DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021688/S-023
NDA 209962

CORRESPONDENCE

Amgen Inc.
Attention: Juliana Sholter, MS, RAC
Manager, Regulatory Affairs
601 13th Street NW, 12th Floor
Washington, D.C. 20005

Dear Ms. Sholter:

Please refer to your Supplemental New Drug Application (NDA) and New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sensipar (cinacalcet hydrochloride) Tablets and Capsules for Sprinkling, respectively.

Pediatric exclusivity (PE) is denied for studies conducted on cinacalcet hydrochloride, under section 505A of the Act. The reasons for this determination are described below.

I. Legislative/Regulatory Background

The basis of a denial of PE can best be understood in light of the structure and context of the PE provisions of Section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 355a (as amended).

As required by Section 505A, the PE process begins with FDA drafting and issuing a Written Request (WR) for information relating to the use of a drug in the pediatric population that may produce health benefits in that population. The Agency has a meaningful opportunity to obtain pediatric information through the PE process, so each WR is designed, within the limits of good science and ethics, to elicit information on the use of the entire active moiety in relevant pediatric populations that will result in labeling for those populations. The Agency drafts each WR to obtain studies that will allow the Agency to determine whether and how the drug should be used in pediatric patients and will permit drug products containing the active moiety to be fully labeled for pediatric populations for whom the drug has been (or is likely to be) prescribed.

In determining the scope of a WR, FDA asks: (1) Is there a health benefit to studying this drug for the proposed indication in the pediatric population; (2) In what age groups in the pediatric population does this indication occur; (3) What information does the Agency currently have regarding use of this drug for this condition in relevant pediatric age groups; and (4) What studies are necessary to fill in the gaps in pediatric information in the Agency's possession and to fully label drug products containing the active moiety for relevant pediatric populations?

The PE, if granted, attaches to all patents and exclusivity protecting the sponsor's drug products containing the active moiety, not just to protections on the particular product, indication, or population studied. A sponsor who obtains PE thus gets six additional months of potential delay of competition for every one of its products containing the active moiety that has existing patent protection or exclusivity. Because of the broad scope of the benefit, WRs are generally crafted to elicit all of the information needed to label all of the sponsor's drug products containing that active moiety for use in relevant pediatric populations.

In reviewing a submission in response to a WR, the statute states that the Secretary's "only responsibility" in accepting or rejecting the reports is to determine "whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing." Section 505A(d)(3) of the FD&C Act.

The Pediatric Exclusivity Board (Board) considers a number of factors when assessing, as required by statute, whether the studies "fairly respond" to a WR.

First, the Board considers the purpose of the PE provision as described in the statute, with reference to the legislative history. The statute makes clear that its purpose is to generate clinical information on the use of drug products in children that will result in a health benefit to pediatric populations. The legislation was enacted to provide an incentive for sponsors to conduct studies to fill in the gaps in safety and efficacy information in product labeling regarding the use of drug products in relevant pediatric populations. The legislative history refers to pediatric populations as "therapeutic orphans" on whom therapies approved for adults are frequently used, but for whom approved and properly labeled therapies are lacking. S. Rep. No. 105-43, at 51 (1997). The legislative history makes clear (and the Agency's experience confirms) that for FDA-regulated products, the health benefit is obtained when the information that a physician needs to properly prescribe a medication is described in the product's labeling. Thus, the provision attempts to ensure that when PE is granted for studies, FDA also may approve labeling describing the results of the studies and providing adequate information for use of the drug in relevant pediatric populations. Id. at 52.

Second, when the pediatric studies are submitted and an exclusivity determination requested, the Board evaluates the information sought in the WR (including any amendments) and the objectives stated in the WR. The Board asks whether the studies were designed and carried out by the sponsor in a way likely to meet those objectives specified in the WR and underlying the exclusivity provision as a whole. The Board looks at the specific requirements that the WR imposed to support these objectives. For example, if a specific number of patients is requested or a specific study duration or endpoint is specified to ensure that the study will generate adequate data to provide a health benefit, failure to comply with these elements of the WR may result in a denial of exclusivity. Denial is likely if, in the absence of compliance, the studies are not expected to be interpretable or will not provide information that otherwise yields a health benefit to pediatric populations. In such cases, the studies are regarded by FDA as not having "fairly respond[ed]" to the WR. In making this determination, the Board also will look at the nature of the drug or class of drugs, the nature of the use (*e.g.*, chronic vs. short term), the adverse event profile in adults, and the nature of the gaps in the existing labeling.

