CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-051

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 20839
Supplement: 051
Drug: Plavix (clopidogrel bisulfate) Tablets
Class: P2Y12 ADP-receptor inhibitor
Sponsor: sanofi-aventis US
Indication: No change in indication with this supplement
Date of re-submission (Class 1): 8 March 2011
PDUFA date: 8 May 2011
Approval date: 6 May 2011

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Medical Reviewer
    - Martin Rose, M.D., JD
  - Regulatory Health Project Manager
    - Alison Blaus
- Office of Clinical Pharmacology
  - Elena Mishina, Ph.D. – Clinical Pharmacology
  - Kevin Krudys, Ph.D. - Pharmacometrics
- Office of Biostatistics, Division of Biometrics I
  - Yeh-Fong Chen, Ph.D.
- Office of Compliance, Division of Scientific Investigations (DSI)
  - Clinical Studies – Sharon Gershon

❖ BACKGROUND

Clopidogrel is a platelet P2Y12 ADP-receptor inhibitor currently marketed for treatment of patients with acute coronary syndrome and those with recent MI, recent stroke, or established peripheral arterial disease. The clopidogrel pediatric developmental program was initiated in 2000 to determine if administration of clopidogrel to infants who had undergone systemic-to-pulmonary artery shunt placement for palliation of congenital heart disease would reduce the risk of shunt thrombosis. The sponsor submitted a proposed pediatric study request and the Agency responded with a Pediatric Written Request (PWR) on 15 October 2001. After completion of a dose-ranging study in children (PICOLO), the sponsor met with the Division to discuss their planned special protocol assessment (SPA) for the Phase 3 safety and efficacy study (CLARINET). This SPA was submitted on 9 May 2006 and the Division responded with a No Agreement letter on 12 July 2006. Subsequently, the PWR was amended to reflect the agreements. The sponsors met with the Agency on 10 May 2010 for a pre-NDA meeting where a number of aspects of this supplement were discussed.

Due to an inability to come to an agreement on how CLARINET should be described in labeling, the Division issued a Complete Response (CR) letter on 14 January 2011 to the original 15 July 2010 submission (S051). The complete labeling history for this supplement is described in detail below.

❖ REGULATORY TIMELINE

- End of Phase 2 Meeting (EoP2 - Pediatrics): 16 July 2006 (minutes dated 8 August 2006)
- Special Protocol Assessment Letter from the Agency dated 16 June 2006
- Pre-NDA Meeting: 10 May 2010 (minutes dated 26 May 2010)
- User fee for this application was paid in full on 21 June 2010 (ID 3010405)
- NDA Filed: 15 July 2010
- Filing Meeting: 16 September 2010
- Priority Designation Letter: 9 September 2010
- 74-day Issues Letter: 27 September 2010
- Mid-cycle Meeting: No meeting needed
- Complete Response Letter Date: 14 January 2011
- PDUFA Date (1st cycle): 15 January 2011
- Teleconference to discuss 18 February 2011 labeling proposal: 4 March 2011
- Class 1 Resubmission: 8 March 2011
- Approval Date: 6 May 2011

❖ LABELING NEGOTIATIONS

Based on the results of CLARINET, sanofi aventis proposed the following labeling changes in the sNDA submitted as amendment 051 to NDA 20839 on 15 July 2010:

(b) (4)

After review of the supplement by the Division, we proposed (on 14 December 2010) to delete subsection 5.6 and to change subsection 8.4, **Pediatric Use**, to the following:

> **8.4 Pediatric Use**
>
> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial neither demonstrated nor ruled out a clinical benefit of administering clopidogrel to neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome include administration of too low a dose of clopidogrel to have an effect and initiation of clopidogrel too long after shunt placement.

On 23 December 2010, sanofi aventis responded to the Division's proposal with the following (which does not differ significantly from their original proposal):

(b) (4)

The Division and the sponsor met via teleconference on 5 January 2011, minutes dated 7 January 2011, to discuss both the Division's and the sponsor labeling proposals and their associated rationale. The Division agreed to eliminate the sentence describing possible factors that may have contributed to CLARINET's outcome and proposed the following:

> **8.4 Pediatric Use**
>
> Safety and effectiveness in pediatric populations have not been established.

> A randomized, placebo-controlled trial neither demonstrated nor ruled out a clinical benefit of administering clopidogrel to neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt.

After considering the suggested wording proposed at the 5 January 2011 meeting, sanofi/BMS responded via email with the following proposal for the label:

(b) (4)

The Division did not agree with the sponsor's new proposed language as it did not incorporate what the Division mentioned at the 5 January teleconference as the fundamental principle to be captured in labeling, which is that CLARINET did not exclude possible benefits of Plavix in the treated population. The Division and the sponsor met again on 13 January 2011 to discuss labeling. Prior to this meeting, the sponsor raised two new proposals for our consideration:

(b) (4)

Both Drs. Temple and Stockbridge reviewed these proposals and at the 13 January 2011 teleconference made an alternative final proposal (conveyed to the sponsor via email after the teleconference):

> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial (CLARINET) did not demonstrate clinical benefit in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. The trial, however, used a relatively low dose of Plavix and randomized patients [X time] post-procedure, so that it did not adequately test for effectiveness.

Upon consideration by the sponsor, they did not agree to the above, but instead proposed another version for the Agency's consideration:

(b) (4)

The above still did not address the Agency's concerns that have been conveyed to the sponsor at both the 5 January and 13 January 2011 meetings. Due to the inability to reach an agreement on labeling, the Division issued a Complete Response Letter on 14 January 2011 noting the final labeling recommendation:

> **8.4 Pediatric Use**
> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial (CLARINET) did not demonstrate clinical benefit in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. The trial, however, used a relatively low dose of Plavix and randomized patients a mean of 20 days post-procedure, so that it did not adequately test for effectiveness.

The Division met with the sponsors again on 4 March 2011 to discuss the sponsor's following proposal (submitted to the NDA on 18 February 2011 in track changes from the Complete Response Letter – the deletions are not reflected in track changes):

> **8.4 Pediatric Use**
> Safety and effectiveness in the pediatric populations have not been established.
>
> A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the timing of initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

After a brief discussion, the Division and sponsor agreed on the final labeling below to describe CLARINET:

> **8.4 Pediatric Use**
> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

❖ REVIEWS

Below are the conclusions reached by the Plavix pediatrics team members, organized by role or discipline.

Office Memorandum
n/a

Divisional Memorandum
Dr. Stephen Grant completed a Divisional Memo on 5 May 2011.

Cross-Discipline Team Leader (CDTL) Review
n/a

Medical Review (dated 27 December 2010 and 2 May 2011)
Dr. Rose noted in his review that the sponsor proposed Plavix labeling should be amended to describe the inconclusive nature of the CLARINET results. He added that the Division should recommend to the Pediatric Exclusivity Board that the Pediatric Exclusivity for clopidogrel should be denied.

Biostatistics Review (dated 29 November 2010)
Dr. Chen highlighted in her review that the data from the only efficacy study (EFC5314/CLARINET) did not show that clopidogrel had an effect in reducing all-cause mortality and shunt-related morbidity in neonates of infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.

