CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-839/SE1-019

Correspondence

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo Inc
Phone:	(610) 889-6425
Subject:	marked up draft labeling
Date:	2-14-02
Pages including this sheet:	19
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

The Division's first marked-up draft of your proposed labeling for NDA 20-839/S-019 accompanies this cover sheet. As we have not completed yet our review of your proposed labeling, there may be some additional changes. However, Dr. Lipicky asked that I forward you a copy of our initial marked-up draft for your consideration. He suggested that you review our changes, decide which of our changes you can accept, revise the labeling accordingly, and submit the revised labeling (as draft labeling) to the sNDA. At that point, additional labeling negotiations may be necessary. Please let me know if you have any questions.

/S/

Regards,
Colleen

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	4-6463
Attention:	Mary Ann Holovac
Company Name:	HFD-093
Phone:	
Subject:	patent info for N 20-839/S-019
Date:	9/7/01
Pages including this sheet:	3
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Mary Ann,

As requested, here's the patent info.

Regards,
Colleen /S/

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 34,663

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Reference is made to your correspondence dated August 8, 2001, requesting a waiver for pediatric studies under 21 CFR 314.55(c) for clopidogrel in the indication of Acute Coronary Syndrome, the subject of your August 21, 2001 submitted supplemental application to NDA 20-839.

We have reviewed the information you have submitted and agree that a waiver is justified for Plavix (clopidogrel bisulfate) in Acute Coronary Syndrome for the pediatric population.

Accordingly, a waiver of the pediatric study requirements for your August 21, 2001 supplemental application submitted to NDA 20-839 is granted under 21 CFR 314.55 at this time.

If you have questions, please contact:

Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332

/S/

Sincerely,

{See appended electronic signature page}

Raymond Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Raymond Lipicky
8/29/01 03:18:43 PM

Locicero, Colleen L

From: Lipicky, Raymond J
Sent: Friday, August 24, 2001 11:01 AM
To: Locicero, Colleen L
Subject: RE: CURE sNDA

Yes and Yes.
Desrves a priority review.
Acute coronary syndrome does not occure in children.

-----Original Message-----
From: Locicero, Colleen L
To: Lipicky, Raymond J
Sent: 8/23/01 11:48 AM
Subject: CURE sNDA

Dr. Lipicky,

The CURE sNDA (clopidogrel, efficacy supp for new indication in ACS) is here. Sanofi requests a priority review for the following reasons:

"...reference is made to the 27 March 2001 pre-sNDA Meeting (see Attachment 2), in which the Division acknowledged the Sponsor's request for an expedited review of the CURE supplemental application "in light of the clinical significance of the CURE findings." Due to this clinical significance, the Division identified key submission materials that would be minimally necessary for review of the sNDA in order to expedite the process, thereby confirming an urgency consistent with the purpose of priority review regulations.

Clinical evidence is presented in this sNDA that demonstrates a significant improvement over existing approved therapies for Acute Coronary Syndrome. This can be assessed from the CURE data on primary outcome that demonstrate Plavix significantly reduces the risk of major outcomes such as stroke, myocardial infarction or cardiovascular death with a 20% relative risk reduction over background therapy including aspirin and any other treatments given in patients with Acute Coronary Syndrome. Sanofi-Synthelabo maintains that these findings represent a basis for priority review status, and are hereby requesting said status."

Additionally, the sponsor requests a full waiver (all age groups) of the pediatric study requirement for clopidogrel in this indication (we have drafted a WR for clopidogrel in prevention of shunt thrombosis). A summary of their justification for the waiver is as follows:

1. Not likely to be used in a substantial # of pediatric patients. They estimate that the number of pediatric patients with ACS is well below 50,000, the cut-off for a substantial # of pediatric patients described under 63 FR 66632 (according to Sanofi).

2. No potential for meaningful therapeutic benefit. They state that the rare peds patient with atherosclerosis (& the potential for ACS) is currently treated with a "statin" to lower lipid levels in response to the underlying etiology of their disease. They do not believe clopidogrel's mechanism of action supports a meaningful therapeutic benefit on this basis.

If you would like the full submission, please let me know and I'll send it to you. If not, please answer the following two questions:

Do you designate this supplement a priority review?

Do you grant a full waiver (all age groups) of the pediatric study requirement for this supplemental application?

