JM:RAB/WMP
F.#2006R00987

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

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UNITED STATES OF AMERICA

- against -

AMGEN INC.,

Defendant.

I N F O R M A T I O N

Cr. No. 12-760 (SJ)
(T. 21, U.S.C., §§ 331(a), 333(a)(1), 334(a)(1), 334(a)(2), 352(f)(1) and 853(p); T. 18, U.S.C., §§ 2 and 3551 et seq.; T. 28, U.S.C. § 2461(c))

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THE UNITED STATES ATTORNEY CHARGES:

INTRODUCTION

At all times relevant to this Information, unless otherwise indicated:

I. The Defendant

1. The defendant AMGEN INC. ("AMGEN") was a California biotechnology corporation with its headquarters and principal place of business located in Thousand Oaks, California.

2. AMGEN manufactured and sold, among other items, erythropoiesis-stimulating agents ("ESAs"). ESAs were approved for the treatment of anemia or low red blood cell levels resulting from chronic kidney failure, chemotherapy and some treatments for Human Immunodeficiency Virus, and also for reducing the number of blood transfusions required during and after some major surgeries. ESAs worked by stimulating the bone marrow to produce red blood cells.

3. AMGEN manufactured the first ESA called epoetin alfa in 1984 for the treatment of anemia, which it trademarked as Epogen. Epogen was intended to treat anemia caused by chronic kidney disease in patients on dialysis to lessen the need for red blood cell transfusions. In 1985, Johnson & Johnson ("J&J") acquired the licensing rights from AMGEN to market epoetin alfa in the non-dialysis market. J&J trademarked epoetin alfa as Procrit and, over time, expanded the uses for Procrit.

4. In the late 1990s, AMGEN developed a new compound, darbepoetin alfa, an analog of epoetin alfa. AMGEN trademarked this new generation ESA as Aranesp and launched the drug into direct competition with Procrit in the non-dialysis market.

5. AMGEN held the United States patents and trademarks for Aranesp, which was manufactured in Puerto Rico and distributed into interstate commerce throughout the United States, including in the Eastern District of New York.

II. The FDA and the FDCA

6. The United States Food and Drug Administration ("FDA") was a federal agency responsible for protecting the health and safety of the public by enforcing the Federal Food, Drug and Cosmetic Act ("FDCA"), set forth at 21 U.S.C. §§ 301 et seq.

7. The FDCA and its implementing regulations required that, with exceptions not relevant here, before a new drug could

legally be introduced into interstate commerce, the drug's sponsor had to submit and obtain approval of a New Drug Application ("NDA") from the FDA.

8. The FDCA and its implementing regulations required that the NDA include proposed labeling for the proposed intended uses of the drug, which included, among other things, the conditions for therapeutic use. The NDA was also required to contain, to the satisfaction of the FDA, data generated in adequate and well-controlled clinical trials that demonstrated that the drug would be safe and effective when used in accordance with the proposed labeling for the proposed intended uses.

9. An NDA sponsor was not permitted to promote and market a new drug until the FDA approved its NDA, including approval for the proposed labeling. Moreover, if approved, the sponsor was permitted to promote and market the drug for the medical conditions of use, known as "indications," and for dosages specified in the approved labeling. Uses not approved by the FDA, including dosages not approved in the drug's approved labeling, were known as "unapproved" or "off-label" uses.

10. The FDCA and its implementing regulations required a sponsor to file a supplemental NDA ("sNDA") in order to label or promote a drug for uses and dosages different from the indications and dosages specified in the approved labeling. The sNDA was required to include both a description of the newly

proposed indication or indications for use and evidence consisting of well-controlled clinical studies sufficient to demonstrate that the drug was safe and effective for the new intended use or uses.