Due to the unexpectedly similar bleeding event rates between the clopidogrel 0.2 mg/kg dose group and placebo, a concern of insufficient dose used was raised and a letter was sent by the Agency to the sponsor for clarification. The sponsor insisted that the chosen dose was endorsed by the Platelet Aggregation Committee, Steering Committee, and FDA. Dr. Chen found that based on the sponsor provided closed meeting minutes for the first interim analysis, the sponsor was indeed informed repeatedly that the used dose could be too low to demonstrate clopidogrel's efficacy.

Clinical Pharmacology & Pharmacometrics Review (dated 23 December 2010)
In Drs. Mishina and Krudys' joint review, they noted that pediatric Plavix® dosing recommendations could not be derived because an effective dose had not been identified in the clinical studies. The clopidogrel dose (0.2 mg/kg) used in the pivotal CLARINET study was potentially inadequate to demonstrate efficacy. They noted that the dose selection was based on response to ADP-induced platelet aggregation targeting similar proportional reduction to that of adults. This strategy is potentially flawed because the baseline responses among neonates, infants and adults are remarkably different. Furthermore, the formulation used in the CLARINET study was administered via naso-jejunal route in most of the neonates, thus potentially leading to decreased bioavailability, as clopidogrel is practically insoluble at neutral pH. If clopidogrel or another drug in the same class is considered for future evaluation for this indication, the pivotal trial should include multiple doses, one of which must achieve drug levels similar to those observed in adult patients at the approved dose. Also, the impact of different routes of administration on the bioavailability must be taken into consideration.

Office of New Drug Quality Assessment (ONDQA), Branch I, Review (dated 13 January 2011)
Dr. Srinivasachar noted in his review that the other review disciplines have questioned the appropriateness of the studies carried out (dose selection, bioavailability of formulation used etc.), but that these issues were not within the scope of a CMC review. What was clear to Dr. Srinivasachar, however, was that there will be no commercial pediatric formulation at this

time and consequently, no changes to the Description and How Supplied sections of the package insert labeling were warranted.

Office of New Drug Quality Assessment (ONDQA), Biopharmaceutics (dated 12 January 2011)
In Dr. Dorantes' review, she had the following comments:

1. It should be noted that at the time the BA study was conducted (2002) the assay for the active metabolite was not available. However, currently it is feasible to measure the parent compound and the active metabolite. Therefore, if we were to evaluate this BA study to currents standards, it would not be acceptable.
2. Although, the pediatric formulation used in the CLARINET trial is a solution, it includes (b) (4). (b) (4) is an inactive ingredient that has an effect on the small intestine transit (SIT) time and influences the bioavailability of the formulations, independently if they are solid dosage forms (tablets/capsules) or solutions. Increasing the rate of SIT reduces the time available for drug absorption and may contribute to impaired absorption of luminal contents. Therefore, the incorporation of an excipient like (b) (4) into a pharmaceutical formulation would lead to reduced bioavailability.
3. Additionally, there are other factors that may had affected the bioavailability of the formulation used in the CLARINET trial such as; 1) the lack of (b) (4) in the formulation, 2) the precipitation of clopidogrel in the non-acidic environment of the small intestine, 3) the fact that the formulation used in the CLARINET study was administered via naso-jejunal route in some of the neonates. It is not known whether the pediatric clopidogrel solution administered via a naso-gastric or naso-jejunal tube results in the same bioavailability as the oral administration. The sponsor did not present any data to address this issue. At present, it is not known what levels of clopidogrel are achieved when the solution is administered through these routes.
4. The sponsor states that the all the clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution. Therefore, these formulations are considered pharmaceutical equivalent*. The sponsor is not correct, because the concentration of the active ingredient is different (b) (4)) and the route of administration for some of the pediatric subjects was different (oral vs. naso-gastric or naso-jejunal tube), therefore, the formulations used in the pediatric program cannot be considered to be pharmaceutically equivalent. In addition of that the formulation used in the CLARINET trial also presents a potential bioavailability/bioequivalence problem. Therefore, the formulations used in the pediatric program are not pharmaceutically equivalent, nor therapeutically equivalent**.

*Pharmaceutical Equivalents: Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.

**Therapeutic Equivalents: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2)they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that(a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.

5. Although, the pediatric-formulation used in the BA study and the pediatric formulation used in the CLARINET pediatric-pivotal clinical trial are both solution formulations; because 1) the formulations are different, 2) the concentration of the active drug is different, 3) the percentage of (b) (4), an inactive ingredient presenting a potential bioavailability/bioequivalence problem is different, and 4) the route of administration was different for some pediatric patients; these formulations are not pharmaceutically nor therapeutically equivalent. Therefore, the pediatric formulation used in the pediatric trial CLARINET cannot qualify for a BA/BE waiver.
6. In conclusion, contrary to the recommendation given in the pediatric written request* that clearly states that the relative bioavailability of the formulation to-be-used in clinical studies (each study) should be characterized; the applicant never evaluated the bioavailability of the pediatric formulation used in the CLARINET trial, neither the impact that the route of administration could have on the bioavailability of this pediatric formulation.

> *Pediatric Written Request - FORMULATION ISSUES
> The studies described below should use an age-appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

7. Overall, without having the data from a bioavailability study (i.e., four way crossover study) evaluating;
    a. the BA of the approved Plavix® tablets vs. the pediatric formulation used in the CLARINET study using the oral route of administration
    b. the BA of the approved Plavix® tablets given by oral route vs. the pediatric formulation used in the CLARINET study administered by naso-gastric tube, and
    c. the BA of the approved Plavix® tablets given by the oral route vs. the pediatric formulation used in the CLARINET study administered by naso-jejunal tube, one could speculate that these differences would not result in differences in bioavailability (resulting in dissimilar exposures), but one would never be able to provide a complete answer for the following relevant questions;
        i. WHY DID THE CLARINET TRIAL FAIL?
        ii. WAS THE FAILURE DUE TO THE USE OF AN INADEQUATE FORMULATION?
        iii. WAS THE ROUTE OF ADMINISTRATION A MAJOR CONTRIBUTOR TO THE TRIAL FAILURE?

❖ CONSULTS

Division of Scientific Investigations (DSI) Review (dated 11 January 2011)
Five clinical investigator sites, 3 domestic and 2 foreign, were inspected in support of this application. No significant regulatory violations were noted during the inspections and no Form FDA-483 was issued to any clinical investigator. Although some protocol deviations as well as recordkeeping deficiencies were discussed with Dr. Tugertimur, the deficiencies are isolated in nature and unlikely to significantly impact data reliability. According to DSI, the data are considered reliable in support of this supplement.

As the review division was concerned about the delays in randomization post-surgery, DSI's inspection assignments specifically requested that the field investigators evaluate and assess the reasons for delayed randomizations at each site. The mean time for randomization to surgery ranged from 25.7 days to 45.4 days for 4 sites and for one site it was between 0-8 days after the intercardiac line was removed. DSI notes that Protocol EFC5314 Section 6.1 only stated that "Eligible patients were to be randomized and treated with the study drug as early as possible following shunt placement." The protocol did not specifically mandate a certain amount of time. With respect to whether the delays in randomization were "appropriate given the clinical status of the patient," the consistent reason provided across sites is that the PI waited to ensure that the subjects were stable. Additional reasons (as stated by the CI at the 2 foreign Argentinian sites) were delays in referral from other hospitals, and giving families several weeks time to read the Informed Consent Document and understand the protocol. Based on what was stated, DSI considers the cited reasons reasonable, especially as the protocol was not specific as to when subjects should be randomized post-surgery. DSI considers subject safety as a very reasonable and appropriate reason to delay randomization; however, DSI defers to the specialty experts in the review division to evaluate the appropriateness of the physician's rationale for delays in randomization as outlined above.

