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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. _____ **COMPLAINT FOR PATENT INFRINGEMENT, CONVERSION, AND UNFAIR COMPETITION (CAL. BUS. & PROF. CODE § 17200)** **JURY TRIAL DEMANDED**

Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Plaintiffs"), by and through their undersigned attorneys, for their Complaint against Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH (collectively, "Defendants") hereby allege as follows:

NATURE OF THE ACTION

1. This lawsuit is necessary because Defendants refuse to follow the rules. Defendants' unlawful efforts are part of a scheme to sell a copy of one of Plaintiffs' most successful therapeutic products. Defendants are seeking approval from the United States Food and Drug Administration ("FDA") to sell their biosimilar product under a new abbreviated approval pathway, but they have not followed all the statutory requirements that must be met before Defendants' product can legally be sold. Specifically, Defendants' failure to follow the rules Congress put in place to resolve patent disputes with innovators such as Plaintiffs has caused harm to Plaintiffs and necessitates this action.

2. Defendants' unlawful activities arise in connection with their effort to gain approval to market and sell a version of NEUPOGEN® (filgrastim), a highly successful product invented by Plaintiff Amgen Inc. ("Amgen") for treating the side effects of certain forms of cancer therapy. NEUPOGEN® (filgrastim) was major advance in the field of oncology and has benefited millions of cancer patients since it was introduced in 1991. NEUPOGEN® (filgrastim) is a biotechnology product—it is made using recombinant DNA technology and was the result of substantial original research and development by Amgen.

3. Since NEUPOGEN® (filgrastim) is regulated by the FDA as a biologic product, Amgen had to conduct extensive clinical trials and then submit the results of those trials to the FDA in order to prove that NEUPOGEN® (filgrastim) is safe, pure, and potent. Over the years, Amgen has accumulated and submitted to FDA a large amount of clinical trial results showing NEUPOGEN® (filgrastim) to be safe and effective in treating various conditions.

4. Prior to 2010, any other company wishing to sell its own version of NEUPOGEN® (filgrastim) would have had to undertake the same extensive effort to prove to the FDA that their proposed version was also safe, pure and potent. In 2010, Congress created a new the statutory framework, known as the Biosimilars Price Competition and Innovation Act ("BPCIA"), that governs the regulatory approval, marketing, and sale of biological products known as "biosimilars." The BPCIA reflects Congress's efforts to balance the rights of innovators, such as Amgen, and the rights of applicants, such as Defendants, who seek to develop biosimilar versions of innovators' drugs.

5. Developing new therapeutic products from scratch is extremely expensive: current studies estimate the cost of obtaining FDA approval of a new drug as more than $1 billion. The BPCIA allows a biosimilar applicant to avoid this expense by taking advantage of the extensive and costly clinical trials previously conducted by the original creator of the biologic product to show that it is safe, pure, and potent. But there is also another side to this procedure: the BPCIA requires a biosimilar applicant to disclose its FDA application (known as a Biologics Licensing Application or "BLA") and manufacturing information to the innovator within 20 days of filing that application. That disclosure allows the innovator to assess which patents the biosimilar applicant's activities could infringe and, critically, to start a process that will allow the innovator to bring its patent claims before the applicant can begin selling an infringing product and thereby irreparably damage the market.

6. Based on a letter that Defendants sent to Amgen and on other public information, Defendants have submitted a BLA that seeks approval under the provisions of the BPCIA to market a biosimilar copy of NEUPOGEN® (filgrastim). But they have refused to provide Amgen with the BLA and manufacturing information in a timely manner, except under conditions nowhere imposed by the BPCIA, and to otherwise comply with what the statute requires them to do.

7. Defendants' scheme to follow only those parts of the BPCIA they consider helpful and to flaunt the part they consider unhelpful to them is unlawful. In particular, these acts constitute unfair competition under California Business & Professions Code § 17200, et

seq. and conversion under California common law. Defendants have also committed a statutory act of patent infringement under the United States patent law, 35 U.S.C. § 271(e)(2)(C)(ii), by submitting an application for approval of a biological product and failing to provide the BLA and manufacturing information as required by the BPCIA. Despite Amgen's requests, Defendants refuse to honor their obligations under the BPCIA. Accordingly, Plaintiffs turn to this Court for protection of their legal rights. Plaintiffs seek injunctive relief, restitution, attorneys' fees, costs, and expenses.

THE PARTIES

8. Amgen Inc. ("Amgen") is a corporation existing under the laws of the State of Delaware, with its principal place of business at One Amgen Center Drive, Thousand Oaks, California 91320. Amgen discovers, develops, manufactures, and sells innovative therapeutic products based on advances in molecular biology, recombinant DNA technology, and chemistry.

9. Amgen Manufacturing, Limited ("AML") is a corporation existing under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. AML manufactures and sells biologic medicines for treating particular diseases in humans.

10. Upon information and belief, Sandoz Inc. is a corporation existing under the laws of the state of New Jersey, with its principal place of business at 506 Carnegie Drive, Suite 400, Princeton, New Jersey 08540. Upon information and belief, acting in concert with Defendants Sandoz International GmbH and Sandoz GmbH, Sandoz Inc. is in the business of developing, manufacturing, and marketing biopharmaceutical products that are distributed and sold in the State of California and throughout the United States. Upon information and belief, Sandoz Inc. is also the United States agent for Sandoz International GmbH and Sandoz GmbH for purposes including, but not limited to, filing regulatory submissions to and corresponding with the FDA.

11. Upon information and belief, Sandoz International GmbH is a corporation existing under the laws of Germany with its principal place of business at Industriestrasse 25, 83607 Holzkirchen, Germany. Upon information and belief, acting in concert with

Defendants Sandoz Inc. and Sandoz GmbH, Sandoz International GmbH is in the business of developing, manufacturing, and marketing biopharmaceutical products that are distributed and sold in the State of California and throughout the United States.

12. Upon information and belief, Sandoz GmbH is a corporation existing under the laws of Austria with its principal place of business at Biochemiestraße 10, 6250 Kundl, Austria. Upon information and belief, acting in concert with Defendants Sandoz Inc. and Sandoz International GmbH, Sandoz GmbH is in the business of developing, manufacturing, and marketing biopharmaceutical products that are distributed and sold in the State of California and throughout the United States.

13. Upon information and belief, Sandoz GmbH operates as a subsidiary of Sandoz International GmbH.

14. Upon information and belief, Sandoz Inc. operates as a subsidiary of Sandoz International GmbH.

15. Upon information and belief, Defendants collaborate to develop, manufacture, seek regulatory approval for, import, market, distribute, and sell biopharmaceutical products (including products intended to be sold as biosimilar versions of successful biopharmaceutical products developed by others) in the State of California and in the United States.

JURISDICTION AND VENUE

16. This Court has subject matter jurisdiction over Plaintiffs' patent infringement claim under 28 U.S.C. § 1331 and 1338(a).

17. The Court also has subject matter jurisdiction over Plaintiffs' unfair competition and conversion claims under 28 U.S.C. §§ 1367 and 1338(b).

18. In the alternative, this Court has subject matter over the case under 28 U.S.C. § 1332 because there is diversity among the parties and the amount in controversy, without interest and costs, exceeds $75,000.

19. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 (b) and (c), and 28 U.S.C. § 1400(b). Upon information and belief, the Defendants collaborate to develop,

manufacture, seek regulatory approval for, import, market, distribute, and sell biopharmaceutical products for sale and use throughout the United States, including in this federal judicial District.

20. For purposes of intradistrict assignment pursuant to Civil Local Rules 3-2(c) and 3-5(b), this Intellectual Property Action is to be assigned on a district-wide basis.

21. This Court has personal jurisdiction over each of the Defendants for the reasons set forth below.

A. Sandoz Inc.

22. Upon information and belief, Sandoz Inc. develops, manufactures, seeks regulatory approval for, markets, distributes, and sells biopharmaceuticals for sale and use throughout the United States, including in California and this federal judicial District.

23. This Court has personal specific jurisdiction over Sandoz Inc. because Sandoz Inc. has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement and the tortious acts of unfair competition and conversion that have led to foreseeable harm and injury to Amgen, a corporation with its principal place of business in California. In particular, Sandoz, Inc. collaborates to develop, manufacture, seek approval for, and sell the disputed biosimilar product, which will cause tortious injury to Plaintiffs. For example, Amgen received a letter from in-house counsel for Sandoz Inc. dated July 25, 2014, that informed Amgen that Defendants' application for the Sandoz biosimilar product had been accepted by the FDA for review. Moreover, upon information and belief, Sandoz Inc., following any FDA approval of the biosimilar product, will sell the Sandoz biosimilar product that is the subject of the patent infringement, unfair competition, and conversion claims in this action in California and throughout the United States.

24. This Court has personal general jurisdiction over Sandoz Inc. by virtue of, *inter alia*, its having conducted business in this District, having availed itself of the rights and benefits of California law, and having engaged in substantial and continuing contacts with California. Upon information and belief, Sandoz has regular and continuous commercial

business dealings with representatives, agents, distributors, and customers located in California and this district. In addition, Sandoz has availed itself of this Court as a patent infringement plaintiff, *see, e.g.*, *Sandoz Inc. v. Amgen Inc.,* 3:13-cv-02904-MMC (N.D. Cal.) (appeal pending, Fed. Cir. Appeal No. 2014-1693), and consented to the personal jurisdiction of this Court in numerous other legal proceedings. *See, e.g.*, *Genentech, Inc. v. Sandoz Inc.,* 3:11-cv-01925-JSW (N.D. Cal.); *Takeda Pharmaceutical, Co., Ltd. v. Sandoz Inc.,* 5:13-cv-02418-LHK (N.D. Cal.); *Takeda Pharmaceutical, Co., Ltd. v. Sandoz Inc.,* 3:12-cv-00446-JCS (N.D. Cal.).

B. Sandoz International GmbH (Germany)

25. Upon information and belief, Sandoz International GmbH collaborates with Sandoz Inc. to develop, manufacture, seek approval for, and sell FDA-approved biopharmaceutical drugs, which are being marketed, distributed, and sold in California and in the United States.

26. Upon information and belief, Sandoz International GmbH exercises considerable control over Sandoz Inc. with respect to biosimilar products, and approves significant decisions of Sandoz Inc. such as allowing Sandoz Inc. to act as the agent for Sandoz International GmbH in connection with preparing and filing the Sandoz BLA, and acting as Sandoz International GmbH's agent in the United States. For example, the Sandoz Management Team includes "Richard Francis, the Global Head of Sandoz," and "Peter Goldschmidt, President of Sandoz US and Head of North America." Upon information and belief, Mr. Francis is the head of Sandoz International GmbH, Mr. Goldschmidt is the President of Sandoz Inc. as well as the Head of North American Operations at Sandoz International GmbH, and Mr. Goldschmidt directly or indirectly reports to Mr. Francis.

27. In addition, Sandoz International GmbH and Sandoz Inc. hold themselves out as a unitary entity and have represented to the public that the activities of Sandoz International GmbH and Sandoz Inc. are directed, controlled, and carried out by a single entity, namely, Sandoz. For example, Sandoz maintains an Internet website at the URL www.sandoz.com attached hereto as Ex. A, which states that it is "the website of Sandoz

International" and on which Sandoz states that all of the worldwide generic pharmaceutical businesses owned by Novartis operate "under one single global brand as known today: Sandoz."

28. Upon information and belief, Sandoz International GmbH is actively involved with planning Sandoz Inc.'s new products and filing the Sandoz BLA for the biosimilar product in dispute. For example, Sandoz Inc.'s President, Mr. Goldschmidt, is also the Head of North American Operations at Sandoz International GmbH.

29. Upon information and belief, Sandoz International GmbH acted in concert with Sandoz Inc. to develop a biosimilar version of Plaintiffs' NEUPOGEN® (filgrastim). Upon information and belief, Sandoz International GmbH acted in concert with, directed, and/or authorized Sandoz Inc. to file a BLA seeking approval from the FDA to market and sell the Sandoz biosimilar product in the State of California and throughout the United States, which directly gives rise to Plaintiffs' claims of patent infringement. For example, Novartis AG, the ultimate corporate parent of both Sandoz International GmbH and Sandoz Inc., issued a press release on July 24, 2014 from Holzkirchen, Germany announcing that the FDA had accepted Sandoz's application for biosimilar filgrastim. *See* Press Release, Novartis, FDA Accepts Sandoz Application For Biosimilar Filgrastim (July 24, 2014), http://www.novartis.com/newsroom/media-releases/en/2014/1835571.shtml, attached hereto as Ex. B. Upon information and belief, the press release announcing the FDA's acceptance of the Sandoz's BLA, which is the subject of Plaintiffs' claims, was issued on behalf of Sandoz International GmbH.

30. Upon information and belief, Sandoz International GmbH acted in concert with, directed, and/or authorized Sandoz Inc. to communicate with Amgen after receiving FDA notification of the FDA's acceptance and to unlawfully withhold the BLA for the Sandoz biosimilar product from Amgen while at the same time obtaining the benefits of the

§ 262(k) pathway (such as making use of the FDA's prior determinations as to the safety, purity, and potency of Plaintiffs' NEUPOGEN® (filgrastim)), which directly gives rise to Plaintiffs' claims of unfair competition and conversion. For example, Amgen received correspondence from Sandoz International GmbH dated September 4, 2014 that refers to "**our** decision not to disclose our application to Amgen." (emphasis added). Similarly, Amgen received further correspondence from Sandoz International, GmbH dated October 20, 2014 that refers to an earlier communication from Sandoz, Inc. as "our July 8, 2014 letter" and to an appeal filed by Sandoz, Inc. in co-pending litigation with Amgen as "our appeal." Letter from Julia Pike, Head, Global IP Litigation, Sandoz Int'l GmbH, to Wendy A. Whiteford, Vice President Law, Amgen Inc. (Oct. 20, 2014). These communications evidence that Sandoz International, GmbH and Sandoz, Inc. are working in concert in their scheme to unlawfully withhold from Amgen the information concerning the Sandoz biosimilar product that is required to be provided under 42 U.S.C. § 262(l)(2)(A).

31. Upon information and belief, the acts of Sandoz Inc. complained of herein were done, in part, for the benefit of Sandoz International GmbH. Upon information and belief, Sandoz International GmbH, following any FDA approval, will directly or indirectly manufacture and/or sell the Sandoz biosimilar product that is the subject of the infringement, unfair competition, and conversion claims in this action in California and throughout the United States.

32. This Court has personal specific jurisdiction over Sandoz International GmbH because Sandoz International GmbH has directly, or through its agent, committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement and the tortious acts of unfair competition and conversion that have led to foreseeable harm and injury to Amgen, a corporation with its principal place of business in California.

33. Additionally, and in the alternative, Plaintiffs allege that to the extent Sandoz International GmbH is not subject to the jurisdiction of the courts of general jurisdiction of the State of California, Sandoz International GmbH likewise is not subject to the jurisdiction

of the courts of general jurisdiction of any state, and accordingly is amenable to service of process based on its aggregate contacts with the United States, including but not limited to the above described contacts, as authorized by Rule 4(k)(2) of the Federal Rules of Civil Procedure.

B. Sandoz GmbH (Austria)

34. Upon information and belief, Sandoz GmbH collaborates with Sandoz Inc. to develop, manufacture, seek approval for, and sell FDA-approved biopharmaceutical drugs, which are being marketed, distributed, and sold in California and in the United States.

35. Sandoz GmbH and Sandoz Inc. hold themselves out as a unitary entity and have represented to the public that the activities of Sandoz GmbH and Sandoz Inc. are directed, controlled, and carried out by a single entity, namely, Sandoz. For example, Sandoz maintains an Internet website at the URL www.sandoz.com, attached hereto Ex. A, which states that it is "the website of Sandoz International" and on which Sandoz states that all of the worldwide generic pharmaceutical businesses owned by Novartis operate "under one single global brand as known today: Sandoz."

36. Upon information and belief, Sandoz GmbH is actively involved with planning Sandoz Inc.'s new biosimilar filgrastim products and filing Defendants' BLA for the biosimilar product in dispute. 42 U.S.C. § 262(k)(2)(A)(V) provides that a biosimilar application submitted to the FDA under the § 262(k) pathway "shall include" information demonstrating "the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent." Upon information and belief, the Sandoz biosimilar product that is the subject of Defendants' BLA is manufactured at Sandoz GmbH facilities. Therefore, upon information and belief, Sandoz GmbH actively participated in the preparation of Defendants' BLA, for example by providing information regarding the facilities in which the Sandoz biosimilar product is manufactured, processed, packed, or held. Upon information and belief, Sandoz GmbH has provided similar information for biosimilar filgrastim products in Europe and manufactures those European products. For example, Sandoz GmbH applied for approval to market biosimilar filgrastim in

Europe, which it manufactures and sells as ZARZIO®. Sandoz GmbH has also stated that its Kundl facility is the "API manufacturing facility" of ZARZIO®. *See* Sandoz Company Presentation (May 15, 2012), attached hereto as Ex. C.

37. Upon information and belief, Sandoz GmbH acted in concert with Sandoz Inc. to develop a biosimilar version of Plaintiffs' NEUPOGEN® (filgrastim). Upon information and belief, Sandoz GmbH acted in concert with, directed, and/or authorized Sandoz Inc. to file a BLA seeking approval from the FDA to market and sell the Sandoz biosimilar product in the State of California and throughout the United States, which directly gives rise to Plaintiffs' claims of patent infringement. For example, Sandoz GmbH provided ZARZIO® to the then-Global Medical Director at Sandoz International GmbH, Michael Muenzberg, to assess ZARZIO®'s biosimilarity to Plaintiffs' NEUPOGEN® (filgrastim) product. *See* M. Muenzberg et al., *Development of a New G-CSF Product Based on Biosimilarity Assessment*, 21 ANNALS OF ONCOLOGY 1419 (2010), attached hereto as Ex. D.

38. Upon information and belief, Sandoz GmbH acted in concert with, directed, and/or authorized Sandoz Inc. to communicate with Amgen after receiving FDA notification of the FDA's acceptance and to unlawfully withhold the BLA for the Sandoz biosimilar product from Amgen while at the same time obtaining the benefits of the § 262(k) pathway (such as making use of the FDA's prior determinations as to the safety, purity, and potency of Plaintiffs' NEUPOGEN® (filgrastim)), which directly gives rise to Plaintiffs' claims of unfair competition and conversion.

39. Upon information and belief, the acts of Sandoz Inc. complained of herein were done, in part, for the benefit of Sandoz GmbH. Upon information and belief, Sandoz GmbH, following any FDA approval, will directly or indirectly manufacture and/or sell the Sandoz biosimilar product that is the subject of the infringement, unfair competition and conversion claims in this action in California and throughout the United States.

40. This Court has personal specific jurisdiction over Sandoz GmbH because Sandoz GmbH has directly, or through its agent, committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement and the

tortious acts of unfair competition and conversion that have led to foreseeable harm and injury to Amgen, a corporation with its principal place of business in California

41. Additionally, and in the alternative, Plaintiffs allege that to the extent Sandoz GmbH is not subject to the jurisdiction of the courts of general jurisdiction of the State of California, Sandoz GmbH likewise is not subject to the jurisdiction of the courts of general jurisdiction of any state, and accordingly is amenable to service of process based on its aggregate contacts with the United States, including but not limited to the above described contacts, as authorized by Rule 4(k)(2) of the Federal Rules of Civil Procedure.

AMGEN OBTAINS FDA APPROVAL FOR ITS INNOVATIVE G-CSF BIOLOGICAL PRODUCT, NEUPOGEN®, UNDER 42 U.S.C. § 262(a)

42. A company seeking to market a biological product for human therapeutic use in the United States must first file a BLA seeking to obtain a license from the FDA. Prior to seeking FDA approval, developers of innovative biological products typically go through three clinical development phases before their developers seek FDA approval: Phase I, which typically tests safety, tolerability, and pharmacologic properties on healthy human volunteers, and Phases II and III, which typically test safety and efficacy on, respectively, a small and then a larger group of afflicted patients. If testing in each phase succeeds, the developer may be in a position to submit a BLA for FDA approval. The BLA includes, among other things, technical data on the characterization and composition of the biological product, toxicology studies in animals, the means for manufacturing, clinical trial results to establish the safety and efficacy of the biological product, and labeling for use of the biological product for which approval is requested. *See* 21 C.F.R. §§ 601 et seq.

43. After submission of the BLA, innovative developers must pass demanding stages of clearance. For example, innovative developers are required to demonstrate to the FDA that "the biological product that is the subject of the application is safe, pure, and potent" (42 U.S.C. § 262(a)(2)(C)(i)(I)); and "the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(II). If

the FDA determines that the biological product or the facility does not meet the requirements, the BLA will be denied.

44. Not surprisingly, the development of innovative pharmaceutical products requires the investment of enormous amounts of time and money. For example, the time to develop a drug is ten to fifteen years, and the average cost to develop a drug (including the cost of failures) was $1.2 billion or higher in the early 2000s. *See* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, 2013 PROFILE: BIOPHARMACEUTICAL RESEARCH INDUSTRY, at 32, attached hereto as Ex. E; Christopher Paul Adams & Van Vu Brantner, *Spending on New Drug Development*, 19 HEALTH ECONOMICS 130, 139, 141 (2010), attached hereto at Ex. F (finding that the cost of drug development (or the net revenue needed to make investment in new drugs profitable) is over $1 billion: "a firm would need expected net revenue of over $1 billion to develop one more drug for the market").

45. Amgen went through each of the requirements of 42 U.S.C. § 262(a) (the "§ 262(a) pathway") to obtain a license from the FDA for its innovative biological product NEUPOGEN® (filgrastim). In 1991, the FDA approved NEUPOGEN® (filgrastim), pursuant to BLA No. 103353, for decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. The FDA later approved a series of additional indications for the therapeutic use of NEUPOGEN® (filgrastim), including the treatment of patients with severe chronic neutropenia, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients receiving bone marrow transplant, and patients undergoing peripheral blood progenitor cell collection and therapy. Each of these new indications necessitated Amgen's further investment to conduct additional clinical testing, submit a supplemental BLA, and prove to the FDA's satisfaction that NEUPOGEN® (filgrastim) was safe, pure, and potent for each new indication. These approvals are the direct result of very significant investments by Amgen in the development and clinical trials of

NEUPOGEN® (filgrastim). The biological product license to NEUPOGEN® (filgrastim) is owned by Amgen and exclusively licensed to AML.

46. The active ingredient in NEUPOGEN® is filgrastim, a recombinantly expressed, 175-amino acid form of a protein known as human granulocyte-colony stimulating factor or "G-CSF." NEUPOGEN® (filgrastim) is also known as recombinant methionyl human granulocyte-colony stimulating factor. By binding to specific receptors on the surface of certain types of cells, NEUPOGEN® (filgrastim) stimulates the production of a type of white blood cells known as neutrophils. Neutrophils are the most abundant type of white blood cells and form a vital part of the human immune system. A deficiency in neutrophils is known as neutropenia, a condition which makes the individual highly susceptible to infection. Neutropenia can result from a number of causes; it is a common side effect of chemotherapeutic drugs used to treat certain forms of cancer. NEUPOGEN® (filgrastim) counteracts neutropenia. The availability of NEUPOGEN® (filgrastim) represented a major advance in cancer treatment by protecting chemotherapy patients from the harmful effects of neutropenia and by thus facilitating more effective chemotherapy regimes.

47. Another major advance provided by NEUPOGEN® (filgrastim) is for patients undergoing peripheral blood progenitor cell collection and transplant. In order to successfully treat certain forms of blood cancer, patients undergo hematopoietic progenitor cell transplants. NEUPOGEN® (filgrastim) is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization with NEUPOGEN® (filgrastim) allows for the collection of increased numbers of hematopoietic progenitor cells capable of engraftment compared with collection without the use of NEUPOGEN® (filgrastim) or from bone marrow harvest. Furthermore, transplantation with an increased number of hematopoietic progenitor cells can lead to faster engraftment, which may result in a faster recovery for the patient after transplant.

THE BPCIA REFLECTS A CONGRESSIONAL BALANCE OF THE INTERESTS OF INNOVATORS AND BIOSIMILAR APPLICANTS UNDER THE 262(k) PATHWAY

48. On March 23, 2010, the BPCIA was enacted, creating an abbreviated approval pathway for FDA licensure of biological products upon a determination that the biological product is "biosimilar" to a previously licensed "reference product." 42 U.S.C. § 262(k). The BPCIA defines a "biosimilar" to be a biological product that is (1) "highly similar to the reference product notwithstanding minor differences in clinically inactive components"; and (2) has "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." 42 U.S.C. §§ 262(i)(2)(A), (B). The BPCIA defines a "reference product" to be "a single biological product licensed under subsection (a) against which the biological product is evaluated in an application submitted under subsection (k)." 42 U.S.C. §§ 262(i)(4).

49. As opposed to applicants under the § 262(a) pathway, biosimilar applicants are permitted to make use of the FDA's prior determinations as to the safety, purity, and potency of the reference product that was already approved by the FDA. Specifically, the § 262(k) pathway may only be used where the prior applicant of the reference product has submitted an application under 42 U.S.C. § 262(a) for approval of a "reference product," and FDA has determined that the reference product sponsor has demonstrated that "the biological product that is the subject of the application is safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). A biosimilar applicant may only request FDA evaluation for biosimilarity under the § 262(k) pathway with respect to no more than one reference product § 262(k)(5)(A) and must submit to the FDA "publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent." 42 U.S.C. § 262(k)(2)(A)(iii)(I). Consequently, the § 262(k) pathway allows the biosimilar applicant to cut short the time and expensive cost of clinical testing, and gain licensure to commercialize its biological product in the market sooner as a biosimilar than it could have done through an independent demonstration of safety, purity, and potency under the § 262(a) pathway. The § 262(k) pathway is thus referred to as an "abbreviated" approval pathway.

50. The purpose of the BPCIA is to establish "a biosimilars pathway balancing innovation and consumer interests." Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, § 7001(b), 124 Stat. 119, 804 (2010) (amending 42 U.S.C. § 262). The statutory provisions of the BPCIA reflect Congressional intent to achieve this balance. In addition to saving the time and expense of the traditional approval pathway under § 262(a), approval under the § 262(k) pathway offers other benefits to the biosimilar applicant. A product that is approved as a biosimilar can take advantage of the existing market for the reference product created by the reference product sponsor. Specifically, the the Patient Protection and Affordable Care Act (PPACA) created a higher Medicare payment rate for biosimilars in the physician clinic setting. Pub. L. No. 111-148, § 3139(a), 124 Stat. 119, 439 (2010) (amending 42 U.S.C. § 1395w-3a). In the case of drugs (both biologics and small molecule drugs) other than biosimilars, the Medicare payment rate is the Average Sales Price (ASP)[1] of the drug plus 6 percent of that ASP. 42 U.S.C. § 1395w-3a(b)(1). Under the PPACA amendments, the Medicare payment rate for biosimilars is the ASP of the biosimilar, plus 6 percent of the *reference product's* ASP. 42 U.S.C. § 1395w-3a(b)(8). This results in a higher payment rate for physicians, assuming the ASP of the reference product is higher than that of the biosimilar. *See* Michael McCaughan, *Biosimilar Reimbursement Under The Sequester: The Lower The Price, The Bigger The Spread*, THE PINK SHEET DAILY (Aug. 8, 2014), attached hereto as Ex. G.

51. Further, a biosimilar product can be approved as "interchangeable" if it meets certain criteria, *i.e.*, the biosimilar product "can be expected to produce the same clinical result as the reference product in any given patient" and "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference

[1] ASP is calculated by the Centers for Medicare & Medicaid Services based on sales information reported to the agency by manufacturers. 42 U.S.C. § 1395w-3a(c).

product is not greater than the risk of using the reference product without such alternation or switch." 42 U.S.C. §§ 262(k)(4)(A), 262(k)(4)(B). The designation of a biosimilar product as interchangeable provides additional value to the biosimilar applicant by permitting the product to be "substituted for the reference product without the intervention of the health care provider who prescribed the reference product" (42 U.S.C. §§ 262(i)(3)); and providing the biosimilar applicant with market exclusivity compared to other biosimilar products. 42 U.S.C. §§ 262(k)(6) (specifying time periods and conditions for exclusivity).

52. On the other hand, the BPCIA also sets forth a detailed and elaborate procedure adopted by Congress as a way of balancing the interests of reference product sponsors and biosimilar applicants under the § 262(k) pathway. Of particular relevance to this lawsuit, the BPCIA sets forth particular requirements that the biosimilar applicant must follow in order to obtain the benefits of filing its BLA under the § 262(k) pathway. 42 U.S.C. § 262(l). Among other things, these provisions require the biosimilar applicant to provide a copy of its BLA, together with other information necessary to describe the process(es) for manufacturing the biosimilar product to the reference product sponsor. *See* 42 U.S.C. § 262(l)(2). This permits the reference product sponsor to evaluate whether it can assert patent claims against the biosimilar applicant for making, using, offering to sell, selling, or importing into the United States the biosimilar product.

53. Specifically, 42 U.S.C. § 262(l) provides the following carefully crafted series of steps for the identification of patents potentially blocking commercialization of the proposed biosimilar, as well as specific times for completing these steps that are emphasized in bold below:

a. ***Within 20 days*** after the FDA has accepted its abbreviated application, the biosimilar applicant must provide the reference product sponsor: (i) a copy of the biosimilar application and (ii) other information describing the process(es) for manufacturing the biosimilar product. 42 U.S.C. § 262(l)(2). The reference product sponsor must keep the BLA and manufacturing information confidential, and may only use such material to evaluate infringement. 42 U.S.C. § 262(l)(1).

b. ***Within 60 days*** after receiving the BLA and manufacturing information, the reference product sponsor must provide the biosimilar applicant with a list of all patents that the reference product sponsor reasonably believes are infringed, such that they could be

asserted by either the reference product sponsor or a patent owner that has granted exclusive rights to the reference product sponsor. 42 U.S.C. § 262(l)(3)(A). The reference product sponsor must also identify which, if any, of these patents it would be prepared to license to the biosimilar applicant. 42 U.S.C. § 262(l)(3)(A)(ii).

c. ***Within 60 days*** after receiving the foregoing list from the reference product sponsor, the biosimilar applicant may provide to the reference product sponsor a list of patents that the biosimilar applicant believes could be subject to a claim of patent infringement. 42 U.S.C. § 262(l)(3)(B)(i). ***Within the same 60 days***, regarding any patents listed by the reference product sponsor or the biosimilar applicant, the biosimilar applicant must also provide: (I) a statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent is invalid, unenforceable, or not infringed; or (II) a statement that the biosimilar applicant does not intend to market until the patent expires. 42 U.S.C. § 262(l)(3)(B))ii). The biosimilar applicant must also provide a response to the reference product sponsor's identification of any patents it would be prepared to license. 42 U.S.C. § 262(l)(3)(B)(iii).

d. ***Within 60 days*** after receiving the information described immediately above, the reference product sponsor must provide, regarding each patent discussed in (I) above, a reciprocal statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent will be infringed as well as a response to any statement regarding validity and enforceability. 42 U.S.C. § 262(l)(3)(C).

e. After this exchange of information, both parties must engage in good faith negotiations to identify which patents, if any, should be subject to patent infringement litigation. 42 U.S.C. § 262(l)(4)(A). If the parties reach agreement ***within 15 days*** of starting negotiations, the reference product sponsor must bring an "immediate" patent infringement action against the biosimilar applicant on the negotiated list of patents ***within 30 days*** of such agreement. 42 U.S.C. § 262(l)(6)(A). If the parties do not reach agreement ***within 15 days*** of starting negotiations, the biosimilar applicant must notify the reference product sponsor of the number of patents it will provide in a second list, and the parties then simultaneously exchange within five days of this notice a list of patents that each party believes should be the subject of infringement litigation. 42 U.S.C. § 262(l)(5). ***Within 30 days*** after exchanging these lists, the reference product sponsor must bring an "immediate" patent infringement action against the biosimilar applicant on all patents on these simultaneously exchanged lists. 42 U.S.C. § 262(l)(6)(B).

f. Even after the immediate litigation of 42 U.S.C. § 262(l)(6)(B) has commenced, the reference product sponsor may identify additional patents that are newly issued or licensed after the reference product sponsor provided its patent list under 42 U.S.C. § 262(l)(3)(A). Specifically, the reference product sponsor may, not later than 30 days after the issuance or licensing supplement that list with the newly issued or licensed patent(s). 42 U.S.C. § 262(l)(7).

54. The mandatory time periods set forth in 42 U.S.C. § 262(l) give the reference product sponsor a limited time after receiving the biosimilar applicant's BLA and

manufacturing information, the biosimilar applicant's contentions, and the biosimilar applicant's response to initial licensing opportunities to consider patent infringement before filing a lawsuit against the biosimilar applicant. Specifically, 42 U.S.C. § 262(l) provides the reference product sponsor with 225 days after receiving the BLA and manufacturing information to exchange patent lists, provide detailed statements of infringement, validity, and enforceability, and engage in good faith negotiations regarding such patent lists prior to filing the "immediate" patent infringement action against the biosimilar applicant. *See* ¶¶ 53(b), (c), (d), (e), *supra.* These procedures provide the reference product sponsor with the benefit of certainty, both as to the scope of the patent disputes and also the characteristics of the biosimilar product.

