IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMGEN INC., Plaintiff, v. THOMAS E. PRICE, M.D., in his official capacity as SECRETARY, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, and SCOTT GOTTLIEB, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, Defendants.	Civil Action No. 17-1006 (RDM)

AMGEN INC.'S SUPPLEMENTAL MEMORANDUM

Pursuant to the Court's request at the June 2 hearing, Amgen submits this supplemental memorandum to provide additional information about FDA's grant of pediatric exclusivity for Ortho Tri-Cyclen (ethinyl estradiol; norgestimate). Amgen also supplements the record to provide the *Merck* brief the Court requested, to address a concern the Court flagged about FDA's inclusion in drug labeling of pediatric studies that were inconclusive due to insufficient completers, and to respond to the "confidential" exclusivity letter that FDA attached to its memorandum of last night.

1. Ortho Tri-Cyclen's Exclusivity Determination

In November 2002, FDA issued a written request for pediatric studies for Ortho Tri-Cyclen to Ortho-McNeil. That written request called for two studies:

- Study 1: A randomized, double-blind, placebo-controlled study to assess the effect of ORTHO TRI-CYCLEN on bone mineral density (BMD) of the lumbar spine and hip in patients with anorexia nervosa (AN). Study 1 was designed to evaluate patients for one year (13 cycles), with the primary efficacy analyses to be performed after cycle 6.

- Study 2: A pharmacokinetics (PK) study to assess the single-dose and steady-state PK of ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in post-menarcheal pediatric patients with AN.

Ex. A. at 1–2 (11/12/2002 Written Request to Ortho-McNeil). [1]

At that time, Ortho Tri-Cyclen was protected by four patents set to expire on September 26, 2003. Ex. B (Orange Book 23rd ed., 2003). FDA set a September 26, 2003 deadline for Ortho-McNeil to submit the requested studies – meaning that the study reports were due the same day the relevant patents expired. Ex. A at 3. The statute at that time did not provide for the current 9-month buffer between expiration of the underlying patent exclusivity and the grant of pediatric exclusivity; that provision was added in 2007.

Ortho-McNeil submitted its study reports on September 25 – one day before FDA's deadline. As is common, in addition to requesting pediatric exclusivity, Ortho-McNeil also separately requested a new pediatric indication on the product's label "for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa." Ex. E at 5. Also at that time, FDA had only 90 days, not 180 days, to make pediatric exclusivity determinations. *See* 21 U.S.C. § 355a(d)(3) (2003). That meant that FDA had to make its pediatric exclusivity determination *before* completing its review of the studies or resolving Ortho-McNeil's request for the new indication.

[1] FDA subsequently issued two amendments to the Written Request: the first, modifying the entry criteria for patients in Study 1, in January 2013; and the second, further modifying those entry criteria and providing an alternative approach to conducting Study 2, in August 2003. Ex. C (WR Amendment 1); Ex. D (WR Amendment 2).

FDA granted pediatric exclusivity to Ortho Tri-Cyclen on December 18, 2003 – 84 days after Ortho-McNeil submitted its request and several months before the clinical pharmacology and biopharmaceutics review was completed. The grant of pediatric exclusivity extended the total market exclusivity for the drug until March 26, 2004. Ex. E at 12. Amgen has been unable to find any publicly available document in which FDA explains the basis for this decision.

As was typical during that time period, FDA had not completed its review of the studies at the time it granted pediatric exclusivity. Over two months after exclusivity was granted, in March 2004, an FDA reviewer found the results of the requested studies "unacceptable due to the sparsity of the data." More specifically:

> Results of this study were confounding. The sampling technique ultimately used by the sponsor was a hybrid method somewhere between a single-trough and full population PK sampling design, but failed to hit either mark. . . . Since the sponsor was unable to conduct this study in a manner consistent with recognized protocol, the value of the calculated apparent clearance is clearly suspect. This finding is apparently consistent with the sponsor's, as they are not requesting a labeling change to include apparent clearance for this pediatric population at this time.