Thanks,
Colleen

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
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5600 Fishers Lane
Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6901
Attention:	Ann Hards
Company Name:	Sanofi
Phone:	(610) 889-8521
Subject:	contact form
Date:	8/3/98
Pages including this sheet:	2

From: **Colleen Locicero**
Phone: **301-594-5312**
Fax: **301-594-5494**

Dr. Hards,

I failed to attach a copy of Dr. Ganley's Draft Contact Form to the June 25 meeting minutes regarding IND 34 663 that I faxed to you earlier. I am sending a copy of this form now, so that you may attach it to the meeting minutes for reference. Please let me know that you have received this fax.

Sincerely,
Colleen LoCicero

cc: orig IND 34,663
HFD-110
HFD-110/CLoCicero

Draft Contact Form (used when the final visit is not an office visit)

1. When was the last office visit prior to this contact? Month/Day/Year
2. Has successful contact been made concerning the patient? Yes No
3. Date of this contact? Month/Day/Year
4. Date this form was completed? Month/Day/Year
5. Who made the contact?
   ____Investigator/subinvestigator
   ____study nurse or coordinator
   ____other qualified profession
6. How was contact made? (check one or more)
   ____home visit
   ____written communication
   ____phone communication
   ____other, explain_____
7. Who was contacted? (check one or more)
   ___patient
   ___patient's G.P. or other physician [Date patient last seen or contacted: Month/Day/Year]
   ___other qualified health professional [Date patient last seen or contacted: Month/Day/Year]
   Name:_____
   ___relative/caregiver, name: _____
   ___other, please explain_____
8. Did the patient experience anyone of the following since the last office visit?

	Yes	No	Unknown	If Yes, Date
Death	☐	☐	☐	MM/DD/YY
MI	☐	☐	☐	MM/DD/YY
Stroke	☐	☐	☐	MM/DD/YY
PTCA/CABG	☐	☐	☐	MM/DD/YY
Severe Ischemia	☐	☐	☐	MM/DD/YY
Hospitalization	☐	☐	☐	MM/DD/YY
Refractory Ischemia	☐	☐	☐	MM/DD/YY

Name and Signature of person making the contact_____

Name and Signature of Investigator_____

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo Inc
Phone:	(610) 889-6425
Subject:	marked up draft labeling
Date:	2-14-02
Pages including this sheet:	19
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

The Division's first marked-up draft of your proposed labeling for NDA 20-839/S-019 accompanies this cover sheet. As we have not completed yet our review of your proposed labeling, there may be some additional changes. However, Dr. Lipicky asked that I forward you a copy of our initial marked-up draft for your consideration. He suggested that you review our changes, decide which of our changes you can accept, revise the labeling accordingly, and submit the revised labeling (as draft labeling) to the sNDA. At that point, additional labeling negotiations may be necessary. Please let me know if you have any questions.

/S/
Regards,
Colleen

2.2.1 Proposed Labeling

17 pages redacted from this section of the approval package consisted of draft labeling

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo Inc.
Phone:	(610) 889-6425
Subject:	request/NDA 20-839/S-019
Date:	1-28-02
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

Please provide a response to the questions on the following page to assist Dr. Throckmorton in his review of this application. Please provide the response as an amendment to the sNDA.

Regards,
Colleen /S/

1. The revised labeling included in your August 21, 2001 submission proposes the following language:

a. The use of GPIIb/IIIa inhibitors was an exclusion criterion in the CURE trial. What data do you have to support the efficacy of clopidogrel in patients receiving GPIIb/IIIa inhibitors? What instructions were given to investigators that administered GPIIb/IIIa inhibitors following randomization (around 6% of the patients)?

b. Please submit the incidence of the first primary endpoint according to the use of either heparin or LMWH at time of randomization along with any additional data you believe support the efficacy of clopidogrel in these populations.

2. Additionally, the revised labeling proposes the following language:

a. What data do you have that support the efficacy of clopidogrel in patients who undergo CABG (assuming that is what is meant by surgical cardiac revascularization)?

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo
Phone:	(610) 889-6425
Subject:	request for information/N 20-839/S-019
Date:	1-24-02
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

Please complete the table on the following page to assist Dr. Throckmorton in his review. Please provide the completed table as an amendment to the supplemental application.

Regards, /S/
Colleen

Table xxx Bleeding in CURE[a].