55. 42 U.S.C. § 262(l) also requires the biosimilar applicant provide the reference product sponsor notice at least 180 days before the biosimilar applicant's first commercial marketing of the biosimilar. 42 U.S.C. § 262(l)(8)(A). The biosimilar applicant's obligation to provide this advanced notice of commercial marketing is not conditioned on performance of any act by the reference product sponsor nor exempted in the circumstance of a biosimilar applicant having failed to make the initial disclosures pursuant to 42 USC § 262(l)(2)(A). Rather, 42 U.S.C. § 262(l)(8)(A) simply provides that the "subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of first commercial marketing of the biological product licensed under subsection (k)."

56. The advanced notice of commercial marketing does, however, enable the reference product sponsor to seek a preliminary injunction before commercial marketing of the biosimilar product has commenced. 42 U.S.C. § 262(l)(8)(B) permits the reference product sponsor to seek a preliminary injunction enjoining the biosimilar applicant from commercially manufacturing or selling the biosimilar product until the court decides the disputed patent issues with respect to any patent that is on the exchanged patent lists, but which were not listed, by negotiation or exchange, for immediate litigation. Accordingly, this provision gives the courts an opportunity to consider the reference product sponsor's motion for preliminary injunction

before the status quo has changed; and gives the reference product sponsor the opportunity to stop the biosimilar applicant from launching its product before the patent issues are resolved.

57. This Court has determined that the notice of commercial marketing must take place on or after FDA approval; that decision is currently on appeal. *See Sandoz Inc. v. Amgen Inc.,* No. C-13-2904, 2013 WL 6000069, at *2 (N.D. Cal. Nov. 12, 2013) (appeal pending, Fed. Cir. Appeal No. 2014-1693) ("Sandoz cannot, as a matter of law, have provided a 'notice of commercial marketing' because, as discussed above, its etanercept product is not 'licensed under subsection (k).'").

58. After receiving the notice of commercial marketing and before such date of first commercial marketing of such biological product, the reference product sponsor may seek a preliminary injunction prohibiting the biosimilar applicant from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent identified for immediate patent litigation in the lists described above (*see* ¶ 53(e), *supra*). 42 U.S.C. § 262(l)(8)(B). This provision gives the courts an opportunity to consider the reference product sponsor's motion for preliminary injunction before the status quo has changed and gives the reference product sponsor the opportunity to stop the biosimilar applicant from launching its product before the patent issues are resolved.

DEFENDANTS' BIOSIMILAR APPLICATION UNDER 42 U.S.C. 262(k)

59. Upon information and belief, Defendants filed a BLA with the FDA under § 351(k) of the Public Health Service Act, codified as 42 U.S.C. § 262(k), to obtain approval to commercially market, manufacture, import and sell a biosimilar version of NEUPOGEN® (filgrastim) for treating particular diseases in the United States.

60. Upon information and belief, the biosimilar product that is the subject of Defendants' BLA is designed to copy and compete with Plaintiffs' NEUPOGEN® (filgrastim). Upon information and belief, Defendants will instruct or direct others to administer the Sandoz biosimilar product to certain patients for treating particular diseases in

the United States in the same way that Plaintiffs' NEUPOGEN® (filgrastim) is administered. Upon information and belief, Defendants are seeking FDA approval for one or more indications for which NEUPOGEN® (filgrastim) is already approved.

61. Upon information and belief, Defendants' BLA is the first application that the FDA has accepted under the § 262(k) pathway.

62. Upon information and belief, Defendants have not and do not seek to independently demonstrate to the FDA that their biological product is "safe, pure, and potent" pursuant to 42 U.S.C. 262(a), as Amgen did in its BLA for its innovative biological product NEUPOGEN® (filgrastim). Rather, upon information and belief, Defendants have requested that FDA evaluate the suitability of their biological product for licensure, expressly electing and seeking reliance on Amgen's FDA license for NEUPOGEN® (filgrastim). Accordingly, Defendants submitted to the FDA publicly-available information regarding the FDA's previous licensure determination that NEUPOGEN® (filgrastim) is "safe, pure, and potent." 42 U.S.C. 262(k)(2)(A)(iii)(I).

63. Upon information and belief, Defendants "received notification from the FDA on July 7, 2014" that the FDA had accepted their BLA for the Sandoz biosimilar product. Letter from Robin Adelstein, Vice President, Legal, IP & Compliance, Sandoz Inc., to Wendy A. Whiteford, Vice President Law, Amgen Inc. (July 25, 2014). Pursuant to the Biosimilar Biological Product Authorization Performance Goal and Procedures, which sets forth FDA goals for fiscal years 2013-2017, the FDA is committed to reviewing and acting "on 70 percent of original biosimilar biological product application submissions within 10 months of receipt" for biosimilar biological product applications filed in 2014.[1] Therefore, the FDA will complete its final review of Sandoz's biosimilar product at least by May 2015. Upon information and belief, Defendants believe that they may secure FDA approval of the Sandoz biosimilar product before

[1] FDA, Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 through 2017, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf, attached as Ex. I.

May 2015. *See* Letter from Robin Adelstein, Vice President, Legal, IP & Compliance, to David J. Scott, General Counsel and Secretary, Amgen Inc. (July 8, 2014) (Defendants' "reasoned belief" is that their BLA for the Sandoz biosimilar product "will be approved by the FDA in or around Q1/2 of 2015."); Letter (Oct. 20, 2014), *supra* ¶ 30 (confirming that "Sandoz continues to expect FDA approval in or around Q1/2 of 2015").

64. Defendants' receipt of FDA notification that their BLA had been accepted for review triggered the mandatory obligations set forth in 42 U.S.C. § 262(l). Specifically, the following provisions are required of Defendants, and would have been required of Amgen and FDA but for Defendants' failure to timely comply with their initial disclosure pursuant to 42 U.S.C. § 262(l)(2)(A):

Provision	**Date**
FDA notifies Defendants that their application for the Sandoz biosimilar product has been accepted for review.	Thursday, July 7, 2014
Subsection (k) application information. Not later than 20 days after Defendants' receipt of FDA notification: • Defendants "shall provide" to Amgen a copy of the application submitted to the FDA under § 262(k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application. 42 U.S.C. § 262(l)(2).	On or before Monday, July 28, 2014
List and description of patents. Not later than 60 days after Amgen's receipt of Defendants' BLA and manufacturing information: • Amgen "shall provide" to Defendants a list of patents for which Amgen believes a claim of patent infringement could reasonably be asserted by Amgen. 42 U.S.C. § 262(l)(3)(A)(i). • Amgen "shall provide" to Defendants an identification of the patents on such list that Amgen would be prepared to license to Defendants. 42 U.S.C. § 262(l)(3)(A)(ii).	On or before Friday, September 26, 2014
List and description by subsection (k) applicant. Not later than 60 days after Defendants' receipt of Amgen's patent list: • Defendants "may provide" to Amgen a list of patents that Defendants believes could reasonably be asserted by	On or before Tuesday, November 25, 2014

Provision	Date
Amgen. 42 U.S.C. § 262(l)(3)(B)(i). • Defendants "shall provide" to Amgen with respect to each patent on Plaintiffs' list a detailed statement describing on a claim by claim basis, the factual and legal basis of Defendants' opinion that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the Sandoz biosimilar product; or a statement that Defendants do not intend to begin commercial marketing of the Sandoz biosimilar product before the date that such patent expires. 42 U.S.C. § 262(l)(3)(B)(ii). • Defendants "shall provide" to Amgen a response regarding each patent identified by Amgen in its patent list. 42 U.S.C. § 262(l)(3)(B)(iii).	
Description by reference product sponsor. Not later than 60 days after Amgen's receipt of Defendants' list and statement: • Amgen "shall provide" to Defendants a detailed statement that describes, with respect to each patent described in Defendants' detailed statement, on a claim by claim basis, the factual and legal basis of Plaintiffs' opinion that such patent will be infringed by the commercial marketing of the Sandoz biosimilar product and a response to Defendants' statement concerning validity and enforceability. 42 U.S.C. § 262(l)(3)(C).	On or before Monday, January 26, 2015
Patent resolution negotiations. After Defendants receive Plaintiffs' detailed statement: • Amgen and Defendants "shall engage" in good faith negotiations to agree on which, if any, patents listed by Amgen and Defendants shall be the subject of an action under 42 U.S.C. § 262(l)(6) for patent infringement. 42 U.S.C. § 262(l)(4).	
Immediate patent infringement action if agreement on patent list. If there is agreement, then not later than 30 days after such agreement: • Amgen "shall bring" an action for patent infringement with respect to each patent. 42 U.S.C. § 262(l)(6)(A).	On or before Wednesday, February 25, 2015, assuming negotiations began on Monday, January 26, 2015.
Patent resolution if no agreement. If there is no agreement, then within 15 days of beginning negotiations:	On or before Monday, February 16, 2015,

Provision	Date
• Defendants "shall notify" Amgen of the number of patents that Defendants will provide to Amgen. 42 U.S.C. §§ 262(l)(4)(B), 262(l)(5)(A). • Within 5 days after Defendants notifies Amgen, the parties "shall" simultaneously exchange the list of patents that each party believes should be the subject of an action for patent infringement under 42 U.S.C. § 262(l)(6). 42 U.S.C. § 262(l)(5)(i).	assuming that Defendants notified Amgen on Tuesday, February 10, 2015.
Immediate patent infringement action if no agreement on patent list. Not later than 30 days after the exchange of second patent lists if there is no agreement: • Amgen "shall bring" an action for patent infringement with respect to each patent that is included on such lists. 42 U.S.C. § 262(l)(6)(B).	On or before Wednesday, March 18, 2015
Notification and publication of the Complaint. Not later than 30 days after Amgen serves a complaint to Defendants in an action for patent infringement under 42 U.S.C. § 262(l)(6): • Defendants "shall provide" the FDA with notice and a copy of such complaint. 42 U.S.C. § 262(l)(6)(C)(i). • The FDA "shall publish" in the Federal Register notice of the received complaint. 42 U.S.C. § 262(l)(6)(C)(ii).	On or before Friday, March 27, 2015 if there were agreement On or before Friday, April 17, 2015 if there were no agreement

65. In addition, Defendants are required under 42 U.S.C. § 262(l)(8)(A) to provide notice to Amgen not later than 180 days before the date of first commercial marketing, which this Court has held can only take place on or after FDA approval, as discussed above in ¶ 57.

66. After receiving such notice and before such date of the first commercial marketing, Amgen may seek a preliminary injunction prohibiting Defendants from engaging in the commercial manufacture or sale of the Sandoz biosimilar product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that is on the exchanged patent lists, but not on the negotiated or exchanged lists for immediate litigation. 42 U.S.C. § 262(l)(8)(B). This provision is intended to permit Amgen

to seek an injunction in time to prevent irreparable harm to Plaintiffs, *i.e.,* before Defendants first market commercially or launch the Sandoz biosimilar product.

67. Upon information and belief, Defendants are attempting to obtain the benefits of the BPCIA by filing their BLA under the § 262(k) pathway without complying with the requirements that Congress also imposed through the BPCIA on biosimilar applicants. For example, Defendants made a deliberate decision not to provide Amgen with a copy of its BLA, together with other information necessary to describe the process(es) for manufacturing the biosimilar product, within 20 days of receiving notification of FDA acceptance of their application. Under 42 U.S.C. § 262(l)(2), Sandoz was required to provide Amgen with such materials by Monday, July 28, 2014. To date, Amgen still has not received such materials, and Defendants continue to enjoy the benefit of FDA review of their application in reliance on Amgen's prior biological product license for filgrastim.

68. Instead of providing their BLA and manufacturing information, Defendants proposed to Amgen that the parties exchange information without following the mandatory provisions of 42 U.S.C. § 262(l)(2). On July 28, 2014, Amgen received a letter from Defendants stating that they "opted not to provide Amgen with Sandoz's biosimilar application within 20 days of the FDA's notification of acceptance." Letter (July 25, 2014), *supra* ¶ 63. Upon information and belief, Defendants' failure to provide their BLA and manufacturing information was an attempt to prevent Amgen from learning the details of their process(es) for manufacture, to avoid patent infringement litigation on any manufacturing patents, and to avoid the patent exchanges required by the statute; and instead to go directly to litigation. Defendants indicated that they wished to sidestep the entire procedure laid out by the statute in their correspondence. *Id.* ("Amgen is entitled to start a declaratory judgment action"). They confirmed this point in their subsequent letter as well. Letter from Julia Pike, Head of Global IP Litigation, to Wendy A. Whiteford, Vice President Law, Amgen Inc. (Sept. 4, 2014) (Amgen's "next step *under the BPCIA can only be* starting a declaratory judgment action as specified in that statute") (emphasis in original).

69. In addition, Defendants proposed in July 8, 2014 and July 21, 2014 Letters that they provide Amgen with their BLA pursuant to an Offer of Confidential Access. Letter (July 25, 2014), *supra* ¶ 63; *see also* Letter (July 8, 2014), *supra* ¶ 63 (also proposing an Offer of Confidential Access). In both letters, Defendants proposed exchanging their BLA, but not manufacturing information. In the July 8, 2014 Letter, Defendants also proposed that Amgen forfeit its right to use the exchanged BLA information as a basis to allege infringement under 35 § 271(g), which provides that "[w]hoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent." 42 U.S.C. § 262(l)(1)(A) permits the biosimilar applicant and the reference product sponsor to agree to alternative provisions for the exchange of confidential information. But, this provision applies only to the confidentiality terms that will apply to the information exchanged. The sequence and content of the exchanges, and the obligations imposed on the biosimilar applicant and reference product sponsor, by 42 U.S.C. § 262(l)(2) through 42 U.S.C. § 262(l)(8) are mandatory regardless of what confidentiality provisions may be agreed under 42 U.S.C. § 262(l)(1). Further, in the absence of agreement ("unless otherwise agreed to" by the biosimilar applicant and the reference product), the statute requires that the parties proceed with the confidentiality provisions provided in 42 U.S.C. § 262(l)(1)(A). Defendants' Offer of Confidential Access purported to replace the requirements of 42 U.S.C. § 262(l)(2) through 42 U.S.C. § 262(l)(8) with an entirely different procedure under which Amgen would have been obligated to commence any patent infringement litigation within 60 days of its receipt of Defendants' BLA information; attempted to limit the exchange of information to Defendants' BLA and not include any manufacturing information; and in the July 8, 2014 Letter, attempted to limit Amgen's cause of actions for patent infringement to exclude process patents. Defendants' attempts to modify the statutory provisions is not legally permissible.

70. Amgen responded that it was not willing to agree to Sandoz's Offers of Confidential Access that each attempted to narrow the scope of Defendants' disclosures

compared to that set forth in the statute, and reminded Defendants of their statutory obligation to provide its BLA and manufacturing information to Amgen. Letter from Wendy A. Whiteford, Vice President Law, Amgen Inc., to Robin Adelstein, Vice President, Legal IP & Compliance, Sandoz Inc. (Aug. 22, 2014). After Amgen responded, Defendants sent Amgen another letter dated September 4, 2014, asserting that Defendants had decided "not to disclose our application to Amgen" and chosen not to exercise their "right to use the patent information exchange process of the BPCIA." Letter (Sept. 4, 2014), *supra* ¶ 68. Defendants sent another letter on October 20, 2014, purporting to "remind" Amgen of "our July 8, 2014 letter which provided you with Sandoz's notice of commercial marketing pursuant to 42 U.S.C. 262(l)(8)(A)." Letter (Oct. 20, 2014), *supra* ¶ 30.

71. Upon information and belief, Defendants' violation of 42 U.S.C. § 262(l)(2) is part of a carefully orchestrated scheme to deprive Amgen of the substantive and procedural benefits of the BPCIA.

72. In particular, receipt of the BLA and manufacturing information gives the reference product sponsor the opportunity to evaluate the manufacturing processes used by the biosimilar applicant to determine whether those processes would infringe any patents held by the reference product sponsor, including under 35 U.S.C. § 271(g). The purpose of the statutory provisions of 42 U.S.C. § 262(l)(2) is, *inter alia*, to permit such an evaluation, as in the absence of such a disclosure, the reference product sponsor has no access to the BLA and manufacturing information. Had Defendants provided Amgen with a copy of their BLA and manufacturing information, Amgen would have been in a position: (1) to provide to Defendants a list of patents for which Amgen believes a claim of patent infringement could reasonably be asserted as to the Sandoz biosimilar product, and (2) to identify to Defendants whether Amgen would be prepared to grant a license to Defendants under any of the patents included on such a list. *See* 42 U.S.C. § 262(l)(3)(A). Amgen has an extensive portfolio of patents relating to various aspects of the manufacture of biological products. However, because Defendants' manufacturing process for the Sandoz biosimilar product is secret, without the disclosure required under 42 U.S.C. § 262(l)(2) Amgen's ability to

conduct a full and complete evaluation of its patent portfolio with respect to Defendants' specific product, process(es) of manufacture, and uses is undermined and delayed. By unlawfully withholding the information required under 42 U.S.C. § 262(l)(2) Defendants have thereby frustrated the statutory purpose and deprived Plaintiffs of the opportunity to seek redress for potential infringement.

73. One patent which Amgen believes could have been identified on its list pursuant to 42 U.S.C. § 262(l)(3)(A)(i), is U.S. Patent No. 6,162,427 ("the '427 patent"), which covers a method of using NEUPOGEN® (filgrastim) to treat a disease requiring peripheral stem cell transplantation in a patient in need of such treatment. However, Amgen holds numerous other patents directed to processes for manufacturing products such as the Sandoz biosimilar product. As noted above, had Defendants provided Amgen with a copy of their BLA and information necessary to describe the process(es) for manufacturing the Sandoz biosimilar product, Amgen would have complied with its obligations under 42 U.S.C. § 262(l)(3) and identified any patents to which a claim of patent infringement could reasonably be asserted. Amgen therefore reserves the right to seek leave to assert additional patents following eventual receipt of Defendants' BLA and manufacturing information and other relevant information to be produced in discovery in this action under the Federal Rules.

74. Further, had Defendants complied with the statutory requirements, then Amgen could have brought a patent infringement action, if necessary, against Defendants under 42 U.S.C. § 262(l)(6) in February or March 2015. Because Defendants did not comply with the mandatory disclosure requirements of 42 U.S.C. § 262(l)(2), however, Amgen was deprived of any opportunity to review Defendants' BLA and manufacturing information, identify a comprehensive list of infringed patents, and review Defendants' contentions, and, possibly, licensing position, prior to bringing an action. Amgen also lost the benefit of the time provided in 42 U.S.C. § 262(l)(2) for Amgen and Defendants to identify potentially disputed patents, the time to evaluate those patents, the substantive exchange of statements concerning those patents, and the ability to identify more patents after exchanging patent lists prior to Amgen bringing a patent infringement action. Defendants' actions also create the

substantial and continuing risk that Plaintiffs may not be able to obtain manufacturing information regarding Defendants' biosimilar product that would permit Plaintiffs to assert their process patents prior to commercialization of the biosimilar product. Forcing Plaintiffs to assert one or more of their patents (including process patents) after Defendants' commercial entry into the market harms Plaintiffs by diminishing the value of such patents.

75. Additionally, Defendants violated the statute by not providing Amgen with a legally operative notice of commercial marketing. Upon information and belief, Defendants do not intend to provide Amgen with a notice of commercial marketing on or after FDA approval. Therefore, Defendants intend to and/or will violate the BPCIA absent an order of the Court compelling Defendants to comply.

76. Each of Defendants' unlawful acts (violation of 42 U.S.C. § 262(l)(2)(A) and violation of 42 U.S.C. § 262(l)(8)(A)) independently deprive Amgen of the benefits afforded under the statute and which Congress provided to reference product sponsors. Defendants' failure to provide the BLA and manufacturing information to Amgen under 42 U.S.C. § 262(l)(2)(A) deprives Plaintiffs of the opportunity to seek a preliminary injunction enjoining Defendants from engaging in the commercial manufacture or sale of the Sandoz biosimilar product in time to prevent irreparable harm to Plaintiffs, *i.e.,* after FDA approval of the Sandoz biosimilar product but before Defendants' commercial marketing of the biosimilar product. In addition, Defendants' failure to provide a legally operative notice of commercial marketing deprives Plaintiffs of the opportunity to seek a court intervention to prevent Plaintiffs from suffering irreparable harm. This too prevents Plaintiffs from enjoining Defendants in time to prevent irreparable harm.

FIRST CAUSE OF ACTION
(UNFAIR COMPETITION UNDER CAL. BUS. & PROF. CODE § 17200 et seq.)

77. The allegations of ¶¶ 1-76 are repeated and incorporated herein by reference.

78. Defendants' actions in filing a BLA with the FDA under the § 262(k) pathway for approval to commercially market, manufacture, import and sell a biosimilar version of Plaintiffs' product NEUPOGEN® (filgrastim), and in planning the launch of a biosimilar

version of Plaintiffs' product NEUPOGEN® (filgrastim) is a business practice under California state law of unfair competition.

79. Defendants have violated Cal. Bus. & Prof. Code § 17200 et seq. by seeking FDA approval for Sandoz biosimilar product under the BPCIA's abbreviated approval pathway of § 262(k), while refusing to comply with other statutory requirements of the BPCIA, specifically those that protect the interest of Amgen (the reference product sponsor). As set forth in ¶¶ 50-58 and ¶ 64 above, Defendants' receipt of FDA notification that their BLA was accepted for review triggers a set of deadlines requiring, among other things, Defendants to provide their BLA and manufacturing information to Amgen within twenty days. Defendants have unlawfully withheld from Amgen the BLA and manufacturing information that Defendants were required to disclose under 42 U.S.C. § 262(l)(2)(A).

80. In addition and as a separate and independent unlawful act, Defendants have failed and/or will imminently fail to meet its statutory obligation under 42 U.S.C. § 262(l)(8)(A) to provide notice of commercial marketing to Amgen upon or after FDA approval. Defendants' violations of the BPCIA satisfy the "unlawful" prong of § 17200.

81. By reason of, and as a direct and proximate result of, Defendants' independent acts of unlawful conduct, Plaintiffs have suffered and will continue to suffer injury to its business and property. As set forth in ¶¶ 64-76 above, Defendants' actions deprive Amgen of the BLA and manufacturing information, Defendants' patent list(s), and Defendants' detailed statements, all of which are required under the statute. Accordingly, Plaintiffs do not have sufficient information to identify patents and infringement claims; and Plaintiffs' determination of whether to file a patent infringement action and which patent claims to assert against Defendants is delayed. Further and as an independent ground, Defendants' conduct threatens to deprive Plaintiffs of the opportunity to seek a preliminary injunction in time to prevent irreparable harm, *i.e.,* after FDA approval of the Sandoz biosimilar product but before Defendants' commercial marketing of the biosimilar product.

82. By reason of and as a direct and proximate cause of Defendants' unlawful conduct, Plaintiffs have suffered economic injury to their business in the form of lost money

that was spent to monitor and respond to Defendants' acts of unfair competition. Plaintiffs will also suffer lost profits and increased costs if Defendants are permitted to commercially market the Sandoz biosimilar product without satisfying their obligations under 42 U.S.C. § 262(l). In addition, Plaintiffs will suffer loss of value of their patents as a result of Defendants' actions by forcing Plaintiffs to assert one or more of their patents (including process patents) after Defendants' commercial entry into the market as discussed in ¶ 74 above.

83. Plaintiffs are entitled to full restitution for the revenues, earnings, profits, compensation, and benefits that Plaintiffs will lose and Defendants obtain as a result of such unlawful business practices. For example, if Defendants are permitted to commercially market the Sandoz biosimilar product without providing the required 180-day notice to Amgen that would have allowed Plaintiffs to bring a motion for preliminary injunction, then Plaintiffs are entitled to restitution for the period of time between Defendants' market entry and a court's decision on Plaintiffs' motion for preliminary injunction.

84. The unlawful conduct alleged herein is continuing and there is no indication that Defendants will cease the conduct.

85. Plaintiffs are entitled to an order enjoining Defendants from commercially marketing the biosimilar product until Plaintiffs are restored to the position they would have been had Defendants met their obligations under the BPCIA, *e.g.,* providing Amgen with the BLA and manufacturing information and the equivalent information and time required under 42 U.S.C. § 262(l) for evaluating Defendants' BLA and manufacturing information so that Plaintiffs may bring a patent infringement action and/or preliminary injunction in time to prevent irreparable harm to Plaintiffs (after FDA approval of the Sandoz biosimilar product but before Defendants' commercial marketing of the biosimilar product).

86. Plaintiffs are entitled to an order compelling Defendants to provide Amgen with notice of commercial marketing on or after FDA licensure of its biosimilar product, and no later than 180 days before Defendants' first commercial marketing of that product.

SECOND CAUSE OF ACTION
(CONVERSION)

87. The allegations of ¶¶ 1-86 are repeated and incorporated herein by reference.

88. The FDA is charged by Congress with promoting "the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner." 21 U.S.C. § 393. The FDA pursues this mission vigorously and effectively in cooperation with applicants who market or seek to market regulated products. One important function of the FDA is to prescribe standards and measure compliance with a multistep process for approval for drugs and biological products.

89. As discussed above in ¶ 43, for reference products, FDA approval requires a demonstration that the "the biological product that is the subject of the application is safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). The same demonstration is not required for FDA approval of biosimilar products under the § 262(k) pathway. Rather, a biosimilar applicant under the § 262(k) pathway selects a single reference product for which it seeks FDA evaluation of its biological product as a biosimilar, and submits to the FDA "publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent." 42 U.S.C. § 262(k)(2)(A)(iii)(I). In order to obtain the benefit of the BPCIA's abbreviated approval pathway for biosimilar products, § 262(k) pathway, including reliance of the reference product sponsor's prior FDA licensure, applicants must follow the BPCIA's procedures set forth in 42 U.S.C. § 262(l) regarding the disclosure of information to the reference product sponsor, the exchange of contentions, the negotiation of disputes for resolution or litigation, and notice of commercial marketing to the reference product sponsor.

90. The biological license for NEUPOGEN® (filgrastim) is owned by Amgen and exclusively licensed to AML. Plaintiffs have a legitimate claim to exclusivity in the license because of the significant effort, investment, and expertise required to obtain the license: Amgen expended considerable time, expense, and resources in research and design; Amgen conducted the appropriate tests and compiled the necessary data; Amgen prepared the BLA

for NEUPOGEN® (filgrastim) and engaged in negotiations with the FDA regarding the BLA; Amgen demonstrated to the FDA that NEUPOGEN® (filgrastim) is safe, pure, and potent; and Amgen supplemented its BLA with the FDA. In addition, Amgen's license has value because it enables biosimilar applicants, such as Defendants, to secure approval of a biological product as biosimilar NEUPOGEN® (filgrastim) without the delay, burden, or expense of demonstrating to the FDA that such biosimilar product is independently "safe, pure, and potent." Thus, the license to NEUPOGEN® (filgrastim) owned by Amgen and exclusively licensed to AML is a property right that is recognized by the law in that Plaintiffs' interest is precisely defined and capable of exclusive possession.

91. Defendants' use of the license for NEUPOGEN® (filgrastim) to obtain a governmental privilege (FDA approval to market, manufacture, import, and sell the Sandoz biosimilar product for use in the United States) for Defendants' own benefit and profit is an act of conversion. Specifically, Defendants filed a BLA for the Sandoz biosimilar product that intentionally uses Amgen's prior demonstration of the safety, purity, and potency of NEUPOGEN® (filgrastim), but without Plaintiffs' authorization or permission and without satisfying the mandatory provisions of 42 U.S.C. § 262(l) that apply to biosimilar applicants. By filing their BLA for the Sandoz biosimilar product under the § 262(k) pathway rather than the § 262(a) pathway, Defendants seek to obtain a valuable benefit from the license for NEUPOGEN® (filgrastim). Without Amgen's efforts, the information relied on by Defendants for the safety, purity, and potency of the Sandoz biosimilar product would not exist. As a result, Defendants have converted property belonging to Plaintiffs.

92. By reason of and as a direct and proximate cause of Defendants' wrongful acts of conversion, Plaintiffs have suffered and will continue to suffer damages due to the lost value of Amgen's biological license for NEUPOGEN® (filgrastim). The detriment caused by Defendants' conversion is presumed to include the value of Plaintiffs' property at the time of conversion. *See* Cal. Civ. Code § 3336. Here, Defendants have derived and will continue to derive value from Amgen's license by seeking approval under the abbreviated § 262(k) pathway rather than the § 262(a) pathway. Had Defendants not wrongfully

converted Plaintiffs' property, Defendants would have had to incur the time and money for filing a BLA under the § 262(a) pathway, just as Amgen did to obtain its license for NEUPOGEN® (filgrastim).

93. In addition, Defendants' conduct will diminish the value of the NEUPOGEN® (filgrastim) license that is owned by Amgen and exclusively licensed to AML. If Defendants are permitted to convert Plaintiffs' property—without authorization or permission and without satisfying the mandatory provisions of 42 U.S.C. § 262(l) that apply to biosimilar applicants—and obtain FDA approval to launch the Sandoz biosimilar product, then the biological license will no longer be exclusive. Consequently, Plaintiffs will suffer economic injury to their business in the form of lost sales, revenue, market share, and asset value.

94. By reason of and as a direct and proximate cause of Defendants' wrongful acts of conversion, Plaintiffs have suffered economic injury to their business in the form of lost money that was spent to monitor and respond to Defendants' acts of conversion. The detriment caused by Defendants' conversion is presumed to include fair compensation for the time and money properly expended by Plaintiffs in pursuit of their property. *See* Cal. Civ. Code § 3336.

95. Upon information and belief, Defendants' conversion of Plaintiffs' property is oppressive and malicious. As a result of such conduct, Plaintiffs are entitled to punitive damages. *See* California Civil Code § 3294.

96. The unlawful conduct alleged herein is continuing and there is no indication that Defendants will cease the conduct.

97. Plaintiffs are entitled to an order enjoining Defendants from continuing to seek FDA review of their § 262(k) application and/or compelling Defendants to suspend FDA review of their § 262(k) application until Defendants have obtained permission from Plaintiffs to use the NEUPOGEN® (filgrastim) license or require Defendants to restore to Amgen the benefits afforded to reference product sponsors in the statute, *e.g.,* providing Amgen with the equivalent information and time required under the statute for evaluating

Sandoz's BLA and manufacturing information, exchanging patent lists and information, negotiating patent lists, receiving Defendants' notice of commercial marketing, and bringing patent infringement actions and preliminary injunction motions.

THIRD CAUSE OF ACTION
(PATENT INFRINGEMENT)

98. The allegations of ¶¶ 1-97 are repeated and incorporated herein by reference.

99. Amgen is the owner of all right, title and interest in the '427 patent.

100. The '427 patent is titled "Combination of G-CSF With a Chemotherapeutic Agent for Stem Cell Mobilization" and was duly and legally issued by the USPTO on December 19, 2000. The inventors of the '427 patent are Matthias Baumann and Peter-Paul Ochlich. A true and correct copy of the '427 patent is attached hereto as Ex. H.

101. Upon information and belief, the purpose of Defendants' BLA for the Sandoz biosimilar product is to obtain approval to engage in the commercial marketing, manufacture, import, and sale of a biological product for treating particular diseases in the United States, one use of which is claimed in the '427 patent before the expiration of such patent. Upon information and belief, Defendants seek to market, manufacture, import, distribute, sell, and/or offer to sell the Sandoz biosimilar product for treating particular diseases in the United States immediately upon receipt of FDA approval and prior to the expiration of the '427 patent.

102. Defendants have committed a statutory act of infringement under 35 U.S.C. § 271(e)(2)(C)(ii) of the '427 patent by virtue of their submission of the BLA for the Sandoz biosimilar product and failure to provide the required BLA and manufacturing information to Amgen within 20 days after the FDA notified Defendants on July 7, 2014 that their BLA was accepted for review.

103. Upon information and belief, Defendants intended to violate the statute by failing to disclose the required BLA and manufacturing information to Amgen within 20 days after the FDA accepted Defendants' BLA, and Defendants chose to disclose their non-

compliance to Amgen one day after the 20 day period had expired. Defendants' actions constitute a knowing and willful infringement under 35 U.S.C. § 271(e)(2)(C)(ii).

104. Plaintiffs are entitled to injunctive relief under 35 U.S.C. § 271(e)(4)(B) preventing Defendants' from profiting by their deliberate non-compliance with the mandatory provisions of 42 U.S.C. § 262(l) by issuing an appropriately tailored injunction against the commercial manufacture, import, offer for sale, or sale of Sandoz's biosimilar product, and restoring Plaintiffs to the position in which they would have been but for such non-compliance. Defendants must restore to Amgen the benefits afforded to reference product sponsors in the statute, *e.g.,* providing Amgen with the equivalent information and time required under the statute for evaluating Sandoz's BLA and manufacturing information, exchanging patent lists and information, negotiating patent lists, receiving Defendants' notice of commercial marketing, and bringing patent infringement actions and preliminary injunction motions.

105. Plaintiffs are further entitled to injunctive relief against Defendants to prevent the commercial manufacture, use, offer to sell, or sale within the United States of the Sandoz biosimilar product. *See* 35 U.S.C. § 271(e)(4)(B).