Ultimately, the Board considers a "fair response" to the WR to be one that responds to the specific elements in the WR in light of the objective stated in the WR and the overall purpose of the PE legislation. In determining whether a submission "fairly responds" to a WR, FDA considers whether the submission is sufficient to enable it to approve pediatric labeling (including negative pediatric labeling) for all of the age groups and indications requested based on the studies conducted. Where a WR is capable of more than one interpretation, the Board considers a fair response to be one that interprets the WR in a manner likely to generate information that will provide a health benefit (including meaningful pediatric labeling) in the relevant populations that the WR asked the sponsor to study. If the studies submitted fairly respond to the WR, the Board will recommend that PE be granted (assuming the other statutory requirements for PE are met). If, on the other hand, the sponsor responds to the WR in such a way that the possibility of a health benefit (including meaningful pediatric labeling) from the studies conducted is not likely, the Board is likely to conclude that the submission does not "fairly respond" to the WR.

II. Summary of Factual Background

FDA originally issued a WR on May 5, 2010, to obtain the information needed to understand (and describe in labeling) the safety and effectiveness of the long term use of cinacalcet in children 28 days to < 18 years of age. The main objective of WR was to establish the benefits of cinacalcet use for the chronic treatment of hyperparathyroidism (HPT) secondary to end-stage renal disease in pediatric patients receiving either hemodialysis or peritoneal dialysis, and to adequately characterize the risks associated with this intended use in pediatric patients. The clinical studies included in the WR were to generate the clinical data necessary to label cinacalcet for use in children 28 days to < 18 years of age.

The following facts summarize the interactions between FDA and Amgen pertinent to this WR:

- On May 4, 2007, Amgen submitted a Proposed Pediatric Study Request (PPSR) to IND 056010.
- On June 20, 2007, A teleconference between FDA and Amgen was held to discuss the PPSR.
- On June 29, 2007, Amgen submitted a summary of the discussions held at the June 20, 2007, teleconference (IND 56010).
- On September 4, 2007, FDA denied issuance of a Written Request but encouraged Amgen to submit a new PPSR that addressed the recommendations made at the June 20, 2007, teleconference and in the denial letter.
- On April 11, 2008, Amgen submitted a new 5 mg pediatric capsule presentation to IND 56010.
- On May 23, 2008, FDA in an email communication asked that this new presentation be handled in a new IND (109361).
- On June 20, 2008, Amgen requested feedback from FDA on a key juvenile chronic toxicology study to support the conduct of pediatric studies for a new PPSR.
- On July 23, 2008, FDA responded to Amgen's questions on the key juvenile chronic toxicology study to support the conduct of pediatric studies for a new PPSR.