See Ex. F at 1–2 (Clinical Pharmacology and Biopharmaceutics Review).

The FDA reviewer also noted that Ortho-McNeil had not shown that the enrolled patient population met the relevant enrollment criteria. In particular, the FDA reviewer concluded that "76 of the 123 treated subjects in [Ortho-McNeil's study] (i.e. 61.8% of treated subjects) had a baseline Body Mass Index (BMI) at or above the 10th percentile for age and should not have been enrolled into the study…." *Id.* at 38. It appears that FDA did not take into consideration the deficient enrollment in deciding to award pediatric exclusivity.

Ultimately, FDA denied Ortho-McNeil's request for a new pediatric indication on the product's label, just as it denied a new pediatric indication for SENSIPAR. Ex. E (Clinical Review).

FDA's grant of pediatric exclusivity for Ortho Tri-Cyclen confirms the agency's limited authority under the statute to determine whether a drug sponsor's reported studies "fairly respond" to the written request. Although the agency reviews the study reports carefully to determine whether to *approve a new indication and/or update the labeling*, its *exclusivity* determination is not so comprehensive. As FDA recognized in its briefing during the *Merck* litigation:

> Under the statute, the determination of whether a company qualifies for pediatric exclusivity must be made within 90 days, well before the expiration of the agency's 10 or 12 month review goals for applications and supplements, agreed to under the Prescription Drug User Fee Act. Thus, under the pediatric exclusivity statute, ***FDA must award or deny pediatric exclusivity without the benefit of a full review of the submitted studies***.

Ex. G at 10 (Fed. Defs.' Mem. in Opp., *Merck & Co., Inc. v. FDA*, 01-1342 (D.D.C. June 22, 2001)) (emphasis added). FDA also admitted that "at the time it makes its exclusivity determination, FDA does not, and indeed, cannot know whether the data generated by the studies will support actual label changes…." *Id.*

Although FDA now has more time to make exclusivity determinations, the standard for doing so has not changed. The mere fact that the deadline for exclusivity determinations is now 180 days rather than 90 days does not alter the meaning of "fairly respond"; that statutory phrase remains unchanged, as the Government points out in its brief here. *See* Gov. Opp. 30 ("If Congress meant to limit the scope of the 'fairly respond' standard, not only would it do so directly, but it would have made such clarification when it amended this section before 2007."). Now, as then, whether a *study* supports meaningful labeling changes bears no relevance to whether the study *report* "fairly responds" to a written request for exclusivity purposes.

2. FDA's Practice With Respect to Including Inconclusive Studies in Drug Labeling

At the June 2 hearing, the Court asked whether FDA would ever update drug labeling to indicate that pediatric studies had been inconclusive because of an insufficient number of completers, or due to some other externality – as opposed to simply inconclusive results at the close of a study that satisfied all of the written request's particulars. As FDA is well aware, many labels do exactly that, including for SENSIPAR itself.

On May 17, 2017, FDA proposed that the following language be included in the labeling for SENSIPAR, to advise prescribing physicians of the insufficiency of the data in Study 3 due to the low number of completers (*i.e.*, "poor retention of patients"):

> **8.4 Pediatric Use.**
>
> The safety and efficacy of Sensipar have not been established in pediatric patients.
>
> The use of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis was evaluated in two randomized, controlled studies where 49 pediatric patients aged 6 years to less than 18 years of age received at least one dose of Sensipar (Study 1 and Study 2) and in one single-arm study where 17 pediatric patients aged 28 days to less than 6 years received at least one dose of Sensipar (Study 3). Dosing with Sensipar in Study 1 was stopped because of a fatality in a Sensipar treated individual. The individual was noted to be severely hypocalcemic at the time of death and a contribution of Sensipar to the death could not be excluded *[see Warnings and Precautions (5.1)]*. Instructions for dosing and titration in Study 1 were similar to instructions used in the adult population and these were deemed inadequate to prevent severe hypocalcemia in the pediatric patient population. The instructions for dosing and titration in pediatric Study 2 and Study 3 were changed following the fatality to minimize the risk of severe hypocalcemia. In Study 2, use of Sensipar had no effects on PTH, calcium, or phosphorus. ***Early termination of Study 1 and poor retention of patients in Studies 2 and 3 resulted in insufficient data to establish the safety and effectiveness of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis.*** In aggregate, the pediatric studies did not establish a safe and effective Sensipar dosing scheme in the pediatric population.[2]