106. As set forth in ¶¶ 72-73 above, Plaintiffs reserve the right to seek leave to assert additional patents following eventual receipt of Defendants' BLA and manufacturing information and other relevant information to be produced in discovery in this action under the Federal Rules.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court enter judgment in their favor against Defendants and grant the following relief:

A. Declaring that Defendants have engaged in unfair competition under Cal. Bus. & Prof. Code § 17200 et seq.;

B. Awarding Plaintiffs restitution for Defendants' acts of unfair competition, including Defendants' unlawful proceeds such as gross profits;

C. Enjoining Defendants from commercially marketing the biosimilar product until Amgen is restored to the position it would have been had Defendants met their obligations under the BPCIA;

D. Enjoining Defendants from commercially marketing the biosimilar product until Defendants have provided Amgen with notice of commercial marketing on or after FDA licensure of its biosimilar product, and no later than 180 days before Defendants' first commercial marketing of that product;

E. Enjoining Defendants from continuing to seek FDA review of their § 262(k) application and/or compelling Defendants to suspend FDA review of their § 262(k) application until Defendants have obtained permission from Plaintiffs to use the NEUPOGEN® (filgrastim) license or require Defendants to restore to Amgen the benefits afforded to reference product sponsors in the statute;

F. Awarding Plaintiffs compensatory damages for Defendants' acts of conversion;

G. Awarding Plaintiffs restitution for Defendants' acts of conversion, including Defendants' unlawful proceeds such as gross profits;

H. Awarding Plaintiffs punitive damages for Defendants' acts of conversion;

I. Adjudging and decreeing that Defendants have committed a statutory act of infringement under 35 U.S.C. § 271(e)(2)(C)(ii) of the'427 patent by submitting their BLA to the FDA for approval of the Sandoz biosimilar product without providing the required BLA and manufacturing information to Amgen;

J. Declaring that Defendants' infringement under 35 U.S.C. § 271(e)(2)(C)(ii) is and/or will be willful and that this is an exceptional case under 35 U.S.C. § 285;

K. Enjoining Defendants, their respective officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringing the '427 patent, or inducing anyone to do the same, including the manufacture, use, offer to sell, sale, importation or distribution of any current or future versions of the Sandoz biosimilar product described in Defendants' BLA while the litigation is pending;

L. Permanently enjoining Defendants, their respective officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringing the '427 patent, or inducing anyone to do the same, including the manufacture, use, offer to sell, sale, importation or distribution of any current or future versions of the Sandoz biosimilar product described in Defendants' BLA;

M. Awarding Plaintiffs their attorneys' fees, costs, and expenses; and

N. Awarding Plaintiffs such other and further relief as this Court may deem to be just and proper.

DEMAND FOR A JURY TRIAL

Plaintiffs hereby demand a jury trial on all issues so triable.

Date: October 24, 2014

___/s/ Vernon M. Winters_____
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EXHIBIT A

SANDOZ
a Novartis company

ABOUT US OUR PRODUCTS CAREERS CORPORATE RESPONSIBILITY MEDIA CENTER

SHAPING THE FUTURE OF HEALTHCARE

Going beyond standard generics, we use innovation and expertise to develop even the most complex medicines for patient healthcare – from biosimilars and complex injectables to respiratory and specialty generics.

FOLLOW US ON

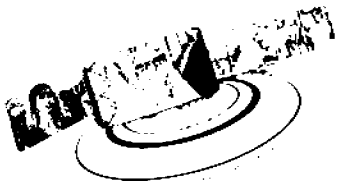
NEWS

Sandoz' Mark McCamish discusses US Biosimilars landscape on Biocentury TV

Read more news about Sandoz ›

SANDOZ RESPIRATORY SHARES PRODUCTS AND STRATEGY AT ERS 2014

Sandoz Respiratory shares products and strategy at ERS 2014 ›



SANDOZ TV

SANDOZ WORLDWIDE

Sandoz Websites →

RECENTLY ON TWITTER

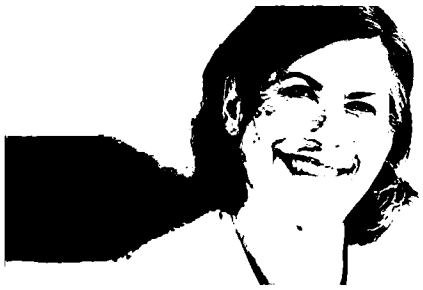
Sandoz

Biosimilars help increase patient access to biologics. Deviating from established IP/TL system will limit this access.

Sandoz

Mandating different INN for [illegible] create barrier to more affordable alternatives for physicians patients

FOLLOW US ON



SANDOZ HISTORY

The Early Years 1886 – 1939 ˅

The Start of Anti-infectives 1946 – 1963 ˅

Expansion and Diversification 1964 – 1982 ˅

A New Corporate Structure 1990 – 1998 ˅

A Global Generics Business 2000 – 2013 ^

2000

2001

2002

2003

2004

2005

2006

2007

2008 [illegible]

2009 - [illegible]

2010 - [illegible]

2011 - [illegible]

2012 [illegible]

SANDOZ WORLDWIDE

Sandoz Websites:

You are on the website of Sandoz International. Please select from the above dropdown to visit a local website.

RECENTLY ON TWITTER

Sandoz

[illegible] represents 25% of [illegible] medicines supply to the WHO & we reach approx. 500 000 people a year who are living with #TB

Sandoz

Check out this map showing TB's global reach – and the rise of multi-drug resistant TB

FOLLOW US ON

EXHIBIT B

SANDOZ
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Media Release | Medienmitteilung | Communiqué Aux Médias

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FDA accepts Sandoz application for biosimilar filgrastim

- *Sandoz is the first company to announce it has filed for approval of a biologic under the biosimilars pathway created in the Biologics Price Competition and Innovation Act of 2009 (BPCIA).*
- *FDA's acceptance of Sandoz's filing is an important first step in increasing US patient access to affordable, high-quality biologics*
- *Sandoz is a global leader in biosimilars with over 50% share of the global biosimilars market [1]*

Holzkirchen, July 24, 2014 – Sandoz, a Novartis Group company, announced today that the US Food and Drug Administration (FDA) has accepted its Biologics License Application for filgrastim, which was filed under the new biosimilar pathway created in the Biologics Price Competition and Innovation Act of 2009 (BPCIA).

The reference product – Amgen's NEUPOGEN® – is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.

"This filing acceptance represents a significant step toward making high-quality biologics more accessible in the US and we applaud FDA for its progress in making this a reality," said Mark McCamish, M.D., Ph.D., and Head of Global Biopharmaceutical & Oncology Injectables Development at Sandoz. "As they've done in Europe and other highly-regulated markets around the world, biosimilars are poised to increase US patient access to affordable, high-quality biologics, while reducing the financial burden on payers and the overall healthcare system."

Under the brand name ZARZIO®, the Sandoz biosimilar filgrastim has been marketed in more than 40 countries outside the US, generating nearly six million patient-exposure days of experience. ZARZIO is the number one biosimilar filgrastim globally and is the leading daily G-CSF in Europe with 30 percent volume market share.

Sandoz is a pioneer in biosimilars and the global market leader with over 50% share of all biosimilars approved in the highly-regulated markets of Canada, Europe, Japan and Australia. Sandoz currently markets three biosimilars outside the US; each of which occupies the #1 biosimilar position in its respective category. Sandoz biosimilars are sold in over 60 countries and have generated over 200 million patient-exposure days in experience. Sandoz also has an unrivalled pipeline with several molecules in various stages of development. Sandoz now has six molecules in Phase III clinical trials/filing preparation, more than any other company in the industry.

[1] Includes products approved in North America, Europe, Japan and Australia

SANDOZ
a Novartis company

Media Release | Medienmitteilung | Communiqué Aux Médias

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Disclaimer

This press release contains forward-looking statements that can be identified by words such as "first step," "poised," "pipeline," or similar terms, or by express or implied discussions regarding potential marketing approval for biosimilar filgrastim, or regarding potential future revenues from biosimilar filgrastim. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that biosimilar filgrastim will be approved for sale in any market, or at any particular time. Nor can there be any guarantee that biosimilar filgrastim will be commercially successful in the future. In particular, management's expectations regarding biosimilar filgrastim could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Sandoz

Sandoz, the generic pharmaceuticals division of Novartis, is a global leader in the generic pharmaceutical sector. Sandoz employs over 26,500 employees and its products are available in more than 160 countries, offering a broad range of high-quality, affordable products that are no longer protected by patents. With USD 9.2 billion in sales in 2013, Sandoz has a portfolio of approximately 1,100 molecules, and holds the #1 position globally in biosimilars as well as in generic injectables, ophthalmics, dermatology and antibiotics, complemented by leading positions in the cardiovascular, metabolism, central nervous system, pain, gastrointestinal, respiratory, and hormonal therapeutic areas. Sandoz develops, produces, and markets these medicines, as well as active pharmaceutical and biotechnological substances. Nearly half of Sandoz's portfolio is in differentiated products, which are defined as products that are more difficult to scientifically develop and manufacture than standard generics.

In addition to strong organic growth since consolidating its generics businesses under the Sandoz brand name in 2003, Sandoz has benefitted from strong growth of its acquisitions, which include Lek (Slovenia), Sabex (Canada), Hexal (Germany), Eon Labs (US), EBEWE Pharma (Austria), Oriel Therapeutics (US), and Fougera Pharmaceuticals (US).

Sandoz is on Twitter. Sign up to follow @Sandoz_global at http://twitter.com/Sandoz_Global.

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SANDOZ
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Media Release | Medienmitteilung | Communiqué Aux Médias

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Neupogen® is a registered trademark of Amgen Inc.

EXHIBIT C

MCI MANAGEMENT CENTER INNSBRUCK

Agenda

- Introduction to Sandoz
- Benefits of collaboration - academia and industry
- Master Thesis of Ian Wallace

Introduction Sandoz GmbH

Clemens Achmüller
Innsbruck, May 15, 2012

a Novartis company

Sandoz is a Novartis Group Company

Environment

Patient needs

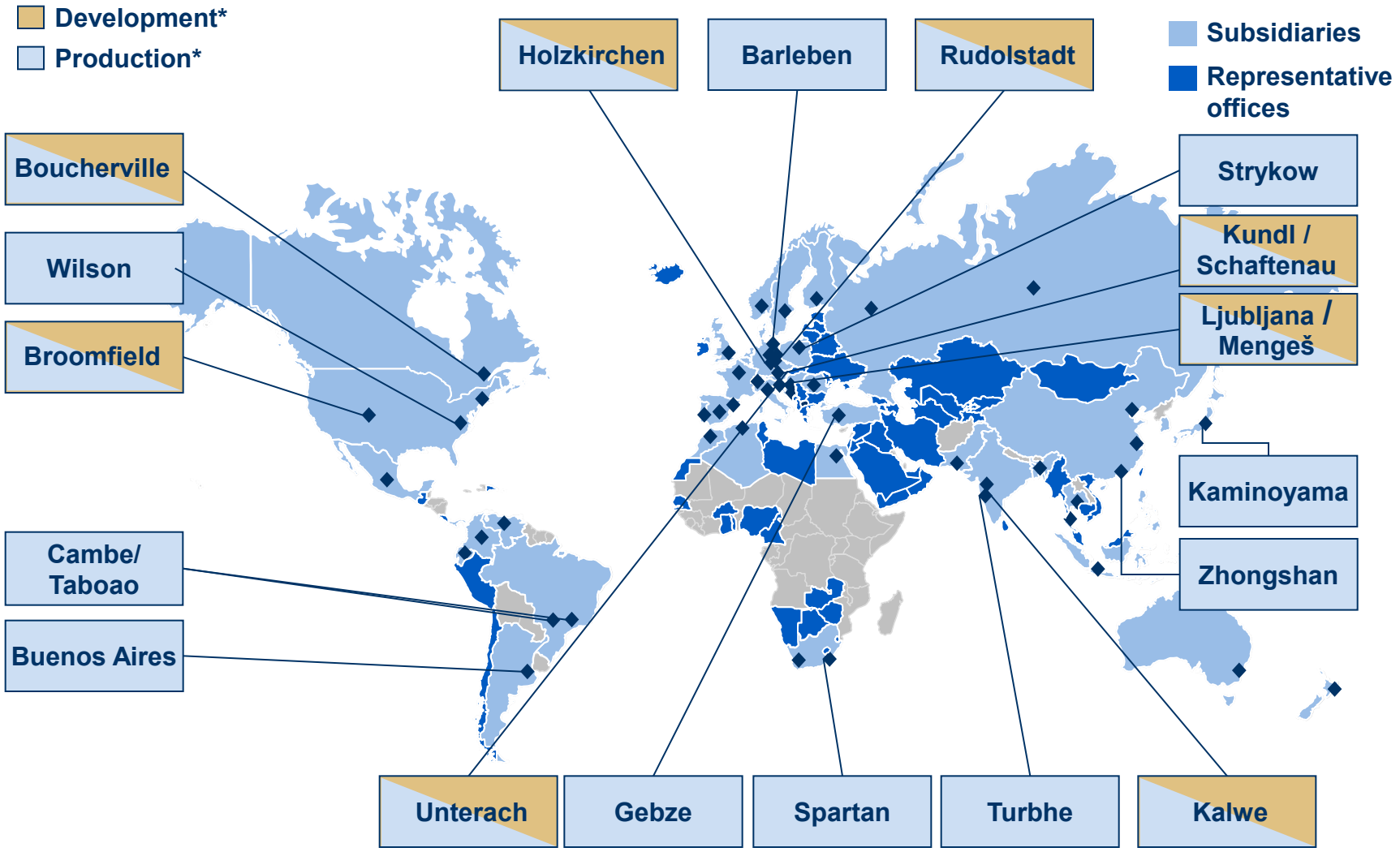
- Innovative medicines
- Prevention
- Affordable options
- Self-care

Full range of healthcare options

Novartis portfolio[1]	2011 sales USD billion
Pharmaceuticals	32.5
Eye Care[2] (Alcon, CIBA VISION)	10
Sandoz – Generics	**9.5**
Consumer Health (OTC, Animal Health)	4.6
Vaccines and Diagnostics	2

SANDOZ

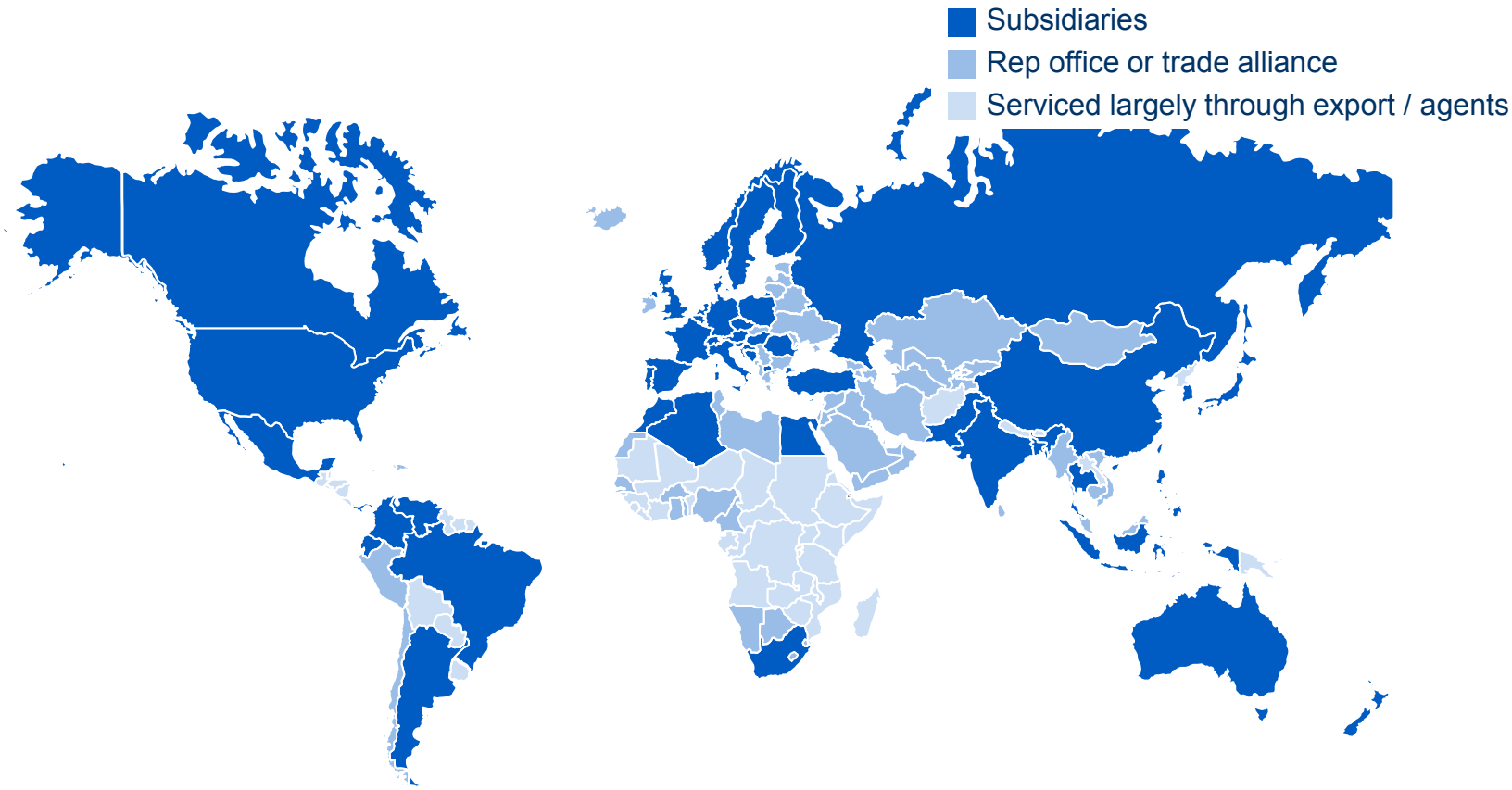
Sandoz operates in 130 countries globally



** Sample Sandoz manufacturing and development sites.*

SANDOZ

Global presence: Affordable medicines for all



Sandoz medicines are available to 90% of world population

SANDOZ

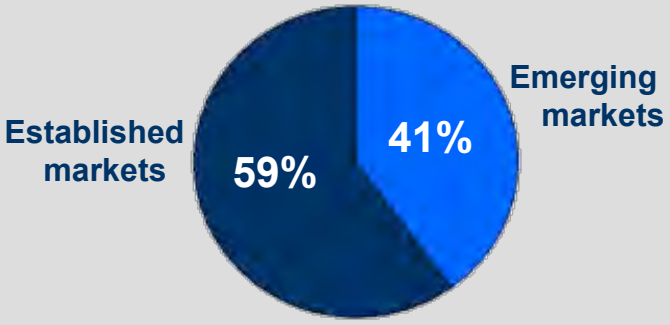
Sandoz is a global leader in generics

- Global #2 in generics
- No.1-3 in roughly half of global market
- Present in > 130 countries
- Strong portfolio of ~1.000 compounds
- Rich pipeline with > 800 projects
- Global development center network
- More than 30 manufacturing sites globally
- Global headquarters near Munich, Germany
- Leader in differentiated (difficult to make) generics
- Pioneer of biosimilars

Sandoz key figures 2011

Net sales:	**USD 9.5 billion**
Net income:	**USD 1.4 billion**
Employees worldwide:	**23 500**

Sales



SANDOZ

Growth

Sandoz continues to strengthen its leadership in differentiated products

Key categories	Global Gx market position	2011 highlights[1]
 **Biosimilars**	**#1**	▪ **Sales +37% vs. PY** and **+48% in Q4** ▪ Initiated multiple **phase III clinical studies**
 **Injectables**	**#1**	▪ **2011 Enox sales of over USD 1 billion** – likely the first time for any generic product ▪ **Retail Anti-Infective sales +10% vs. PY**
 **Ophthalmics**	**#1**	▪ **Successful integration** of Alcon's former generics business ▪ **Growth of +24% vs. PY (+8% vs. TGT)**
 **Respiratory**	**Top 5**	▪ **Continued progress on US and European pipeline**

[1] *All figures in local currency*

SANDOZ

Sandoz biosimilars: #1 with 3 marketed products

Omnitrope®
(human growth hormone; hGH)

- First biosimilar in EU; approved May 2006
- Broad global launch (e.g., US, Japan & LATAM)

Zarzio®
(filgrastim)

- Feb. 2009 EU approval
- Growing rapidly across EU markets

2006 **2007** **2008** **2009** **2010**

Binocrit®
(epoetin alfa)

- Introduced for nephrology in Oct. 2007
- First EPO biosimilar in EU
- Launched in Oncology (2009 & 2010)

SANDOZ

Biosimilars development requires substantive investment and time

	Generics*	Biosimilars*	Originators*
Development investment	USD 2 – 3m	USD 75 - 250m	USD 800m
Time to market	2 – 3 yrs	7 – 8 yrs	8 – 10 yrs
# of patients for approval[1]	20 – 50 pts	~ 500 pts	800 – 1000 pts

* Industry average

[1] Average estimates for biopharmaceutical trials, e.g., oncology

Source: Sandoz internal estimates

SANDOZ

Sandoz sites in Austria

Kundl

- Largest research and production site of Sandoz worldwide
- Antibiotics, recombinant proteins, enzymes, hormones

Schaftenau

- Enzymes, hormones, recombinant proteins (cell culture)

Unterach

- Acquisition of former EBEWE Pharma in 2009
- Center of excellence for generic oncology injectables

Vienna

- Marketing and sales for Sandoz Austria domestic market

Sandoz GmbH, site Kundl

Largest research and production site of Sandoz worldwide

Kundl, Austria

- Fermentation
- Synthesis (ß-lactams)
- Sterile Precipitation (ß-lactams)
- Process Enzymes
- Rec. Proteins
- FDFs
- Pilot Plants

SANDOZ

Sandoz GmbH: Key Strenghts

Manufacturing of fermentation-derived products

- Fermentation of microbial strains: fermenter scales ranging from 3 m^3 to 250 m^3
- Isolation and purification in multipurpose facilities
- Downstream scales corresponding to fermenter sizes
- FDA-approved facilities
- Full cGMP manufacturing

SANDOZ

Biosimilars

Kundl and Schaftenau are Novartis' centers of excellence for Biosimilars

Kundl (~ 430 associates working in „BP“)

- Center for **microbiotic** API development and production
- API manufacturing facility of **Omnitrope® and Zarzio®**
- Biosimilars-Competence-Center for:
  - developing Finished Dosage Forms and devices
  - Analytical development incl. characterization
  - registration

Schaftenau (~140 associates working in „BP“)

- Global production center for process development of **cell cultures and antibodies**
- Manufacturing facility for **innovative biopharmaceuticals** required from our parent company Novartis

SANDOZ

Future

- **Further expansion** in Anti-Infectives
- **Strengthening** of leading position in "differentiated products"
- **Future growth market** Biopharmaceuticals
- **Ongoing investments** in high-tech facilities
- **Continuous education** and trainings for employees
- **Attract,** retain and develop the **best talent**
- **"Diversity and Inclusion":** Valuing diversity as key factor for success
- **Corporate Social Responsibility**

SANDOZ

MCI MANAGEMENT CENTER INNSBRUCK

BENEFITS OF COLLABORATION ACADEMIA AND INDUSTRY

Benefits of collaboration academia and industry

- Cutting edge scientific and engineering knowledge
  - Latest scientific advances
- Networking
  - Mutual understanding
  - Trust
  - Exchange
- Fund raising
  - Project cooperation

Benefits of collaboration academia and industry

MCI MANAGEMENT CENTER INNSBRUCK

- Collaboration on teaching
  - Lectures
  - Laboratory courses
  - Support of bachelor and master theses
  - Topics:
    Biotechnology – Analytics
    Biotechnology – Fermentation
    Biotechnology – Dowstream Processing
    Process Simulation
    Thermodynamics

- Further education
  - Accessed by employees of Sandoz Kundl (+40)
  - Full day / extra occupational (if offered)

Benefits of collaboration academia and industry

- Support of Bachelor and Master Theses
  - Currently support of 3 master theses
  - Supervision
    - Shared MCI and Sandoz
  - Content
    - Agreed between MCI and Sandoz
    - Topic of industrial relevance
    - CDA in place
  - Practical part of the work
    - Hands-on in Sandoz facility

MCI MANAGEMENT CENTER INNSBRUCK

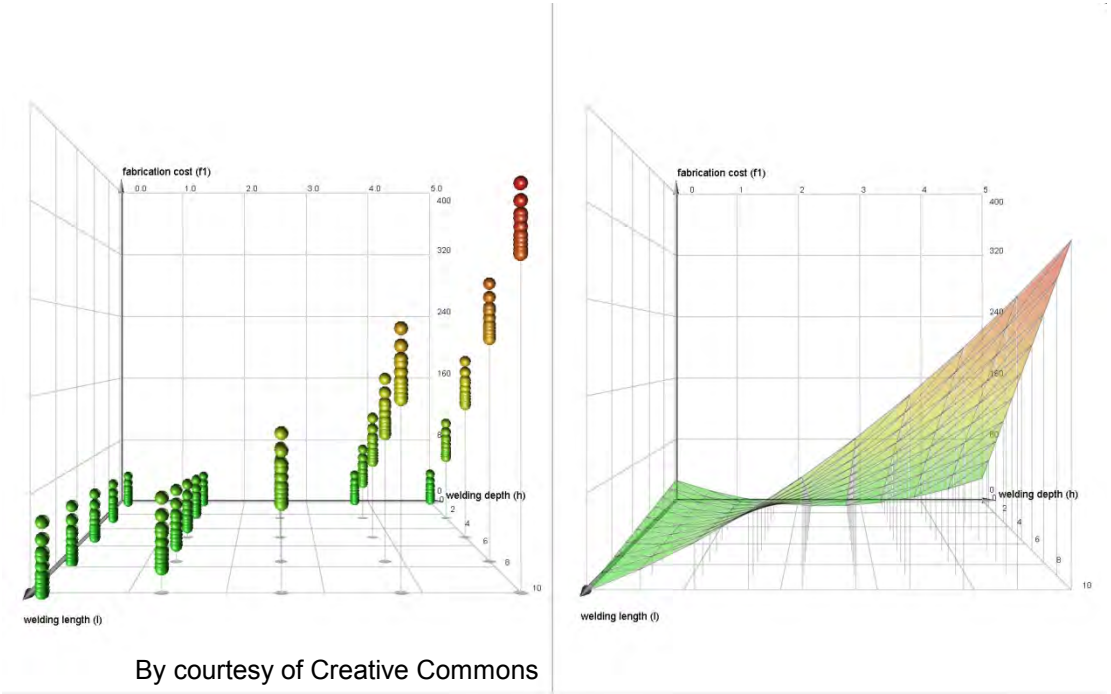
MASTER THESIS OF IAN WALLACE – AN OVERVIEW

Topic

Microbial Expression Systems for the Production of Recombinant Proteins

- A continuation of various Sandoz projects past and present
- Split research between HTS And Process Optimisation
- Fine-tuning of established processes in respect to difficult-to-express proteins (e.g. disulfide bond formation, folding, post-translational modifications etc.)
- Determination of critical parameters in the expression of rec. proteins at various scales

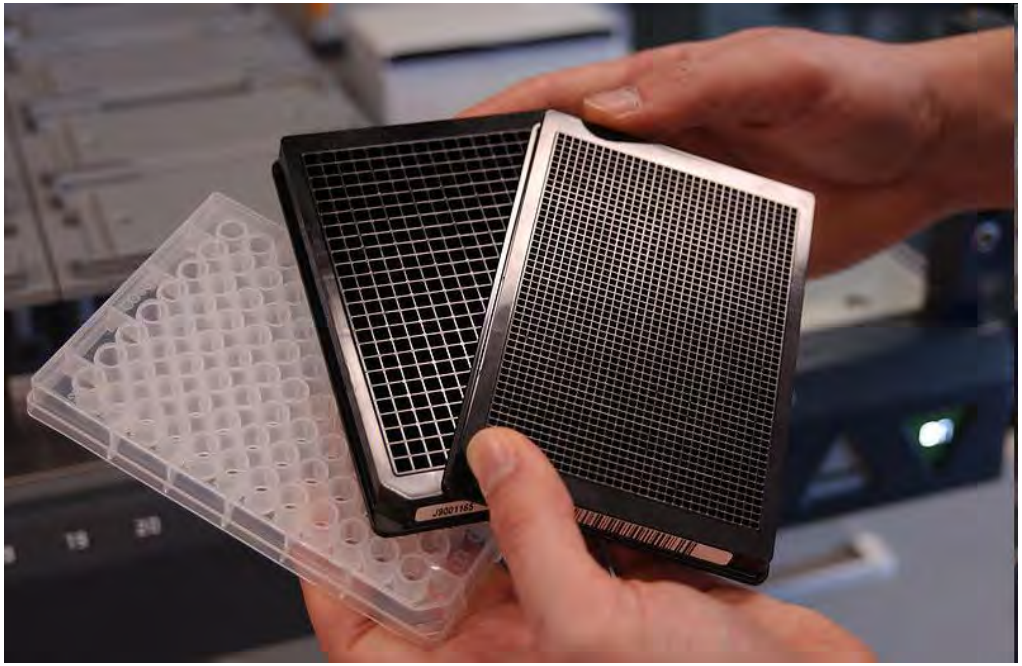
Experimental Planning and Design



Fully factorial planning

Design of Experiments (DoE)

Comparison of an expression system across various platforms and scales



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Microtiter Plates

- Well-plates designed for high throughput screening

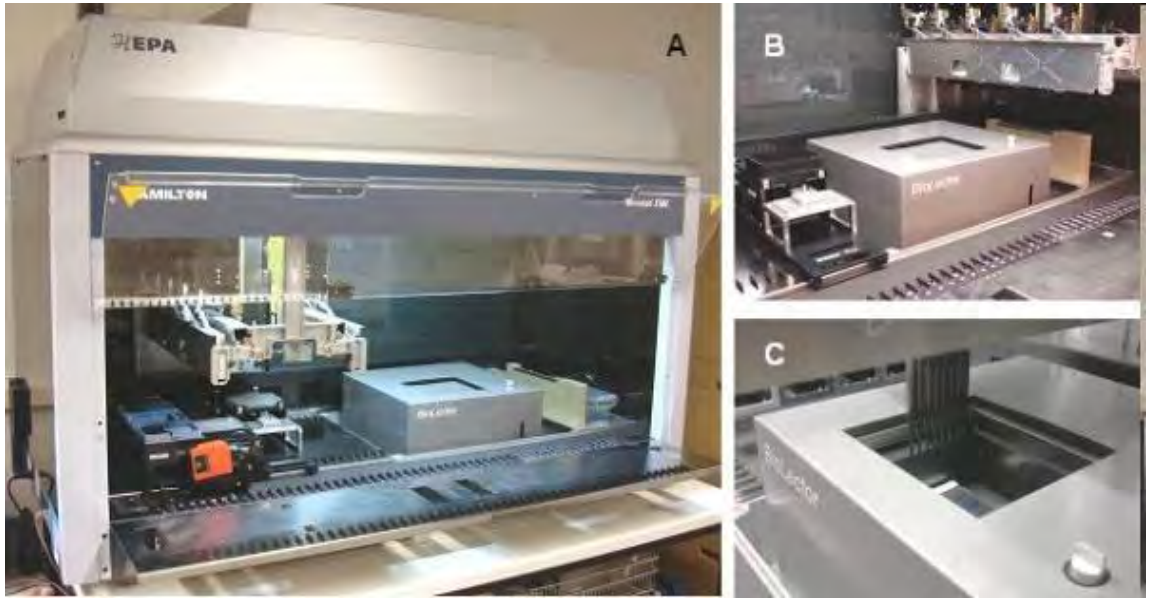
Shake Flasks

- Classical platform for testing culture parameters

Comparison of an expression system across various platforms

Automated HTS

- For strain screening, media and process optimisation, etc.
- Many online measurements possible (pH, pO_2, Biomass, fluorescence, etc.)



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Comparison of an expression system across various platforms

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Fermenters

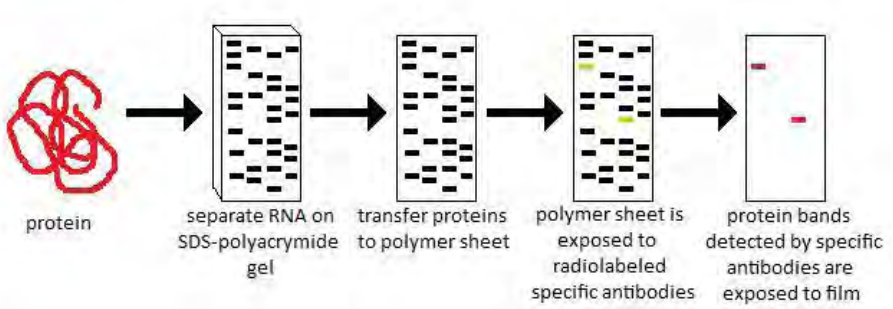
- Large scale fermentation
- Automatic dosage of feed-medium, pH stabilisation, etc.

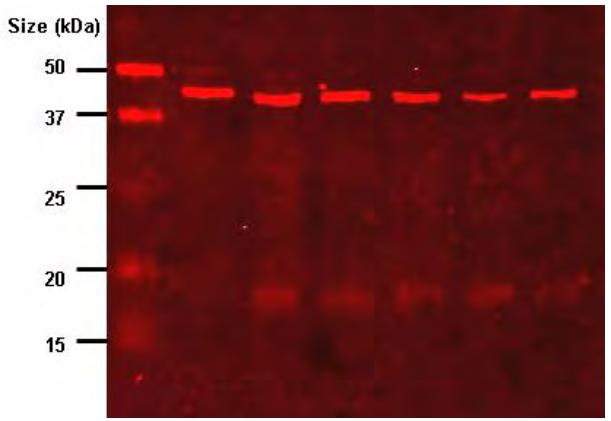
Typical point-measurements

- OD_{600}
- pH
- Sugars
- Posphates
- Nitrates
- Biomass (Dry/Wet)
- Etc.