- On December 22, 2009, Amgen submitted a new Proposed Pediatric Study Request for cinacalcet to IND 056010.
- On March 17, 2010, A teleconference between FDA and Amgen was held to address FDA questions related to the new PPSR.
- On April 25, 2010, Minutes of the discussions for the March 17, 2010, teleconference were submitted to IND 56010.
- On May 5, 2010, FDA issued a WR for cinacalcet.
- On June 24, 2010, Amgen requested modification of, and submitted a proposed first amendment to, the WR.
- On September 7, 2010, A teleconference between FDA and Amgen was held to discuss proposed changes to the WR.
- On September 15, 2010, Minutes of the discussions for the September 7, 2010, teleconference were submitted to IND 56010.
- On December 14, 2010, FDA issued an amended WR to allow for extrapolation of efficacy in patients 28 days to 6 years of age. Therefore, a new safety study (Study 3) was added to account for this change (because additional safety information is required when extrapolation of efficacy is accepted).
- On February 08, 2011, Amgen submitted correspondence to IND 109361 requesting clarification of FDA's December 14, 2010 WR amendment.
- On March 25, 2011, FDA amended the WR a second time to adjust the number of patients in Studies 1 and 2 and responded to Amgen's January 20, 2011, list of clarifying questions.
- On June 7, 2011, Amgen submitted draft protocol 20110100 (WR Study 3) requesting FDA review and comments.
- On June 28, 2011, FDA responded to Amgen's June 7, 2011, request for draft protocol 20110100 (WR Study 3) review and comments.
- On December 27, 2012, a 14-year old patient enrolled in WR Study 2 (20070208) died
- On January 31, 2013, Amgen notified FDA by email of their intent to submit "Dear Investigator Letters" notifying investigators in WR Study 2 (20070208) and Study 3 (20110100) of their intent to immediately suspend dosing in both studies based on a preliminary review of the fatality. Amgen also notified FDA that the fatality had erroneously been reported to IND 056010.
- On January 31, 2013, FDA notified Amgen by telephone to suspend dosing in all pediatric studies and asked that the treatment allocation for the case be revealed.
- On February 7, 2013, FDA issued a clinical hold letter for pediatric studies and asked that Amgen submit details of the fatality and other pertinent information related to pediatric safety.
- On July 8, 2013, Amgen requested a meeting with FDA to seek agreement on Amgen's plan to discontinue the WR studies, on Amgen's assessment that the data collected in the clinical pediatric program was sufficient to inform product labeling, and on potential modifications to the WR to reflect that Amgen can qualify for pediatric exclusivity without conducting any additional pediatric studies.
- On September 4, 2013, a teleconference between FDA and Amgen was held to address Amgen's July 8, 2013 questions to FDA. FDA did not agree that the data collected in the cinacalcet pediatric program was sufficient to inform product labeling and did not agree to amend the WR to eliminate the need for Amgen to conduct further pediatric studies.

- On October 5, 2013, Minutes of the September 4 2013 teleconference were issued.
- On December 13, 2013, FDA notified Amgen that they could resume dosing pediatric patients in the single dose WR Study 1 (20090005) and asked the applicant to submit a finalized protocol for WR Study 4 (20130356) to resolve the hold on dosing pediatric patients in multiple dose studies.
- On December 20, 2013, Amgen submitted a meeting request to seek FDA agreement on a plan to resume the cinacalcet pediatric program with added dosing safeguards and their intent to seek an amendment to the WR.
- On February 4, 2014, FDA met with Amgen to discuss Amgen's plan to resume the pediatric program and to seek an amendment to the WR.
- On March 14, 2014, FDA notified Amgen that they could resume dosing in pediatric patients in the multiple dose studies (including WR Study 4 (20130356)).
- On March 31, 2014, Amgen requested a third amendment to the WR.
- On July 29, 2014, FDA issued a third amendment to the WR that allowed early termination of WR Study 2 and added WR Study 4 to support an adequate evaluation of safety and efficacy in patients 6 years to < 18 years of age, given the early termination of WR Study 2.
- On December 12, 2014, Amgen requested for a fourth amendment to the WR to reduce the required number of completers in WR Study 4.
- On April 9, 2015, FDA amended the WR a fourth time, allowing for a reduction in the number of completers in WR Study 4.
- On June 19, 2015, Amgen submitted a request to amend the WR a fifth time to redefine the efficacy assessment phase and make it easier for the WR term to be met, to remove language related to the statistical power required for WR Study 4 to meet its objective, and the requirement that Amgen seek FDA agreement on the final statistical analysis plan prior to study completion.
- On October 14, 2015, FDA issued a fifth amendment to the WR allowing for Amgen's requested changes to Study 4.
- On December 3, 2015, Amgen requested that FDA amend the WR for a sixth time to reduce the number of completers required in the WR for Study 3 and Study 4.
- On December 24, 2015, FDA declined to amend the WR for a sixth time as Amgen had requested (see Section III below).
- On July 1, 2016, Amgen requested a meeting to discuss their intent to submit an NDA for a pediatric indication.
- On September 21, 2016, a meeting between FDA and Amgen was held to discuss the overall cinacalcet pediatric development program and Amgen's intent to submit an NDA for a pediatric indication.
- On November 23, 2016, Amgen submitted NDAs 209962 and 021688/S-023 with a request for a pediatric exclusivity determination for cinacalcet.