11. Under the FDCA, a drug was "misbranded" if its labeling did not contain "adequate directions for use." 21 U.S.C. § 352(f)(1). "Adequate directions for use" meant directions under which a layperson could use a drug safely and effectively for the purposes for which it was intended. 21 C.F.R. § 201.5. A prescription drug, by definition, could not bear adequate directions for use by a layperson, but an FDA-approved prescription drug, bearing the FDA-approved labeling, could be exempt from the adequate directions for use requirement if it was sold for an FDA-approved use. A prescription drug that was intended for non-approved, off-label uses did not qualify for this exemption and therefore was misbranded. 21 C.F.R. § 201.100.

12. FDA regulations define "intended use" by reference to the "objective intent of the persons legally responsible for the labeling of drugs," which intent may be demonstrated by, among other things, "oral or written statements by such persons or their representatives" and "the circumstances that the article is, with the knowledge of such persons or their representatives,

offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. § 201.128.

13. The FDCA prohibited introducing or causing the introduction into interstate commerce of any drug that was misbranded.

14. The FDCA did not prohibit doctors from prescribing drugs for any purpose the doctor deemed medically appropriate, including off-label uses.

III. The Aranesp Approval Process

15. The FDA approved Aranesp at specific doses to treat patients suffering from anemia caused by (i) chronic renal failure ("CRF"), and (ii) chemotherapy in patients with nonmyeloid malignancies.

A. The Nephrology Label

16. On or about March 18, 2001, AMGEN submitted an NDA seeking approval for Aranesp for treatment of anemia associated with CRF.

17. On or about September 17, 2001, the FDA approved Aranesp for the treatment of anemia caused by CRF. The FDA approved a starting dose for the correction of anemia in CRF patients of 0.45 micrograms per kilogram ("mcg/kg") of body weight, administered once weekly ("QW"). For patients converting from epoetin alfa to Aranesp, due to Aranesp's longer serum half-life, the FDA approved Aranesp at a QW dosing cycle if a

patient was receiving epoetin alfa 2 to 3 times weekly and once every 2 weeks ("Q2W") if a patient was receiving epoetin alfa QW.

B. The Oncology Label

18. On or about September 18, 2001, AMGEN submitted an sNDA seeking approval for Aranesp for treatment of anemia caused by chemotherapy.

19. On or about July 19, 2002, the FDA approved Aranesp for the treatment of chemotherapy-induced anemia ("CIA") in patients with non-myeloid malignancies, meaning anemia not caused by cancer. The recommended starting dose for Aranesp was 2.25 mcg/kg, administered QW. On or about March 23, 2006, the FDA approved every-three-week ("Q3W") dosing of Aranesp for the treatment of CIA in patients with non-myeloid malignancies.

IV. The Compendia

20. The compendia were reference books providing medical professionals with information regarding practitioners' uses of drugs in clinical practice. Pursuant to Title 42 of the United States Code and the regulations issued by the Centers for Medicare & Medicaid Services (CMS), the Medicare and Medicaid programs could reimburse for a drug prescribed for an off-label use so long as that use was supported by one of the compendia designated by CMS. One such compendium was the United States Pharmacopeia - Drug Information ("USP-DI"), a reference book published by the U.S. Pharmacopeia ("USP"), a scientific not-for-profit organization, that contained standard drug usages,

including some off-label uses. Once a drug obtained a listing for an off-label use in the USP-DI or one of the other compendia designated by CMS, that use was typically reimbursed by the Medicare and Medicaid programs and by many private insurers. Consequently, obtaining a compendia listing for an off-label use of a drug created the possibility for more widespread use of the drug in the off-label manner because it became financially practical for doctors and patients to use the drug in that manner.

21. As alleged herein, AMGEN sought and obtained listings in the USP-DI for off-label doses for Aranesp to treat CRF and for the off-label use of treating anemia of cancer ("AOC"). The off-label use to treat AOC was not supported by any other compendium designated by CMS.

V. AMGEN's Misbranding of Aranesp

22. In or about and between September 2001 and March 2007, AMGEN introduced into interstate commerce Aranesp that was misbranded, in that its labeling lacked adequate directions for intended uses and dosages that were not approved by the FDA. AMGEN continued to receive the benefits of its misbranding at least until the first quarter of 2009.