With respect to whether the "actions taken by the sponsor to ensure early randomization, were reasonable and appropriate in response to the situation," the FDA field investigators noted that Newsletters were sent to sites requesting that randomization occur as soon as possible. DSI considers this as reasonable as the protocol was silent with respect to the specific timeframes that should be adhered to with from surgery to randomization. As the time from surgery to randomization was considered critical, then perhaps the protocol and/or amendments should have required a specific time from surgery to randomization.

It is important to note that the observations noted above for 2 domestic sites (Sullivan and Pizarro) and the 2 foreign sites (Somoza and Marantz) are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

❖ CONCLUSION

Pediatric Exclusivity was granted, effective 20 January 2011, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). The sponsor was notified by Alison Blaus, via email, of this decision on 24 January 2011.

A Complete Response (CR) Letter (cleared by OCC on 12 January 2011) was issued for this application and signed by Dr. Norman Stockbridge, Division Director, on 14 January 2011.

Subsequently, a Class 1 resubmission was received on 8 March 2011. An Approval Letter to incorporate pediatric labeling (language agreed upon at the 4 March 2011 teleconference) was drafted and signed by Stephen Grant, Deputy Division Director, on 6 May 2011. The letter was appended with the final agreed-upon label.

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

/s/

ALISON L BLAUS
05/06/2011

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

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❖ BACKGROUND

Clopidogrel is a platelet P2Y12 ADP-receptor inhibitor currently marketed for treatment of patients with acute coronary syndrome and those with recent MI, recent stroke, or established peripheral arterial disease. The clopidogrel pediatric developmental program was initiated in 2000 to determine if administration of clopidogrel to infants who had undergone systemic-to-pulmonary artery shunt placement for palliation of congenital heart disease would reduce the risk of shunt thrombosis. The sponsor submitted a proposed pediatric study request and the Agency responded with a Pediatric Written Request (PWR) on 15 October 2001. After completion of a dose-ranging study in children (PICOLO), the sponsor met with the Division to discuss their planned special protocol assessment (SPA) for the Phase 3 safety and efficacy study (CLARINET). This SPA was submitted on 9 May 2006 and the Division responded with a No Agreement letter on 12 July 2006. Subsequently, the PWR was amended to reflect the agreements. The sponsors met with the Agency on 10 May 2010 for a pre-NDA meeting where a number of aspects of this supplement were discussed.

❖ REGULATORY TIMELINE

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❖ LABELING NEGOTIATIONS

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(b) (4)

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A randomized, placebo-controlled trial neither demonstrated nor ruled out a clinical benefit of administering clopidogrel to neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome include administration of too low a dose of clopidogrel to have an effect and initiation of clopidogrel too long after shunt placement.

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❖ REVIEWS

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Dr. Rose noted in his review that the sponsor proposed Plavix labeling should be amended to describe the inconclusive nature of the CLARINET results. He added that the Division should recommend to the Pediatric Exclusivity Board that the Pediatric Exclusivity for clopidogrel should be denied.

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potentially flawed because the baseline responses among neonates, infants and adults are remarkably different. Furthermore, the formulation used in the CLARINET study was administered via naso-jejunal route in most of the neonates, thus potentially leading to decreased bioavailability, as clopidogrel is practically insoluble at neutral pH. If clopidogrel or another drug in the same class is considered for future evaluation for this indication, the pivotal trial should include multiple doses, one of which must achieve drug levels similar to those observed in adult patients at the approved dose. Also, the impact of different routes of administration on the bioavailability must be taken into consideration.

Office of New Drug Quality Assessment (ONDQA), Branch I, Review (dated 13 January 2011)
Dr. Srinivasachar noted in his review that the other review disciplines have questioned the appropriateness of the studies carried out (dose selection, bioavailability of formulation used etc.), but that these issues were not within the scope of a CMC review. What was clear to Dr. Srinivasachar, however, was that there will be no commercial pediatric formulation at this time and consequently, no changes to the Description and How Supplied sections of the package insert labeling were warranted.

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1. It should be noted that at the time the BA study was conducted (2002) the assay for the active metabolite was not available. However, currently it is feasible to measure the parent compound and the active metabolite. Therefore, if we were to evaluate this BA study to currents standards, it would not be acceptable.
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3. Additionally, there are other factors that may had affected the bioavailability of the formulation used in the CLARINET trial such as; 1) the lack of (b) (4) in the formulation, 2) the precipitation of clopidogrel in the non-acidic environment of the small intestine, 3) the fact that the formulation used in the CLARINET study was administered via naso-jejunal route in some of the neonates. It is not known whether the pediatric clopidogrel solution administered via a naso-gastric or naso-jejunal tube results in the same bioavailability as the oral administration. The sponsor did not present any data to address this issue. At present, it is not known what levels of clopidogrel are achieved when the solution is administered through these routes.
4. The sponsor states that the all the clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution. Therefore, these formulations are considered pharmaceutical equivalent*. The sponsor is not correct, because the concentration of the active ingredient is different ((b) (4) and the route of administration for some of the pediatric subjects was different (oral vs. naso-gastric or naso-jejunal tube), therefore, the formulations used in the pediatric program cannot be considered to be pharmaceutically equivalent. In addition of that the formulation used in the CLARINET trial also presents a potential bioavailability/bioequivalence problem. Therefore, the formulations used in the pediatric program are not pharmaceutically equivalent, nor therapeutically equivalent**.

*Pharmaceutical Equivalents: Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.

**Therapeutic Equivalents: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2)they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that(a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.

5. Although, the pediatric-formulation used in the BA study and the pediatric formulation used in the CLARINET pediatric-pivotal clinical trial are both solution formulations; because 1) the formulations are different, 2) the concentration of the active drug is different, 3) the percentage of (b) (4) an inactive ingredient presenting a potential bioavailability/bioequivalence problem is different, and 4) the route of administration was different for some pediatric patients; these formulations are not pharmaceutically nor therapeutically equivalent. Therefore, the pediatric formulation used in the pediatric trial CLARINET cannot qualify for a BA/BE waiver.
6. In conclusion, contrary to the recommendation given in the pediatric written request* that clearly states that the relative bioavailability of the formulation to-be-used in clinical studies (each study) should be characterized; the applicant never evaluated the bioavailability of the pediatric formulation used in the CLARINET trial, neither the impact that the route of administration could have on the bioavailability of this pediatric formulation.

*Pediatric Written Request - FORMULATION ISSUES
The studies described below should use an age-appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

7. Overall, without having the data from a bioavailability study (i.e., four way crossover study) evaluating;
    a. the BA of the approved Plavix® tablets vs. the pediatric formulation used in the CLARINET study using the oral route of administration
    b. the BA of the approved Plavix® tablets given by oral route vs. the pediatric formulation used in the CLARINET study administered by naso-gastric tube, and
    c. the BA of the approved Plavix® tablets given by the oral route vs. the pediatric formulation used in the CLARINET study administered by naso-jejunal tube, one could speculate that these differences would not result in differences in bioavailability (resulting in dissimilar exposures), but one would never be able to provide a complete answer for the following relevant questions;
        i. WHY DID THE CLARINET TRIAL FAIL?
        ii. WAS THE FAILURE DUE TO THE USE OF AN INADEQUATE FORMULATION?

iii. WAS THE ROUTE OF ADMINISTRATION A MAJOR CONTRIBUTOR TO THE TRIAL FAILURE?