Typical Product Analysis for rec. Proteins

- SDS-PAGE
- Western Blotting
- Capillary electrophoresis
- Chromatography
- etc.





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Internal Support

- Weekly meetings
- Support by Sandoz Lab people: assistance and guidance
- Novartis Knowledge Centre
- Various ad hoc discussions with other members of staff
- Open communication ethic
- Constructive and positive environment

Good Laboratory Practice

- Data integrity
- Effective communication between colleagues
- A high level of responisibility and awareness
- Laboratory safety paramount

Outcome

- Nature of the thesis allows for great level of hands-on, industry experience
- Scientists in the professional community can work directly with MCI postgraduates, sharing their advice and knowledge

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Thank you for your attention!

mentoring the motivated.

EXHIBIT D

original article

Annals of Oncology 21: 1419–1429, 2010
doi:10.1093/annonc/mdp574
Published online 17 December 2009

Development of a new G-CSF product based on biosimilarity assessment

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Received 15 September 2009; accepted 9 November 2009

Background: Zarzio®, a new recombinant human granulocyte colony-stimulating factor (filgrastim), was evaluated in healthy volunteers and neutropenic patients in phase I and III studies.

Patients and methods: Healthy volunteers in randomized, two-period crossover studies received single- and multiple-dose s.c. injections of 1 μg/kg (n = 24), 2.5 μg/kg (n = 28), 5 μg/kg (n = 28), or 10 μg/kg (n = 40), as well as single-dose i.v. infusions of 5 μg/kg (n = 26), of Zarzio® or the reference product (Neupogen®). Filgrastim serum levels were monitored; pharmacodynamic parameters were absolute neutrophil count (all studies) and $CD34^+$ cells (multiple-dose studies). Supportive efficacy and safety data were obtained from an open phase III study in 170 breast cancer patients undergoing four cycles of doxorubicin and docetaxel (Taxotere) chemotherapy, receiving Zarzio® (300 or 480 μg) as primary prophylaxis of severe neutropenia.

Results: The results of the studies in healthy volunteers confirm the comparability of the test and reference products with respect to their pharmacodynamics and pharmacokinetics. Confidence intervals were within the predefined equivalence boundaries. In the phase III study in breast cancer patients, the administration of Zarzio® was efficacious and safe, triggering no immunogenicity.

Conclusion: The results of these studies demonstrate the biosimilarity of Zarzio® with its reference product Neupogen®.

Key words: biosimilar, clinical trial, filgrastim, neutropenia, recombinant human granulocyte colony-stimulating factor

introduction

The current treatment of cancer with combination cytotoxic chemotherapy targeting proliferating cells usually leads to bone marrow damage, anemia, thrombocytopenia, and, most importantly, neutropenia, resulting in impaired host defense [1]. A severe neutropenia predisposes to serious infection. Life-threatening gastrointestinal and pulmonary infections, as well as sepsis, may occur as long as the severe neutropenia prevails [2]. In addition, this may lead to delays in subsequent chemotherapy cycles.

The recovery of the bone marrow is stimulated by various growth factors, the most important for the recovery of neutrophils being granulocyte colony-stimulating factor (G-CSF). G-CSF is a 20 000 Da glycoprotein hormone that stimulates the proliferation of neuropoietic progenitor cells and their differentiation to granulocytes and functionally activates mature neutrophils [3].

Human G-CSF is a single polypeptide chain protein of 174 amino acids with *O*-glycosylation at one threonine residue. It acts by binding to a specific transmembrane receptor (G-CSF receptor), a member of the class I cytokine receptor family expressed on various hematopoietic cells, such as stem cells, multipotent progenitors, myeloid-committed progenitors, neutrophils, and monocytes [4]. The effects of G-CSF [and of recombinant human G-CSF (rhG-CSF)] are mediated via a single affinity class of receptors. The same mechanism of action and receptor-mediated biological activity mobilizes mature neutrophils into the circulating neutrophil pool and accelerates granulopoiesis.

Zarzio® (filgrastim) is an rhG-CSF produced in *Escherichia coli*. Its amino acid sequence is identical to that of natural human G-CSF, except for the addition of an N-terminal methionine necessary for the expression in *E. coli*. Moreover, it is not glycosylated like its reference product, Neupogen® (Amgen, Thousand Oaks, CA). Zarzio® was approved in the EU in February of 2009 for the same indications as Neupogen®.

The development of Zarzio® included four comparative clinical pharmacology studies in healthy adult volunteers and one phase III study in breast cancer patients receiving cytotoxic

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chemotherapy. The bioequivalence of Zarzio® and the reference product, Neupogen®, was assessed at various dose levels in terms of pharmacodynamics (PD) and pharmacokinetics (PK) using both the s.c. and the i.v. routes of administration. This publication presents the PK/PD results obtained with Zarzio® in healthy volunteers, as well as efficacy and safety in a neutropenic cancer patient population.

patients and methods

The methodology of the four phase I studies (s.c. administration: EP06-101, EP06-103, and EP06-105; i.v. administration: EP06-102) and of the phase III study (EP06-301) is described below.

study population

All studies were conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines and approved by the pertinent ethics committee and regulatory authorities. All individuals gave their written informed consent.

Main inclusion and exclusion criteria are presented in Table 1.

study design

All phase I studies were randomized, double-blind, crossover, single- or multiple-dose studies. Study designs are summarized in Table 2.

The phase III study EP06-301 was an open, single-arm, multicenter trial that evaluated the safety and efficacy of Zarzio® as primary prophylaxis of severe neutropenia in breast cancer patients receiving doxorubicin and docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ) chemotherapy (Table 2). Treatment consisted of daily Zarzio® s.c. bolus injection from day 2 of each chemotherapy cycle for up to 14 days or until absolute neutrophil count (ANC) reached 10×10^9/l after the expected nadir, repeated for up to four cycles. The total daily dose was 300 μg (30 MIU) for women weighing <60 kg and 480 μg (48 MIU) for women weighing ≥60 kg.

On day 1 of each chemotherapy cycle, patients received an i.v. bolus infusion of doxorubicin (60 mg/m^2) followed ∼1 h later by an i.v. infusion of docetaxel (75 mg/m^2). Full-dose chemotherapy on day 1 of the next cycle (days 22–25 of the previous cycle) was not to be started unless the patient had an ANC $>1 \times 10^9$/l and a platelet count $>100 \times 10^9$/l.

study drugs

Zarzio®, containing 300 μg (30 MIU)/0.5 ml or 480 μg (48 MIU)/0.5 ml filgrastim, was provided by Sandoz GmbH (Kundl, Austria) as a clear, colorless to slightly yellowish, sterile solution ready for injection in prefilled syringes.

The reference product was the marketed formulation of Neupogen® containing 300 μg or 480 μg/0.5 ml filgrastim (Amgen GmbH, Munich, Germany), a clear, colorless, sterile solution ready for injection in prefilled syringes.

study end points and analytical methods

pharmacodynamics. PD biosimilarity was used as a surrogate parameter for efficacy. Blood samples were taken regularly up to 14 days after injection and were analyzed for ANC (all phase I studies) and CD34$^+$ cells (studies EP06-101 and EP06-103) using validated flow cytometry assays: Sysmex XT-2000i (Nordenstadt, Germany) for ANC and FACSCalibur Flow cytometer (BD Biosciences, San Jose, CA) for CD34$^+$.

pharmacokinetics. Blood was sampled at predetermined times and filgrastim serum concentrations were determined with a validated enzyme-linked immunosorbent assay. The lower limit of quantification was 0.039 ng/ml. The inter-day precision of the calibration standards of filgrastim was ≤8.3%, with a relative error (accuracy) within ±2.3%. The intra-day precision of the control samples ranged from 3.2% to 8.5%.

Table 1. Main inclusion and exclusion criteria in studies conducted with Zarzio®

	Inclusion criteria	Exclusion criteria
Phase I studies	Healthy male and female Caucasian adults	Smoker
		Any evidence of a clinically significant medical condition
		Acute infection within 2 weeks preceding first study drug administration
		History of drug or alcohol abuse
		History of allergy to *Escherichia coli*-derived proteins, filgrastim, and/or related drugs and their components
		History of hypersensitivity to multiple drugs
Phase III study	Chemotherapy-naïve adult women	Previous treatment with G-CSF preparation
	Documented locally advanced/advanced breast cancer or high-risk stage II breast cancer	Severe neutropenia
	Scheduled for treatment with doxorubicin and docetaxel	Previous or concurrent malignancy
	Estimated life expectancy of >6 months	Concurrent or prior radiotherapy within 4 weeks of study start
	ECOG performance status ≤ 2	WBC count $>50 \times 10^9$/l
	ANC $\geq 1.5 \times 10^9$/l	Total bilirubin higher than the upper limit of normal
	Platelet count $\geq 100 \times 10^9$/l	Creatinine >1.5 × upper limit of normal
	AST and ALT level <3 × upper limit of normal, providing that the alkaline phosphatase level was <5 × upper limit of normal	Prior bone marrow or stem cell transplant
		Systemic anti-infective treatment within 72 h of chemotherapy

G-CSF, granulocyte colony-stimulating factor; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

efficacy parameters. The main efficacy parameters in the phase III study were the overall incidence of severe neutropenia and febrile neutropenia and the incidence and duration (time to recovery to ANC $\geq 1.0 \times 10^9$/l or number of consecutive days with ANC $<0.5 \times 10^9$/l during the cycle) of severe neutropenia during cycles 1 to 4.

Febrile neutropenia was defined as an oral temperature ≥38.2°C with ANC $<0.5 \times 10^9$/l measured on the same day or the day after the temperature elevation.

Table 2. Design of the phase I studies

	EP06-101	EP06-102	EP06-103	EP06-105
Type of study	Randomized, double-blind, two-way crossover, single center	Randomized, double-blind, two-way crossover, single center	Randomized, double-blind, two-way crossover, with two-dose groups, single center	Randomized, double-blind, two-way crossover, single center
Number of subjects	40	26	2 × 28	24
Study population	Healthy volunteers	Healthy volunteers	Healthy volunteers	Healthy volunteers
Duration of exposure	2 weeks (7 days per substance) Washout period of 28 days	2 days (1 day per substance) Washout period of 12–18 days	2 weeks (7 days per substance) Washout period of 28–40 days	2 days (1 day per substance) Washout period of 14 days
Dose (μg/kg)	10	5	2.5 or 5	1
Frequency of dosing	Multiple s.c. injections	Single i.v. infusion	Multiple s.c. injections	Single s.c. injection
Objectives	Primary: evaluate PK bioequivalence Secondary: compare PD, safety, local tolerance	Primary: evaluate PK bioequivalence Secondary: compare PD, safety	Primary: evaluate PD equivalence Secondary: safety, local tolerance, PK	Primary: evaluate PD equivalence Secondary: safety, local tolerance, PK

PK, pharmacokinetics; PD, pharmacodynamics.

To analyze any potential influence of a fixed dose regimen on the efficacy and safety of Zarzio®, administered doses were stratified according to patients' body weight. Five dose groups were generated according to the mean administered dose during all cycles.

safety assessments. Safety assessments in the phase I studies consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), assessments of physical condition, vital signs, electrocardiogram, and monitoring of laboratory values. Local tolerance was evaluated by self-assessment of the subjects using a visual analog scale and by the investigators using the injection site reaction score.

Safety assessments in study EP06-301 included reporting all AEs, their severity, and causal relationship to study drug and/or chemotherapy, injection site evaluations, clinical laboratory tests, vital signs, and mortality. AEs commonly associated with G-CSF treatment, i.e. increases in lactate dehydrogenase (LDH), alkaline phosphatase, serum uric acid, and serum aspartate aminotransferase (AST), as well as musculoskeletal events coded as arthralgia, myalgia, back pain, bone pain, and pain in extremities, were summarized as 'G-CSF-associated AEs', separately from other AEs ('non-G-CSF-associated AEs').

immunogenicity. For antibody analysis, blood was collected in the phase I studies before each period and at study end; in the phase III study, blood was collected at baseline, at day 1 of cycle 2, at day 21 of cycle 4 and at study termination.

Evaluation of the immunogenicity of rhG-CSF injection was made by a three-step procedure:

- Screening of the sera for binding of ^{125}I-rhG-CSF by immunoglobulin G present in the serum [screening radio immuno-precipitation (RIP) assay].
- Specificity of the binding (confirmatory RIP assay).
- Inhibitory effect [neutralizing antibody (NAB) assay].

statistical analysis

The following PK/PD parameters were determined using WinNonLin (Pharsight, Mountain View, CA) and the statistical analysis was carried out using the SAS software (Cary, NC):

- PD parameters $AUEC_{0-last}$ (area under the effect–time curve from time of administration until the last scheduled blood sampling), E_{max} (maximal effect) and $t_{max,E}$ (time of the maximal effect).
- PK parameters area under the serum concentration-time curve, maximum serum concentration (C_{max}), and t_{max}.

For all PK/PD parameters, the 95% (PD) or 90% (PK) confidence interval (CI) for the ratio of means was calculated, except for t_{max} and $t_{max,E}$ where the CIs were determined for the differences in medians. CIs were derived by parametric methods as well as by nonparametric methods for t_{max} and $t_{max,E}$, and if data were not normally distributed.

The primary PD equivalence assessment was based on the per-protocol population applying the predefined equivalence boundaries chosen to contain at least 85% of the observed difference between Neupogen® and placebo in terms of E_{max} as reported in the literature [5].

The phase III data were summarized using descriptive statistics as this was a single-arm study. Two-sided 95% CIs were calculated for mean or median values as appropriate. Results were compared to historical data for filgrastim [6, 7].

results

patients

The demographic data of all studies carried out with Zarzio® are summarized in Table 3.

In the crossover phase I studies, 146 healthy volunteers (81 males and 65 females) were treated with Zarzio® and Neupogen®.

In the phase III study, 170 female patients were treated with Zarzio®. The clinical stage at screening was high risk (stage II), locally advanced (stage III), and advanced metastatic breast cancer (stage IV) for 3%, 66%, and 30% of the patients, respectively. Clinical staging was not reported for one patient. The mean extent of exposure to Zarzio® was 31 days (range 6–48 days).

pharmacodynamic analysis

Filgrastim-induced response in the phase I studies was assessed by ANC, spanning the linear (1–10 μg/kg) portion of the dose–response curve, as well as by the response in the $CD34^+$ cells (for the dose range of 2.5–10 μg/kg, after multiple dosing).

The mean ANC–time profiles after s.c. administration of various doses of Zarzio® and Neupogen® are shown in

Table 3. Demographic characteristics of the phase I and III studies

	Phase I study: EP06-101	Phase I study: EP06-102	Phase I study: EP06-103		Phase I study: EP06-105	Phase III study: EP06-301
Number of subjects	40 enrolled and 32 completed	26 enrolled and 24 completed	28 enrolled and 28 completed	28 enrolled and 27 completed	24 enrolled and 24 completed	170 enrolled and 153 completed the treatment period
Number of subjects eligible for PK/PD analysis	32	24	28	27	23	n.a.
Dose (μg/kg)	10	5	2.5	5	1	300 μg for women weighing <60 kg and 480 μg for women weighing ≥60 kg
Route	s.c.	i.v.	s.c.	s.c.	s.c.	s.c.
Gender enrolled (completed)	21M/19F (17M/15F)	14M/12F (14M/10 F)	19M/9F (19M/9F)	14M/14F (13M/14F)	13M/11F (13M/11F)	170F
Age (years), mean (SD) [min–max]	35 (6) [25–45]	30 (5) [23–39]	37 (10) [22–54]	40 (8) [21–53]	40 (9) [21–53]	52 (10) [24–78]
Weight (kg), mean (SD) [min–max]	69.9 (9.1) [55.7–89.1]	75.9 (10.6) [58.5–101.0]	79.2 (13.1) [55.5–111.8]	71.2 (10.1) [54.9–93.1]	76.3 (11.6) [61.2–95.1]	73.2 (14.5) [43.2–130.0]
Height (cm), mean (SD) [min–max]	173.0 (9.7) [155–193]	176.1 (9.3) [162–199]	177.6 (10.5) [155.0–205.0]	173.5 (7.1) [162–191]	175 (9.3) [158–190]	161.3 (6.4) [147–178]
Body mass index (kg/m^2), mean (SD) [min–max]	23.3 (1.8) [19.2–27.0]	24.4 (1.9) [21.4–27.8]	24.9 (2.1) [20.2–27.2]	23.6 (2.3) [19.5–28.4]	24.7 (2.0) [21.6–27.3]	28.1 (5.4) [18.2–47.2]
Reason for discontinuation	3 failure during check-in laboratory 2 due to AEs 1 due to personal reason 1 due to noncompliance 1 due to drug failure during check-in testing	2 due to AEs	–	1 due to multiple protocol violation	–	9 on patient's decision 1 on investigator's decision 3 due to AEs 4 due to protocol violations
Number of volunteer- or patient-years (Zarzio®)	0.69	0.07	0.54	0.53	0.07	14.4

Table 3. (*Continued*)

	Phase I study: EP06-101	Phase I study: EP06-102	Phase I study: EP06-103		Phase I study: EP06-105	Phase III study: EP06-301
Number of volunteer- or patient-years (Neupogen®)	0.69	0.07	0.54	0.54	0.07	n.a.

PK, pharmacokinetics; PD, pharmacodynamics; M, Male; F, female; SD, standard deviation; n.a., not available; n.a., not available.

Figure 1. Zarzio® and Neupogen® profiles were superimposable for all dose levels and all routes (i.v. administration not shown). There were no significant differences between the two products at any point in time. After s.c. injection, the increase of ANC was reversible and returned to baseline values ~48 h after single or the last repeated administration. Following multiple s.c. dosing, the seventh administration triggered a larger increase in ANC than following the first administration. This effect was also observed between the two periods of each study, affecting both treatments equally (data not shown).

Table 4 shows the results of the primary efficacy end points for all routes and all dose levels, as well as the results of the statistical test for equivalence.

After 7 days of s.c. administration, both Zarzio® and Neupogen® exhibited a clear dose-dependent response. The mean Zarzio® AUEC for ANC increased from 4.2 $h \cdot 10^6/\mu l$ for the 2.5 μg/kg group to 5.2 $h \cdot 10^6/\mu l$ for the 5 μg/kg dose group and 6.5 $h \cdot 10^6/\mu l$ for the 10 μg/kg dose group (Table 4).

Each individual phase I study showed a remarkable concordance of the observed effects between Zarzio® and Neupogen®, with CIs for ANC well within the predefined equivalence boundaries (Table 4).

$CD34^+$ counts were investigated as a secondary efficacy assessment after repeated daily s.c. administration. Increasing doses from 2.5 to 10 μg/kg raised $CD34^+$ counts for both products (Figure 2). The results for $CD34^+$ counts showed comparable effects of Zarzio® and Neupogen®, with CIs well within the predefined equivalence boundaries (data not shown).

pharmacokinetic analysis

The results of the PK parameters of filgrastim following single i.v. infusion of 5 μg/kg are summarized in Table 5. Zarzio® and Neupogen® showed similar PK characteristics, with 90% CIs for AUC_{0-last} and C_{max} within the predefined standard bioequivalence limits of 80%–125% (Table 5).

Following s.c. injection, mean serum filgrastim concentration–time profiles of different doses of Zarzio® and Neupogen® are displayed in Figure 3. Analysis of the PK results demonstrated bioequivalence between Zarzio® and Neupogen® (data not shown).

clinical efficacy

The incidence and duration of severe neutropenia are shown in Table 6; results obtained with Zarzio® are compared with published results for Neupogen® [6, 7].

The mean ANC curve for each cycle is shown in Figure 4. ANC curves were congruent for all cycles from days 1 to 11. As expected, the depth of the ANC nadir was greatest in cycle 1 compared with the subsequent three cycles.

Zarzio® was administered as a fixed dose of 300 or 480 μg according to the patient's body weight. This resulted in a mean dose by body weight of 6.1 ± 0.9 μg/kg per day (range 3.7–8.4 μg/kg). To analyze any potential influence of this fixed dose regimen on the efficacy and safety of Zarzio®, administered doses were classified according to patients' body weight. Table 7 shows the proportion of patients in the corresponding dose

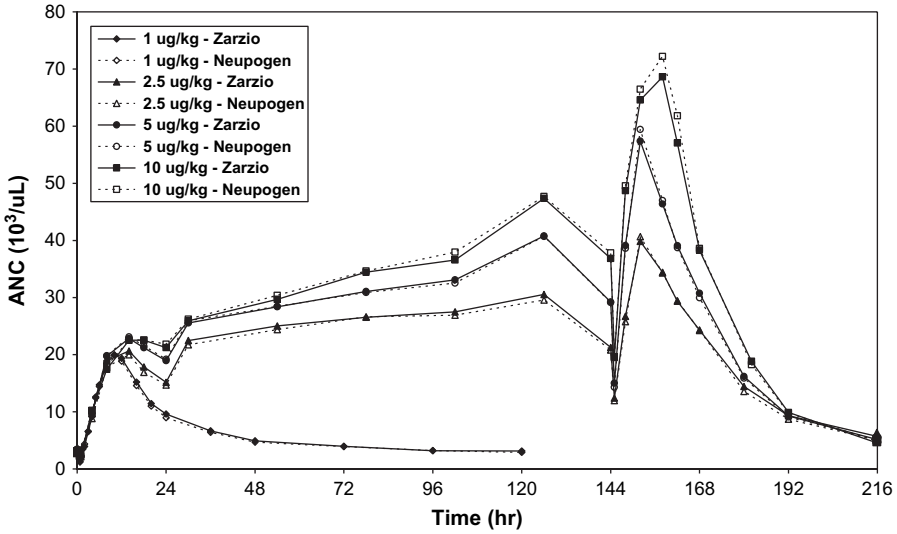

Figure 1. Mean absolute neutrophil count (ANC) profiles after s.c. administration of 1 μg/kg Zarzio® (—♦—), 1 μg/kg Neupogen® (—◇—), 2.5 μg/kg Zarzio® (—▲—), 2.5 μg/kg Neupogen® (—Δ—), 5 μg/kg Zarzio® (—●—), 5 μg/kg Neupogen® (—○—), 10 μg/kg Zarzio® (—■—), and 10 μg/kg Neupogen® (—□—) to healthy volunteers.

groups at baseline. The overall incidence of grade 3 or 4 neutropenia (ANC $<1.0 \times 10^9$/l) according to the dose per body weight is summarized in Table 7. The stratified analysis shows that there was no relationship ($P = 0.66$) between the overall and the by-cycle incidences of grade 3 or 4 neutropenia and the respective doses per body weight.

Ten (6%) patients (95% CI 2.9% to 10.6%) experienced febrile neutropenia during the first treatment cycle, and febrile neutropenia was not observed during any subsequent treatment cycle.

Febrile neutropenia caused hospitalization of six (3.5%) patients during the first treatment period, with a mean ± standard deviation duration of hospitalization of 12 ± 8.1 days. None of these patients were treated in the intensive care unit. Antibiotics were administered i.v. to only nine (5.3%) patients during the first treatment period, all for febrile neutropenia. Only one (0.6%) patient required a blood transfusion due to anemia.

safety

safety in healthy volunteers. Study drug-related AEs frequently observed in healthy volunteers under Zarzio® or Neupogen® treatment were as expected (musculoskeletal pain, leukocytosis, thrombocytopenia, and headaches). There were no clinically relevant differences between Zarzio® and Neupogen® in the frequency or type of AEs by system organ class and severity (all generally mild or moderate). No SAEs were observed and no deaths occurred during any of these studies.

Results from the laboratory tests, vital signs measurements, and physical examinations confirmed the absence of marked changes in the subjects' state of health.

safety in neutropenic patients. Summary results for AEs in study EP06-301 are displayed in Table 8. Regarding the 1494 'non-G-CSF-associated AEs', a relationship to study chemotherapy was suspected for most of them (85%). Of the 89 'G-CSF-associated events', 44 (49%) were considered to be related to Zarzio®, while 48 (54%) were suspected to be chemotherapy related. The intensities of the G-CSF-associated AEs were mainly mild (89%) or at most moderate (11%).

Local tolerability was found to be excellent with Zarzio®.

In addition, the analysis of 'G-CSF-associated events' based on the five body weight-adjusted dose strata showed that the incidences were similar across the dose groups.

immunogenicity. During this clinical development of Zarzio®, 1060 serum samples were tested with the screening RIP assay and 29 samples were analyzed with the confirmatory RIP assay. Among them, three samples were tested positive for binding antibodies. These three samples belonged to a healthy volunteer in study EP06-102 and included the baseline sample. Thus, the result in the RIP assay was positive already at baseline and no increase was detected during treatment. No neutralizing antibodies were detected in these serum samples in the NAB assay. In conclusion, none of the subjects developed anti-rhG-CSF binding antibodies.

discussion

For the demonstration of clinical efficacy of biosimilar rhG-CSF, the European authorities state in their guidelines that comparative PK/PD studies in healthy subjects between the similar biological medicinal product and its reference may be sufficient to demonstrate clinical comparability [8]. At least one PD marker should be considered accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker should be well known.

Since the duration of treatment, the mechanism of action and the pharmacological properties of rhG-CSF are fundamentally the same in healthy volunteers and neutropenic patients, and as duration of severe neutropenia (ANC $< 0.5 \cdot 10^9$/l) is accepted as the primary measure of efficacy in patients undergoing myelotoxic chemotherapy, a proper dose response in a comparative PD study in healthy volunteers was considered

Table 4. Pharmacodynamics of the primary parameter absolute neutrophil count after i.v. and s.c. administration of rhG-CSF to healthy volunteers

Dosage group	Parameter	Zarzio® geometric mean (SD)	Neupogen® geometric mean (SD)	Point estimate[a]	95% CI
5 µg/kg i.v. single dose	*N*	24	24		
	$AUEC_{0–last}$ ($h·10^3/µl$)	945 (169)	950 (291)	99.42%	94.51% to 104.59%
	E_{max} ($10^3/µl$)	21.7 (3.9)	21.5 (6.4)	100.83%	93.37% to 108.88%
	$t_{max,E}$ (h)	11.9 (8.0–16.0)[b]	11.7 (8.0–16.0)[b]	0.01 h	−0.03 to 1.00 h
1 µg/kg s.c. single dose	*N*	23	23		
	$AUEC_{0–last}$ ($h·10^3/µl$)	741 (125)	725 (133)	102.11%	96.68% to 108.09%
	E_{max} ($10^3/µl$)	19.9 (3.8)	20.0 (4.3)	99.73%	94.26% to 105.42%
	$t_{max,E}$ (h)	10.0 (8.0–12.0)[b]	10.0 (8.0–12.0)[b]	0.03 h	0.00 to 1.00 h
	$AUEC_{0–24}$ ($h·10^3/µl$)	313 (48)	309 (57)		
2.5 µg/kg/day s.c. repeated doses over 7 days	*N*	28	28		
	$AUEC_{0–last}$ ($h·10^3/µl$)	4224 (1048)	4135 (951)	102.16%	99.49% to 104.91%
	E_{max} ($10^3/µl$)	38.7 (9.8)	39.7 (9.0)	97.50%	93.48% to 101.70%
	$t_{max,E}$ (h)	152.0 (152.0–158.0)[b]	152.0 (152.0–158.0)[b]	0.00 h	0.00 to 0.00 h
	$AUEC_{0–24}$ ($h·10^3/µl$)	362 (88)	346 (72)	104.47%	98.92% to 110.34%
	$E_{max,\ sd}$ ($10^3/µl$)	20.4 (5.3)	19.7 (4.2)	103.76%	97.03% to 110.96%
	$t_{max,E,\ sd}$ (h)	14.0 (8.0–24.0)[b]	14.0 (8.0–18.0)[b]	0.01 h	−0.01 to 0.03 h
5 µg/kg/day s.c. repeated doses over 7 days	*N*	27	27		
	$AUEC_{0–last}$ ($h·10^3/µl$)	5192 (1250)	5177 (1087)	100.61%	98.01% to 103.29%
	E_{max} ($10^3/µl$)	56.1 (11.8)	58.1 (12.2)	96.74%	92.69% to 100.97%
	$t_{max,E}$ (h)	152.0 (152.0–152.0)[b]	152.0 (152.0–158.0)[b]	0.00 h	−0.01 to 0.00 h
	$AUEC_{0–24}$ ($h·10^3/µl$)	405 (94)	404 (103)	100.68%	95.27% to 106.39%
	$E_{max,\ sd}$ ($10^3/µl$)	22.4 (5.1)	22.6 (5.9)	99.81%	94.59% to 105.31%
	$t_{max,E,\ sd}$ (h)	14.0 (8.0–18.0)[b]	14.0 (8.0–24.0)[b]	−0.01 h	−2.01 to 0.01 h
10 µg/kg/day s.c. repeated doses over 7 days	*N*	32	32		
	$AUEC_{0–last}$ ($h·10^3/µl$)	6475 (1458)	6515 (1839)	99.37%	96.30% to 102.54%
	E_{max} ($10^3/µl$)	71.2 (27.3)	73.3 (35.0)	97.10%	88.36% to 106.70%
	$t_{max,E}$ (h)	152.0 (152.0–158.0)[b]	152.0 (152.0–158.0)[b]	0.00 h	−0.07 to 2.98 h
	$AUEC_{0–24}$ ($h·10^3/µl$)	406 (108)	407 (131)	100.22%	93.39% to 107.56%
	$E_{max,\ sd}$ ($10^3/µl$)	24.3 (7.8)	23.7 (7.5)	97.72%	90.68% to 105.29%
	$t_{max,E,\ sd}$ (h)	16.0 (14.0–24.0)[b]	18.0 (14.0–24.0)[b]	−1.00 h	−3.00 to 1.00 h

Predefined equivalence intervals: 1 µg/kg/day: 80%–125%; 2.5 µg/kg/day: 87.25%–114.61%; 5 µg/kg/day: 86.50%–115.61%.

[a]Ratio of means for AUEC and E_{max}, difference of medians for $t_{max,E}$.

[b]Median (range).

rhG-CSF, recombinant human granulocyte colony-stimulating factor; SD, standard deviation; CI, confidence interval; *N*, number of subjects; $AUEC_{0–last}$, area under the effect–time curve from time of administration until the last scheduled blood sampling; E_{max}, maximal effect; $t_{max,E}$, time of the maximal effect; $AUEC_{0–24}$, area under the effect–time curve from time of administration until the 24-h blood sampling; $E_{max,\ sd}$, maximal effect after single-dose administration; $t_{max,E,\ sd}$, time of the maximal effect after single-dose administration.

sufficient to support marketing authorization from an efficacy perspective. In addition, the fact that bone marrow in healthy subjects, in contrast to myelosuppressed patients, is fully responsive to G-CSF treatment actually makes a healthy volunteer study a more sensitive model for rhG-CSF efficacy assessment than a study in chemotherapy-treated patients.

The phase I studies conducted with Zarzio® in healthy volunteers were similar in design to provide a large pool of data for efficacy assessments. ANC and $CD34^+$ cell count were used as surrogate markers for efficacy. ANC qualifies as a valid marker, as it essentially drives diagnosis (e.g. grade of neutropenia), predicts prognosis (duration of severe neutropenia correlates with the risk of infection), and is utilized to monitor rhG-CSF treatment effects; $CD34^+$ represents a useful marker for the selection and characterization of cells necessary for both short- and long-term engraftment of stem cells in recipients after myeloablative therapy [9, 10].

Each individual phase I study showed a remarkable concordance of the observed effects between Zarzio® and Neupogen®. ANC curves were superimposable whatever the route and the dose, with a very tight range in the corresponding ratios (99%–102%) achieved between Zarzio® and Neupogen®. All CIs for ANC were well within the predefined equivalence boundaries. Therefore, Zarzio® showed a highly similar PD effect to Neupogen®.

In addition to ANC, $CD34^+$ counts further confirmed Zarzio® efficacy. Higher $CD34^+$ yields are known to be achieved with the commonly used clinical dose of 10 µg/kg for stem cell mobilization, a fact also confirmed in study EP06-101. Broad interindividual variation in the capacity of normal subjects to mobilize progenitor cells were noted, a finding that is in line with literature reports [11].

With regard to the PK of filgrastim administration, the results obtained in the phase I studies are clearly in agreement

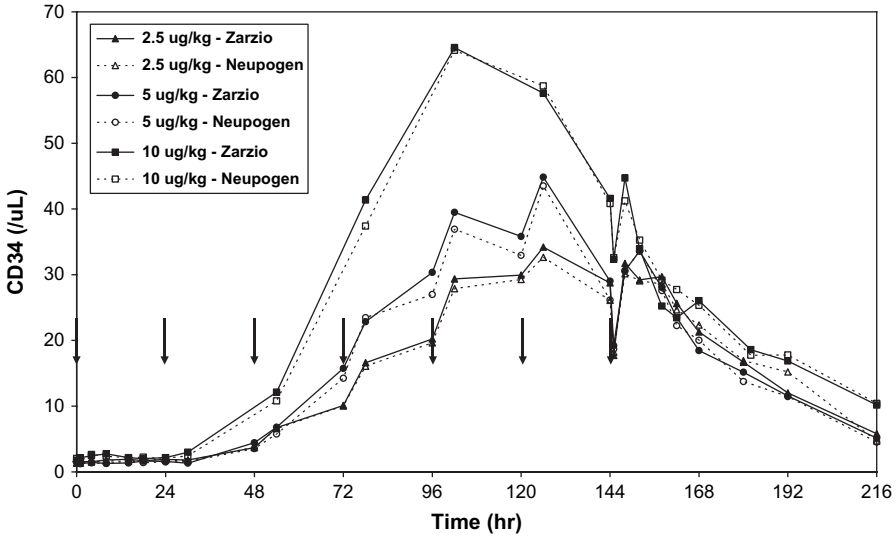

Figure 2. Mean $CD34^+$ profiles after s.c. administration of 2.5 μg/kg Zarzio® (—▲—), 2.5 μg/kg Neupogen® (—Δ—), 5 μg/kg Zarzio® (—●—), 5 μg/kg Neupogen® (—○—), 10 μg/kg Zarzio® (—■—), and 10 μg/kg Neupogen® (—□—) to healthy volunteers. Arrows represent drug administration.