III. Basis for Denial of Pediatric Exclusivity for Cinacalcet

The following four studies are included in the WR as amended and were conducted under IND 109361:

1. WR Study 1 (20090005): An open-label, single-dose, pharmacokinetics (PK) and pharmacodynamics (PD) study to characterize the single-dose PK and PD profiles and the safety of a single dose of cinacalcet in pediatric patients ages 28 days to less than 6 years with chronic kidney disease (CKD) and secondary HPT receiving dialysis.

2. WR Study 2 (20070208): A 30-week, randomized, double-blind, placebo-controlled, efficacy and safety study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to less than 18 years with CKD and secondary HPT receiving dialysis. This study was to include an assessment of pharmacokinetic (PK) parameters using a sparse sampling design. Study 2 was terminated early and was to be analyzed with available data.

3. Study 3 (20110100): A 26-week or time-until transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to less than 6 years with CKD and secondary HPT receiving dialysis to evaluate the safety of cinacalcet and characterize the PK profile in pediatric patients.

4. Study 4 (20130356): A 20-week, randomized, open-label, controlled efficacy and safety study in pediatric patients ages 6 years to less than 18 years with CKD and secondary HPT receiving dialysis. An open-label extension protocol to Study 4 was to assess longer term safety of cinacalcet for at least 7 additional months.

To place the studies in the amended WR in perspective, we note that the initial (unamended) WR requested two studies:

1. A single-dose PK study in pediatric patients ages 28 days to less than 6 years with CKD and secondary HPT receiving dialysis. This study had to enroll enough patients to properly evaluate PK in two age groups: 28 days to less than 3 years, and 3 years to less than 6 years.

2. A 30-week, randomized, double-blind, placebo-controlled, efficacy and safety study in patients 28 days to less than 17 years of age that was to be followed by a 26-week single arm, open-label, safety extension. This study was to enroll a minimum of 100 patients.

As stated above, Amgen requested that FDA amend this WR six times.

In the first amendment, among other things, FDA revised Study 2 to allow for the extrapolation of efficacy to younger patients (28 days to less than 6 years) from data gathered for older pediatric patients (6 to l8 years) and removed the younger age group from the scope of that study. Because additional safety information is required when extrapolation of efficacy is accepted, a third study was added to adequately characterize the risks of cinacalcet in the younger patient population during long-term use. Accordingly, this study (Study 3) would be a 26-week (or time until transplantation, whichever happened first) open-label study in patients 28 days old to less than 6 years. FDA requested that a minimum of 15 patients complete Study 3 and specified that patients who terminate the study prematurely to undergo kidney transplant may be considered completers if they have been enrolled for at least 12 weeks.

In the second amendment, among other things, FDA relaxed some of the requirements for Study 1, and clarified that while 100 patients should be enrolled in Study 2, 70 patients were required to complete the 30-week double-blind portion, and that 30 patients were required to complete the open-label extension.

The third amendment, among other things, acknowledged that Study 2 had been terminated early and available data would be analyzed. It decreased the number of patients in Study 2 from 100 to 40 to account for the early termination. It also added Study 4, which would have at least 48 patients.

The fourth and fifth amendments, among other things, included a reduction in the number of patients who were required to complete Study 4, and a reduction in the exposure time required to define completion. In amendment 4, FDA agreed to lower the number of patients required to complete Study 4 from 48 patients with 20 weeks of data to a minimum of 40 patients with at least 12 weeks of data. In amendment 5, FDA agreed to loosen the definition for the efficacy assessment phase for Study 4, to remove language related to the required power for Study 4 and to remove language requiring that Amgen seek FDA agreement on the final statistical analysis plan prior to study completion.

Amgen then requested that FDA amend the WR a sixth time, proposing to further decrease the number of completers required in Study 3 and Study 4. FDA denied this amendment request because the number of patients enrolled in Study 4 had already been reduced in previous amendments and because reducing the number of required completers in Study 3 as Amgen proposed was not likely to yield sufficient information to adequately characterize the safety of the product for its intended chronic use in patients 28 days to 6 years of age, and therefore was unlikely to satisfy the purpose of the WR (see further discussion below).