❖ CONSULTS

Division of Scientific Investigations (DSI) Review (dated 11 January 2011)
Five clinical investigator sites, 3 domestic and 2 foreign, were inspected in support of this application. No significant regulatory violations were noted during the inspections and no Form FDA-483 was issued to any clinical investigator. Although some protocol deviations as well as recordkeeping deficiencies were discussed with Dr. Tugertimur, the deficiencies are isolated in nature and unlikely to significantly impact data reliability. According to DSI, the data are considered reliable in support of this supplement.

As the review division was concerned about the delays in randomization post-surgery, DSI's inspection assignments specifically requested that the field investigators evaluate and assess the reasons for delayed randomizations at each site. The mean time for randomization to surgery ranged from 25.7 days to 45.4 days for 4 sites and for one site it was between 0-8 days after the intercardiac line was removed. DSI notes that Protocol EFC5314 Section 6.1 only stated that "Eligible patients were to be randomized and treated with the study drug as early as possible following shunt placement." The protocol did not specifically mandate a certain amount of time. With respect to whether the delays in randomization were "appropriate given the clinical status of the patient," the consistent reason provided across sites is that the PI waited to ensure that the subjects were stable. Additional reasons (as stated by the CI at the 2 foreign Argentinian sites) were delays in referral from other hospitals, and giving families several weeks time to read the Informed Consent Document and understand the protocol. Based on what was stated, DSI considers the cited reasons reasonable, especially as the protocol was not specific as to when subjects should be randomized post-surgery. DSI considers subject safety as a very reasonable and appropriate reason to delay randomization; however, DSI defers to the specialty experts in the review division to evaluate the appropriateness of the physician's rationale for delays in randomization as outlined above.

With respect to whether the "actions taken by the sponsor to ensure early randomization, were reasonable and appropriate in response to the situation," the FDA field investigators noted that Newsletters were sent to sites requesting that randomization occur as soon as possible. DSI considers this as reasonable as the protocol was silent with respect to the specific timeframes that should be adhered to with from surgery to randomization. As the time from surgery to randomization was considered critical, then perhaps the protocol and/or amendments should have required a specific time from surgery to randomization.

It is important to note that the observations noted above for 2 domestic sites (Sullivan and Pizarro) and the 2 foreign sites (Somoza and Marantz) are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

❖ CONCLUSION

A Complete Response (CR) Letter (cleared by OCC on 12 January 2011) was issued for this application and signed by Dr. Norman Stockbridge, Division Director, on 14 January 2011.

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

/s/

ALISON L BLAUS
01/14/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 11, 2011

TO: Alison Blaus, Regulatory Project Manager
Martin Rose, MD, Medical Officer
Division of Cardiovascular and Renal Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA 20-839/S-051

APPLICANT: Sanofi Aventis

DRUG: Plavix (clopidogrel bisulfate)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Prevention of thrombotic events in children and neonates with congenital heart disease palliated with shunt surgery.

CONSULTATION REQUEST DATE: August 24, 2010

DIVISION ACTION GOAL DATE: January 15, 2011

PDUFA DATE: January 15, 2011

I. BACKGROUND: Sanofi Aventis submitted this application for the use of PLAVIX (clopidogrel bisulfate) ®, for the prevention of thrombotic events in children and neonates with congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g. modified Blalock Taussig shunt). In this current sNDA, the Sponsor is submitting study results to fulfill a Pediatric Written Request, and has proposed associated labeling changes, based on results of a single study, Study EFC5314 (or CLARINET) entitled: "International, randomized, double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g. modified Blalock Taussig shunt)."

Around the world, heart defects are among the most common birth defects, and are the world's leading cause of birth-defect related-deaths, accounting for more than half of all deaths from congenital anomalies. About 35,000 infants are born with heart defects each year in the U.S. The defect may be so slight that the baby appears healthy for many years after birth, or so severe that his/her life is in immediate danger. In the U.S., studies suggest that approximately 2.3 per 1000 live births require invasive treatment or result in death in the first year of life due to congenital heart disease.

For children with congenital heart disease such as hypoplastic left heart syndrome, pulmonary atresia with or without intact ventricular septum, single ventricle with pulmonary stenosis or atresia, management includes 3 stages of surgery: 1) the initial stage of palliation shunt, 2) the second stage of creating the bidirectional superior cavo-pulmonary connection; and then, later, 3) the definitive corrective surgery. These 3 stages of surgery include a window of high risk for sudden death between the initial and second stage. The risk is highest when patients have been discharged from the hospital to grow and prepare for the second stage. This is despite the remarkable improvements in immediate postoperative and hospital survival after the initial surgery. However, advances in diagnosis and surgical treatment have led to dramatic increases in survival for children with serious heart defects.

One of the complications of the corrective procedures are the occurrences of thrombotic events. Clopidogrel selectively inhibits the binding of ADP to its platelet receptor, thereby inhibiting platelet aggregation. Clopidogrel has been tested extensively in adults, and has been used by about 50 million people worldwide. Because of its proven efficacy in reducing thrombotic events and its good safety profile compared to ASA, it is hypothesized that clopidogrel therapy in children with systemic-to-pulmonary artery shunts would be safe and effective for reducing the risk of shunt thrombosis. The investigational product was a reconstituted solution of clopidogrel at (b) (4) and the route of administration was oral or enteric.

The primary objective of Study EFC5314 was to evaluate the efficacy of clopidogrel 0.2 mg/kg once daily versus placebo for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants (age ≤ 92 days at the time of randomization) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The

secondary objective of the study was to assess the safety of clopidogrel 0.2 mg/kg once daily in the study population. Safety was evaluated by the incidence of adverse events and serious adverse events, including bleeding.

The single study submitted in this sNDA (EFC5314 or AKA CLARINET) was audited. A total of 5 clinical investigator sites were inspected in support of this application, 3 domestic and 2 foreign (Argentina). The sites selected for inspection had higher numbers of subjects and longer than average times from surgery to randomization. Additionally, in December 2010, it was brought to DSI's attention that (b) (6) recommended that FDA carefully evaluate the largest South American site involved in the Plavix studies (no further information was provided) and subsequently, the two Argentinian sites were inspected.

The review division was specifically interested in 1) evaluation of the delays in randomization post-surgery, 2) whether the delays were appropriate given the clinical status of the patient, and 3) if the actions taken by the sponsor to ensure early randomization appeared reasonable and appropriate to the situation. The concern was that widespread delays in randomization and starting study drug (clopidogrel or placebo) post-surgery may have biased the results against a showing of efficacy.

The review division was also interested in the following: 1) if and how aspirin was administered to infants in the post-operative period, and if so, how soon after surgery, 2) evaluation of the feeding status of infants to determine how soon after surgery "partial" or "full feeding" began, as the thinking was that a child on an oral diet or being given oral aspirin would seem plainly able to take an oral medication and need not have been kept out of the study.