A. Misbranding in Nephrology

23. Despite the differences in molecular structure of Aranesp and Procrit and the FDA's dosing approvals, doctors

generally deemed Aranesp and Procrit to be therapeutically equivalent to treat patients with anemia caused by CRF. At the time the FDA approved Aranesp in September 2001, doctors used Procrit extensively to treat such patients.

24. Faced with the task of competing with the well-established Procrit for market share, AMGEN sought to capture the nephrology ESA market by emphasizing the primary difference between Aranesp and Procrit, which was that Aranesp possessed a longer serum half-life and had thus been approved for a less frequent dosing regimen than Procrit. However, AMGEN soon realized that promoting Aranesp for the on-label dosage of Q2W if a patient was receiving Procrit QW did not effectively differentiate Aranesp from Procrit because a large number of doctors already used Procrit on an off-label Q2W dosing schedule to treat patients with anemia caused by CRF.

25. To better differentiate Aranesp from Procrit and increase Aranesp's sales, AMGEN representatives made oral and written statements to promote Aranesp for the off-label dose of once a month ("QM") for the treatment of anemia caused by CRF. AMGEN encouraged its marketing and sales representatives in nephrology to spread the QM dosing message to doctors and other health care professionals and aggressively promote the conversion of CRF patients with anemia to QM dosing intervals. Promoting QM dosing for Aranesp for treatment of anemia caused by CRF was

AMGEN's business plan to distinguish Aranesp from Procrit and move anemic CRF patients to an ESA dosing regimen where Procrit could not compete.

26. AMGEN knew that its strategy of introducing Aranesp into the ESA market using the off-label QM dose for CRF patients with anemia would be pointless if doctors and patients were unable to obtain reimbursement for using the QM dose. Therefore, AMGEN sought and obtained a listing in the USP-DI for Aranesp for QM dosing, which in turn allowed for reimbursement for doctors who switched to the QM dose. As part of its strategy to increase sales of Aranesp, AMGEN instructed its sales representatives to distribute laminated reprints of the Aranesp compendia listing for the QM dose to health care professionals with the intent that the health care professionals would use Aranesp for QM dosing, for which they would be reimbursed.

27. AMGEN was very successful in using the off-label QM dose to increase its market share for CRF patients, which prompted one of its account managers, in June 2004, to state: "Doctors are so used to writing Procrit and we have pushed extended dosing [QM dosing] so much that they forget that they can use Aranesp Q2W."

28. In or about January 2005, to further increase Aranesp's share in the nephrology market, AMGEN promoted the unapproved QM dosing regimen through the concept of "Freedom

Time." The Freedom Time chart, which was created by an AMGEN sales representative, promoted QM dosing by highlighting the alleged lifestyle benefits to patients and economic benefits to doctors that followed a conversion from QW or Q2W to QM dosing. Senior AMGEN sales executives promoted the use of the Freedom Time chart and the attendant sales messages to AMGEN sales representatives across the United States and provided incentives to sales representatives who were able to convert accounts from Procrit to Aranesp. In response to an email showing that the Freedom Time chart and sales messages were being circulated to regional sales directors, district sales managers and sales representatives across the country, the Senior National Sales Director in Nephrology wrote to a regional sales director, senior marketing executives and others: "Great direction to your team. Thanks for sharing. This is a great way to follow up from our managment [sic] call."

29. In addition to the Freedom Time chart, AMGEN provided its sales representatives with clinical studies that supported the unapproved QM dosage of Aranesp and encouraged them to use these studies to promote QM dosing under the guise of "reactive" marketing, which was a marketing technique that took advantage of the sales representatives' supposed ability to react to doctor-initiated questions about an off-label use by providing the doctors with information in their possession concerning that

use. In reality, AMGEN trained its sales representatives to elicit questions from doctors about QM dosing that AMGEN believed gave the sales representative the necessary cover to provide the doctors with the off-label QM studies because Amgen intended that the drug be used for the off-label QM dosing, notwithstanding that Aranesp labeling lacked adequate directions for use for the off-label QM dosing.