	Clopidogrel N=6259	Placebo N=6303	p-Value
TIMI Major Bleeding			
TIMI Minor Bleeding			
TIMI Major Bleeding in Subset Undergoing PCI			
TIMI Minor Bleeding in Subset Undergoing PCI			
Intracranial Hemorrhage	7 (0.11%)	5 (0.08%)	
Retroperitoneal Hemorrhage			

a. xxxx

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Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo
Phone:	(610) 889-6425
Subject:	request /NDA 20-839/S-019
Date:	1-9-02
Pages including this sheet:	1
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

The following is a request from Dr. Throckmorton regarding NDA 20-839/S-019:

You have indicated that there were 28 CURE study sites with individuals who failed to submit the required financial disclosure information. Please provide the following information regarding these sites:

1. The number of patients enrolled (total) from these sites.
2. Confirm that only one Principal Investigator [redacted] failed to complete his/her financial information.

Regards,
Colleen

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo
Phone:	(610) 889-6425
Subject:	questions/NDA 20-839/S-019
Date:	1-9-02
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

Dr. Throckmorton has the following requests regarding NDA 20-839/S-019:

1. Please provide the case report forms for the four patients in CURE reported to have had severe hepatic adverse events.

2. Please confirm that there were no cases of renal failure associated with glomerulonephritis reported in CURE.

3. Please elaborate on why cardiovascular death could not occur in patients prior to PCI, as reported in your December 20, 2001 amendment to the sNDA (question #3).

4. Please complete the following table for those individuals who had their PCI during their initial hospitalization. According to the paper this amounts to 65% of the PCIs, 1730/2658 PCI procedures.

Table 3.4e.2 Cardiovascular Events Before and After PCI in a Subset from CURE[a].

Endpoint	Placebo N=xxx	Clopidogrel N=xxx	Relative Risk (95% C.I.)
Events Before PCI			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI			
CV Death			
MI			
MI or Refractory Ischemia[b]			
Events To Day 30 After PCI			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI			
CV Death			
MI			
MI or Refractory Ischemia[b]			
Events From PCI to End of F/U			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI			
CV Death			
MI			
MI or Refractory Ischemia[b]			

a. From sponsor's submission dated 12.20.01.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.
c. Not calculated as CV death was not definable prior to PCI.

Please provide your responses in an amendment to the sNDA.

Regards,
Colleen

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Rockville, MD 20857

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Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo
Phone:	(610) 889-6425
Subject:	questions/NDA 20-839/S-019
Date:	12-14-01
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

Accompanying this cover sheet are requests from Dr. Throckmorton regarding NDA 20-839/S-019. Please provide your responses in an amendment to the supplemental application. If you have any questions, please let me know.

Regards,
Colleen

1. In your recent submission that summarizes the outcomes before and after the amendment of August 16, 1999, the hazard ratio in the pre-amendment population with ECG changes appears to be significantly higher (0.96) than the hazard ratio observed after the amendment (0.78), although the same population for this subset would have been enrolled. Are the demographics of the pre-amendment with ECG change population different from the with ECG population after the amendment? Aside from the small sample size you cite in your report, do you have other speculation(s) for the sizable observed change in hazard ratio?

2. You analyzed the sub-group efficacy of clopidogrel in Figure 4 of the NEJM paper. Please provide additional details about when these demographics were obtained.

3. In the Lancet August 2001 paper, the incidence rates in table 2 are reported for events other than stroke. Please verify the included data, and provide the missing data for the following table.

Cardiovascular Events Before and After PCI in a Subset from CURE[a].

Endpoint	Placebo N=1345	Clopidogrel N=1313	Risk Reduction (95% C.I.)
Events Before PCI			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI			
CV Death			
MI	68 (15.3%)	47 (3.6%)	0.68 (0.47-0.99)
MI or Refractory Ischemia[b]	206 (15.3%)	159 (12.1%)	0.76 (0.62-0.93)
Events To Day 30 After PCI			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI	86 (6.4%)	59 (4.5%)	0.70 (0.50-0.97)
CV Death	13 (1.0%)	14 (1.1%)	1.10 (0.52-2.35)
MI	51 (3.8%)	28 (2.1%)	0.56 (0.35-0.70)
MI or Refractory Ischemia[b]			
Events From PCI to End of F/U			
CV Death/ MI/ Stroke			
CV Death/ MI/ Stroke/ Refractory Ischemia			
CV Death/ MI	108 (8.0%)	79 (6.0%)	0.75 (0.56-1.00)
CV Death	31 (2.3%)	32 (2.4%)	1.07 (0.65-1.75)
MI	85 (6.4%)	59 (4.5%)	0.71 (0.51-0.99)
MI or Refractory Ischemia[b]			

a. From Lancet, August 18, 2001 article, and from sponsor at reviewer's request.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.