II. RESULTS (by Site):

Site # Name of CI	No. of Subjects	Inspection Dates	Classification
Site # 840010 Christian Pizzaro, MD, Alfred I. Dupont Hospital for Children, Nemours Cardiac Center, 1600 Rockland Rd, Wilmington, DE	8	11/1-8/2010	Pending (preliminary classification of NAI)
Site # 840013, Janice E Sullivan MD, University of Louisville, Kosair Charities Pediatric Clinical Research Unit, 231 E. Chestnut St, Louisville, KY	12	11/1-5/2010	Pending (preliminary classification of NAI)
Site # 840507, Aykut Tugertimur, MD, The Congenital Heart Institute, 50 West Sturtevant St, Orlando, FL 32806	24	10/28 – 11/5/2010	NAI

Site # Name of CI	No. of Subjects	Inspection Dates	Classification
Site # 032503, Pablo Marantz, MD, Hospital Italiano, Gascon 450, Buenos Aires, Argentina	22	12/6-9/2010	Pending (preliminary classification of NAI)
78ySite # 032504, Filipe Jorge Somoza, MD, Esperanza Unidad Perinatal del Sanatorio Frances, Baigorri 749, Cordoba, Argentina	9	12/13-16/2010	Pending (preliminary classification of NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Christian Pizzaro, MD**,
   Alfred I. Dupont Hospital for Children,
   Nemours Cardiac Center,
   1600 Rockland Rd,
   Wilmington, DE 19803 USA

   a. **What was inspected**: The FDA audit was conducted November 1-8, 2010. This site screened 25 subjects, enrolled 8 subjects, and 5 subjects completed the study. The FDA field investigator reviewed case report forms for all 8 subjects, and compared medical records against CRFs for 5 of 8 subjects. The FDA field investigator reviewed the following specific items: adverse events, serious adverse events, primary efficacy endpoints, **time between surgery and randomization for all 8 subjects, and aspirin usage for all 8 subjects.** The FDA field investigator was unable to collect data on feeding status of infants, as this question was raised by the review division after the inspection had been completed

   b. **General observations/commentary**:
   In general, the study appeared to have been conducted adequately at this site. The FDA field investigator reported that all records were in good order, and that all adverse events and serious adverse events were reported in a timely manner. The FDA field investigator specifically asked Dr. Pizzaro about the reason for delays between the patient's first surgery and randomization (range of 8-84 days). Dr. Pizarro stated that he wanted to make sure that the subject was sufficiently stable before being randomized into the study. With respect to any Sponsor efforts to speed up delays in randomizations, the FDA field investigator reported there did not appear to be evidence that the sponsor was concerned about delays between surgery and

randomizations. However, it should be noted that the FDA field investigator did not make note of any correspondences from the sponsor or monitor, such as newsletters and/or emails.

The following Table contains data collected during the inspection, relating to number of days between the subject's first (shunt) surgery and randomization.

Subject No.	Date of Birth	Date of Shunt Surgery	Date of Randomization	Days from (shunt) Surgery to Randomization (mean 38.6)
001				
002				
003				
004				
005				
006				
007				
008				

(b) (6)

When asked about aspirin usage, Dr. Pizzaro stated that it is not hospital policy to use aspirin with patients in the cardiac center. Medical records reflected that no subjects received aspirin post-operatively. The FDA field investigator did not gather information with respect to oral feedings of subjects; she reported that the primary endpoints were verifiable. Note that Protocol EFC5314 Section 8.9.1 for Permitted Concomitant therapy specifies the following: "The concomitant use of aspirin will be allowed according to the investigator's judgment and usual practice." Per the protocol, ASA usage was not specifically required.

At the conclusion of the inspection, no Form FDA 483 was issued.

c. **Assessment of data integrity**: No major regulatory violations were found during the inspection at this site. As per the Clinical Investigator, the delay between surgery and randomization (mean 38 days) was due to concerns for patient safety, i.e., waiting for the patient to stabilize. DSI considers this a reasonable rationale for delay in randomization; however, defers to the review division for final assessment of rationale. Again, there was no aspirin use for these subjects at this site, and the FDA field investigator did not collect information with respect to oral feedings at this site, as this question was not asked until after the inspection was completed. In general,

the study was conducted adequately, and DSI recommends the data at this site as reliable, and be used in support of the respective indication.

NOTE: **Observations noted above are based on e-mail communications with the FDA field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

2. **Janice E Sullivan MD,**
University of Louisville,
Kosair Charities Pediatric Clinical Research Unit,
231 E. Chestnut St, N-97
Louisville, KY

a. **What was inspected**:
The FDA audit was conducted Nov 1-5 and Nov 8, 2010. A total of 47 subjects were screened, and 12 subjects were randomized. A 13th subject signed the ICD prior to shunt surgery, but was not randomized because he/she failed to meet inclusion criteria due to bleeding prior to reaching 92 days of age.

The FDA field investigator reported that all subjects completed a study endpoint: Subjects 1-3, 5 and 8-11 had Glenn surgery after 120 days of age. Subject 4 had a cardiac/thrombotic event prior to 120 days of age and did not meet primary efficacy endpoint. Subject 6 was on study drug from 10/27/08 – 3/26/09 until a parent decided to stop study drug (reported to the NDA). Subject 7 was on study drug from 12/8/08 – 6/10/09 when Dr. Austin (sub investigator and cardiac surgeon) requested that the subject stop study drug (reported in the NDA). Subject 7 was followed via medical chart review until 1 year old. Subject 12 was followed to only 120 days of age because the study was ending. Subject 12 had a Glenn surgery about 6.5 months after the end of study visit.

The field investigator reviewed the following: Informed Consent Documents for all 12 subjects; study binders including paper copies of key medical records (i.e. shunt surgery); electronic medical records for Subjects 1, 4, 6-7 and 11-12 (randomized to study drug, not placebo) from birth to one year old, specifically for unreported AEs or SAEs or concomitant medications; primary efficacy endpoint data; protocol violations; data on aspirin use; reasons for delay between shunt surgery and randomization;
sponsor communications to the site encouraging faster randomization. <u>The FDA field investigator did not collect data on feeding status of infants, as this question was raised by the review division after the inspection had been completed</u>

b. **General observations/commentary**:
In general, the study was conducted adequately at this site. The FDA field investigator reported that study records were generally adequate, and there was no evidence of underreporting of adverse events or serious adverse events. The FDA field investigator reported there were no significant protocol violations during the study.

At this site, the FDA field investigator collected information on aspirin usage, route of administration and how soon aspirin was begun after surgery, and asked the Clinical Investigator for the reasons for delays between shunt surgery and randomization. The FDA field investigator reported that during the study, aspirin was generally administered to study subjects between 3 -13 days after shunt surgery. The route of administration of the ASA was reported as oral (po), enteral (NG tube), and rectal. In some cases, the infant had all 3 routes of ASA administration. The FDA field investigator reported that despite oral aspirin use by some, according to the Clinical Investigator, the subject was not considered for randomization until the intercardiac line had been removed, and there was no evidence of bleeding (considered as a patient safety issue at this site). As per Dr. Sullivan, "if bleeding occurs when the intercardiac line is removed, pooling of blood in the heart would send the infant into cardiac arrest." After the intercardiac line was removed, Subjects 1, 4, 6-7 & 11-12 were randomized 0 – 8 days later. The FDA field investigator did not collect information about 'feeding status' of infants during the inspection, as the inspection at the site was completed before the question was asked.