Table 5. Pharmacokinetics (PK) of filgrastim after single i.v. infusion of rhG-CSF to healthy volunteers

PK parameter	Zarzio® ($n = 24$) geometric mean (SD)	Neupogen® ($n = 24$) geometric mean (SD)	Point estimate (%)	90% CI
C_{max} (ng/ml)	186.4 (19.8)	188.7 (25.2)	98.82	95.76% to 101.98%
AUC_{0-last} (ng·h/ml)	632.1 (105.8)	634.2 (112.6)	99.68	96.94% to 102.47%
$AUC_{0-\infty}$ (ng·h/ml)	635.8 (106.7)	637.5 (113.1)	99.74	97.01% to 102.56%
$t_{½}$ (h)	12.47	11.12	112.12	100.87% to 124.62%

rhG-CSF, recombinant human granulocyte colony-stimulating factor; SD, standard deviation; CI, confidence interval; C_{max}, maximum serum concentration; AUC_{0-last}, area under the serum concentration–time curve from 0 h to the last quantifiable concentration; $AUC_{0-\infty}$, area under the serum concentration–time curve from 0 h to infinity; t_{max}, time point of maximal serum concentration; $t_{½}$, half-life of drug elimination.

with what has been previously described [5,12–14]. G-CSF stimulates the proliferation of myeloid precursors and accelerates neutrophil release from the bone marrow [15]. The number of G-CSF receptors thus substantially increases with time after its administration, leading to a faster elimination and an enhanced effect on neutrophils. This time-dependent nonlinear PK was very clearly evidenced in the repeated administration studies, where C_{max} decreased by more than 50% between the first and the seventh administration.

As supportive evidence of Zarzio® efficacy, study EP06-301 was designed as a single-arm phase III study in patients with breast cancer receiving treatment with combination chemotherapy of doxorubicin and docetaxel. This chemotherapy is known to be associated with a high risk for severe neutropenia [16].

The mean duration of severe neutropenia with Zarzio® was 1.8 days in cycle 1 compared with the historical expectation of up to 7 days without growth factor support [17]. Duration of severe neutropenia in this study was comparable to historical data with Neupogen® [6, 7], even though the incidence of severe neutropenia in the various cycles was lower compared with published data (47% in cycle 1 for Zarzio® versus 79% and 83% for Neupogen®). To some extent, this lower incidence can be explained by heterogeneity across the studies in a number of patients' characteristics. In study EP06-301, women were chemotherapy naïve, with a bone marrow less vulnerable and more responsive than in chemotherapy-pretreated patients. In contrast, ∼20% of patients in the literature studies were previously chemotherapy treated, a known risk factor for severe neutropenia. This is also evidenced by the same duration of recovery from severe neutropenia in patients treated with Zarzio® compared with Neupogen®. This observation is further supported by the fact that 90 patients (53%) in study EP06-301 experienced severe neutropenia at least once during the whole study period, which is in line with other published data for chemotherapy-naïve breast cancer patients [18], for whom an incidence rate of 46% across all four chemotherapy treatment cycles was reported.

Zarzio® and Neupogen® are available in prefilled syringes containing either 300 or 480 μg of filgrastim; for practical reasons, patients thus received a fixed filgrastim dose, which reflects clinical routine [6]. The corresponding individual dose based on body weight ranged between 3.7 and 8.4 μg/kg. This is consistent with the range of the daily dose of 4.0–8.4 μg/kg used in randomized clinical studies with Neupogen® in cancer patients receiving cytotoxic chemotherapy [19, 20]. Thorough

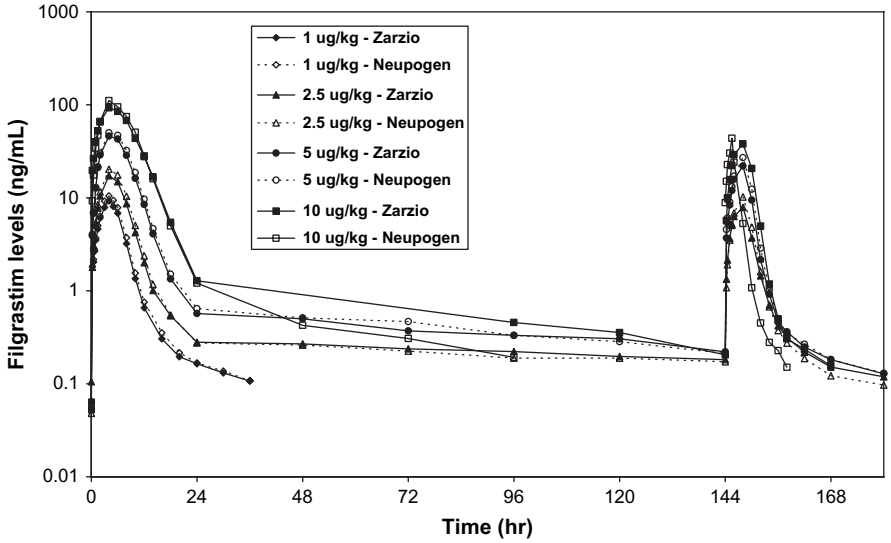

Figure 3. Mean serum filgrastim profiles after s.c. administration of 1 μg/kg Zarzio® (—♦—), 1 μg/kg Neupogen® (—◇—), 2.5 μg/kg Zarzio® (—▲—), 2.5 μg/kg Neupogen® (—Δ—), 5 μg/kg Zarzio® (—●—), 5 μg/kg Neupogen® (—○—), 10 μg/kg Zarzio® (—■—), and 10 μg/kg Neupogen® (—□—) to healthy volunteers.

Table 6. Incidence and duration of severe neutropenia

Cycle	Incidence				Duration (days)			
	Zarzio®		Neupogen®		Zarzio®		Neupogen®	
	N	*n* (%)	Green et al. [6] (*N* = 75), %	Holmes et al. [7] (*N* = 151), *n* (%)	Mean ± SD[a]	Mean ± SD[b]	Green et al. [6], mean ± SD[b]	Holmes et al. [7], mean ± SD[b]
1	170	80 (47)	83	116 (79)	2.2 ± 0.9	1.8 ± 1.4	1.6 ± 1.1	1.8 ± 1.4
2	162	25 (15)	54	81 (56)	1.8 ± 0.6	1.3 ± 0.5	0.9 ± 1.0	1.1 ± 1.1
3	159	33 (21)	53	86 (60)	1.9 ± 0.9	1.4 ± 0.6	0.9 ± 1.1	1.2 ± 1.4
4	154	27 (18)	49	78 (55)	2.1 ± 0.8	1.7 ± 0.6	1.0 ± 1.3	1.3 ± 1.5

[a]Recovery to ANC ≥1.0 × 109/l, i.e. number of days from the first day with ANC <0.5 × 10^9/l to the first day with ANC ≥1.0 × 10^9/l.
[b]Number of consecutive days with ANC <0.5 × 10^9/l during the treatment cycle.
SD, standard deviation; ANC, absolute neutrophil count.

analysis of the effects of Zarzio® on patients stratified by dose per kg body weight demonstrated similar therapeutic efficacy, along with a comparable safety profile for all dose groups. The result that the incidence of grades 3–4 neutropenia in study EP06-301 was not higher in heavier patients, who had received a relatively lower filgrastim dose than recommended in the label, is also in accordance with literature data [21].

Zarzio® effectively reduced the risk of febrile neutropenia and the incidence in cycle 1 was 7.6%, comparing well to incidences reported from Amgen-sponsored studies [6, 7]. In contrast, the median risk of developing febrile neutropenia with the same chemotherapy regimen (3-week schedule of doxorubicin and docetaxel), without rhG-CSF, was reported to be 17.5% (range 15%–21%) [22–25].

The safety profiles of Zarzio® and Neupogen® in healthy volunteers were comparable. Drug-related AEs were consistent with those reported in normal donors as described in the Summary of Product Characteristics (SPC) of Neupogen® [19] and were similar for both products. Overall, these data support the comparability of both products.

Zarzio® was very well tolerated by cancer patients in the phase III study. The overall incidence of AEs was in the range of that reported with the reference product. Notably, for musculoskeletal events, an incidence of 21% for Zarzio® was reported versus 26% for Neupogen® in the literature [7] or 13% in the SPC [19]; transient reversible increases in AST and LDH were in the range of those previously reported with rhG-CSF [26].

As with any other biopharmaceutical, a major focus of safety assessment was on the potential development of antidrug antibodies in the treated subjects. Antibodies directed against a therapeutic protein may have neutralizing activity and interfere with the efficacy of treatment [27]. The reports on anti-G-CSF antibodies are sparse and rather indicate that positive testing is due to unspecific binding and causes no clinical consequences for the individual patient [28]. For Neupogen®, an incidence rate of 3% (11 patients out of 333) of nonneutralizing antibodies in clinical studies has been reported [19]. None of the 316 subjects treated with Zarzio® developed anti-rhG-CSF antibodies, which shows that Zarzio® is safe from an immunological point of view. This observation is in

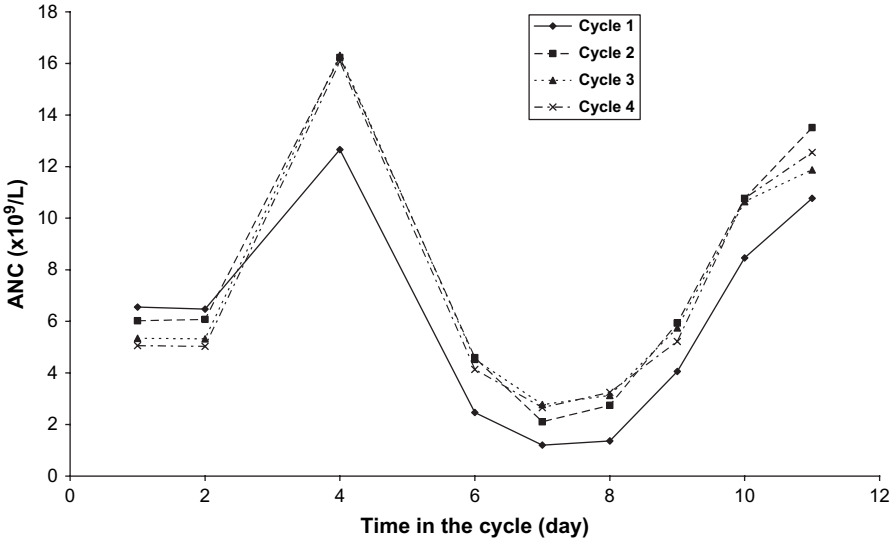

Figure 4. Mean absolute neutrophil count (ANC) curve for each cycle.

Table 7. Overall incidence of grade 3 or 4 neutropenia for doses expressed per body weight

Dose per body weight (μg/kg)	Number of patients (%)	Incidence of neutropenia (grades 3 and 4)[a], *n* (%)				
		Overall	Cycle 1	Cycle 2	Cycle 3	Cycle 4
<4.5	4 (2)	3 (75)	2 (49)	1 (42)	1 (42)	1 (42)
4.5 to <5.5	38 (22)	31 (82)	28 (14)	20 (16)	20 (16)	19 (16)
5.5 to <6.5	71 (42)	60 (85)	50 (11)	24 (11)	31 (12)	32 (12)
6.5 to <7.5	42 (25)	33 (79)	28 (14)	17 (15)	18 (16)	16 (16)
≥7.5	15 (9)	14 (93)	12 (20)	4 (25)	3 (23)	6 (29)

[a]According to the stratification based on mean dose administered and patient's body weight at baseline, even though some patients might have been classified in another dose group during the study due to a change in weight and/or dose.

Table 8. General summary of AEs in study EP06-301

	G-CSF-associated AEs	Non-G-CSF-associated AEs
Number of subjects dosed	170	170
Number of subjects with AEs (%)	39 (23)	168 (99)
Number of AEs	89	1494
Severity, *n* (%)		
Mild	79 (89)	557 (37)
Moderate	10 (11)	311 (21)
Severe	0 (0)	231 (15)
Life-threatening	0 (0)	208 (13)
Death	0 (0)	0 (0)
Relation to study drug, *n* (%)		
Not suspected	45 (51)	187 (13)
Suspected to Zarzio®[a]	44 (49)	50 (3)
Suspected to chemotherapy[a]	48 (54)	1264 (85)

[a]An AE can be related to both Zarzio® and chemotherapy.
AE, adverse event; G-CSF, granulocyte colony-stimulating factor.

line with published data on the absence of immunogenicity of rhG-CSF in long-term maintenance treatment [29].

Taken together, the phase I studies demonstrate the biosimilarity of Zarzio® and Neupogen® with respect to PD and PK profiles, over doses ranging from 1 to 10 μg/kg, following both s.c. and i.v. administration. This was shown in healthy volunteers, a more sensitive model than neutropenic patients under cytotoxic chemotherapy since healthy bone marrow is more responsive to rhG-CSF treatment. Efficacy and safety of Zarzio® were further confirmed in a phase III study in

neutropenic breast cancer patients receiving myelosuppressivechemotherapy treatment.

The phase III study also suggests that the administration of a fixed dose of filgrastim to neutropenic cancer patient receiving chemotherapy, rather than a dose based on body weight, has a similar therapeutic efficacy along with a comparable safety profile.

acknowledgements

The authors would like to thank Dr Jean-Yves le Cotonnec (Triskel Integrated Services) for his assistance in the registration of Zarzio® and for the conception of this publication. The authors would also like to thank the volunteers for participating in the studies and the many individuals involved in planning, conductance, evaluation, and/or reporting of the studies. Specifically, the following individuals made a major overall contribution: Dr Alexander Jetter, Dr Dorota Tomalik-Scharte (Department of Pharmacology, University Hospital, University of Cologne, Cologne, Germany), Hendrik Lück, Dr Irina Müller, Dr Petra Krause (Itecra GmbH & Co. KG, Cologne, Germany).

disclosure

UF is currently conducting research sponsored by Sandoz. FS performs clinical and analytical research for Sandoz. He makes presentations at conferences where they support him. MK-S carried out the clinical studies in healthy volunteers, did study planning, analytics, PK, and assisted reporting. AM has conducted research sponsored by Sandoz. PG, SB, SE, and MM do not have any conflict of interests.

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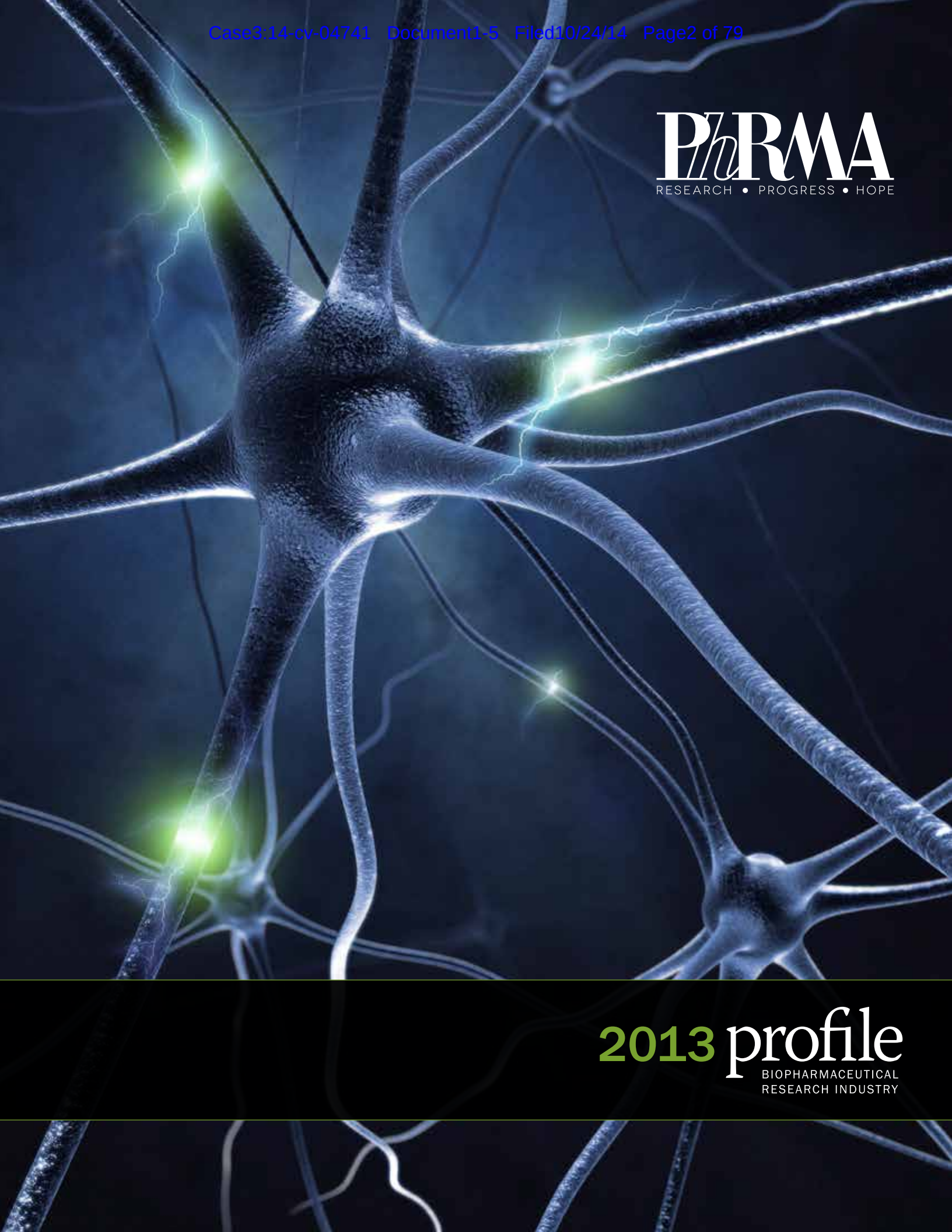
EXHIBIT E



PhRMA
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2013 profile
BIOPHARMACEUTICAL
RESEARCH INDUSTRY

Research and Development (R&D)

Time to develop a drug = 10 to 15 years[1, 2, 3]

Development Costs

Average cost to develop a drug (including the cost of failures): [4, 5]

- Early 2000s = $1.2 billion* (some more recent studies estimate the costs to be even higher [6])
- Late 1990s = $800 million*
- Mid 1980s = $320 million*
- 1970s = $140 million*

R&D Spending

Year	PhRMA members[7]
2012	$48.5 billion (*est.*)
2011	$48.6 billion
2010	$50.7 billion
2009	$46.4 billion
2008	$47.4 billion
2007	$47.9 billion
2006	$43.4 billion
2005	$39.9 billion
2000	$26.0 billion
1990	$8.4 billion
1980	$2.0 billion

Percentage of Sales That Went to R&D in 2012[8]

Domestic R&D as a percentage of domestic sales = 20.7%

Total R&D as a percentage of total sales = 16.4%

Economic Impact of the Biopharmaceutical Sector[9]

Direct jobs = more than 810,000

Total jobs (including indirect and induced jobs) = nearly 3.4 million

Approvals

- Medicines approved 2000–2012 = more than 400[10, 11, 12]
- In the 30 years since the Orphan Drug Act was established, more than 400 orphan drugs have been approved.[13]
- Only 2 of 10 marketed drugs return revenues that match or exceed R&D costs.[14]

Medicines in Development

- Global development in 2011 = 5,400 compounds[15]
- U.S. development 2013 = 3,400[16] — an increase of 40% since 2005[17]
- Potential first-in-class medicines** in clinical development globally = 70%[18]

Value of Medicines

- **Cancer:** Since 1980, 83% of life expectancy gains for cancer patients are attributable to new treatments, including medicines.[19] Another study found that medicines specifically account for 50% to 60% of increases in survival rates since 1975.[20]
- **Cardiovascular Disease:** According to a 2013 statistics update by the American Heart Association, death rates for cardiovascular disease fell a dramatic 33% between 1999 and 2009.[21]
- **HIV/AIDS:** Since the approval of antiretroviral treatments in 1995, the HIV/AIDS death rate has dropped by 85%.[22, 23]

Sales

Generic share of prescriptions filled:[24]

2000 = 49%

2012 = 84%

See inside back cover for references.

* Note: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.

**Note: First-in-class medicines are those that use a different mechanism of action from any other already approved medicine.

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2013 profile
BIOPHARMACEUTICAL RESEARCH INDUSTRY

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Suggested Citation:
Pharmaceutical Research and Manufacturers of America,
2013 Biopharmaceutical Research Industry Profile
(Washington, DC: PhRMA, July 2013).

Pharmaceutical Research and Manufacturers of America
Washington, DC
www.phrma.org
July 2013

Cover image: Neurons firing in the brain.

Letter from PhRMA's President and CEO

Hear more from John J. Castellani here.
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Today in America and around the world we confront daunting health care challenges. The incidence and costs of preventable and manageable chronic diseases like diabetes and asthma are growing. The medical needs of our rapidly aging population are unprecedented. And we face extremely complex diseases like cancer and Alzheimer's disease.

Each of these alone represents an enormous challenge and, in combination, a threat to both individual health and to the U.S. economy. To overcome these challenges we will need many innovative solutions, and research in the biopharmaceutical sector offers an important part of the answer.

Biopharmaceutical research is an engine of progress in the fight against disease and in building a stronger economy. More importantly, drug discovery offers patients around the globe real hope — hope that a once-deadly disease may be prevented, treated, and even cured, hope that a patient may stop being a patient and live a longer, healthier life.

Researchers continue to work toward these goals in spite of many barriers. The science and technology of drug development are increasingly complex, and the length and cost of research and development have continued to grow. Regulatory and business environments add uncertainty to the process.

Still, researchers in our industry are inspired to improve life for patients. This is why biopharmaceutical research companies invested an estimated $48.5 billion in new R&D in 2012 — the largest R&D investment of any sector in the U.S. economy. PhRMA members invest in order to realize the promise of incredible advances in our understanding of basic biology; to help solve the puzzle of cancers and rare diseases; and to help reduce the cost and health burden of disease.

I am pleased to present the ***2013 Biopharmaceutical Research Industry Profile***, which lays out both the challenges we face and the progress we have made. I am proud of the story it tells of a sector striving to achieve the hope we all share for a longer life and a healthier future.

John J. Castellani
President and Chief Executive Officer
Pharmaceutical Research and Manufacturers of America

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Committed to Patients, Health, and the Economy

New medicines have been an important part of transforming many diseases in recent years. They are putting rheumatoid arthritis into remission, greatly increasing the chances of survival for children with cancer, curing hepatitis in many patients, and reducing hospitalizations for HIV patients.

The biopharmaceutical industry is a dynamic, knowledge-driven sector. The work of its researchers brings hope to millions of patients and benefits to local and national economies. Biopharmaceutical companies invest heavily in research and development; in the past year, Pharmaceutical Research and Manufacturers of America (PhRMA) members surpassed the $500 billion mark in research and development (R&D) spending since 2000.

Developing a new medicine is challenging and the chances of success are extremely low, particularly in recent years. The 44 new medicines approved by the U.S. Food and Drug Administration (FDA) in 2012 represented the highest total in 15 years, a proud landmark for an industry whose mission is to save and improve lives.

In addition to their health benefits, medicines are an important part of the solution to rising health care costs through their role in reducing the need for hospital stays, surgeries, and

other costly interventions. The biopharmaceutical sector also supports hundreds of thousands of high-quality, well-paying jobs in the United States that contribute significantly to the health of our communities and the nation's economy.

The *2013 Biopharmaceutical Research Industry Profile* provides an overview of the essential contributions the industry makes to the lives and health of people and to the U.S. economy. Chapter 1 examines the enormous value of medicines developed by biopharmaceutical companies for patients around the world. Chapter 2 discusses the role that prescription medicines play in improving the quality and value of health care, and in controlling its cost. Chapter 3 describes the impact of the biopharmaceutical industry on local, state, and the national economies. Chapter 4 captures the R&D process that brings us new medicines. Chapter 5 reflects on our growing knowledge of disease, which is providing the most promising platform ever for developing new medicines and new ways to save lives. And Chapter 6 looks ahead at the hurdles facing the sector and how biopharmaceutical companies are meeting those challenges.

1 Impacting Patients

Impacting Patients

New medicines save and improve lives every day. For patients, new medicines can mean getting back to work, avoiding doctors visits and surgeries, feeling better, and living longer.

In recent years, we have seen accelerated progress in the fight against many diseases as a result of biopharmaceutical innovation. In 2012, the U.S. Food and Drug Administration (FDA) approved 44 new medicines[1,2] — the largest number in 15 years.[3] Of those, 39 were approved by the Center for Drug Evaluation and Research and 5 by the Center for Biologics Evaluation and Research.

Novel therapies were approved in a wide variety of disease areas, including:[4]

- **Cystic Fibrosis:** The first therapy that targets the underlying cause of cystic fibrosis. This personalized medicine treats a subset of patients with a specific mutation.[5]
- **Skin Cancer:** The first medicine approved for treatment of metastatic basal cell carcinoma, the most common form of skin cancer.[6]

- **Tuberculosis:** The first new tuberculosis medicine in 40 years, which will be used in combination with other medicines to treat multi-drug resistant tuberculosis infection.[7]
- **Leukemia:** Three new therapies that treat chronic myelogenous leukemia, a rare blood and bone marrow disease.[8]
- **Cushing's Disease:** Two new medicines to treat Cushing's disease, a rare disease that affects the pituitary gland causing a host of problems throughout the body. One medicine treats patients with endogenous Cushing's syndrome and the other is the first medicine that addresses the underlying mechanism of the disease.[9,10]
- **Respiratory Distress Syndrome:** A new medicine to treat respiratory distress syndrome in premature infants.[11]

> *These accomplishments could not have been achieved without the innovations of the biopharmaceutical industry and the dedication and skill of FDA's drug review staff.*[12]
>
> ► Food and Drug Administration on 2012 approvals

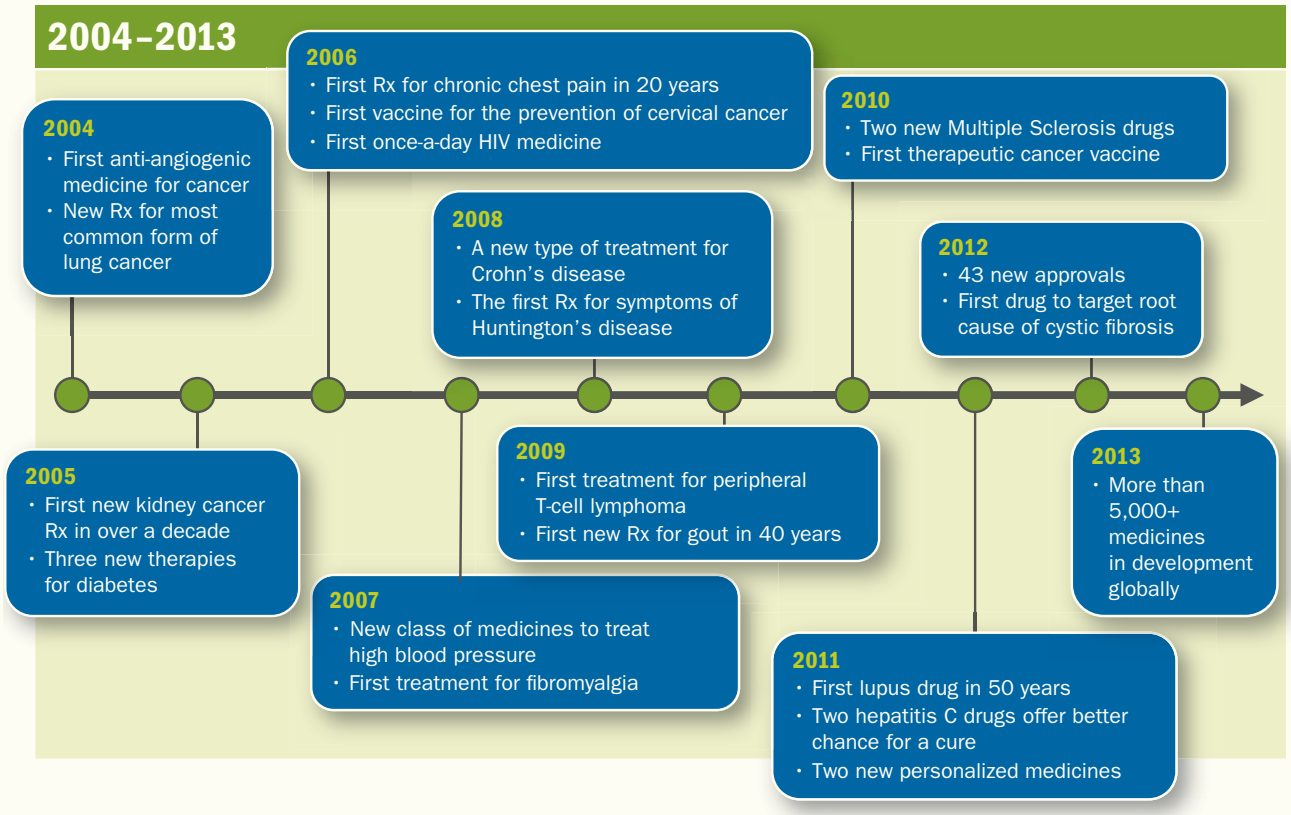
Fighting Rare Diseases

This year marks the 30th anniversary of the enactment of the Orphan Drug Act, which was pivotal in creating incentives for the development of new treatments for rare diseases. The Act transformed the landscape of drug development for rare diseases: more than 400 medicines have been approved to treat rare diseases since 1983, compared with fewer than 10 in the 1970s.[13,14]

Researchers have made tremendous progress against rare diseases in recent years. In fact, the FDA notes that approximately one-third of all new medicines approved in the last 5 years have been designated as "orphan drugs" — the term used for medicines that treat rare diseases affecting fewer than 200,000 patients in the United States.[15] In 2012, 13 orphan drugs were approved by the FDA.[16]

Although each of the nearly 7,000 rare conditions affects a small number of people, their impact on public health is anything but small; rare diseases overall affect more than 30 million Americans.[17] Because 85% to 90% of rare diseases are serious or life threatening, bringing new medicines to patients is especially important.[18] (See Chapter 5, page 46 for information about treatments currently in development for rare diseases.)

Figure 1: A Decade of Innovation—Selected Advances



SOURCES: U.S. Food and Drug Administration. Available at www.fda.gov (accessed February 2013); Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

Progress Against Disease

Medicines improve patients' lives in many different ways. Appropriate use of medications can have a huge impact on the health and well-being of patients and their caregivers by extending life, halting or slowing disease progression, minimizing complications, improving quality of life, preventing hospitalizations and surgeries, preventing disease, and reducing side effects. Following are just a few specific examples of the positive impact therapies have had on patient care.