30. In December 2005, AMGEN applied to the FDA to obtain approval for QM dosing for the treatment of anemia for patients with CRF. In July 2006, the FDA issued a complete response letter that did not approve QM dosing for the treatment of anemia for patients with CRF. The FDA told AMGEN that the studies submitted were inadequate to obtain an approval for QM dosing, and that AMGEN required "at least one randomized, controlled clinical study that provides robust evidence of safety and efficacy." AMGEN never submitted such a study to the FDA. Instead, AMGEN promoted Aranesp for the treatment of anemia caused by CRF at the QM dose by using some of the same studies that the FDA had found insufficient to establish the safety and efficacy of the QM dose. AMGEN's sNDAs submitted in 2007 and 2008 to obtain approval for QM dosing for the treatment of anemia for patients with CRF were also not approved by the FDA.

B. Misbranding in Oncology - Q2W Dosing

31. Similar to nephrologists, oncologists generally deemed Aranesp and Procrit to be therapeutically equivalent to treat patients with CIA. At the time the FDA approved Aranesp for the treatment of CIA in patients with non-myeloid malignancies at a QW starting dose, Procrit was already being used extensively by doctors at the off-label starting dose of QW.

32. As part of its strategy to introduce Aranesp into the oncology ESA market, Amgen sought to differentiate Aranesp from Procrit and increase Aranesp's sales by pointing doctors to language in the Dosage and Administration portion of the Aranesp label, which stated that the drug possessed a "longer serum half-life" and "should be administered less frequently than epoetin alfa." AMGEN used this language as justification for its promotion of a Q2W starting dose of Aranesp for the treatment of patients with CIA. This strategy was critical to AMGEN's business plan for Aranesp in the oncology field, which focused on establishing a Q2W starting dose for the treatment of CIA at the time of the drug's oncology launch in July 2002. AMGEN's internal marketing documents openly stated that the "launch strategy" was to "build a compelling clinical study around 200mcg 2QW" and to "utilize [an off-label study that supported the Q2W dose] on each call to solidify Q2W dosing with the 200 mcg." Despite these oral and written statements that reflected the

intended use of Aranesp for Q2W dosing in oncology, the Aranesp label did not contain adequate directions for use for Q2W dosing.

33. AMGEN improperly trained its sales representatives that the "less frequently than epoetin alfa" language in the Aranesp label meant that they could promote Aranesp for a Q2W starting dose. Indeed, AMGEN's promotion of the Q2W starting dose for the treatment of patients with CIA was so pervasive that some sales representatives were unaware that the Q2W starting dose was an off-label dosage. In training materials, AMGEN told its sales representatives that one of the "keys to success" was the "ability to maintain provider confidence in the 200 mcg Q2W dose."

34. Similar to AMGEN's marketing strategy for Aranesp in the nephrology field, AMGEN sought and obtained a listing in the USP-DI for Aranesp for the Q2W starting dose, which in turn allowed doctors to obtain reimbursement if they used this off-label dose. As it did in its nephrology campaign, AMGEN also encouraged its oncology sales force to promote Aranesp for the Q2W starting dose by instructing sales representatives to elicit questions from doctors about the off-label use of Aranesp and then provide the doctors with clinical studies that supported the off-label Q2W starting dose under the guise of "reactive" marketing.

35. In its September 18, 2001 sNDA, AMGEN applied for and submitted a Phase II study in support of the Q2W starting dose for the treatment of CIA, but the FDA did not approve Aranesp for this dose. Amgen nevertheless instructed its sales representatives to promote the off-label starting dose of Q2W for the treatment of patients with CIA using the same study that the FDA found insufficient to support approval of that dose.

C. Misbranding in Oncology - Anemia of Cancer

36. AMGEN introduced Aranesp into the oncology field for the treatment of AOC, which was an off-label use.

37. Prior to Aranesp's approval for the treatment of CIA, AMGEN's marketing group highlighted the fact that AOC was "a relatively large market with significant opportunities for future growth."