With respect to whether the sponsor or monitor encouraged the site to randomize as soon as possible following shunt surgery, the FDA field investigator found a CLARINET study newsletter #5 dated 10/31/07 that discussed randomization timeframes as follows:

"*We reviewed blinded date about patient characteristics, and have found that more than 50% of patients are randomized more than 2 weeks after the initial surgery. As you may know, the greatest incidence of adverse thrombotic or fatal events after shunt palliation occurs in the early post-operative period. We are convinced that if clopidogrel is effective in this patient population, then these early thrombotic or fatal events may potentially be avoided. We therefore strongly recommend that patients entering the trial are randomized as soon as possible after shunt palliation, as soon as they are able to tolerate oral medications.*"

The following table displays data collected during the inspection, relating to days between shunt surgery and randomization, as well as aspirin usage.

Subject No.	Initial (shunt) Surgery Date	Randomized Date	Days between Surgery and Randomized (mean 35.8)	Aspirin Start Date/route	Days from Surgery to Aspirin Start
001	(b) (6)				

	(b) (6)
002	
003	
004	
005	
006	
007	
008	
009	
010	
011	
012	

No significant deficiencies were observed and no Form FDA-483 was issued.

c. Assessment of data integrity: No major regulatory violations were found during the inspection at this site. During the inspection, Dr. Sullivan indicated that she generally did not randomize the subjects into the study until after the intercardiac line had been removed (bleeding was no longer a risk). Following removal of this intercardiac line, mean time to randomization was 4.2 days (range 1-15). DSI considers this a reasonable rationale for delay in randomization; however, defers to the review division for final assessment of rationale. Aspirin, by oral or rectal routes, was generally administered beginning 8 -13 days after surgery. The FDA field investigator did not collect data on feeding status of infants, as this question was raised by the review division after the inspection had been completed. In general, the study was conducted adequately, and the data generated by this site may be used in support of the respective indication.

NOTE: **Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

3. **Aykut Tugertimur, MD,**
The Congenital Heart Institute,
50 West Sturtevant St,
Orlando, FL 32806

a. **What was inspected**: The FDA audit was conducted between October 28 – November 5, 2010. At this site, 38 subjects were screened, 24 subjects enrolled, and 12 subjects completed the study. Two subjects were discontinued from the study, but were followed through to their second stage palliation. The FDA field investigator addressed questions with respect to time to randomization following first surgery, and aspirin use during the study. The FDA field investigator did not obtain data about subject feeding status, as this question was asked by the review division after the inspection had been completed.

The field investigator reviewed records of all 24 enrolled subjects. Specific items covered were adverse events, serious adverse events, verification of study endpoints, subject eligibility, protocol waivers, adherence to study blinding and randomization procedures, documentation of concomitant medications, adherence to protocol visit schedules, completion of required study questionnaires, completion of all diagnostic and biospecimen testing, maintenance of subject contact records, and consistency between data in subject records and data submitted to FDA. In addition, the inspection reviewed: all drug accountability records (i.e., temperature logs, IVRS forms, drug accountability logs, medication administration records, shipping invoices); monitoring visit logs and monitoring reports; documented protocol deviations; protocol approvals, reviews, and correspondences between the site, the Central Ethics Committee (CEC), the Local Ethics Committee (LEC), and the sponsor.

b. **General observations/commentary**: In general, the study appeared to have been conducted adequately at this site. Although no Form FDA 483 was issued, the following items were discussed at the closeout visit:

1) Documentation of the informed consent (IC) process. Specifically, the IC document for Subject 840507016 was signed by a parent/guardian on 07/08/2008, and the subject randomized the next day on 07/09/2008. There was no documentation of who discussed the ICD or study guidelines with the subject's parent/guardian prior to randomization. **DSI does not consider this item significant to impact data reliability.**

2) Accuracy of documentation in case report forms. Specifically, source records document that Subject 840507017 had 2 stage one surgeries on (b) (4), whereas the CRF documents the second surgery as 09/24/2008. **DSI considers this an isolated recordkeeping error with respect to the 2nd surgery date.**

3) Reporting of adverse events. Specifically, source records documented that Subject 840507022 was taken to the ER due to crying, not sleeping well and suspected abdominal pain on (b) (4) and these AEs were not reported to the Sponsor. According to Dr. Tugertimur, this ER visit was not a medically significant event and will not be recorded as an AE. **DSI acknowledges the**

response and given that this is isolated in nature, this finding is unlikely to significantly impact data reliability.

4) Timely reporting to IRB. Specifically, Subject 840507010 experienced an SAE of viral syndrome and upper respiratory congestions requiring hospitalization on (b) (4). The IRB was not notified until 12/18/2007. In addition, the site did not notify the IRB of three out-of-window visits for 3 subjects. **The SAE was reported to the sponsor.**

5) Delegation of Authority Log & Training. Specifically, Dr. Tugertimur did not delegate any responsibilities for study conduct to himself, and all trainings to support that each individual qualified to perform duties was not maintained. **DSI considers this a recordkeeping deficiency unlikely to impact data reliability.**

When asked about the delay in randomization following surgery, Dr. Tugertimur stated that there was no 'intentional' delay in randomizing infants, and that both subject randomization and use of aspirin were based on clinical judgment of when the medications could be tolerated by the subjects. The field investigator noted that aspirin administration was typically begun in the hospital once the subject was able to ingest the medication. The route of administration of ASA at this site was either oral (po) or enteral (NG tube).

With respect to the sponsor communications for earlier randomizations, the FDA field investigator reported that the sponsor communicated with the site twice on this issue: 1) by a 5th newsletter from the Steering Committee, dated 10/31/2007; and 2) during a teleconference on 11/5/2007 (Note: Subject randomizations occurred between 10/25/2006 and 8/15/2009). The newsletter and teleconference notes stated the following:

"…..we reviewed blinded data about patient characteristics, and found that more than 50% of patients are randomized > 2 weeks after the initial surgery…..we strongly recommend that patients entering the trial are randomized as soon as possible after shunt palliation, as soon as they are able to tolerate oral medications."

The following Table displays data collected during the inspection, relating to time between surgery and randomization, and aspiring usage.

Subject No.	Initial (shunt) Surgery Date	Aspirin Start Date	Days Between Surgery and Aspirin Start Date (mean ~ 17 days)	Randomization Date	Days Between Surgery and Randomization Date (mean ~ 35 days)
001	(b) (6)				
002					
003					
004					
005					
006					
007					
008					
009					
010					
011					
012					
013					
014					
015					
016					
017					
018					
019					
020					
021					
022					
023					
024					

c. **Assessment of data integrity**: While minor deviations from the study plan were discussed with the site at the conclusion of the inspection, they were generally isolated issues and do not appear to significantly impact reliability of efficacy and safety data generated by the site. During the inspection, Dr. Tugertimur stated that he began oral aspirin use when he felt the subject could tolerate the drug, and randomized the infant when he considered the subject ready. DSI considers this reasonable rationale for delay in randomization; however, defers to the review division for final assessment of rationale, especially as the protocol was silent as to the exact timing of randomization post-surgery. No information was gathered on the feeding status of infants, as this question was posed by the review division, after the inspection had been completed. The study appears to have been conducted adequately, with the exception of items noted above. In general, the data generated by this site appear acceptable in support of the respective indication.