4. Please provide demographic and outcome data for the subset of patients who did not undergo PCI. The outcome data should include the incidence of the following endpoints: both primary endpoints from CURE, CV death, all-cause death, death/MI, stroke, and MI. I am interested in the incidence at 30 days and to the end of F/U.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo
Phone:	(610) 889-6425
Subject:	CURE questions
Date:	12-5-01
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Nancy,

Dr. Throckmorton requests a response to the following questions concerning NDA 20-839/S-019. Please provide your response as an amendment to this supplemental application. If you have any questions, please let me know.

Regards,
Colleen /S/

1. Please provide the incidence of co-primaries in the two populations of entry as described on page 14/76 or the original protocol dated 8.12.98 (along with RR and 95% CI). The results from the population over 60 without ECG changes will necessarily be based on a smaller sample size, as enrollment of those patients was discontinued after the first 5000 patients.

2. Please clarify the timing of the decision not to enroll the patients over the age of 60 without objective signs of cardiac ischemia relative to the decision to increase the sample size and add the co-primary endpoint. A timeline for major milestones, including protocol amendments to the protocol would be one approach.

3. Please provide exposure information, as follows:

   Confirm the accuracy of the following table, and fill in the empty cells.

	≥10 Days	≥30 Days	≥90 Days	≥180 Days	≥270 Days	≥365 Days	≥540 Days
Placebo	6303	5957	5779	4664	3600	2388	
Clopidogrel	6259	5984	5866	4779	3644	2418	

4. Please provide the incidence by treatment group of, and CRFs for, the following reported adverse events:

   All renal failure requiring dialysis or reported using 'uremia'.
   All renal SAEs
   Aplastic anemia
   Thrombotic Thrombocytopenic Purpura

5. In table (10.1) 1 you enumerate the people who 'Completed Treatment', a group that is smaller than the number listed in (10.1) 2 for 'Completed Follow-up'. What was the definition used for 'Completed Treatment' (is it the same as the number who completed at least three months of therapy with study drug, regardless of whether they completed 12 months of follow-up)?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-839/S-019

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Plavix (clopidogrel bisulfate) Tablets

NDA Number: 20-839

Supplement Number: S-019

Review Priority Classification: Priority (P)

Date of Supplement: August 21, 2001

Date of Receipt: August 21, 2001

This supplement proposes the addition of a new indication for the early and long-term reduction of atherothrombotic events in patients with Acute Coronary Syndrome.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 20, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 21, 2002.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note your August 8, 2001 correspondence to the Investigational New Drug application for clopidogrel (IND 34,663) requesting a full waiver of the pediatric study requirement for this supplemental application and our August 29, 2001 correspondence waiving this requirement.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332.

Sincerely yours,

{See appended electronic signature page}

/s/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
8/29/01 03:47:18 PM
For Natalia Morgenstern.

MAY 13

IND 34,663

Sanofi Pharmaceuticals, Inc.
Attention: Ann Hards, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Hards:

Please refer to your Investigational New Drug Application (IND) for Plavix (clopidogrel bisulfate) Tablet.

In reviewing your submission of October 14, 1998, our Statistician has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence.

If you have any questions, please contact:

Ms. Colleen LoCicero
Consumer Safety Officer
(301) 594-5312

Sincerely yours,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
Dr. Hung's review

cc:
Archival IND 34,663
HFD-110/Div. Files
HFD-110/cll

Drafted by: cll/May 5, 1999
Initialed by: J Hung/5/6/99
Z McDonald for N Morgenstern
final:sb/5/11/99
filename: 34663gc990511.doc

GENERAL CORRESPONDENCE

In response to the discussions during the protocol meeting of 06/25/98 with the Agency, the sponsor submitted for review the process to be used for assessing myocardial infarctions in the CURE study and the final CURE protocol. This review pertains to the statistical plan of the protocol.

CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial is a Phase III randomized, multi-center, double-blind, parallel group clinical trial. The primary objective of this study is to evaluate whether clopidogrel is superior to placebo in preventing ischemic complications in patients with unstable angina or myocardial infarction without ST segment elevation (acute coronary syndrome [ACS]) who are receiving aspirin therapy.

The duration of follow-up will be a minimum of 3 months and a maximum of 12 months. Follow-up will end on a fixed date, which will be equivalent to 90 days after the randomization of the last patient (called Study End Date). A patient is considered to have a complete follow-up if the final visit is at least 365 days after randomization or the final visit is on or after the fixed Study End Date.