38. A year after the FDA approved Aranesp for the treatment of CIA, AMGEN sought and obtained a listing in the USP-DI concerning the use of Aranesp to treat AOC, providing the USP-DI with information about two AOC studies. Senior AMGEN sales executives treated the USP listing as the functional equivalent of FDA approval. AMGEN's internal marketing materials trumpeted that Aranesp in AOC was the "next big thing" and would give AMGEN a "fifty-one percent market share." AMGEN instructed its sales representatives to distribute laminated reprints of the USP-DI listing for Aranesp to treat AOC to health care

professionals with the intent that the health care professionals would use Aranesp for AOC. AMGEN also sought and obtained reimbursement for the use of Aranesp to treat AOC and trained its sales representatives to provide the written USP-DI listing to convince doctors to switch their AOC patients from Procrit to Aranesp. AMGEN encouraged its sales representatives to use off-label studies to promote Aranesp for the treatment of AOC and trained them to elicit questions about off-label uses of Aranesp to permit sales representatives to provide the studies to doctors under the guise of "reactive" marketing. At no time did the Aranesp label contain adequate directions for use for this intended use.

39. As early as 2001, AMGEN was in discussions with the FDA about obtaining an AOC indication for Aranesp. At that time, the FDA told AMGEN that it required a robust study of safety in AOC patients before it could approve Aranesp for that use. AMGEN nevertheless promoted Aranesp for the treatment of AOC using the less-robust studies that would have been insufficient to gain FDA approval. In 2007, AMGEN completed the required robust study and informed the FDA of the results. In response, in March 2007, the FDA mandated that a "black box" warning be added to Aranesp's label stating, among other things, that Aranesp "increased the risk of death . . . in patients with active malignant disease receiving neither chemotherapy nor

radiation." AMGEN ceased its promotion of Aranesp for the treatment of AOC at or about the time the FDA issued this "black box" warning.

INTRODUCTION OF A MISBRANDED DRUG INTO INTERSTATE COMMERCE

40. The allegations contained in paragraphs 1 through 39 are realleged and incorporated as though fully set forth in this paragraph.

41. In or about and between September 2001 and March 2007, both dates being approximate and inclusive, within the Eastern District of New York and elsewhere, the defendant AMGEN, together with others, did introduce into interstate commerce, and cause the introduction into interstate commerce of, Aranesp, a drug within the meaning of 21 U.S.C. § 321(g), for the following intended uses and dosages for which it was not approved by the FDA: (i) the off-label QM dosage for the treatment of anemia in CRF patients; (ii) the off-label Q2W starting dosage for the treatment of anemia in CIA patients; and (iii) the off-label use in the treatment of AOC, which resulted in the drug being misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that its labeling did not bear adequate directions for such intended uses and dosages.

(Title 21, United States Code, Sections 331(a), 333(a)(1) and 352(f)(1); Title 18, United States Code, Sections 2 and 3551 et seq.)

CRIMINAL FORFEITURE ALLEGATION

42. The United States hereby gives notice to AMGEN that, upon conviction of the offense charged in this Information, the government will seek forfeiture in accordance with Title 21, United States Code, Section 334(a)(1) and (a)(2) and Title 28, United States Code, Section 2461(c), which requires any person convicted of such offense to forfeit: (a) any article of food, drug or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce, or while held for sale after shipment in interstate commerce, or which may not, under the provisions of Title 21, United States Code, Sections 334 or 355, be introduced into interstate commerce; (b) any drug that is a counterfeit drug; (c) any container of a counterfeit drug; (d) any punch, die, plate, stone, labeling container, or other thing used or designed for use in making a counterfeit drug or drugs; and (e) any adulterated or misbranded device.

43. If any of the above-described forfeitable property, as a result of any act or omission of AMGEN:

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of AMGEN up to the value of the forfeitable property described in this forfeiture allegation.

(Title 21, United States Code, Sections 334(a)(1), 334(a)(2) and 853(p); Title 28, United States Code, Section 2461(c))

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