4. **Pablo Marantz, MD,**
Hospital Italiano, Gascon 450,
Ciudad de Buenos Aires, Argentina

a. What was inspected:
The FDA inspection at Dr. Marantz' site was conducted December 6-10, 2010. The FDA field investigator conducted the inspection according to the standard Compliance Program for Clinical Investigators. He also addressed the specific questions concerning time delays in randomization, aspirin usage, feeding status of infants, and communications by the sponsor to ensure more rapid randomizations.

b. General **observations/commentary**:
In general, the study appears to have been conducted adequately at this site. The FDA field investigator reported that the delay in randomization was most often seen in infants who were referred from an outside hospital. A total of 12 (of 22) infants were referred from outside hospitals to the site where subjects were randomized. Due to either a late discharge, or being medically unstable, they were not randomized quickly. The FDA field investigator reported that those infants born in Hospital Italiano were often medically unstable. There were at least 2 cases in which the patient was feeding and/or taking ASA via oral route, but the PI did not feel the subject was "stable" enough to randomize. The route of ASA administration was oral.

The following Table displays the data collected during the inspection, relating to surgery dates, randomization dates, ASA usage, and feeding status of infants.

Subject No.	Date of Shunt Surgery	Randomize Date	Referred from outside hospital (date)	(oral) ASA start date	Feeding start date	Days to Randomize (mean ~25)	Days to ASA use (mean ~ 6.2)
001	(b) (6)						
002							
003							
004							
005							
006							
007							
008							
009							
010							

011	[redacted] (b) (6)
012	
013	
014	
015	
016	
017	
018	
019	
020	
021	
022	

* thes

from another hospital, and the medical records were not available at the time of the inspection.

The FDA field investigator observed that the sponsor sent periodic newsletters to the site; of 18 newsletters sent between 02/26/2007 and 02/26/2010, 3 made specific mention about encouraging sites to randomize as early as possible (FDA field investigator collected copies of these 3 newsletters, and language was similar to that written above for other site related inspectional findings).

c. **Assessment of data integrity**: There did not appear to be any regulatory issues noted at this site, and no Form FDA-483 was issued. During the inspection, the FDA field investigator asked Dr. Marantz specific questions about: the delay in randomization following surgery, ASA usage, full feeding status, and communications from the sponsor encouraging more rapid randomizations. Dr. Marantz stated that at least half of the subjects were referred from an outside hospital where surgery had taken place, and that the delay in randomization was because of the delay in subjects arriving to his hospital, or waiting for the subject to become medically stable. Dr. Marantz also indicated that in most cases, oral aspirin use began shortly after surgery, and much sooner than randomization (6 days vs. 25 days). The FDA field investigator collected information about feeding status of infants, and review of this data reveals that oral feedings usually began within a week of surgery, and full feedings began a few weeks later. DSI considers the reasons stated by the site for not randomizing sooner acceptable; however, defers to the review division's clinical assessment of the rationale for delays. In general, the study appears to have been conducted adequately. In general, the data generated by this site appear acceptable in support of the respective indication.

NOTE: **Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions**

change upon receipt and review of the EIR.

5. **Filipe Jorge Somoza, MD**,
Esperanza Unidad Perinatal del Sanatorio Frances,
Baigorri 749, Cordoba, Argentina

a. What was inspected: The inspection at this site was conducted December 13-16, 2010. The FDA field investigator conducted the inspection according to the standard Compliance Program for Clinical Investigators. He also addressed the specific questions concerning time delays in randomization, aspirin usage, feeding status of infants, and communications by the sponsor to ensure more rapid randomizations.

b. General observations/commentary: In general, the study was conducted adequately. No significant violations were noted during the inspection. The Table below contains the data collected during the inspection, relating to the subject's surgery date, randomization date, ASA usage, and feeding status.

Subject No.	Date of Shunt Surgery	Date Randomized	Referring Hospital Discharge Date	Days between Surgery and Randomization (mean ~ 45)	Feeding start date (mean 3 days after surgery)	"Full" feeding achieved (mean ~ 15 days post surgery)
001	(b) (6)					
002						
003						
004						
005						
006						
007						
008						
009						

According to the Dr. Somoza's explanation, "in every case, he would not approach the parents of a potential subject until after the baby was no longer in intensive care" and " he would not randomize a patient until he was absolutely sure the shunt was fully permeable." His three stated conditions for this were 1) an O2 saturation of at least 81%; 2) a clearly audible, continuous murmur from the shunt; and 3) an echocardiogram that showed a permeable shunt. The PI also wanted to make sure the subject did not have pulmonary hypertension that was unrelated to the congenital heart defect. After approaching the subject's parents, he would give them a copy of the Informed Consent Document and allow parents to read it for sometimes up to 2 weeks, before calling them to set-up randomization. Also, according to Dr. Somoza, 'this delay after discharge was because he wanted to ensure the parents fully read and understood the ICD and study, not because of medical concerns.'

All 9 subjects were referred from outside hospitals and no subjects were taking ASA after surgery or at randomization. The delay between the surgery and randomization, according to Dr. Somoza, was due to him waiting until the patients were discharged from the referring hospitals, and due to the timeline that he allowed the parents to review the study and ICF. He also stated that logistical issues with the parents coming to his site were also a factor.

c. Assessment of data integrity: There were no regulatory violations noted at this site during the FDA investigation, and no FDA-483 was issued. DSI considers that the reason stated by Dr. Somoza for delay in randomization (vs. oral feeding status which was on average 3 days after surgery) was acceptable; however, defers to the review division. In general, the study appears to have been conducted adequately, with the exception of items noted above. In general, the data generated by this site appear acceptable in support of the respective indication.

NOTE: **Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites, 3 domestic and 2 foreign, were inspected in support of this application. No significant regulatory violations were noted during the inspections and no Form FDA-483 was issued to any clinical investigator. Although some protocol deviations as well as recordkeeping deficiencies were discussed with Dr. Tugertimur, the deficiencies are isolated in nature and unlikely to significantly impact data reliability. The data are considered reliable in support of the application.

As the review division was concerned about the delays in randomization post-surgery, DSI's inspection assignments specifically requested that the field investigators evaluate and assess the reasons for delayed randomizations at each site. The mean time for randomization to surgery ranged from 25.7 days to 45.4 days for 4 sites and for one site it was between 0-8 days after the intercardiac line was removed. DSI notes that Protocol EFC5314 Section 6.1 only stated that "Eligible patients were to be randomized and treated with the study drug as early as possible following shunt placement." The protocol did not specifically mandate a certain amount of time.

With respect to whether the delays in randomization were "appropriate given the clinical status of the patient," the consistent reason provided across sites is that the PI waited to ensure that the subjects were stable. Additional reasons (as stated by the CI at the 2 foreign Argentinian sites) were delays in referral from other hospitals, and giving families several weeks time to read the Informed Consent Document and understand the protocol. Based on what was stated, DSI considers the cited reasons reasonable, especially as the protocol was not specific as to when subjects should be randomized post-surgery. DSI considers subject safety as a very reasonable and appropriate reason to delay randomization; however, DSI defers to the specialty

experts in the review division to evaluate the appropriateness of the physician's rationale for delays in randomization as outlined above.

With respect to whether the "actions taken by the sponsor to ensure early randomization, were reasonable and appropriate in response to the situation," the FDA field investigators noted that Newsletters were sent to sites requesting that randomization occur as soon as possible. DSI considers this as reasonable as the protocol was silent with respect to the specific timeframes that should be adhered to with from surgery to randomization. As the time from surgery to randomization was considered critical, then perhaps the protocol and/or amendments should have required a specific time from surgery to randomization.

Based on FDA inspections of the 5 clinical investigator sites, the study appears to have been conducted adequately at the sites, and the data are considered reliable in support of the application.