Patients will be given a loading dose of study drug (clopidogrel 300 mg or placebo) as soon as treatment is allocated. Aspirin therapy (75-325 mg once daily) will be started simultaneously with the study drug or the patient should continue with pre-admission aspirin therapy, as applicable.

The primary efficacy outcome is the first occurrence of the composite outcome of cardiovascular death, myocardial infarction and stroke (ischemic, hemorrhagic or of uncertain type). The secondary outcome is the first occurrence of the composite outcome of cardiovascular death, myocardial infarction, stroke and refractory ischemia. Other outcomes are cardiovascular death, total death, myocardial infarction (fatal or non-fatal) stroke, severe ischemia during hospitalization, mechanical or pharmacological coronary revascularization (PTCA, CABG or

thrombolytic therapy). The events will be adjudicated by the Event Adjudication Committee.

The main efficacy analysis will utilize the intent-to-treat approach (i.e., all randomized patients in the study will be included). The primary outcome will be tested using logrank test and statistical significance will be claimed if the computed p-value is ≤ 0.05. Treatment effect will be measured by the hazard ratio and its associated 95% confidence interval obtained from Cox proportional hazards model. The secondary outcome will be analyzed following the same strategy of the primary outcome analysis. The interpretation of the secondary and primary outcomes depends on their coherence and consistency. If the primary outcome is of borderline statistical significance, the secondary outcome will be examined for consistency and similarity of effects.

Interim Analysis The primary efficacy outcome will be monitored using a modified Haybittle-Peto boundary of four standard deviations in the first half of the study and three standard deviations in the second half. The boundary will have to be exceeded on at least two consecutive time points, three months apart. Two interim efficacy analyses are to be performed at approximately 1/3 and 2/3 of expected events. The corresponding nominal alpha levels are 0.00006 and 0.0027, respectively. The nominal alpha level is 0.049 for the final analysis. Conditional power and stochastic curtailment approach as described by Lan and Wittes (1988, Biometrics) will be used to assess futility at the two interim efficacy analysis times. If the upper limit of the 95% CI for the conditional power for the primary outcome falls below 25%, then the DSMB may recommend early termination for futility.

Sample Size Calculation Based on comparing two proportions, it is planned to randomize 9,000 patients in the trial. The sample size is believed to give adequate power to detect a moderate, but clinically meaningful, difference in the primary clinical outcome, as given in the following table.

Table 1. Detectable Relative Risk Reduction

Endpoints	Control Event Rate	80% power	90% power
Primary outcome	12%	15.4%	17.7%
α=0.05 (2-sided)	13%	14.8%	16.9%
	14%	14.1%	16.2%
Secondary outcome	22%	13.2%	14.8%
α=0.01 (2-sided)	24%	12.5%	14.0%

comments

The interim analysis plan and sample size calculation are reasonable.

The proposed plan states that the interpretation of the secondary and primary outcomes depends on their coherence and consistency. Furthermore, if the primary outcome is of borderline statistical significance, the secondary outcome will be examined for consistency and similarity of effects. It is not clear how the consistency or coherence will be examined (by numerical similarity or else?). Table 1 seems to suggest that the secondary outcome may be tested at two-sided α=0.01. The difference between the primary outcome and the secondary outcome lies in the component, refractory ischemia. If the secondary outcome will be a part of the decision tree for drawing the conclusion regarding efficacy of clopidogrel, then I recommend that the secondary outcome be formally tested and a small fraction of total alpha be allocated to this test, for instance, testing the primary outcome at α=0.049 and the secondary outcome at α=0.001. The 0.001 level may be improved by taking advantage of a potentially moderate to large correlation between the primary and secondary outcomes. This approach can protect testing the primary outcome from overly spending alpha for the secondary outcome when refractory ischemia is the major component of the secondary outcome and clopidogrel has null effect on this component. On the other hand, if clopidogrel has a very large effect on refractory ischemia but a small effect on the primary outcome, statistical evidence with a p-value less than the conservative 0.001 level is recommended.

If the size of clopidogrel effect on refractory ischemia is about the same as that on the primary outcome, then a good alternative is the two-stage approach that begins with globally testing the two endpoints at α=0.05 and then testing each endpoint at the same alpha if the global test is significant.

In any event. I strongly recommend that the sponsor look into this issue carefully.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 34,663

SEP - 2 1998

Sanofi Pharmaceuticals, Inc.
Attention: Ann Hards, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Hards:

Please refer to your Investigational New Drug Application (IND) for Plavix (clopidogrel bisulfate) 75 mg. Tablet.