[2] The numbering of studies in the label is different than the numbering in the Written Request. Studies 1, 2, and 3 in the label correspond to Studies 2, 4, and 3, respectively, in the Written Request.

Ex. H (FDA's May 17, 2017 Proposed Labeling for SENSIPAR) at 8.4 (emphasis added).

Similarly, on May 19, 2017, FDA proposed the following draft language for SENSIPAR's labeling, to advise prescribing physicians of the insufficiency of the data in Study 3 due to the low number of completers (*i.e.,* "poor recruitment and retention of patients"):

> **8.4 Pediatric Use**
>
> The safety and efficacy of Sensipar have not been established in pediatric patients.
>
> The use of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis was evaluated in two randomized, controlled studies (Pediatric Study 1 and Study 2) where 47 pediatric patients aged 6 years to less than 18 years received at least one dose of Sensipar and in one single-arm study (Pediatric Study 3) where 17 pediatric patients aged 28 days to less than 6 years received at least one dose of Sensipar. Dosing with Sensipar in Pediatric Study 1 was stopped because of a fatality in a Sensipar-treated individual. The individual was noted to be severely hypocalcemic at the time of death. The cause of death was multifactorial and a contribution of Sensipar to the death could not be excluded *[see Warnings and Precautions (5.1)]*. Changes to Sensipar dosing after the fatality were implemented in Pediatric Study 2 and Study 3 to minimize the risk of severe hypocalcemia. ***Early termination of Study 1 and poor recruitment and retention of patients in Studies 2 and 3 resulted in insufficient data to establish the safety or effectiveness of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis.*** In aggregate, the pediatric studies did not establish a safe and effective Sensipar dosing regimen for the pediatric population.

Ex. I (May 19, 2017 Proposed Labeling for SENSIPAR) at 8.4 (emphasis added).

The final labeling for SENSIPAR also includes information about Study 3 and notes that it was inconclusive. Section 8.4 notes:

> **8.4 Pediatric Use**
>
> The safety and efficacy of Sensipar have not been established in pediatric patients. The use of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis was evaluated in two randomized, controlled studies (Pediatric Study 1 and Study 2) where 47 pediatric patients aged 6 years to less than 18 years received at least one dose of Sensipar and in one single-arm study (Pediatric Study 3) where 17 pediatric patients aged 28 days to less than 6 years received at least one dose of Sensipar. Dosing with Sensipar in Pediatric Study 1 was stopped because of a fatality in a Sensipar-treated individual. The individual was noted to be severely hypocalcemic at the time of death. The cause of death was multifactorial and a

> contribution of Sensipar to the death could not be excluded [see Warnings and Precautions (5.1)]. Study 1 was terminated and changes to Sensipar dosing after the fatality were implemented in Pediatric Study 2 and Study 3 to minimize the risk of severe hypocalcemia. ***The data in Pediatric Studies 2 and 3 were insufficient to establish the safety and efficacy of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis.*** In aggregate, the pediatric studies did not establish a safe and effective Sensipar dosing regimen for the pediatric population.

Ex. J (Final labeling for SENSIPAR) at 8.4 (emphasis added).