NOTE: **Observations noted above for 2 domestic sites (Sullivan and Pizarro) and the 2 foreign sites (Somoza and Marantz) are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Reviewer, Good Clinical Practice Branch 2
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

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

/s/

SHARON K GERSHON
01/11/2011

TEJASHRI S PUROHIT-SHETH
01/11/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 20839 BLA# n/a	NDA Supplement #: 051 BLA STN # n/a	Efficacy Supplement Type - SE5
Proprietary Name: Plavix Established/Proper Name: clopidogrel bisulfate Dosage Form: oral suspension Strengths: 0.2mg/kg/day		
Applicant: sanofi aventis and Bristol-Myers Squibb Agent for Applicant (if applicable): n/a		
Date of Application: 15 July 2010 Date of Receipt: 15 July 2010 Date clock started after UN: n/a		
PDUFA Goal Date: 15 January 2010	Action Goal Date (if different): n/a	
Filing Date: 13 September 2010	Date of Filing Meeting: 11 August 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only): n/a		
Proposed indication(s)/Proposed change(s): No change in indication. This supplement provides for pediatric clinical data from the failed CLARINET trial.		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): n/a				
List referenced IND Number(s): 34,663				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**X**			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***			**X**	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			**X**	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			**X**	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**X**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		**X**		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		**X**		The sponsor is submitting a response to a Pediatric Written Request and if deemed appropriate will be granted 6 additional months exclusivity.

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			**X**	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**X**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**X**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	**X**			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**X**	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		**X**		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			**X**	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			**X**	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			**X**	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***	**X**			Exclusivity Board has been contacted and a meeting has been scheduled to discuss this application on 5Oct10.

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**X**			
Is the PI submitted in PLR format?	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			**X**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		**X**		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		**X**		
REMS consulted to OSE/DRISK?		**X**		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		**X**		
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**X**			DSI Consulted on 25Aug10

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		**X**		
Pre-NDA meeting(s)? **Date(s):** 10 May 2010 ***If yes, distribute minutes before filing meeting***	**X**			Minutes dated 26May10
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		**X**		PWR dated 15Oct01 and amended 24Aug07

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: 16 September 2010

NDA/Supp #: 20-839 / S051

PROPRIETARY NAME: Plavix

ESTABLISHED/PROPER NAME: clopidogrel bisulfate

DOSAGE FORM/STRENGTH: 0.2mg/kg/day oral suspension

APPLICANT: sanofi aventis & Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The sponsor proposes changes to the (b) (4) sections. These changes were in response to the clinical trial data submitted from the failed CLARINET study.

BACKGROUND:
Clopidogrel is a P2Y12 inhibitor currently marketed for treatment of patients with acute coronary syndrome (ACS) and those with recent MI, recent stroke, or established peripheral arterial disease. The clopidogrel pediatric developmental program was initiated in 2000 to determine if administration of clopidogrel to infants who have undergone systemic-to-pulmonary artery shunt placement for congenital heart disease would prevent shunt thrombosis. After meeting with the Division regarding formulation, dosing, appropriate patient population, and trial design, the sponsor submitted a proposed pediatric study request. The Agency responded with a Pediatric Written Request (PWR) on 15 October 15 2001. After completion of a dose-ranging study in children (PICOLO), the sponsor met with the Division to discuss their planned special protocol assessment (SPA) for the Phase 3 safety and efficacy study (CLARINET). This SPA was submitted on 9 May 2006 and the Division responded with a No Agreement letter on 12 July 2006. Subsequently, the PWR was amended, dated 24 August 2007, to reflect the agreements. After CLARINET was initiated, there were a number of revisions to the statistical analysis plan in response to Agency advice (letters dated 9 May 2008, 3 September 2008 and a teleconference on 31 July 2008).

The sponsor met with the Agency on 10 May 2010 for a pre-NDA meeting where a number of aspects of this NDA were discussed. Please refer to the minutes from this meeting dated 26 May 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Quynh Nguyen	Y

Cross-Discipline Team Leader (CDTL)	n/a		n/a
Clinical	Reviewer:	Martin Rose	Y
	TL:	Shari Targum	Y
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Elena Mishina	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	Jim Hung	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Statistics (carcinogenicity)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Quality Microbiology *(for sterile products)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:	n/a	n/a
Other reviewers	n/a		n/a
Other attendees	Norman Stockbridge (DCRP Director), Steve Grant (DCRP Deputy Director), Abraham Karkowsky (Team Leader, Clinical), Kevin Krudys (Pharmacometrics)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**: Dr. Rose does not have any issues for the 74 day letter at this point.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES

If no, explain:	☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Possible 74day letter issues/requests.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Dr. Chen has no issues for the 74 day letter at this point.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL	☒ Not Applicable

(PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**: n/a	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-51	SANOFI AVENTIS US LLC	PLAVIX

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/s/

ALISON L BLAUS
09/16/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: N 20839 S51 **Applicant: Sanofi** **Stamp Date: 15 July 2010**

Drug Name: Clopidogrel **NDA/BLA Type: 505(b)(1) supplement** **SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			**x**	Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	**x**			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	**x**			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.,* are the bookmarks adequate)?	**x**			
5.	Are all documents submitted in English or are English translations provided when necessary?	**x**			
6.	Is the clinical section legible so that substantive review can begin?	**x**			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	**x**			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	**x**			Per agreement, only Mod 1, 2, and 5 are required. Summaries are adequate.
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	Safety data is displayed per our agreement with the sponsor
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	There was only one efficacy study and the applicant is not making an efficacy claim.
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	See item 10.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	**x**			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: PDY4422/PICOLO	**x**			Dose agreed to prior to Phase 3 study start. However, the dose used may have been too low. This does not

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 116 Arms: 5 Location in submission: \\Cdsesub1\evsprod\NDA020839\0068\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\pdy4422				negate satisfaction of the terms of the PWR.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 EFC5314 (CLARINET) Indication: Prevention of events associated with graft closure in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt Pivotal Study #2 (none) Indication:	**x**			Only 1 study is required per the PWR.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**x**			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	**x**			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		No text or relevant statistical analyses were found
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	**x**			
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	**x**			None needed at this time.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	**x**			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	Study size is adequate.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	**x**			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	**x**			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	**x**			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	**x**			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	**x**			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		See item 17
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	**x**			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	**x**			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	**x**			
34.	Are all datasets to support the critical safety analyses available and complete?	**x**			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	**x**			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	**x**			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	**x**			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	**x**			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	**x**			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES__x__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The applicant should provide justification for the application of its foreign data to the US. Preferably, this justification should include both textual (i.e., medical science-based) and statistical (i.e., study data-based) information.

Reviewing Medical Officer Date

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-51	SANOFI AVENTIS US LLC	PLAVIX

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/s/

MARTIN ROSE
09/01/2010

SHARI L TARGUM
09/01/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 20839(S051) **Applicant:** sanofi aventis & BMS **Stamp Date:** 7/15/2010

Drug Name: Plavix (clopidogrel bisulfate) **NDA/BLA Type:** priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidance (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___×_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	×			
Appropriate references for novel statistical methodology (if present) are included.			×	Not relevant
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			×	Not relevant since the only submitted study is unique by its nature.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-51	SANOFI AVENTIS US LLC	PLAVIX

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/s/

YEH FONG CHEN
08/16/2010

HSIEN MING J J HUNG
08/16/2010