We also refer to your letter of August 12, 1998 in which you requested a waiver of the IRB membership requirements as described in 21 CFR 56.107 for the ex-US sites included in your proposed phase III study (EFC3307) [entitled CURE: Clopidogrel in Unstable Angina To Prevent Recurrent Ischemic Events (OASIS-4)] to evaluate clopidogrel versus placebo in patients with acute coronary syndrome (unstable angina or myocardial infarction without ST segment elevation) who are receiving aspirin therapy. You have stated in your letter that the requirements for Institutional Review Board/Independent Ethics Committee (IEC) membership in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline "E6 Good Clinical Practice: Consolidated Guidance" will be used.

We note that the 21 CFR 56.107(b) requirement that "every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender..." is not a requirement in the ICH guideline.

Representation of both genders is critical on an IRB when gender-specific clinical studies are under review or when there are indications that a test article may place one gender more at risk than the other. The study under IND 34,663 however, is not gender specific nor is there any indication of gender related risks. For this reason, it is not necessary to require that an IRB/IEC add a member based solely on gender to ensure that both genders are represented during review of this study.

Therefore, we have concluded, that, based on the requirement that the IRB/IEC membership be in compliance with the requirements for composition as found in section E6. 3.2.1 and the glossary definitions for an IRB and IEC found in E6. 1.27 and 1.31 of the ICH-GCP consolidated guideline, this waiver request is granted.

If you have any questions, please contact:

Ms. Colleen LoCicero
Consumer Safety Officer
(301) 594-5312

Sincerely yours,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc: orig IND 34, 663
HFD-110
HFD-110/LoCicero
HFD-340/D Lepay
HFD-341/Woollen
HFD-343/Zollo
HFD-1/Woodcock
cl/8/26/98;sb/8/28/98
R/D: S Chun/8/26/98
C Ganley/8/26/98
R Fenichel/8/27/98
N Morgenstern/8/28/98

REQUEST GRANTED

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 34,663

AUG 3 1998

Sanofi Pharmaceuticals, Inc.
Attention: Ann Hards, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Hards:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets and to your protocol entitled, "CURE-'Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events' (OASIS 4)."

Under 21 CFR 312.32 you (the holder of the IND) are required to report serious and unexpected adverse drug reactions (as soon as possible but within 7 calendar days by telephone or facsimile for death or life threatening experience and in writing by 15 calendar days of learning of the event) to FDA. Since the major endpoints of the protocol include morbidity and mortality and the trial is designed to determine whether the frequency of such events is affected by treatment with clopidogrel compared to placebo, a treatment relationship cannot be excluded until the trial has been completed and the data analyzed. It is not reasonable, under the circumstance of the trial, to expect reports to FDA of all mortality and serious morbidity you will observe. Such reports are ordinarily requested to be certain that subjects' safety is being protected.

You have a Safety Monitoring Committee whose responsibility is to ensure the safety of the trial as it is ongoing. Consequently, as we have done for a variety of similar circumstances, the following outlines the requirements that fulfill your responsibilities under your IND.

As holder of the IND you are the person responsible for reporting serious and unexpected adverse reactions to the FDA.

The Safety Monitoring Committee should make all judgments with respect to what are serious and unexpected adverse drug reactions to report to you. Your 7 and 15 calendar day limits start upon your receipt of serious and unexpected adverse reaction information from the Safety Monitoring Committee. You have no obligation to us until the Safety Monitoring Committee reports an event to you.

We anticipate that the Safety Monitoring Committee will function in a blinded (e.g., groups A and B) fashion. For purposes of reporting serious and unexpected adverse drug reactions, there is no need to unblind (identifying placebo and or active group; A and B are sufficient) the patients reported. As mortality and serious morbidity are endpoints in your trial, such events should not be considered serious and unexpected." Certainly the Committee will have developed a means for ensuring that the trial is still able to continue morally and ethically. Neither you, nor the FDA, should play a role in that decision-making process.

What the Committee should report to you as "serious and unexpected" is somewhat more difficult to define. For purposes of the trial, adverse events such as hepatic toxicity, bone marrow depression, pancreatitis, etc., where the circumstances are such that your Committee thinks a treatment relationship cannot be excluded and/or when the frequency of such events has had a meaningful (another committee judgment) increase in incidence is what the committee should report to you.

The blind need be broken only when a number of events or disproportion of events between treatment groups reaches a magnitude that could require an alteration in the trial design or in the discontinuation of the trial.