Extending Lives

Childhood Cancers: The chance of survival for children with cancer has greatly improved in recent years. The 5-year relative survival rate increased from 58% in the mid-1970s to 83% in the most recent time period (2002–2008) — a 25 percentage point increase.[19] (See Figure 2.) The American Cancer Society noted that "survival for all invasive childhood cancers combined has improved markedly over the past 30 years due to new and improved treatments."[20]

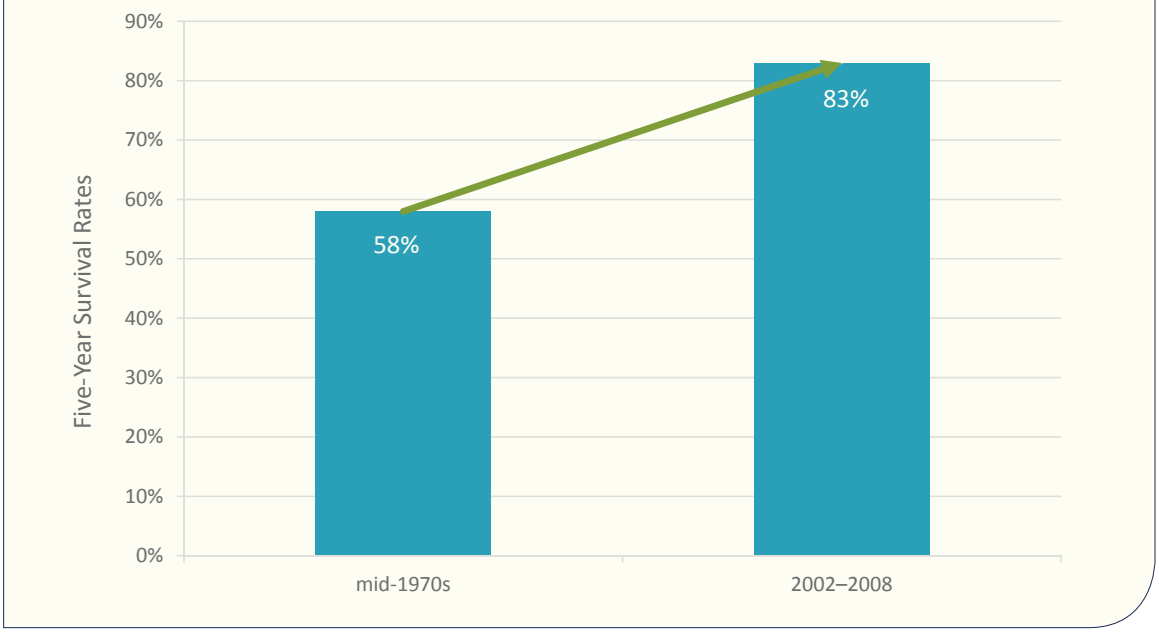
Slowing and Preventing Disease Progression

Cardiovascular Disease: Despite rising obesity levels, Americans have reached a milestone in controlling high cholesterol. The U.S. Centers for Disease Control and Prevention (CDC) reported in 2007 that U.S. adults reached an average cholesterol level in the ideal range (below 200) for the first time in 50 years.[21] (See Figure 3.) Authors of the report attribute the drop to the increased use of cholesterol-lowering medicines in the over-60 population.[22]

Hepatitis C: This viral disease, which affects 3.2 million people in the United States, attacks the liver leading to many complications, including cirrhosis, liver transplants, liver cancer, and death.[23] Sustained virologic response rates improved from 10% in the 1990s to 80% today among hepatitis C patients.[24] Sustained virologic response, defined as the suppression of the virus below detectable levels for 24 weeks after treatment, rose as understanding of the disease grew and treatment moved to today's triple therapy regimens, which include recently approved "direct acting antivirals."[25]

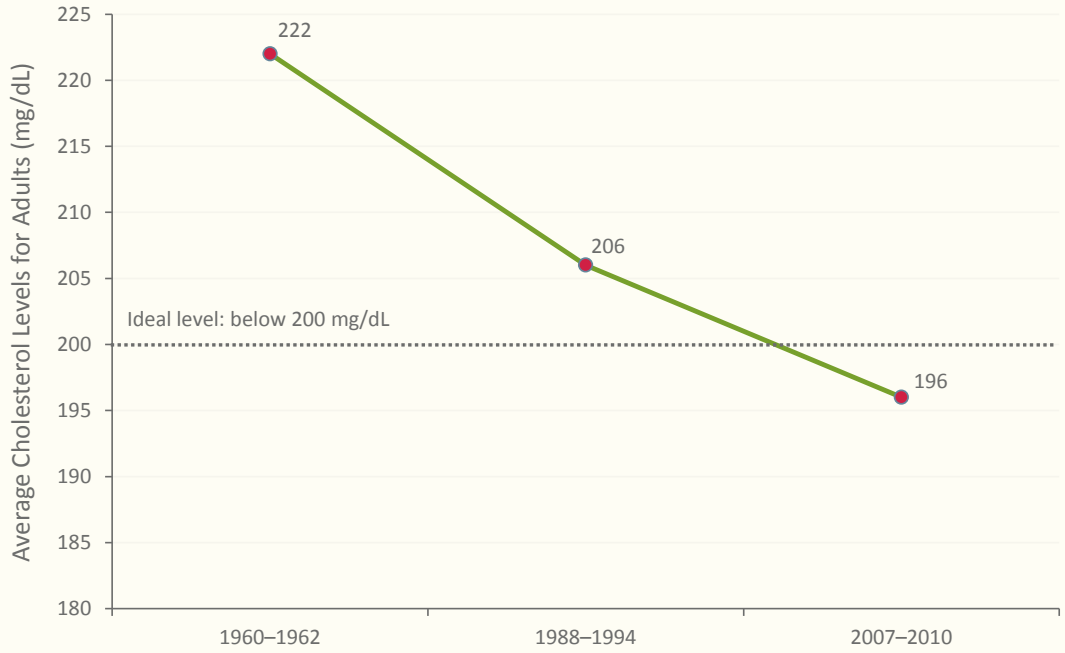
> *We are living in very exciting times. While years ago there were no specific therapies for liver diseases, we now have many different therapies for patients with different types of liver disease and at different stages of disease. One of the most exciting areas is the therapy of hepatitis C, one of the main causes of liver disease in the world.*[26]
>
> ► Guadalupe Garcia-Tsao, M.D., President, American Association for the Study of Liver Diseases

Figure 2: Survival Rates for Childhood Cancers Have Increased 25 Percentage Points over the Last Several Decades



SOURCE: American Cancer Society. "Cancer Facts & Figures, 2013." Atlanta, GA: American Cancer Society, 2013. Available at www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf (accessed February 2013).

Figure 3: In 2007, the Average Cholesterol Level for Adults Reached the Ideal Range, Below 200 mg/dL



SOURCES: S.E. Schober, et al. "High Serum Total Cholesterol—an Indicator for Monitoring Cholesterol Lowering Efforts: U.S. Adults, 2005–2006." *NCHS Data Brief* 2007; 2: 1–8. Hyattsville, MD: National Center for Health Statistics; M.D. Carroll, et al. "Trends in Lipids and Lipoproteins in U.S. Adults, 1988–2010." *JAMA* 2012; 308(15): 1545–1554.

> ***Protein enzymes, receptors, or channels identified by the pharmaceutical industry as 'drugable targets' have led to striking, remarkable, and repeated achievement.***[27]
>
> ► Drs. Myron Weisfeldt and Susan Zieman, Johns Hopkins University, "Advances in the Prevention and Treatment of Cardiovascular Disease," *Health Affairs*, 2007

Preventing Hospitalizations

HIV/AIDS: Since anti-retroviral treatments became available in the mid-1990s, survival rates for HIV patients have grown rapidly, increasing the number of people living with the disease between 1996 and 2000 by 28%. Despite this increase in survival, hospitalization rates fell by 32% in this period.[28] In more recent years, hospitalization rates have continued to fall. Between 2002 and 2007, the hospitalization rate fell from 35 per 100 HIV patients to 27 per 100 patients, a 23% drop.[29]

Diabetes: Over the last several years, many innovative medications for the treatment of diabetes have emerged, giving patients important tools for managing their disease. A recent study found that emergency room visits of patients who took their diabetes medicines as directed were 46% lower than for patients who took their medicines less than 50% of the time. Similarly, the hospitalization rate and the number of days spent in the hospital were 23% and 24% lower, respectively, for adherent patients.[30]

Check out an infographic on the impact of innovation and adherence in improving the lives of diabetes patients.

Scan QR code ▼

HIV/AIDS

THEN... "In the early years of the AIDS epidemic before ART (anti-retroviral treatment) was available, the median survival after an AIDS diagnosis was measured in weeks to months and patient care was confined to diagnosing and treating a complex array of opportunistic infections and AIDS-related types of cancer..."

NOW... "In stark contrast to the early and mid-1980s, if a person aged 20 years is newly infected with HIV today and guideline recommended therapy is initiated, researchers can predict by using mathematical modeling that this person will live at least an additional 50 years — that is, a close-to-normal life expectancy."[31]

► Drs. Carl W. Dieffenbach and Anthony S. Fauci, *Annals of Internal Medicine*, 2011

Learn about progress against HIV from an activist who has seen the disease go from acute and fatal to chronic and manageable.

Scan QR code ►

Improving Quality of Life

Rheumatoid Arthritis: Clinical remission is now possible for patients with severe rheumatoid arthritis (RA).[32] A recent study found that patients treated with combination therapy consisting of both a new and older medicine had a 50% chance of complete clinical remission after 52 weeks of treatment, compared with 28% for those taking only the older medicine. These results would have been "unthinkable" prior to new disease-modifying biological medicines.[33]

Rheumatoid Arthritis

THEN... "Previously the progression of RA from symptom onset to significant disability was often inevitable and, in some cases, rapid."

NOW... "With the availability of medications that can slow or halt disease progression and prevent irreversible joint damage, joint replacement surgery is not always the ultimate outcome and patients with RA may live comfortable and productive lives on medical therapy."[34]

► Drs. Katherine Upchurch and Jonathan Kay, University of Massachusetts Medical School

The Evolving Value of Medicines

Advances against disease like those illustrated above are not typically driven by large, dramatic developments, but more commonly result from a series of incremental gains in knowledge over time. New medicines build on one another step by step. In addition, the best clinical role and full value of a therapy typically emerges years after initial approval as further research is conducted and physicians gain real-world experience. Initial FDA approval often marks the starting point for this additional research, generating a larger body of evidence to help us understand the full value of the medicine and how best to treat patients.

This step-wise transformation in knowledge has led to increased survival, improved patient outcomes, and enhanced quality of life for many patients. In fact, in recent years we have seen the transformation of several diseases that were once thought of as acute and sometimes fatal to chronic, manageable conditions for patients who have access to medication.

Some forms of cancer provide a useful illustration of the different pathways by which our understanding of value can evolve:[35]

- **Use earlier in treatment line or disease state**
  For example: Trastuzumab (Herceptin®) received an additional indication for use as a potential first-line adjuvant therapy, 10 years after originally being approved as a second-line treatment for HER2+ metastatic breast cancer.

- **Use in combination with other therapeutics or biomarkers**
  For example: Subsequent studies of Cetuximab (Erbitux®) indicated that mutations of the KRAS gene could predict response to treatment for patients with a form of metastatic colorectal cancer, allowing for more targeted treatment.

- **Use in additional indications**
  For example: Docetaxel (Taxotere®) was initially approved for the treatment of non-small cell lung cancer, but continued research revealed a significant survival benefit in squamous cell carcinoma of the head and neck; initial evaluation based on early trial results would have substantially underestimated its impact on survival by more than 4.5 years.

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2 Improving the Quality and Value of Health Care

Improving the Quality and Value of Health Care

Improving the quality and value of health care — and controlling its costs — are imperatives for the health of Americans and for our economy. Prescription medicines play an important role in achieving both of those goals, especially in light of our aging population and the large number of people living with chronic conditions.

With optimal use, medicines can improve health outcomes and help to reduce the need for costly health care services, such as emergency room admissions, hospital stays, surgeries, and long-term care. Patients are healthier, and unnecessary medical expenditures are avoided.

As more Americans gain access to health care, it is important that they also have access to the medicines they need. Suboptimal use of prescription medications remains a challenge, and there is a large opportunity for patients and their health care providers to improve the quality and the efficiency of the health care system by improving the use of medicines.

Better Use of Medicines Improves Outcomes

For patients to receive the clinical benefits of medicines, several actions must occur:

- Appropriate and timely diagnosis and prescribing
- Prompt initiation of therapy
- Adherence to prescribed medicines (i.e., patients must take the medicines as prescribed at the right dose and right time)
- Periodic reviews and updates of the medication regimen

All of these dimensions are key to achieving better health outcomes, particularly for patients with chronic diseases. For example:

- **Preventing Hospitalizations:** Poor adherence to prescribed medicines is associated with increased hospitalizations, nursing home admissions, and physician visits.[1,2,3] For instance, research demonstrates that patients who did not consistently take their diabetes medicine were 2.5 times more likely to be hospitalized than were patients who took their medicine as directed more than 80% of the time.[4]
- **Preventing Disease:** Nonadherent patients were 7%, 13%, and 42% more likely to develop coronary heart disease, cerebrovascular disease, and chronic heart failure, respectively, over 3 years than were patients who took antihypertension medicine as directed.[5]
- **Preventing Adverse Events:** Providing counseling to patients to clarify their medication regimen following hospital discharge can dramatically reduce the likelihood of adverse drug events.[6]

Figure 4: Recommended Medicines Can Save Lives and Dramatically Improve Health

"...achieving effective blood pressure control would be approximately equivalent to eliminating all deaths from accidents, or from influenza and pneumonia combined."

—David Cutler, Ph.D., Harvard University

Annual Hospitalizations and Deaths Avoided through Use of Recommended Antihypertensive Medications

	Annual Hospitalizations Avoided	Annual Premature Deaths Avoided
Prevention Achieved: Based on Current Treatment Rates	833,000	86,000
Potential Additional Prevention: If Untreated Patients Received Recommended Medicines	420,000	89,000

SOURCE: D.M. Cutler, et al. "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation." *Health Affairs* 2007; 26(1): 97–110.

The Economic Value of Better Use of Medicines

Used appropriately, medicines also can generate positive economic outcomes across many common diseases. A wide range of studies have shown that improved use of recommended medications is associated with reduced total health care costs.[7] In fact, the link between use of prescription medicines and spending on other health care services was recently acknowledged by the Congressional Budget Office (CBO). In 2012, the CBO announced a change to its scoring methodology to reflect savings in medical spending associated with increased use of medicines in Medicare.[8] (For more on the value of better use of medicines in Medicare Part D, see sidebar on page 15.)

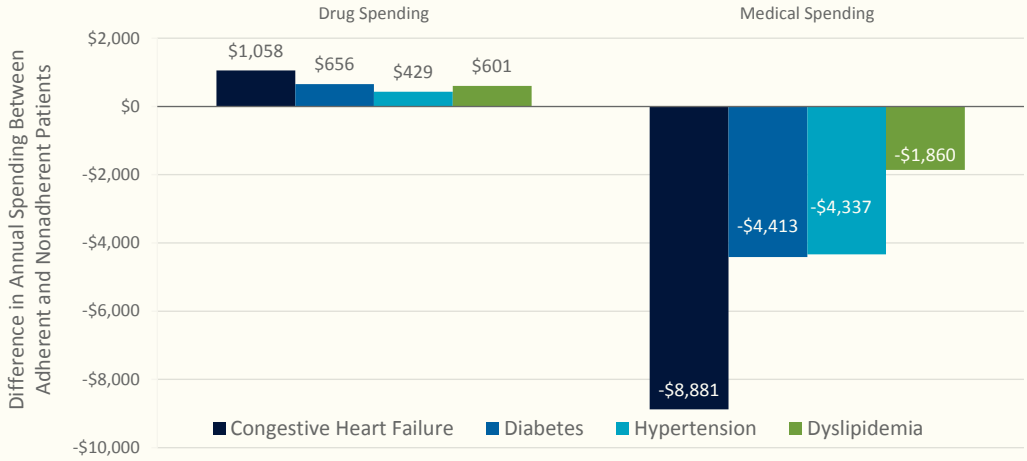
It is estimated that the cost of suboptimal medicine use including nonadherence, undertreatment, administration errors, and underdiagnosis is between $100 and $290 billion annually.[9,10]

Examples of the medical savings resulting from better use of medicine include:

- **High Blood Pressure:** Treating patients with high blood pressure in accordance with clinical guidelines would result in fewer strokes and heart attacks, preventing up to 89,000 deaths and 420,000 hospitalizations annually and saving $15.6 billion a year.[11] (See Figure 4.)
- **Diabetes:** Improving adherence to diabetes medicines would result in an estimated reduction of more than 1 million emergency room visits and hospitalizations annually, for potential savings of $8.3 billion each year.[12]
- **High Cholesterol:** Research has shown that statin therapy reduces low-density lipoprotein cholesterol levels by an average of 19%. Over one year, this reduction in bad cholesterol was associated with roughly 40,000 fewer deaths, 60,000 fewer hospitalizations for

Figure 5: Adherence to Medicines Lowers Total Health Spending for Chronically Ill Patients

Better use of medicines reduces use of avoidable medical care, resulting in reductions in medical spending.



SOURCE: M.C. Roebuck, et al. "Medical Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending." *Health Affairs* 2011; 30(1): 91–99.

heart attacks, and 22,000 fewer hospitalizations for strokes in the United States. From an economic perspective, those prevented hospitalizations translated into gross savings of nearly $5 billion.[13]

- **Chronic Conditions:** For conditions such as diabetes, dyslipidemia, hypertension, and congestive heart failure, patients who had better adherence to prescribed medicines experienced savings of $3 to $10 in non-drug spending for each additional dollar spent on prescriptions — a net savings of $1,200 to $7,800 per patient per year.[14] (See Figure 5.)

Another aspect of the economic impact of medicines is their potential to improve productivity in the workplace through reduced absenteeism or disability leave, which benefits both the individual patient and the economy as a whole. Several of the most common chronic conditions are estimated to cost the economy more than $1 trillion annually in lost productivity.[15] Examples of improved productivity include:

- **Rheumatoid Arthritis:** Researchers at the Integrated Benefits Institute found that high cost sharing for rheumatoid arthritis medications decreased adherence and led to increased incidence and longer duration of short-term disability leave. Researchers estimated that lowering patient copays would improve medication adherence, reducing lost productivity among workers with this disease by 26%.[16]
- **Chronic Conditions:** Research shows that workers diagnosed with diabetes, hypertension, dyslipidemia, asthma, or chronic obstructive pulmonary disease who are adherent to prescribed medicines were absent up to 7 fewer days from work and used 5 fewer days of short-term disability compared with nonadherent workers.[17]

Gaps in Optimal Use of Medicines

Poor use of medicines is a widespread challenge throughout the health care system. Because of the broad scope

Medicare Part D: Improving Seniors' Access to Medicine and Reducing the Cost of Care

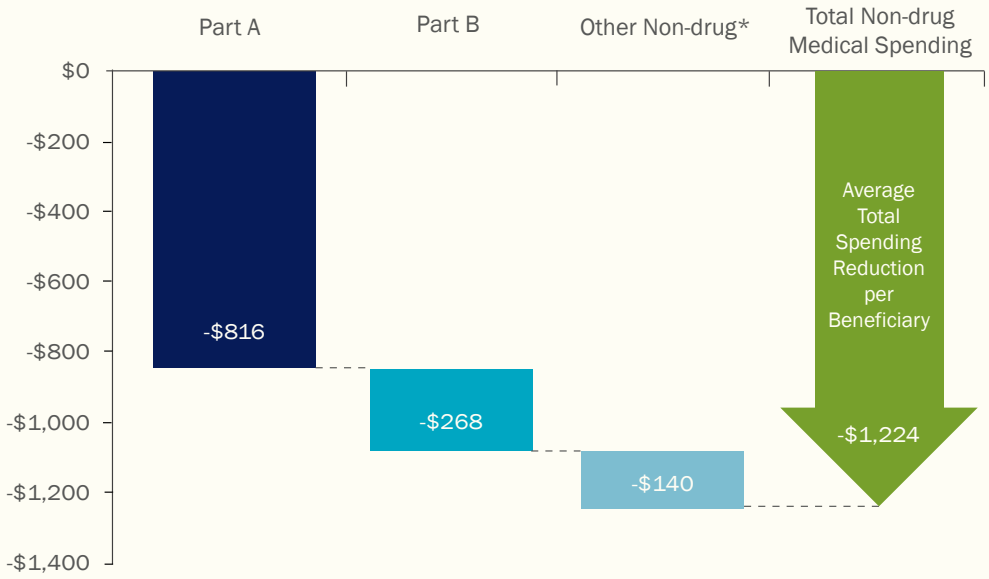
Passed into law in 2003, the Medicare prescription drug program (Part D) began in 2006. The program is working well and exceeding expectations. The current estimates for total spending over the first 10 years of the program are $346 billion lower than initial projections.[18] Additionally, health outcomes for seniors have improved, and beneficiary satisfaction is high.[19] Medicare Part D has improved access to needed medicines and reduced hospitalizations and use of other medical care.[20]

A 2011 study in the *Journal of the American Medical Association* found that for those with limited prior drug coverage who subsequently enrolled in Part D, there was an average savings of $1,200 per beneficiary in total non-drug medical costs in both 2006 and 2007.[21] (See Figure 6.) Better access to medicines through Medicare Part D also has led to declines in costly hospitalizations and skilled nursing care, which provides significant savings to the Medicare program.[22,23]

Today, 32 million people, or almost two-thirds of all Medicare beneficiaries, are enrolled in a Part D plan,[24] and the overwhelming majority of them rate their coverage highly. A recent survey reported that 96% of respondents were satisfied with their Medicare drug coverage, and 96% said their coverage worked well.[25] To learn more about the successes of Medicare's Part D program, visit www.phrma.org/issues/medicare.

Figure 6: Gaining Drug Coverage Reduced Other Medical Spending

The Medicare drug benefit increased access to medicines, reducing non-drug medical spending — an overall savings of $13.4 billion in 2007, the first full year of the program.

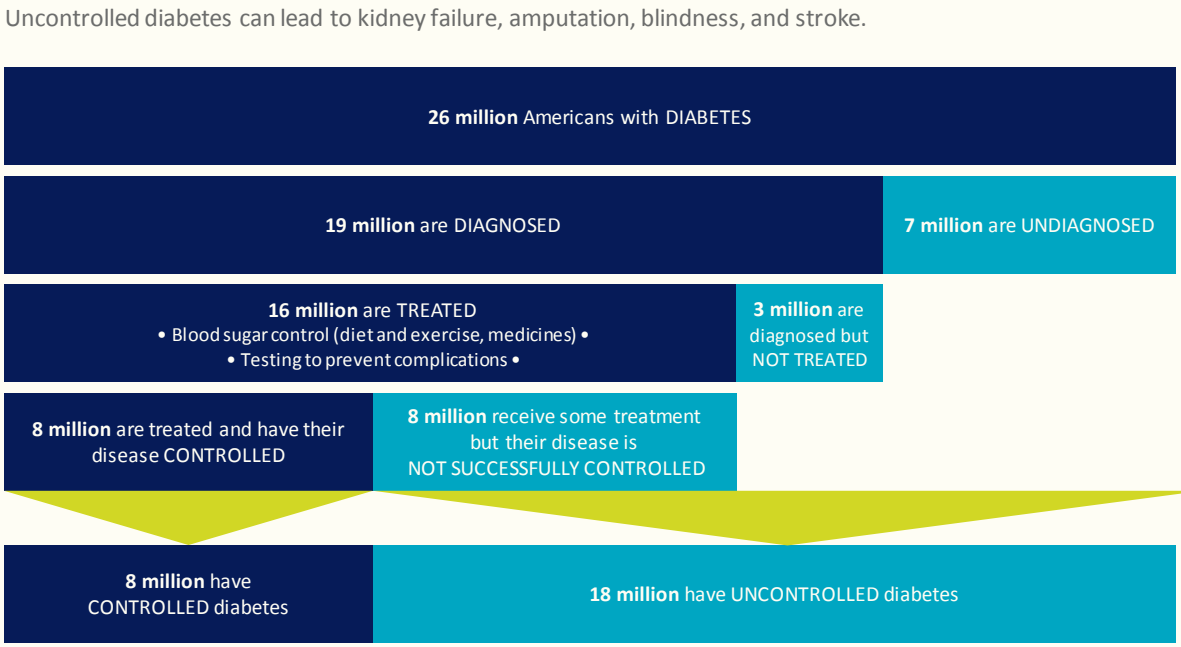


*Home health, durable medical equipment, hospice, and outpatient institutional services.

SOURCES: J.M. McWilliams, A.M. Zaslavsky, and H.A. Huskamp. "Implementation of Medicare Part D and Nondrug Medical Spending for Elderly Adults with Limited Prior Drug Coverage." *JAMA* 2011; 306(4): 402–409; C.C. Afendulis and M.E. Chernew. "State-level Impacts of Medicare Part D." *American Journal of Managed Care* 2011; 17 Suppl 12: S.

Find out more about the successes of Medicare's Part D Program.
Scan QR code ▶

Figure 7: Diabetes: An Example of Underdiagnosis and Undertreatment



SOURCES: U.S. Centers for Disease Control and Prevention (CDC). "National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011." Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf (accessed December 2012); IHS Global Insight Analysis of 2010 NHANES. Available at http://meps.ahrq.gov/mepsweb/ (accessed December 2012).

of the problem, there is a significant opportunity for improving patients' health and the efficiency of the health care system.

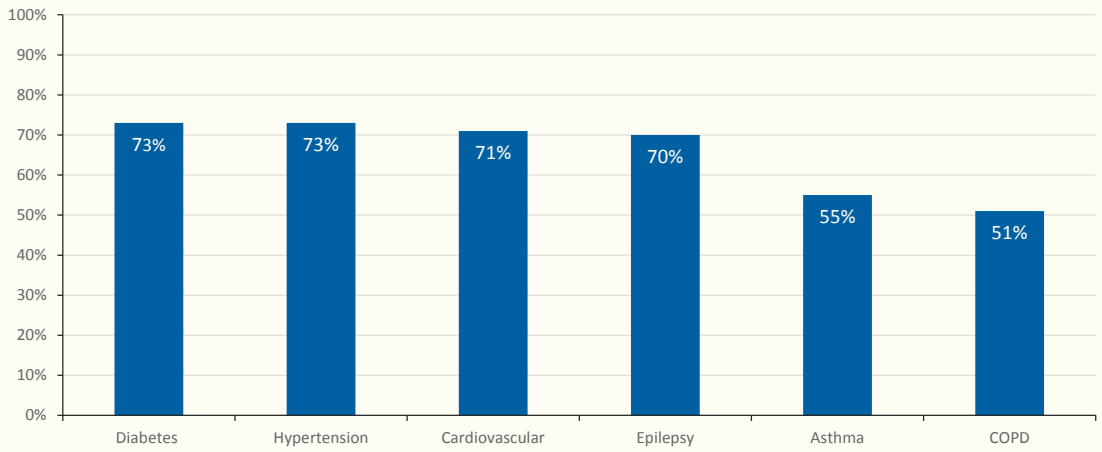
- More than 25% of newly written prescriptions, including those for high blood pressure, diabetes, and high cholesterol, are never brought to the pharmacy to be filled.[26]
- Approximately 50% of medications for chronic diseases are not taken as prescribed.[27]
- Among elderly patients, underuse of recommended medicines outweighs overuse by about 17 to 1.[28]
- A National Community Pharmacists Association poll showed that nearly 75% of adults do not follow their doctors' prescription orders, including not filling the prescription in the first place or taking less than the recommended dose.[29]

Patients do not follow their doctors' prescription recommendations for a wide variety of reasons. Patients may not believe that the treatment will help them or they may not adequately understand their illness and the need for treatment. Some patients may experience or fear potential side effects. Others suffer from cognitive or physical impairments that can reduce their adherence to medication regimens. Complex medication regimens, limited access to medicines, and poor relationships between prescribers and patients may also contribute to nonadherence.[30]

Improving Use of Medicines

Given the potential for better use of medicines, there are clear opportunities for various parts of the health care system to contribute to improvement. Employers, health plans, pharmacists, manufacturers, and other health care

Figure 8: Percentage of Doses Patients Take as Prescribed



SOURCE: A.J. Claxton, J. Cramer, and C. Pierce. "A Systematic Review of the Associations Between Dose Regimens and Medication Compliance." *Clinical Therapeutics* 2001; 23(8): 1296–1310.

stakeholders have taken on the challenge in differing ways. For example:

- To reduce their medical costs, employers and health plans are focusing on comprehensive medication management and decreasing cost sharing, which can pose a significant barrier to taking prescribed medicines.[31]
- Advances in information technology are enabling pharmacies to synchronize refills for patients who have multiple prescriptions to reduce the number of times a patient must go to the pharmacy. Some pharmacies now send out reminders to patients when they need to pick up a prescription and allow physicians to access their patients' medication fill histories to prevent drug interactions.
- The Centers for Medicare and Medicaid Services is tracking medication adherence rates for Part D Medicare Advantage and standalone prescription drug plans.
- Biopharmaceutical companies are continuing to develop innovative new therapies that make it easier for patients to take medicines by simplifying dosing regimens or reducing side effects.

There is no single solution to improving use of medicines. With diverse approaches, patients will gain more value from the medicines prescribed to keep them healthy.

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3 Supporting the Economy

Supporting the Economy

The biopharmaceutical industry continues to make major contributions to the U.S. economy. This sector generates high-quality jobs and powers economic output for the U.S. economy, serving as "the foundation upon which one of the United States' most dynamic innovation and business ecosystems is built."[1] The U.S. biopharmaceutical sector employs more than 810,000 workers, supports a total of nearly 3.4 million jobs across the country, and contributes nearly $790 billion in economic output on an annual basis when direct, indirect, and induced effects are considered.[2]

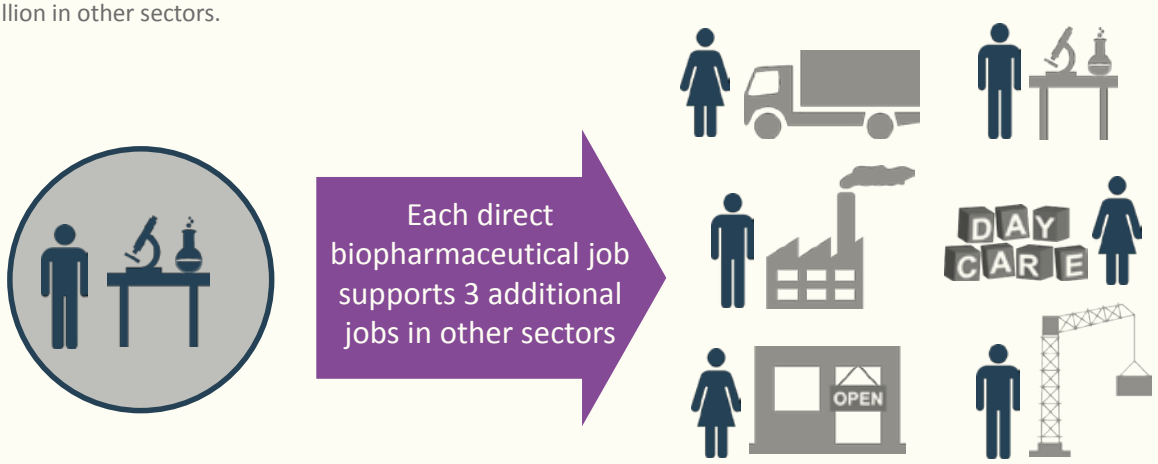
These economic impacts are driven by the industry's research and development (R&D) enterprise. (See Chapter 4 for more on investment in R&D.) The U.S. biopharmaceutical sector accounts for the single largest share of all U.S. business R&D, representing nearly 20% of all domestic R&D funded by U.S. businesses, according to data from the National Science Foundation.[3]

The high number of jobs that are supported indirectly reflects the fact that the industry is a "jobs multiplier," meaning that each biopharmaceutical sector job supports a total of four jobs throughout the economy. (See Figure 9 and sidebar, "Mapping the Impact.") The industry helps support a vibrant scientific and economic ecosystem that is vital to the U.S. economy and our country's competitiveness in the global market. Biopharmaceutical companies put down roots in communities across the country, helping to generate jobs across a whole range of sectors, from suppliers to retail to personal services.

The jobs the industry creates have high wages and require a workforce with diverse skills and educational levels, from Ph.D. scientists, to entry-level technicians, to support staff of all kinds.

Figure 9: The Ripple Effect of High-Value Biopharmaceutical Jobs

The biopharmaceutical sector supported nearly 3.4 million jobs across the economy in 2009, including about 3.3 million in other sectors.



Biopharma Jobs

More than 810,000 Jobs in the U.S. Biopharmaceutical Sector

Total Jobs Supported

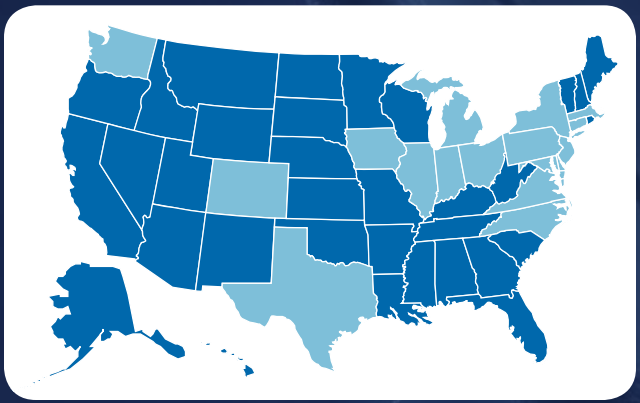
Nearly 3.4 million total U.S. Jobs Supported by the Biopharmaceutical Sector

SOURCE: Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013.

Mapping the Impact

In accomplishing the mission of bringing new medical treatments to the market, the biopharmaceutical industry sustains a very large-scale supply chain — both in R&D and in support of the production and distribution of biopharmaceutical products.

To provide insight into the breadth and depth of the industry's impact in the form of business relationships with vendors large and small, a recent analysis aggregated data from 17 innovative biopharmaceutical companies across 17 states. The analysis found that in 2011, these biopharmaceutical companies spent approximately $53 billion in transactions with vendors and suppliers in these states.[4] The recipient companies provided services and supplies to the industry. Although just a snapshot of the sector's total impact, these findings demonstrate the importance of a strong and vibrant biopharmaceutical industry in helping other businesses to grow and contribute to a strong local economy.



Vendor data from this analysis, broken down by congressional and state legislative district, can be viewed at www.weworkforhealth.org.

WEWORKFORHEALTH
WEWORKFORHEALTH.ORG

Science, technology, engineering, and mathematics (STEM) workers drive our nation's innovation and competitiveness by generating new ideas, new companies, and new industries. STEM workers play a key role in the sustained growth and stability of the U.S. economy and are critical components to helping the U.S. win the future.[5]

► U.S. Department of Commerce

In 2011, the more than 810,000 direct jobs generated $89.9 billion in total personal income—averaging $110,490 in wages and benefits per worker. This was twice the average U.S. private sector compensation of $54,455, an indication of the high-quality jobs the biopharmaceutical industry provides to U.S. workers.[6]

Boosting State and Regional Economies

Clinical trials are the most costly portion of the drug development process, usually accounting for 45% to 75% of the $1.2 billion average cost of developing a new medicine.[7] Trials on average last 7 years and represent a large investment into the communities where they are conducted. Biopharmaceutical companies collaborate with local research institutions across the country — including clinical research centers, university medical schools, hospitals, and foundations — to carry out clinical trials, providing patients access to potential new treatments as well as creating local jobs.