FDA has approved similar labeling language for other drug products where it is necessary and warranted. For example, Sanofi-Aventis's Plavix (clopidogrel) was awarded pediatric exclusivity on January 20, 2011, pursuant to a Written Request issued almost 10 years earlier and amended for the last time in 2007. FDA granted pediatric exclusivity before the FDA review division had approved proposed changes to the labeling describing the studies. Ex. K (NDA 020839, Summary Review (May 5, 2011)) at 2. And the agency awarded pediatric exclusivity despite the fact that "[t]he Pediatric Exclusivity Board members agreed with the Division that the study as conducted 'did not provide interpretable data.'" *Id*. at 6. The studies were deemed deficient in several ways, which rendered their results "far from definitive." *Id*. at 6. In particular, the sponsor used different formulations in the pediatric studies, and did not provide adequate bioavailability data as FDA had requested. As a result, FDA expressed concern that the formulation used may have delivered a sub-therapeutic level of exposure to the study drug. Ex. L (NDA 020839, Medical Officer's Review (December 22, 2010)) at 1-2. After noting other deficiencies – including unaccounted-for delays in randomization for many patients and a lack of clear disclosure of concerns raised by pharmacodynamic data – the FDA reviewer concluded that "the study's results are inconclusive and that they neither confirm nor rule out a beneficial effect of clopidogrel for the shunt palliation indication." *Id*. at 2.

The labeling for Plavix includes the following information in Section 8.4:

> 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.

Ex. M (NDA 020839, Approved Labeling (May 6, 2011)) at Section 8.4 (Pediatric Use).

In short, FDA itself has conceded that even inconclusive studies involving an insufficient number of completers can provide useful information to prescribing physicians. And FDA has specifically made that determination in connection with Study 3, which was included in the labeling for SENSIPAR notwithstanding the insufficient number of completers. By FDA's own standards, then, it should have accepted Amgen's study reports as fairly responsive to the written request. *See* 21 U.S.C. § 355a(j) (inconclusive pediatric study results must be included in labeling).

3. FDA's Secret May 2006 Exclusivity Letter.

FDA has recently surfaced a heavily redacted and previously secret May 2006 memo purporting to summarize the agency's denial of pediatric exclusivity to an unidentified drug for partially redacted reasons. FDA claims that it is now entitled to *Chevron* deference because the secret memo established the agency's new, post-*Merck* interpretation of the pediatric-exclusivity statute. (FDA says nothing of the contents of the *other* seventeen secret decisions the agency has issued denying pediatric exclusivity.)

That claim to deference is misplaced. "Where an agency's interpretation lacks the force of law, it is 'beyond the *Chevron* pale.'" *Pharm. Research & Mfrs. of Am. v. U.S. Dep't of Health & Human Servs.*, 43 F. Supp. 3d 28, 36 (D.D.C. 2014). And here, FDA's interpretation lacks the force of law. In addition to the complete lack of "any formal procedures" that

traditionally accompany notice-and-comment rulemaking and formal adjudications, *N.Y. State Bar Ass'n v. FTC*, 276 F. Supp. 2d 110, 138 (D.D.C. 2003), there is no evidence that FDA intended to imbue its May 2006 memo with the force of law. Most notably, FDA never intended that its May 2006 interpretation be made public. *See FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012) ("A fundamental principle in our legal system is that laws which regulate persons or entities must give fair notice of conduct that is forbidden or required."); *Godinez-Arroyo v. Mukasey*, 540 F.3d 848, 850 (8th Cir. 2008) (collecting cases holding that unpublished BIA determinations lack the force of law and do not warrant *Chevron* deference); *Batterton v. Marshall*, 648 F.2d 694, 701 (D.C. Cir. 1980) ("Advance notice and public participation are required for those actions that carry the force of law.").

As explained more fully in Amgen's brief and reply, an agency may not hold regulated entities to a standard that had not previously been made public. Any effort to do so runs afoul of due process requirements, and it certainly is not entitled to *Chevron* deference.

Respectfully submitted,

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Dated: June 5, 2017

CERTIFICATE OF SERVICE

I hereby certify that on this 5th day of June 2017, I caused a copy of the foregoing Supplemental Memorandum to be served upon all parties using this Court's Electronic Case Filing system.

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