Should you have any questions, please contact:

Ms. Colleen LoCicero
Consumer Safety Officer
Telephone: (301) 594-5312

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FILING SUMMARY/MEETING MINUTES

NDA Number and Drug Name: NDA 20-839/S-019

New Indication: the reduction of atherothrombotic events (myocardial infarction, stroke, cardiovascular death, and refractory ischemia), in combination with aspirin in patients with acute coronary syndrome (unstable angina or non-Q-wave MI) whether or not they undergo cardiac revascularization (surgical or PCI, with or without stent).

Sponsor: Sanofi-Synthelabo Inc.

Therapeutic Classification: P

Date of Application: August 21, 2001

Date of Receipt: August 21, 2001

User Fee Goal: February 21, 2002

User Fee Status: Paid

Submission Complete As Required Under 21 CFR 314.50? Yes

Patent Information Included? Yes

Exclusivity Requested? Yes (3 years for indication)

Debarment Statement Included? Yes

Pediatric Rule addressed? Yes, requirement has been waived.

Pre-NDA Meeting(s)? Yes, minutes attached.

Meeting Participants:

Earl Butler, Ph.D.	Pharmacologist, Non-Clinical Laboratory Studies Branch, Division of Scientific Investigation (HFD-048)
Antoine El Hage, Ph.D.	Branch Chief, Good Clinical Practices Branch II, Division of Scientific Investigation (HFD-045)
James Hung, Ph.D.	Team Leader, Statistical, Division of Biometrics I (HFD-810)
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110

BACKGROUND

This supplemental application proposes a new indication for Plavix in the setting of Acute Coronary Syndrome (see text above) based on the results of the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (OASIS-4) – A phase 3 randomized, double-blind, parallel group clinical study of clopidogrel versus placebo in patients with an acute coronary syndrome (unstable angina or myocardial infarction without ST segment elevation)) study.

In an effort to expedite the submission of this supplemental application due to the potential clinical importance of the CURE findings, the Division accepted the sponsor's proposal to submit an abbreviated supplemental application. The details of the proposal, i.e., the items essential for an adequate review of the application, were discussed and agreed upon at the March 27, 2001 pre-sNDA meeting for this supplemental application.

The application is a fully electronic submission with only those documents requiring an original signature provided in paper copy.

Assigned Reviewers:

DISCIPLINE	REVIEWER
Primary Medical:	Throckmorton
Sec. Medical:	N/A
Pharmacology:	N/A
Chemist:	Zielinski
Statistician:	Hung
Biopharmaceuticist:	N/A
Microbiologist:	N/A
DSI:	N/A
Project Manager:	LoCicero

MEDICAL – It was decided at the filing meeting that a secondary medical review of this supplement will not be necessary. Dr. Throckmorton expects to complete his review of this application within several days of the completion of the statistical review (i.e., the beginning of December 2001).

STATISTICAL – Dr. Hung expects to complete his review of this application by the end of November 2001.

CHEMISTRY – Dr. Zielinski did not attend the filing meeting, as there is no chemistry to review, other than the request for categorical exclusion for environmental assessment.

Did firm request categorical exclusion for environmental assessment? Yes

EIR package transmitted? N/A

Trade Name Review Requested? N/A

DSI – CURE was a large, multi-center study with no single investigator enrolling enough subjects to significantly affect the outcome of the study. Therefore, Drs. Lipicky and Throckmorton agreed that a DSI audit of the CURE study will not be necessary.

MISCELLANEOUS – Dr. Lipicky would like to take this application to the January Advisory Committee meeting, if there is one, but indicated that additional internal discussion will be needed before a final decision on this can be made.

Signature, Minutes/Summary Preparer: /S/ Colleen LoCicero

Concurrence, Meeting Chairperson: /S/ Raymond Lipicky, M.D.

drafted: 10/11/01 finaled: 10/18/01

rd:
Butler
El Hage
Hung/10/12/01
Throckmorton/10/12/01

cc: Division Document Room
S Matthews
A El Hage
C LoCicero

SEP - 2 1998

CSO Overview of IND 34,663/S-188 (request for IRB waiver)
Plavix (clopidogrel bisulfate) 75 mg Tablet
August 28, 1998

Background

The Division received a request from Sanofi Pharmaceuticals, dated August 12, 1998, for a waiver of the IRB membership requirements as described in 21 CFR 56.107 for the ex-US sites in their proposed phase 3 study entitled CURE: Clopidogrel in Unstable Angina To Prevent Recurrent Ischemic Events (OASIS-4).