A PhRMA program called "Research in Your Backyard" helps to illustrate the impact trials have on communities around the country. Sixteen state reports developed by the program have been released, highlighting the biopharmaceutical economic impact on these communities through clinical trials. For example, in Washington State, job growth in the biopharmaceutical industry grew 12% from 2007 through 2011, compared with a 2% decline in jobs for all other industries.[8] Since 1999,

biopharmaceutical companies working with local research institutions have conducted, or are conducting:

- Nearly 3,500 clinical trials in Maryland, including 1,775 for six major chronic diseases (asthma, cancer, diabetes, heart disease, mental illness, and stroke)[9]
- More than 3,000 trials in Colorado, including 1,400 for major chronic diseases[10]
- More than 3,600 trials in Georgia, including 1,800 targeting major chronic diseases[11]
- More than 3,400 trials in Virginia, including more than 1,500 for major chronic diseases[12]

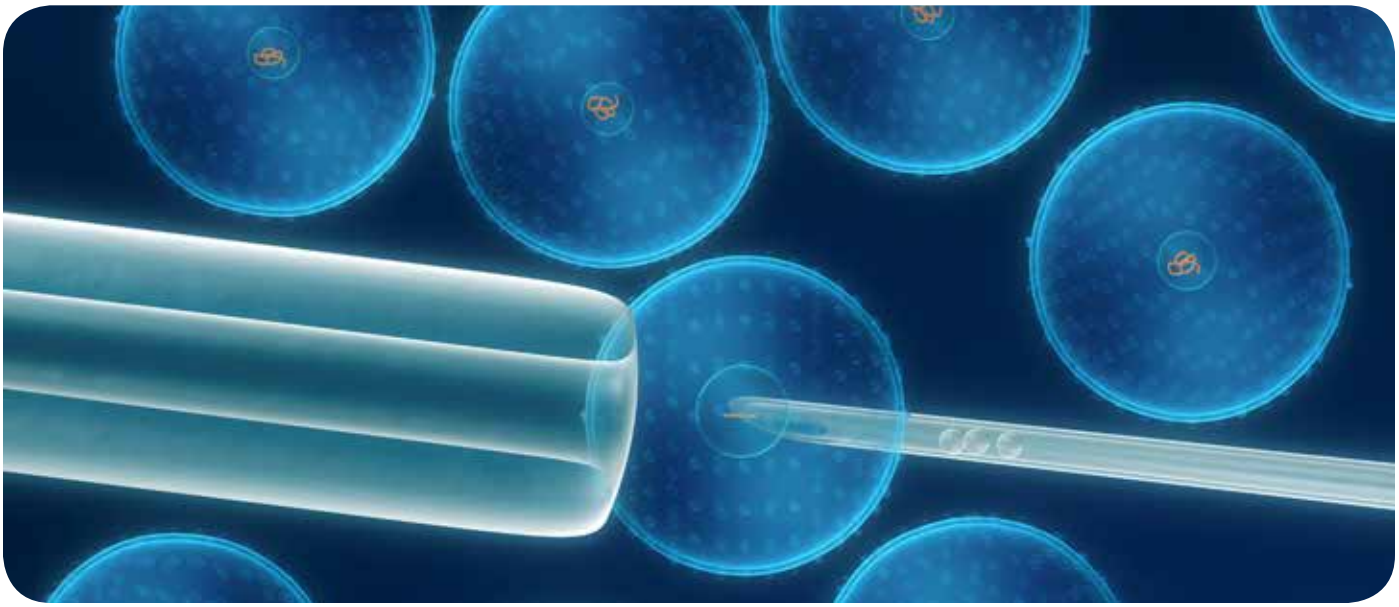
Although clinical trials provide an economic boost for communities, their primary benefit is to offer patients potential therapeutic options. Clinical trials may provide a new avenue of care for some chronic disease sufferers who are searching for the medicines that are best for them.

Ripple Effect of Industry R&D Support

Biopharmaceutical R&D continues to have a strong impact on the overall U.S. economy. PhRMA members have invested more than half a trillion dollars in R&D since 2000, including an estimated $48.5 billion in 2012 alone.[13] The impacts of this spending and the sector's broad support for biomedical research ripple across the economy.

Support for the R&D enterprise extends beyond the confines of any given company. In addition to supporting science, technology, engineering, and mathematics (STEM) education

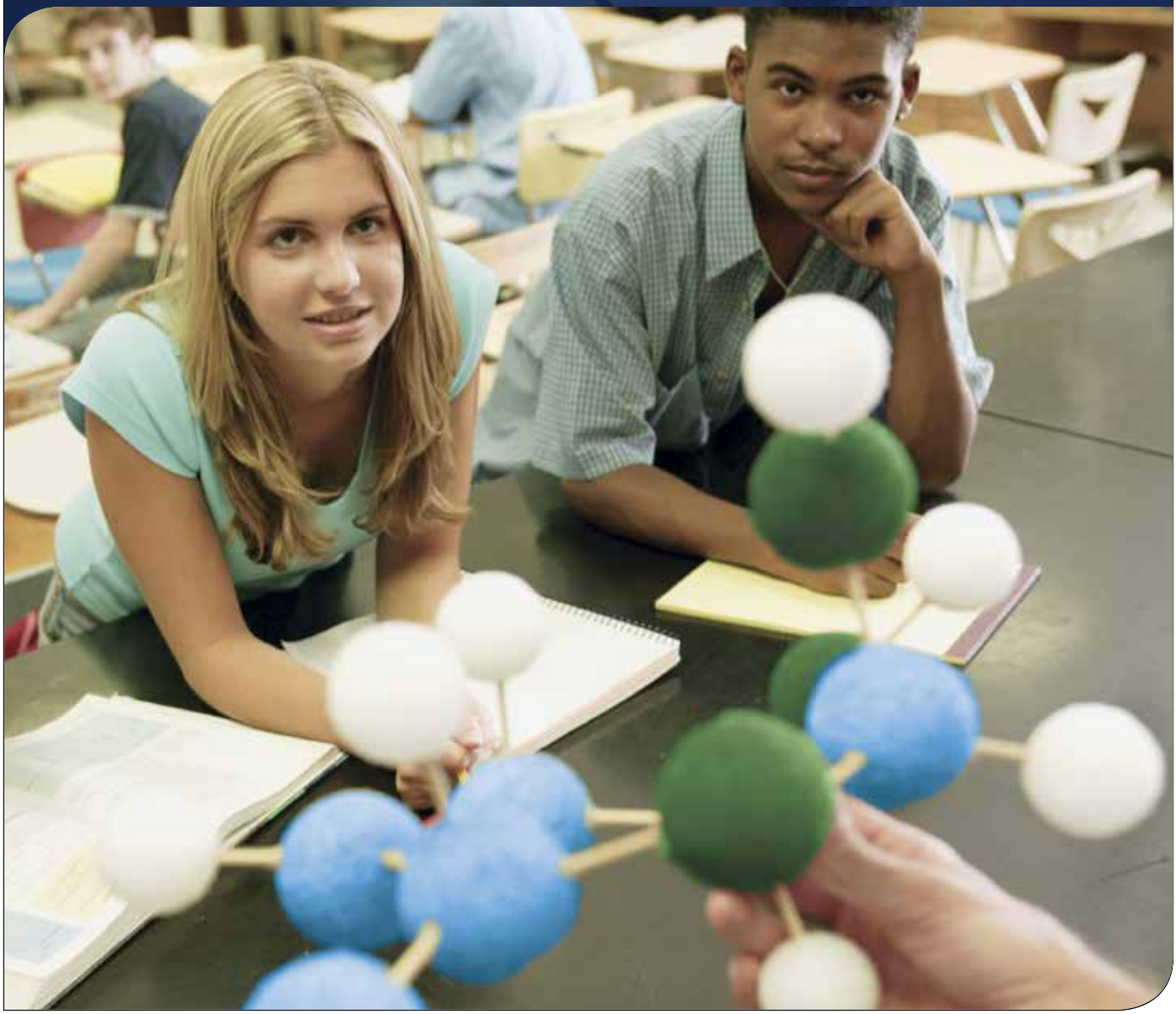
> *The STEM fields and those who work in them are critical engines of innovation and growth: according to one recent estimate, while only about five percent of the U.S. workforce is employed in STEM fields, the STEM workforce accounts for more than fifty percent of the nation's sustained economic growth.*[14]
>
> ► U.S. Department of Labor



STEM Jobs and Education: A Critical Focus for Today and Tomorrow

Science, technology, engineering, and mathematics (STEM) education is critical to continued U.S. global leadership. A workforce with strong STEM skills is essential to providing an adequate supply of workers with the skills necessary for the increasingly complex mission of developing 21st century medicines, and for the U.S. biopharmaceutical industry to maintain its competitive edge globally.

From 2001 to 2008, the biopharmaceutical industry outperformed other major STEM industries in generating jobs, and it is one of the few high-tech manufacturing sectors projected to add STEM-related jobs between 2010 and 2020.[15] However, many of these high-wage, high-value jobs may go unfilled if the United States continues to fall behind other countries in the quality of STEM education it provides its students. Improvements in this area would not only help the industry but also would benefit American workers as the average earnings for STEM workers are nearly twice as high as those of all workers, and STEM workers are also much less likely to experience joblessness.[16] Increasingly, biopharmaceutical companies are supporting STEM efforts around the country in many ways, including providing scholarships, mentoring students in local school districts, and funding and supporting teacher workshops and other professional development in STEM fields.



(see sidebar on page 24), innovative biopharmaceutical companies are engaged in a range of precompetitive research collaborations and partnerships with academic medical centers as well as increasingly supporting start-up and emerging companies through the establishment of corporate venture capital funds. These innovative collaborations not only help to ensure a robust future for the industry and the biopharmaceutical ecosystem, but benefit the larger national economy as well.

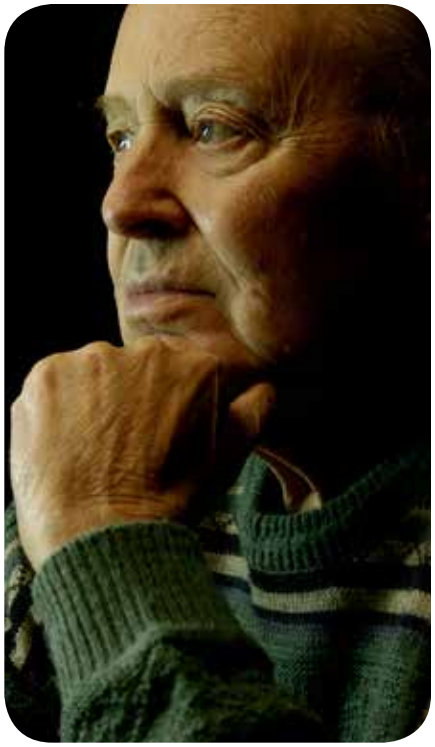
Partnerships Across Sectors

In recent years, biopharmaceutical companies have formed a growing number of partnerships with researchers in government, academia, smaller companies, and other parts of the biomedical ecosystem. The close and synergistic relationship between sectors in the biomedical research ecosystem is critical to ensuring a robust national biomedical research capacity in the United States.

The Tufts Center for the Study of Drug Development recently conducted an analysis of more than 3,000 partnerships of biopharmaceutical companies with academic medical centers (AMCs).[17] The analysis found that the partnerships benefit both industry and academia by providing opportunities for the sectors to work together to explore promising new technologies and address scientific problems that may lead to breakthroughs in treatments for the most challenging diseases and conditions. According to a report by PwC's Health Research Institute, "all large pharmaceutical companies have established at least one AMC partnership, often specific to a disease," and the number of partnerships is rising as the industry adopts a more collaborative approach to R&D.[18]

These relationships vary significantly and are continually evolving. Common partnership models include unrestricted research support, academic drug discovery centers, and precompetitive research centers, which incorporate a collaborative research model that brings together various institutions that ordinarily are commercial competitors to perform early-stage research collectively.

One prominent example of a precompetitive research collaboration is the Alzheimer's Disease Neuroimaging Initiative (ADNI), which includes federal agencies, nonprofit organizations, and industry members. The goal is to identify physical changes in the brain prior to the onset of Alzheimer's disease, track their progression, establish quality standards for imaging data collection and sharing, and validate biomarkers to be used in clinical trials.[19] Data collected from ADNI are made available at no cost to other researchers to analyze and use when designing Alzheimer's disease clinical trials and research projects.[20]



The industry is funding and working collaboratively with the academic component of the public sector on basic research that contributes broadly across the entire spectrum of biomedical R&D, not just for products in its portfolio.[21]

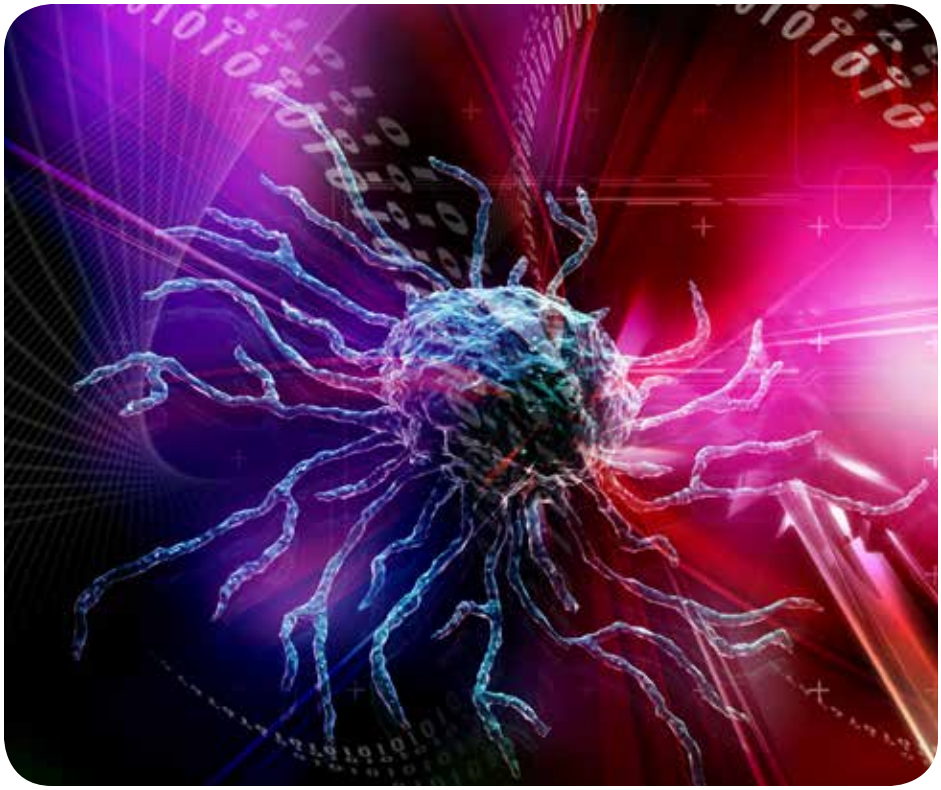
► Tufts Center for the Study of Drug Development, 2012

Corporate Venture Capital Investments

Venture capital (VC) and other forms of private capital are a key form of financing for start-up and emerging biopharmaceutical companies.

As traditional VC has recently declined due to several factors, including regulatory challenges and concerns about coverage and payment for new medical innovations, the corporate venture arms of established biopharmaceutical companies have become an increasingly important source of capital to help fill this gap. Between 2010 and 2012, biopharmaceutical corporate venture capital funds invested nearly $1.2 billion in biotechnology start-ups.[22] And corporate venture activity is on the rise. According to a recent report by the Boston Consulting Group, 63% of the 30 largest biopharmaceutical companies currently participate in corporate venture capital investments — up from 50% in 2007.[23]

> *Corporate venture funds may provide biotech startups with strategic benefits beyond investment capital. These include the opportunity to access technology, research knowledge and capacity, drug development expertise, marketing competence, and (often) a global presence ... Corporate venturing by multinational pharmaceutical and large biotech companies is playing an increasingly important role in financing the development of early stage innovation... and an essential role in the sustainability of the biotech ecosystem, advancing the future of pharmaceutical innovation and biotech entrepreneurship.*[24]
>
> ► Georg von Krogh, et al., *Nature Biotechnology*, 2012



Ensuring Access to Needed Medicines

The Partnership for Prescription Assistance

The biopharmaceutical industry has long provided access to medicines for patients who cannot afford them. The Partnership for Prescription Assistance (PPA) has helped nearly 8 million uninsured and financially struggling patients gain free and confidential access to 475 public and private patient assistance programs, including nearly 200 that are offered by pharmaceutical companies.[25] PPA member programs offer more than 2,500 brand-name medicines and generic drugs. More than 1,300 major national, state, and local organizations have joined the PPA, including the American Academy for Family Physicians, American Cancer Society, American College of Emergency Physicians, Easter Seals, National Association of Chain Drug Stores, United Way, and the Urban League.

Patients can learn about and apply to the PPA by visiting www.pparx.org or calling toll-free 1-888-4PPA-NOW. The call center can provide help in English, Spanish, and about 150 other languages.

Rx Response

Ensuring access to medicines following a major disaster is a critical priority for biopharmaceutical companies. In the aftermath of Hurricane Katrina, the industry realized that the absence of a single point of contact through which federal and state officials could reach the biopharmaceutical supply chain was a serious problem.

Rx Response is a unique collaborative initiative that brings together biopharmaceutical companies, distributors, and dispensers, along with the American Red Cross, to help ensure the continued flow of medicines following a major disaster. In the 6 years since its inception, Rx Response has become an indispensable homeland security and public health asset. In October 2012, Rx Response was activated to address threats to the supply chain posed by Super Storm Sandy.

Among its most valuable resources is the Pharmacy Status Reporting Tool, an online resource that maps the location of open pharmacies in disaster-stricken areas. For additional disaster planning resources and more information about Rx Response, visit RxResponse at www.rxresponse.org.

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[1]Battelle Technology Partnership Practice. "The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation." Columbus, OH: Battelle Memorial Institute, July 2011. Prepared for Pharmaceutical Research and Manufacturers of America.

[2]Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013. Note: The economic impact estimates developed by Battelle and presented here reflect several methodological refinements and thus are not directly comparable to previous estimates prepared for PhRMA. These estimates now more accurately capture the core functions of today's innovative biopharmaceutical industry and better capture headquarters' jobs.

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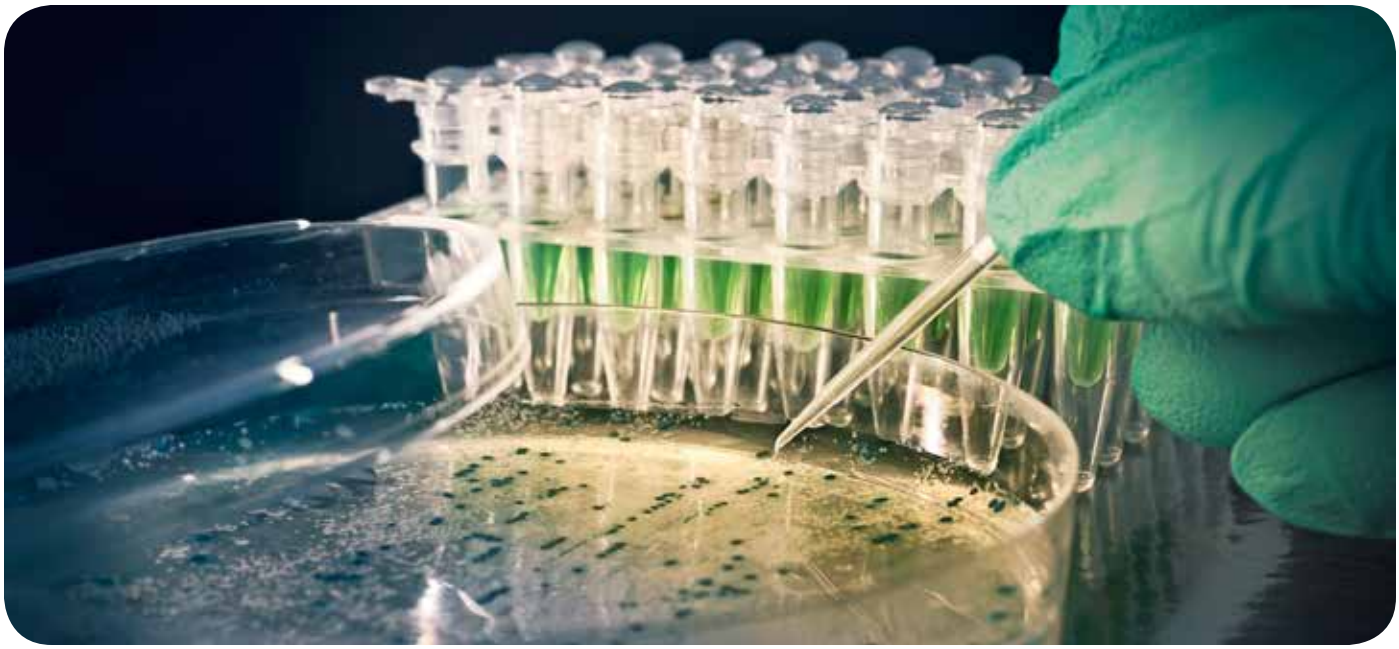
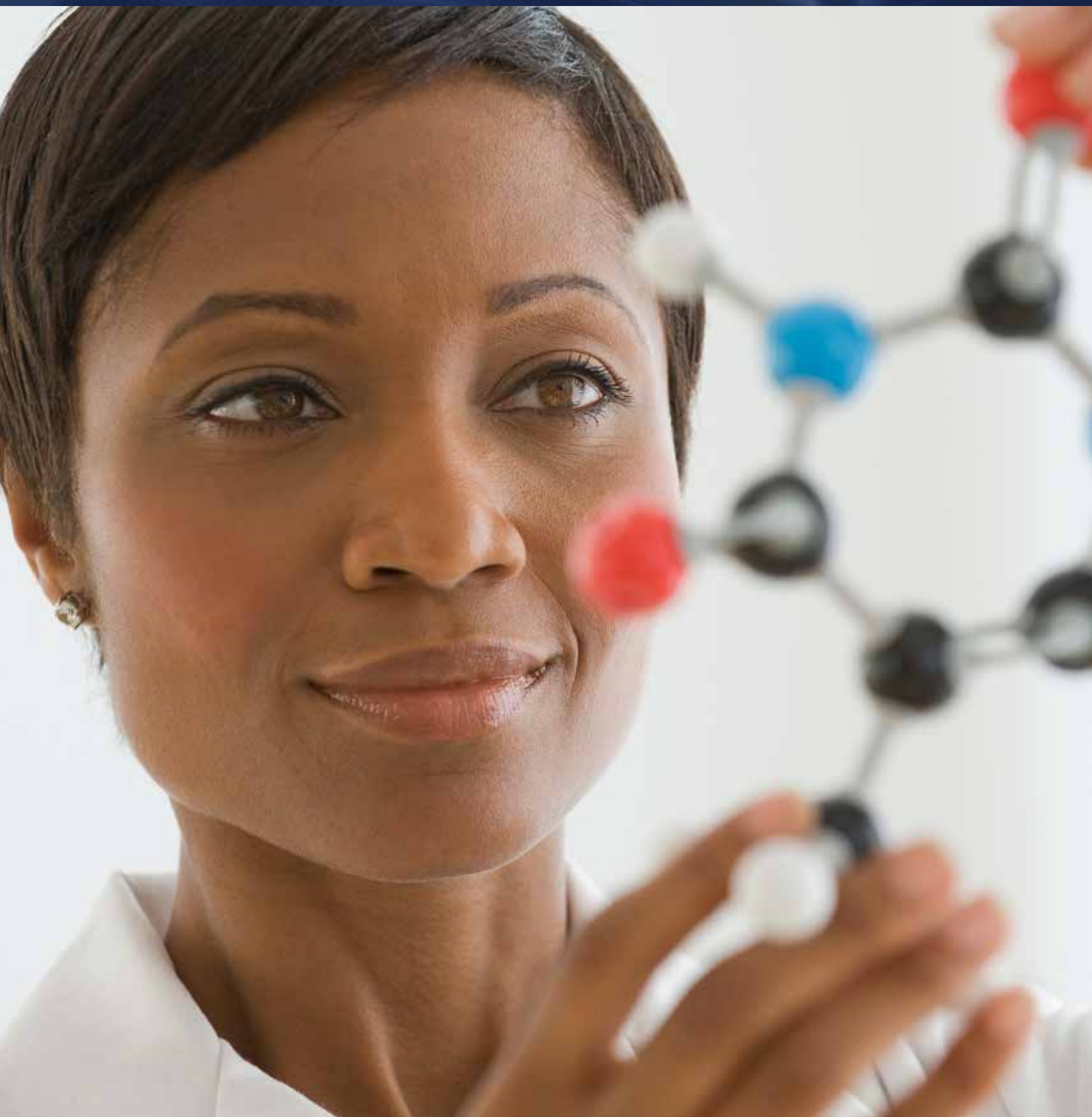


4 R&D: Delivering Innovation



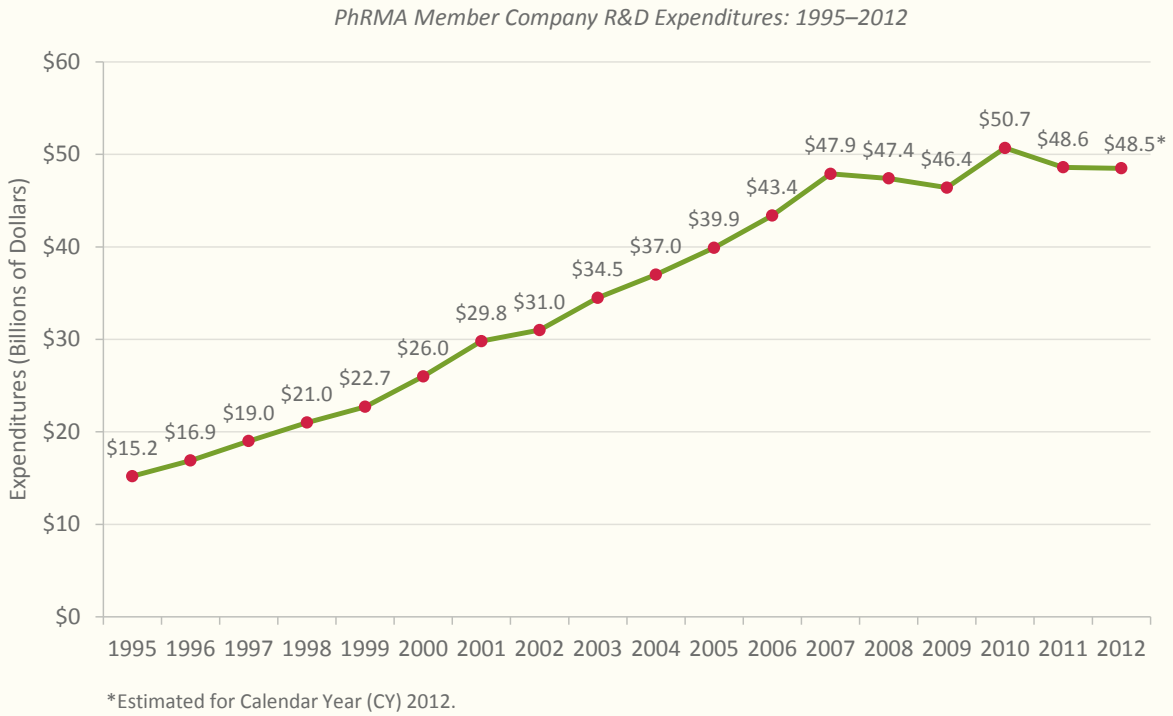
R&D: Delivering Innovation

Discovering and developing new medicines is a long, complex, and costly process, but biopharmaceutical researchers devote their careers to this often frustrating but tremendously gratifying task. The research and development (R&D) process is the road to new medicines — and more often than not it entails many turns, stops, and starts. Substantial progress typically occurs in increments over time, as advances build on each other.

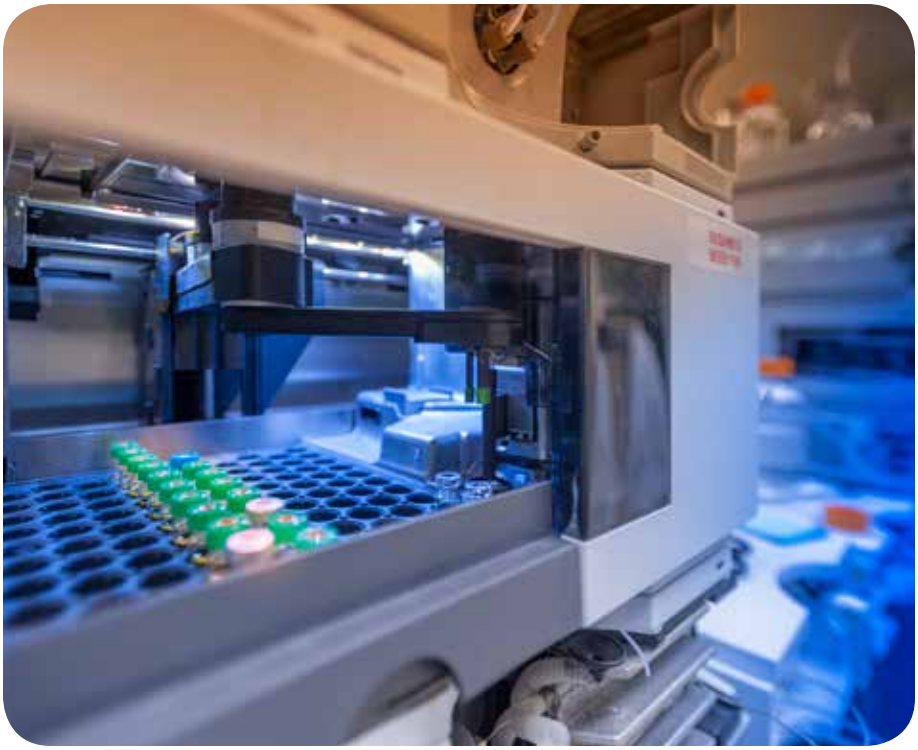
In 2012, Pharmaceutical Research and Manufacturers of America (PhRMA) member companies invested an estimated $48.5 billion in R&D.[1] This strong investment is part of the industry's ongoing commitment to innovation; since 2000, PhRMA members have spent more than half a trillion dollars on R&D.[2] PhRMA members' yearly investments represent the majority of all biopharmaceutical R&D spending in the United States.[3]

According to the Congressional Budget Office, "The pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest

Figure 10: Biopharmaceutical Companies Continue to Invest Strongly in R&D



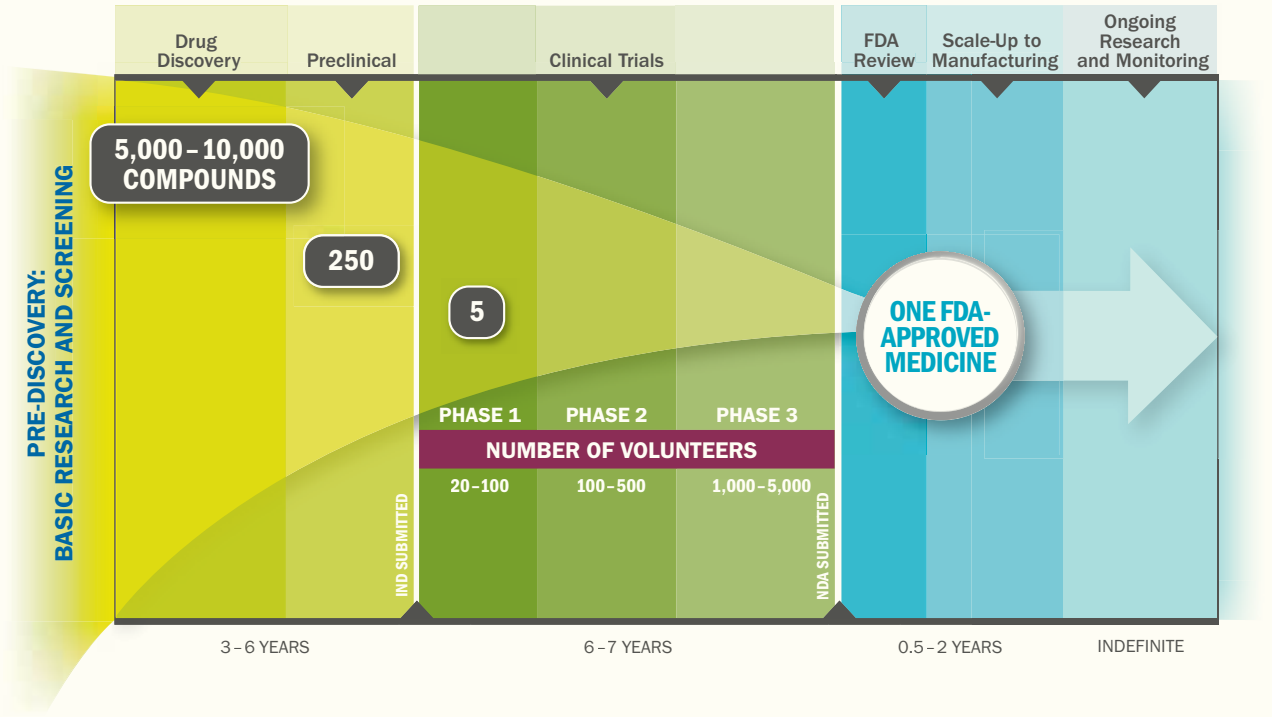
SOURCE: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 1996–2013.



as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm."[4]

Today, more than 5,000 medicines are in clinical trials globally or in U.S. Food and Drug Administration (FDA) review.[5] All of these have the potential to benefit U.S. patients, and each must undergo the same rigorous process to determine safety and efficacy for patient use. (For more information about the many innovative medicines in the pipeline, see Chapter 5.)