Amgen's pediatric studies submitted in response to the October 14, 2015 amended WR for cinacalcet (NDAs 209962 and 021688/S-023) did not meet the terms of the WR, and in particular failed to meet the criteria for Study 3 of the WR, as detailed below. Moreover, even though Amgen has met the literal terms of the WR for Studies 1, 2, and 4, considering Amgen's submission in its entirety, the Board concludes that Amgen has not fairly responded to the amended WR as a whole. The Board reaches this conclusion based on a review of the record relating to the amended WR and after conferring with the Division of Metabolism and Endocrinology Products (Division) on its assessment of the data in the submission. The basis for this conclusion is summarized below.

An insufficient number of patients 28 days to < 6 years of age completed WR Study 3 and clinical data in the submission were insufficient to allow FDA to adequately characterize the risks of cinacalcet for its chronic intended use in this age group.

Study 3 was designed to evaluate the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years of age when used chronically as intended in patients undergoing dialysis, and to characterize the cinacalcet PK profile in these pediatric patients.

The amended WR provides the number of patients required to be studied for Study 3:

"A minimum of 15 patients must complete this 26-week study. Patients who terminate the study prematurely to undergo a kidney transplant may be considered completers to satisfy this study requirement minimum if they have been enrolled in the study for at least 12 weeks."

Cinacalcet is titrated by increasing the dose until it is effective, and is intended to be used chronically in dialysis patients. Safety data for a minimum of 15 patients completing 26 weeks was considered by FDA to be a critical amount of information required to determine whether the product is safe in young pediatric patients for chronic use. Study 3 was set up as a 26-week trial because the protocol relied on a very gradual cinacalcet dosing strategy. The starting dose selected was low, in order to minimize risks to participants, and was not expected to have a therapeutic effect. The dose of cinacalcet was to be increased every 4 weeks according to protocol-specified instructions until the therapeutic target defined in the protocol was reached, or until Week 20 if the therapeutic target was not reached. The design of the trial thus anticipated that attainment of effective doses could necessitate up to five dose increases and take up to 20 weeks. The selected duration of the study ensured that at least 4 weeks (i.e., from Week 20 to 24) of safety data at effective doses would be available from subjects who completed the trial (i.e., completers). Accordingly, the study was designed to provide safety information during both cinacalcet titration and at stable effective doses. In setting the Study 3 exposure (number of patients and duration), the Division also understood that data from Study 4 in older children (≥ 6 years of age to < 18 years) would provide supportive safety information in younger patients assuming that Study 4 provided a robust assessment of safety in those older age children. Such a supporting safety assessment required that an adequate number of older children be included in Study 4 and that cinacalcet dosing be sufficient to attain a therapeutic effect, indicating adequate exposure to the medication. Thus, two sources of safety information on cinacalcet in younger children were to be evaluated: safety information from Study 3 as the primary source, with supportive safety information collected in older patients from Study 4.

In considering whether the WR criteria related to Study 3 were met, the Division reviewed all available data submitted in Amgen's report. The Division noted that only 4 patients were completers with 3 completing 26 weeks and 1 subject, who received a kidney transplant, completing 12 weeks of treatment. *Thus, only 4 patients out of the 15 (or 27%) required by the WR for Study 3 completed the study*. Of note, more than half (i.e., 9 out of 17) of all of the subjects who were enrolled and exposed to cinacalcet failed to complete the study; and, 5 out of those 9 subjects failed to complete due to study closure in June 2016, when Amgen terminated the study. These failures to complete the study resulted in limiting exposure time to cinacalcet and the study not achieving the requested number of completers, as stated in the protocol. Moreover, many of the non-completers who received cinacalcet in Study 3 were exposed to doses that were too low to adequately characterize the safety of the product for its intended use: the safety data collected for most individuals reflect low dose exposure for a majority of the time those individuals were in the study, and does not reflect titration to effect as the protocol specified. Finally, the duration of exposure was also insufficient to adequately characterize the safety of the product for chronic use. Importantly, only a single completer was exposed to cinacalcet for the full duration. The median duration of exposure was only 12 weeks. As noted above, the WR specified that Study 3 should, at a minimum, include 15 completers that should

ideally have been exposed to cinacalcet for 24 weeks,[1] and the median exposure for the 18 patients enrolled fell far short of this minimum level.