In accordance with the draft MaPP (4740.X) *Waiver of Institutional Review Board Requirements* the Division notified the Office of the Center Director and the Division of Scientific Investigation (DSI) that this waiver request had been received for consideration. Upon receipt, the Division verified that the waiver request package was complete and contained all of the information specified in the MaPP.

DSI

The Division forwarded a copy of the request package to DSI for their review and comment. In a memorandum dated August 26, 1998, DSI concurred with the Division's recommendation that the waiver request be granted. DSI also reviewed the approval letter drafted by the Division and agreed that it was acceptable.

Approval letter and request package

The DSI endorsed waiver package that will be forwarded to the Office of the Center Director contains the following:

- An approval letter in final form for the signature of the Director to the applicant. The approval letter clearly states the regulatory requirement being waived and the conditions of the waiver.
- A copy of the e-mail from DSI endorsing the approval letter
- A copy of the memorandum from DSI concurring that the waiver request should be granted.
- A copy of the waiver request. The waiver request contains the following information, as required in the MaPP:

    1. A copy of the study protocol (ATTACHMENT 1)
    2. A copy of the informed consent documents (ATTACHMENT 2)
    3. Identification of the specific provision of 21 CFR Part 56 for which a waiver is requested (WAIVER REQUEST LETTER)
    4. A statement of the specific study activity to which the waiver will apply and the reason this study activity is a special situation (WAIVER REQUEST LETTER)

5. Justification that the waiver would be in the best interest of subjects (WAIVER REQUEST LETTER)
6. A description of the alternative mechanism for assuring the protection of subjects (WAIVER REQUEST LETTTER)
7. A description and documentation of any action that an IRB has taken on a protocol (s) or an informed consent document(s) related to the specific study for which the waiver is requested (WAIVER REQUEST LETTER)

Summary

The waiver package containing the approval letter in final form will be forwarded to the Center Director, Dr. Janet Woodcock, for endorsement and signature. The Division will issue the approval letter, once it has been signed, to the applicant.

/S/

Colleen LoCicero, CSO

cc: orig IND 34,663
HFD-110
HFD-110/LoCicero

SEP - 2 1998

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 26 1998

FROM: Director, Division of Scientific Investigations, HFD-340

SUBJECT: IND 34,663 (Serial No. 188); Protocol EFC3307, CURE: Clopidogrel Bisulfate in Unstable Angina to Prevent Recurrent Ischemic Events - Request to Waive 21 CFR 56.107 Institutional Review Board Membership

TO: Director, Division of Cardio-Renal Drug Products, HFD-110

We concur with the request of Sanofi Pharmaceuticals to waive the institutional review board (IRB) membership requirements specified in 21 CFR 56.107 for the ex-US sites in the CURE study. The requirements for Institutional Review Board/Independent Ethics Committee (IEC) membership in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline "E6 Good Clinical Practice: Consolidated Guidance" will be used.

The submission referenced the requirement in 21 CFR 56.107(b) that "every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender...." There is no corresponding requirement in the ICH guideline.

Representation of both genders is critical on an IRB when gender-specific clinical studies are under review or when there are indications that a test article may place one gender more at risk than the other. However, the study under IND 34,663 is not gender specific nor is there any indication of gender related risks. For this reason, it is not necessary to require that an IRB/IEC add a member based solely on gender to ensure that both genders are represented during review of this study.

The approval for this waiver is based on the requirement that the IRB/IEC membership be in compliance with the requirements for composition as found in section E6. 3.2.1 and the glossary definitions for an IRB and IEC found in E6. 1.27 and 1.31 of the ICH-GCP consolidated guideline.

/S/

David A. Lepay, M.D., Ph.D.

cc:
HFD-110 (Locicero)
HFD-340 (Lepay/Woollen)
HFD-340 RF
HFD-343 (Zollo)
HFD-343 RF
R/D:HFD-343:Zollo:08/24/98

cc: orig IND 34,663
HFD-110
HFD-110/LoCicero

SEP - 2 1998

Printed by Colleen Locicero

Electronic Mail Message

Date: 27-Aug-1998 07:48am
From: Mary Jo Zollo
ZOLLOM
Dept: HFD-343 MPN1 107
Tel No: 301-594-1026 FAX 301-594-1204

Colleen Locicero (LOCICEROC)

ect: Waiver letter

ust read your draft waiver letter for IND 34,663. It looks fine to me.

cc: orig. IND 34,663
HFD-110
HFD-110/LoCicero