As noted above, two sources of safety information on younger children (i.e., those 28 days to < 6 years of age) had been anticipated: results from Study 3 and supportive safety information from Study 4. In addition to the inadequate exposure from Study 3, discussed above, supportive safety information from Study 4 was also limited due to inadequate cinacalcet titration. Study 4 demonstrated no significant therapeutic effect with cinacalcet treatment relative to placebo. The lack of evident efficacy suggests that cinacalcet dosing in this study provided lower than clinically relevant exposures, markedly limiting the utility of safety information relevant to the older age group in this study, as well as supportive information for the younger children in Study 3.

Amgen proposed a sixth amendment to the WR on December 3, 2015 that would have reduced the number of young pediatric patients required to complete Study 3 to reflect the number of anticipated completers. Amgen claimed that this reduction was necessary due to the following issues:

- Difficulty with patient recruitment given the small size of the study population;
- Difficulty with patient retention;
- The fact that the study was placed on a partial clinical hold due to a pediatric fatality;
- Study closure in June 2016 in order to be able to submit the study report within the necessary time frame to obtain pediatric exclusivity prior to patent expiration.

Although acknowledging the challenges with recruitment, the Division was concerned that the significantly lower patient numbers proposed in the amendment would not be expected to provide sufficient information to establish the safety of the product in the younger patient population. Therefore, the Division denied this amendment on December 24, 2015.

To attempt to address the deficiencies described above in the safety database in younger children (28 days to < 6 years), Amgen included additional safety data in 23 patients in a retrospective chart review. However, these data have only limited value to inform about the risks of the drug for its intended use. This retrospective case review is subject to the limitations and biases of retrospective observational chart review, which include voluntary participation, selection bias, uncertainty with regard to how the product was used, uncertainty with regard to exposure in terms of dose and duration of exposure, uncertainty with regard to the dosing regimen used (i.e., administration schedule and titration), uncertainty surrounding the completeness of ascertainment and reporting of safety data, and missing data. Amgen acknowledges these limitations in its submission of these data: "Although a research plan was developed prospectively for this chart review, this review shares similar limitations to other retrospective observational analyses, i.e., propensity for missing data, accuracy and completeness of data quality, and chart selection determination." Although such information can provide supportive

[1] The Division was willing to consider a minimum exposure duration of 12 weeks for a small subset of subjects who underwent a kidney transplant, but the Division expected only a few patients to be in this category, given that Amgen estimated that less than 30% of subjects would get a transplant and the inclusion / exclusion criteria for the study excluded patients who were scheduled for a kidney transplant.

information, this cannot replace the missing robust safety information from a randomized, controlled clinical trial such as Study 3.

In summary, Amgen's failure to provide sufficient safety data in the 28 day to < 6 year old age group prevents FDA from drawing any conclusions about the safety of the product in patients < 6 years of age when used as intended. If the totality of safety information Amgen submitted had provided an appropriate safety assessment in younger children and supported a label description—even if the exact minimum number of patients had not been met in Study 3—this element of the WR could have been adequately satisfied and Amgen's response could be considered a fair response to the WR as a whole. However, in the absence of any robust source of safety information in this vulnerable age group (again, considering Study 3, supportive information from Study 4, and other sources of information), the Board concludes that this criterion was not met. Accordingly, the Board concludes that Amgen has failed to fairly respond to the WR.[2]

IV. Conclusion

Amgen did not fairly respond to the amended WR for cinacalcet. Amgen's failure to meet an important element of the WR also resulted in the lack of sufficient safety data for pediatric patients < 6 years of age with secondary HPT and CKD receiving dialysis. The lack of sufficient safety data in this population has led to the inability to clearly establish the safety profile of the drug for pediatric patients in accordance with objectives of the amended WR. Accordingly, PE is denied for cinacalcet.

In accordance with section 505A(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), a submission of a pediatric study report seeking exclusivity requires the Secretary to make available to the public the medical, statistical, and clinical pharmacology reviews of the same.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Peter Stein, M.D.
Deputy Director
Office of New Drugs
Center for Drug Evaluation & Research

[2] We note that there may be an alternative basis for denial of PE based on the non-completion of a study or studies that were subject of this WR, see section 505A(h) of the FD&C Act, but, since the Board concludes that Amgen has not fairly responded to the WR under section 505A(d)(3) of the FD&C Act, the Board has not reached the separate question under section 505A(h) in making its decision.

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/s/

PETER P STEIN
05/22/2017
Concur with determination