Figure 11: The Research and Development Process



Overview of the R&D Process

For those who do not work directly in drug development, the difficulty of the process can be hard to grasp. Numbers can help give a sense of the gauntlet of challenges each candidate medicine must pass through, and those numbers are daunting:

- On average, it takes about 10 to 15 years for a new medicine to complete the journey from initial discovery to the marketplace.[6,7,8]
- For every 5,000 to 10,000 compounds that enter the pipeline, only one receives approval. Even medicines that reach clinical trials have only a 16% chance of being approved.[9]
- The process is costly. The average R&D investment for each new medicine is $1.2 billion, including the cost of failures,[10] with more recent studies estimating the costs to be even higher.[11]

Each potential new medicine goes through a long series of steps on its way to patients. Figure 11 outlines this process.

Drug Discovery

The first step in developing a new medicine is to understand the disease or condition as thoroughly as possible. The entire biomedical research community contributes to this body of knowledge. In the United States, we are fortunate to have a have a dynamic, collaborative research ecosystem that includes researchers from government, industry, and academia.

From the earliest stages of basic research to drug approval, this collaborative ecosystem is among our greatest strengths in moving medical advances forward and making the United States the worldwide leader in biopharmaceutical innovation. (For more information on this ecosystem and these partnerships, see page 25 in Chapter 3 and Figure 12 below.)

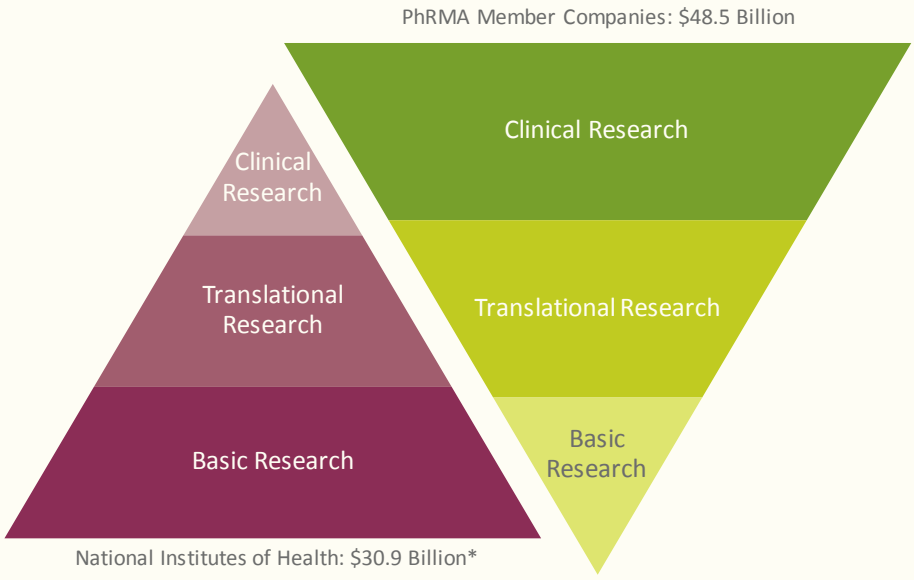
Basic research provides clues about how to treat diseases and potential ways to target the symptoms or underlying causes. Armed with an idea, researchers work to understand biological targets for a potential medicine. A drug target can be a protein, RNA, DNA, or other molecule that is somehow involved in the disease. The investigators conduct studies in cells, tissues, and animal models to determine whether the target can be influenced by a medicine.

Then researchers look for a lead compound — a promising molecule that could influence the target and, potentially, become a medicine. They do this in various ways, including creating a molecule from scratch, using high-throughput screening techniques to select a few promising possibilities from among thousands of potential candidates, finding compounds from nature, and using biotechnology to genetically engineer living systems to produce disease-fighting molecules.

Even at this early stage, investigators already are thinking about the final product. Issues such as the formulation (or "recipe") of a medicine and its delivery system (for example, whether it is taken in pill form, injected, or inhaled) are critical if a compound is to become a successful new medicine.

Figure 12: Government and Industry Roles in Research & Development

Government and biopharmaceutical industry research complement one another.



*NIH spending is for FY 2012. PhRMA member companies' spending is estimated for CY 2012. PhRMA member companies account for the majority of private biopharmaceutical R&D spending. Non-member company data are not included.

SOURCES: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013; National Institutes of Health (NIH), Office of Budget. "History of Congressional Appropriations, Fiscal Years 2000–2012." Bethesda, MD: NIH, 2012. http://officeofbudget.od.nih.gov/pdfs/FY12/Approp.%20History%20by%20IC)2012.pdf (accessed February 2013); Adapted from E. Zerhouni. "Transforming Health: NIH and the Promise of Research." Transforming Health: Fulfilling the Promise of Research. Washington, DC. November 2007. Keynote address. www.researchamerica.org/transforming_health_transcript (accessed January 2013).

Preclinical Testing

The drug discovery phase whittles down thousands of compounds to a few hundred promising possibilities that are ready for preclinical testing. In this stage, scientists conduct laboratory and animal studies to determine whether a compound is suitable for human testing. At the end of this process, which can take several years, around five compounds move to the next stage of testing in humans. The company files an Investigational New Drug Application with the FDA to begin clinical trials.

Clinical Trials

During this stage, a compound is tested in human volunteers. The clinical trials process occurs in several phases and takes on average 6 to 7 years. A potential medicine must successfully complete each phase before being submitted to the FDA for review.

Because this process involves both benefits and risks, companies take great care to protect the safety of trial participants and to ensure that they are thoroughly informed about the trial and its potential risks so that they can provide informed consent to participate, as required by federal regulations. Companies also ensure that the trials are conducted correctly and with integrity and that clinical trial results are disclosed at the appropriate time.

Clinical Trial Principles

PhRMA members have had a longstanding commitment to sponsoring clinical research that fully complies with all legal and regulatory requirements as well as international agreements. In addition, PhRMA has set out voluntary principles to fortify member companies' commitment to the highest standards for ethics and transparency in the conduct of clinical trials. PhRMA's *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* are designed to help ensure that clinical research conducted by America's pharmaceutical research and biotechnology companies continues to be carefully conducted and that meaningful medical research results are communicated to health care professionals and patients.

Learn more about PhRMA's *Principles on Conduct of Clinical Trials.*
Scan QR code ▶

The study design and the informed consent are reviewed, approved, and monitored by an Institutional Review Board (IRB). The IRB is made up of physicians, researchers, and members of the community. Its role is to make sure that the study is ethical and the rights and welfare of participants are protected. This includes ensuring that research risks are minimized and are reasonable in relation to any potential benefits.[12]

Following is a general description of the three primary phases of clinical research:

- **Phase 1** trials test a compound in a small group (e.g., 20 to 100) of healthy volunteers to determine the safety of the compound.
- **Phase 2** trials test the compound in a somewhat larger group (e.g., 100 to 500) of volunteers who have the disease or condition the compound is designed to treat. Phase 2 trials determine effectiveness of the compound, examine possible short-term side effects and risks, and identify optimal dose and schedule.
- **Phase 3** trials test the compound in a much larger group (e.g., 1,000 to 5,000) of participants to generate statistically significant information about safety and efficacy and to determine the overall benefit-risk ratio.

FDA Review and Approval

If the results of all three clinical trial phases indicate that the compound is safe and effective, the company submits a New Drug Application or Biologics License Application to the FDA. This application, which includes reams of data from all stages of testing, is a request for FDA approval to market the new medicine.

Scientists at the FDA carefully review all the data from all of the studies on the compound and, after weighing the benefits and risks of the potential medicine, decide whether to grant approval. Occasionally, the FDA will ask for additional research before granting approval or convene an independent expert panel to consider data presented by the FDA and the company. The panel will then advise the agency on whether to approve the application and under what conditions.

Manufacturing

Approved medicines may be used by millions of people or a small, specific population. Medicines often are in the marketplace for many years. As a result, manufacturing facilities must be carefully planned so that medicines can be consistently and efficiently produced.

Manufacturing facilities must be constructed to the highest standards to ensure that safety and quality are built into each step of the manufacturing process.[13] Companies must adhere to FDA's Good Manufacturing Practices regulations, and they also must constantly update, overhaul, or even rebuild facilities when new medicines are approved, as each new medicine is manufactured differently.

Drug Lifecycle

The R&D process is part of a larger prescription drug lifecycle. The cycle begins with the initial development of the medicine and it ends with generic drugs. Generics provide low-cost access to effective medicines for many years. But we would not have generics if innovator companies did not commit the time, resources, and investment to research and develop new, innovative medicines.

After FDA approval, the average effective patent life of a brand name medicine is about 12 years.[14] Competition often begins soon after approval, with generics frequently coming to the market even earlier through patent challenges, and other competing brand drugs commonly coming to market. During the period of patent protection, the medicine must earn enough revenue to fund the drug development pipeline for other candidates that may someday become new drugs. Only 2 of every 10 brand name medicines earn sufficient revenues to recoup average R&D costs.[15]

After patent protection expires, other companies are allowed to sell generic copies of the innovative drug. These medicines, which are often adopted rapidly, can be offered at low cost because the generic companies can base their approval on the extensive research already conducted to develop the brand name medicine. Today, we estimate that 84% of all drug prescriptions are filled generically,[16] yielding a savings of $1.1 trillion dollars in the past decade.[17] With the passage of the Affordable Care Act, an abbreviated approval pathway was created for biosimilars, which will further increase competition.

Post-Approval Research and Monitoring

Research on a new medicine does not end when the discovery and development phases are over and the product is on the market. On the contrary, companies conduct extensive post-approval research to monitor safety and long-term side effects in patients using the medicine. The FDA requires that companies monitor a medicine for as long as it stays on the market and submit periodic reports on safety issues. Companies must report any adverse events that occur from use of the medicine.

FDA sometimes requires companies to conduct phase 4 clinical trials, which evaluate long-term safety or effects in specific patient subgroups. Companies may conduct post-approval studies to assess the benefits of a medicine for different populations or in other disease areas. In some cases, they may also develop improved delivery systems or dosage forms.

This research phase is critical to improving researchers' and clinicians' understanding of a medicine's potential uses and its full benefits for health and quality of life. Continued research can show whether a medicine has a greater impact on an outcome when it is used earlier in a disease, in combination with other medicines, in different disease indications, or in combination with specific biomarkers (see the section "The Evolving Value of Medicines" in Chapter 1, page 9).

The Evolving R&D Process

As science advances and opens new doors, the R&D process continually changes and adapts. New scientific advances are bringing greater promise but also increasing complexity. Here are just a few examples of the forces that are changing the R&D process:

Working on the molecular level: In recent years, scientists' deepening understanding of the molecular and genetic underpinnings of disease has brought unprecedented opportunities and dramatically changed many aspects of drug development.

Figure 13: Increasing Complexity of Clinical Trials

During the last decade, clinical trial designs and procedures have become much more complex, demanding more staff time and effort, and discouraging patient enrollment and retention.

Trends in Clinical Trial Protocol Complexity

	2000–2003	2008–2011	Percentage Change
Total Procedures per Trial Protocol (median) (e.g., bloodwork, routine exams, x-rays, etc.)	105.9	166.6	57%
Total Investigative Site Work Burden (median units)	28.9	47.5	64%
Total Eligibility Criteria	31	46	58%
Clinical Trial Treatment Period (median days)*	140	175	25%
Number of Case Report Form Pages per Protocol (median)	55	171	227%

*These numbers reflect only the "treatment duration" of the protocol.

SOURCE: K.A. Getz, R.A. Campo, and K.I. Kaitin. "Variability in Protocol Design Complexity by Phase and Therapeutic Area." *Drug Information Journal* 2011; 45(4): 413–420. Updated data provided through correspondence with Tufts Center for the Study of Drug Development.

Researching more complex diseases: Increasingly, clinical investigators are exploring treatment options for more complex diseases such as neurological disorders, cancer, and many rare diseases. For example, in 2003 there were 26 medicines in development for Alzheimer's disease in the United States; today there are 94.[18,19] New scientific opportunities make these new avenues of exploration possible, but the complexities of these uncharted areas also can in some cases mean that research projects are less likely to succeed.

Advancing personalized medicine: With the emergence of personalized medicine — in which the use of a medicine is linked to a diagnostic to determine if a patient will respond well to a medicine — the R&D process has become more complex. Drug developers must coordinate research on a new medicine along with a corresponding diagnostic.

In this increasingly complicated research scheme, it is necessary to dig deeper into how each patient may respond to a therapy and to keep pace with expanding regulatory requirements. As a result of these changes, the burden of executing a clinical trial is growing, with more procedures required, more data collected, more numerous and complex eligibility criteria for study enrollment, and longer study duration.[20] (See Figure 13.) In fact, the form used to collect data from each patient expanded in length by 227% between 2000 and 2011, reflecting the growing challenges of conducting clinical trials.[21]

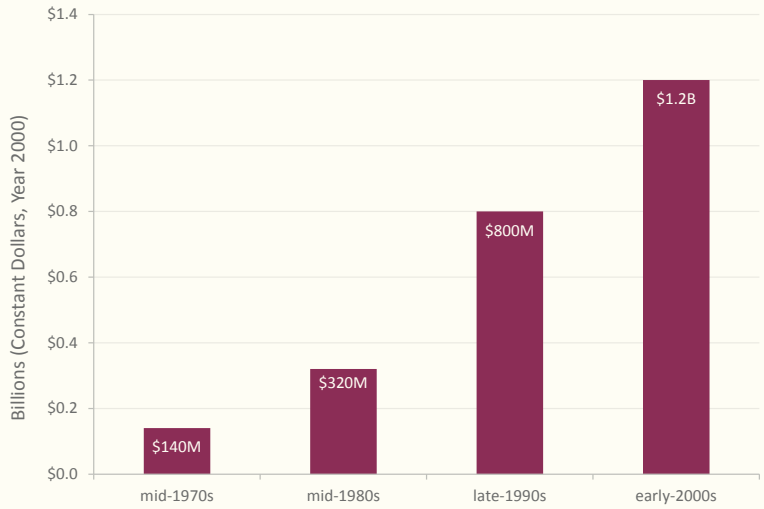
Recruitment of patient volunteers is also an ongoing and growing challenge for researchers. Difficulty recruiting volunteers extends the original timeline of phase 2 to 4 trials by nearly double on average across all therapeutic areas.[22]

The increased complexity of the research environment has contributed to the rising costs of clinical research.[23] Treatment failures and setbacks also contribute to the cost of research. According to the Tufts Center for the Study of Drug Development, the cost of developing a drug (including the cost of failures) grew from $800 million in

Figure 14: Average Cost to Develop One New Medicine

It costs an average of $1.2 billion to develop one new drug, with more recent studies estimating the costs to be even higher.

The Average Cost to Develop One New Approved Drug — Including the Cost of Failures



SOURCES: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185; J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479; More recent estimates range from $1.5 billion to more than $1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.
NOTE: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.

the late 1990s to about $1.2 billion in the early 2000s.[24] (See Figure 14.) Other more recent studies have put the total cost even higher.[25]

Adapting to Changes and Challenges

The biopharmaceutical industry is continually adapting to produce innovative treatments more efficiently. Researchers are exploring ways to reduce development times and increase the odds of success using new research tools, new approaches to patient recruitment, and sophisticated methods of analyzing data.

Companies are working to develop innovative partnerships and collaborative relationships with researchers in academia, government, and in other companies. Precompetitive partnerships, which seek to advance basic research, are a growing part of this approach.[26]

Improving the clinical trials process is another area of active exploration. For example, phase 0 or "microdosing" trials allow researchers to test a very small dose in fewer human volunteers to eliminate more quickly drug candidates that may be metabolically or biologically ineffective.

No one change will transform the R&D process on its own, but with many diverse efforts biopharmaceutical companies will continue to improve the process of innovation.

> ***Companies are developing "new approaches to designing and conducting global clinical trials, including simplifying protocols, maximizing investigative site performance, and reducing the number of protocol amendments."[27]***
>
> ► Tufts Center for the Study of Drug Development, 2011

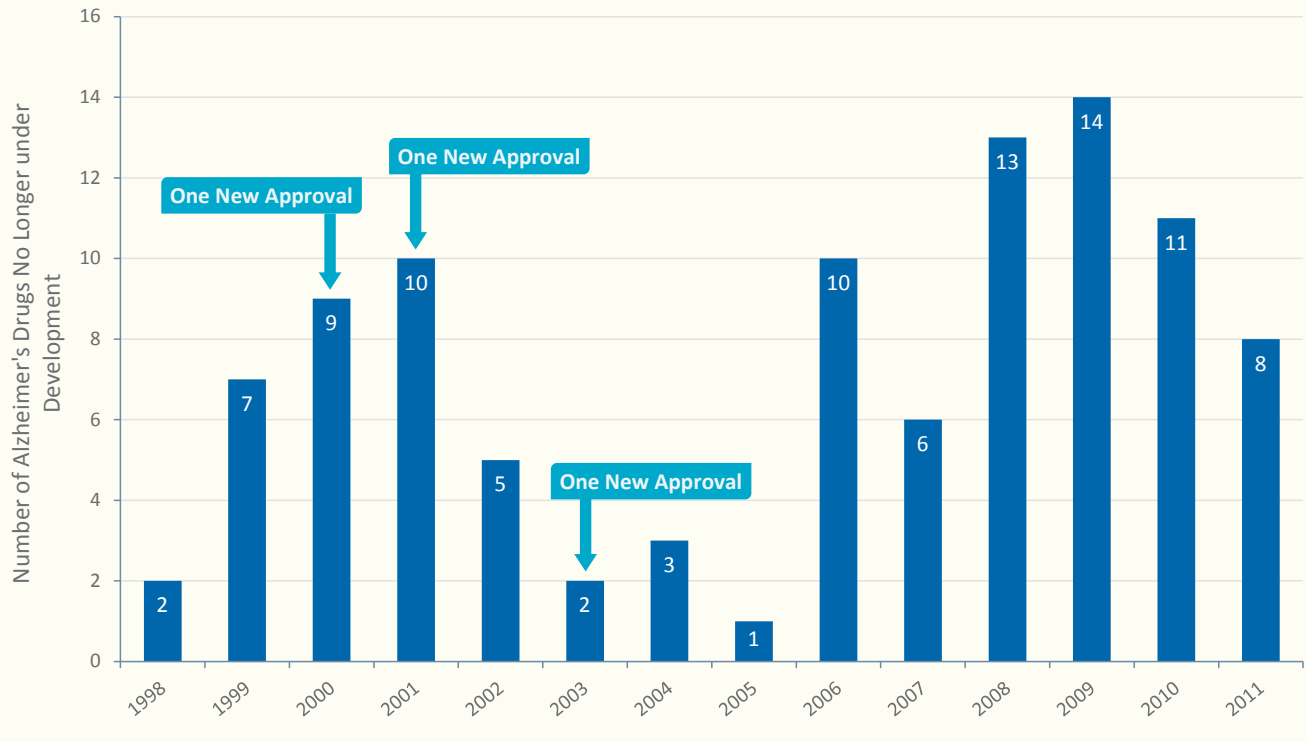
Learning from Setbacks in Alzheimer's Disease Research

Not only do successes build over time, but so do lessons learned from seemingly failed projects and research. Alzheimer's disease is commonly considered one of the most devastating conditions anyone can face and is the sixth leading cause of death in the United States.[28] The disease progressively robs people of their memory, their personality, and their health.[29] What's more, the Alzheimer's Association projects that the disease will cost the U.S. health care system $1.1 trillion annually by 2050.[30]

Today's medicines can address symptoms of Alzheimer's, but medicines that prevent or slow the disease are needed. Although researchers continue to discover and learn more, the underlying causes and mechanisms of this disease remain elusive, and the complex nature of the disease presents huge challenges to scientists.

Since 1998, biopharmaceutical companies have made 101 unsuccessful attempts to develop medicines to treat Alzheimer's while, in the same period, only three medicines have been approved. That means that for every success, companies have experienced 34 so-called "failures."[31] (See Figure 15.) Although these setbacks may be disheartening, they are certainly not failures because they contribute valuable knowledge about Alzheimer's that can be used as building blocks to point researchers in more fruitful directions.

Figure 15: Unsuccessful Alzheimer's Drugs in Development, 1998 – 2011
Total unsuccessful drugs=101



SOURCE: Pharmaceutical Research and Manufacturers of America. "Researching Alzheimer's Medicines: Setbacks and Stepping Stones." Washington, DC: PhRMA, September 2012. Available at http://phrma.org/sites/default/files/1864/alzheimersetbacksreportfinal912.pdf (accessed February 2013).

Understanding the Nature of Progress and Innovation

Occasionally one breakthrough will transform treatment of a disease, but most often discoveries and approvals build on each other over time in a cumulative process resulting in significant clinical advances. To progress from no treatments to effective treatments, the R&D process must be repeated over many years for many drugs, which build upon one another incrementally.

Research on individual medicines also accumulates over time. Although initial market approval by the FDA is a critical first step in ensuring a medicine is reaching patients, the approval often lays the foundation for additional learning and research that will shape the way a product is used in years to come. (See the section on the evolving value of medicines in Chapter 1, page 9.)

Recognizing the step-wise nature of innovation is essential to ensuring that progress continues.

> *Incremental advances can add up to transformative changes.*[32]
>
> ▶ Dr. Siddhartha Mukherjee, *The Emperor of All Maladies*, 2010

Recognizing Researchers and Patient Advocates for Alzheimer's Disease

In September 2012, PhRMA bestowed the first annual Research and Hope Award, honoring individuals and organizations in academia, the biopharmaceutical research sector, as well as the patient and caregiving communities that have contributed significantly to the advancement of medical progress and patient care for Alzheimer's. Information about the award recipients is available at www.phrma.org/awards.

Biopharmaceutical researchers are responding to this complex scientific challenge and are committed to finding treatments for Alzheimer's disease. There are nearly 100 new medicines in development in the United States.[33] As researchers examine the science and clinical data behind both the successes and the stumbling blocks, there is hope for a future in which this devastating disease can be managed successfully or even cured or prevented altogether.

Key Legislation in 2012 Fosters Innovation

In 1992, the Prescription Drug User Fee Act (PDUFA) authorized the FDA to collect user fees from the biopharmaceutical industry to hire additional drug reviewers and safety specialists. These funds supplement Congressional appropriations. In its first 20 years, PDUFA has helped to bring more than 1,500 new medicines to market. It also has increased FDA's staffing and resources and preserved and strengthened FDA's high safety standards, resulting in a drop in approval times for new medicines from 29 months in the early 1990s to an estimated 10 months in 2010.[34,35]

In 2012, the fifth authorization of PDUFA (called PDUFA-V) was enacted as part of the Food and Drug Administration Safety and Innovation Act. In addition to enabling more timely patient access to safe and effective new medicines, PDUFA-V promotes future research and prepares the FDA for a 21st century regulatory framework. It also supports the development of a framework to facilitate evaluations of the benefits and risks of new medicines (including orphan drugs) and integrates patient perspectives into the review process.

Congress also acted last year to make two provisions affecting pediatric research permanent. These provisions, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), work together to encourage pediatric research. The combination of BPCA and PREA, often referred to as the "carrot" and "stick" approach, has resulted in a wealth of useful information about administering drugs to children, including information on dosing, safety, and efficacy. Together, BPCA and PREA have driven research and greatly advanced American children's medical care. Making these two provisions permanent will help create a more predictable and efficient pediatric drug development process, resulting in continued progress to develop new medicines for children. BPCA and PREA already have resulted in significant accomplishments:

- As of December 2012, 193 drugs have received pediatric exclusivity under BPCA.[36,37]
- Following the reauthorization of BPCA and PREA in 2007 and through June 2012, 405 pediatric studies were completed, involving 174,273 patients.[38]
- Since 1998, BPCA and PREA have resulted in 463 labeling changes reflecting important pediatric information.[39]

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[10]J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479.

[11]More recent estimates range from $1.5 billion to more than $1.8 billion. See for exampleJ. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

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[21]*Ibid*.

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[23]M. Allison. "Reinventing Clinical Trials." *Nature Biotechnology* 2012; 30(1): 41–49.

[24]J.A. DiMasi and H.G. Grabowski, *Op. cit.*

[25]More recent estimates range from $1.5 billion to more than $1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

[26]C.P. Milne and A. Malins. "Academic-Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Boston, MA: Tufts Center for the Study of Drug Development, April 2012.

[27]Tufts Center for the Study of Drug Development. "Outlook 2011." Boston, MA: Tufts University, January 2011.

[28]Alzheimer's Association. "Alzheimer's Facts and Figures." Available at www.alz.org/alzheimers_disease_facts_and_figures.asp (accessed February 2013).

[29]Alzheimer's Association. "2012 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia* 2012; 8(2). Available at www.alz.org/downloads/facts_figures_2012.pdf (accessed February 2013).

[30]Alzheimer's Association. "Changing the Trajectory of Alzheimer's Disease: A National Imperative." Washington, DC: Alzheimer's Association, May 2010.

[31]Pharmaceutical Research and Manufacturers Association. "Researching Alzheimer's Medicines: Setbacks and Stepping Stones." Washington, DC: PhRMA, 2012.

[32]S. Mukherjee. *The Emperor of All Maladies: A Biography of Cancer*. New York, NY: Scribner, 2010.

[33]Pharmaceutical Research and Manufacturers Association. "Medicines in Development for Alzheimer's Disease." Washington, DC: PhRMA, September 2012. Available at http://phrma.org/sites/default/files/422/alzheimers2012.pdf (accessed February 2013).

[34]U.S. Food and Drug Administration. "Third Annual Performance Report: Prescription Drug User Fee Act of 1992, Fiscal Year 1995 Report to Congress." Silver Spring, MD: FDA, December 1995.

[35]U.S. Food and Drug Administration. "FY 2011 Performance Report to the President and Congress for the Prescription Drug User Fee Act." Silver Spring, MD: FDA, March 2012.

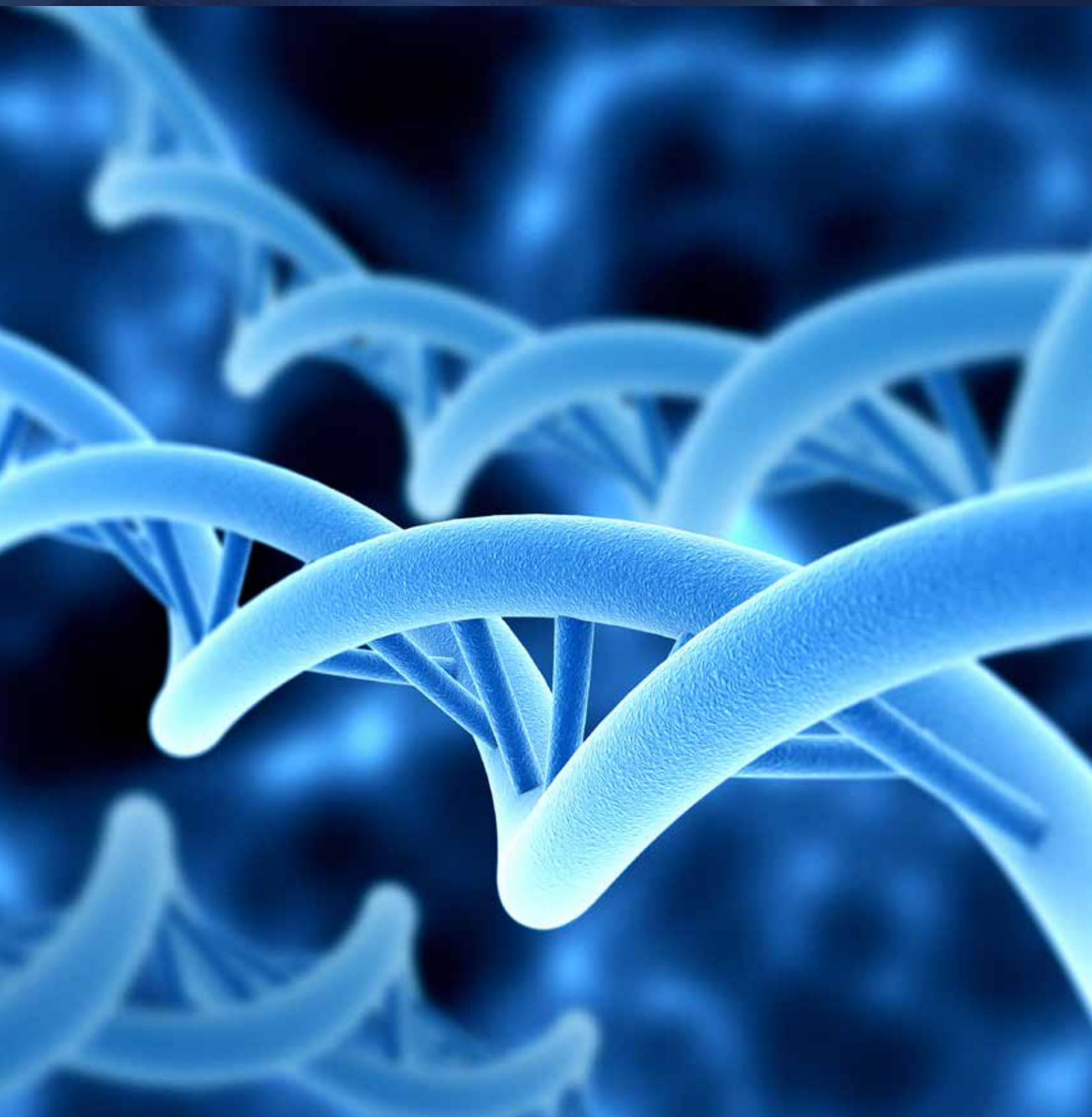
[36]*Ibid*.

[37]U.S. Food and Drug Administration. "Pediatric Exclusivity Granted." January 2013. Available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM223058.pdf (accessed February 2013).

[38]U.S. Food and Drug Administration. "Breakdown of FDAAA Completed Pediatric Studies." 6 December 2012. Available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm (accessed February 2013).

[39]U.S. Food and Drug Administration. "New Pediatric Labeling Information Database." 13 December 2012. Available at www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase (accessed February 2013).

5 A Promising Pipeline



A Promising Pipeline

Our growing understanding of human disease gives us the most promising platform ever to find medicines that treat disease in new ways. Today, more than 5,000 medicines are in development globally, all of which have the potential to help patients in the United States and around the world.[1] (See Figure 16.) According to another data source, there are 3,400 medicines in development today just in the United States, an increase of 40% since 2005.[2,3] The quantity and quality of new drugs in the pipeline reflect a robust research ecosystem. Both basic research and the biopharmaceutical pipeline are thriving. As a result, the potential for new treatments and cures for patients is unprecedented.

Biopharmaceutical researchers are working tirelessly to develop medicines that attack diseases in novel ways. They are exploring new scientific approaches while expanding their knowledge and understanding of human diseases. The increase in the number and variety of scientific tools over the last 20 years has enabled researchers to better understand the molecular and genetic bases of disease and to develop targeted treatments that work more precisely and effectively. Researchers are steadily applying this knowledge to a range of different diseases and conditions, and the result is unprecedented potential for improvements in human health around the world.

Examining the Pipeline

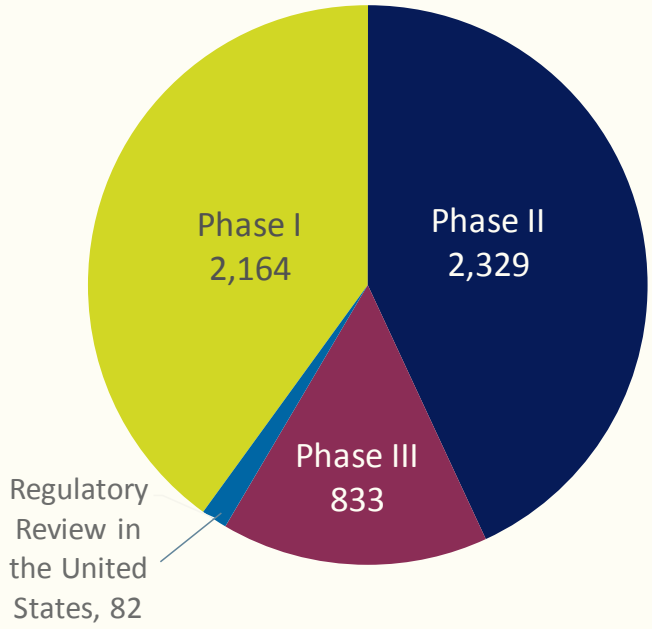
According to a recent report by Analysis Group, which uses various data sources to examine innovation in the pipeline from several different angles, 70% of the more than 5,000 new molecular entities (NMEs) being investigated are potential first-in-class medicines, meaning that they are in a unique pharmacologic class distinct from any other marketed drugs.[4] Such medicines offer new potential treatment options for patients, particularly for those who have not responded to existing therapies or for whom no existing treatment options are available. These medicines may improve the outlook for patients by providing greater efficacy or fewer side effects. Subsequent medicines in the class may provide patients with different side effect or efficacy profiles.

These data "hint at an exciting new Spring of medical innovation for patients. The last thing we want to do — or can afford to do — is stop it cold."[5]

► John C. Lechleiter, Ph.D., Chairman, President, Chief Executive Officer, Eli Lilly and Company

Figure 16: Medicines in Development by Regulatory Phase

In 2011, 5,408 medicines* were in clinical development worldwide.

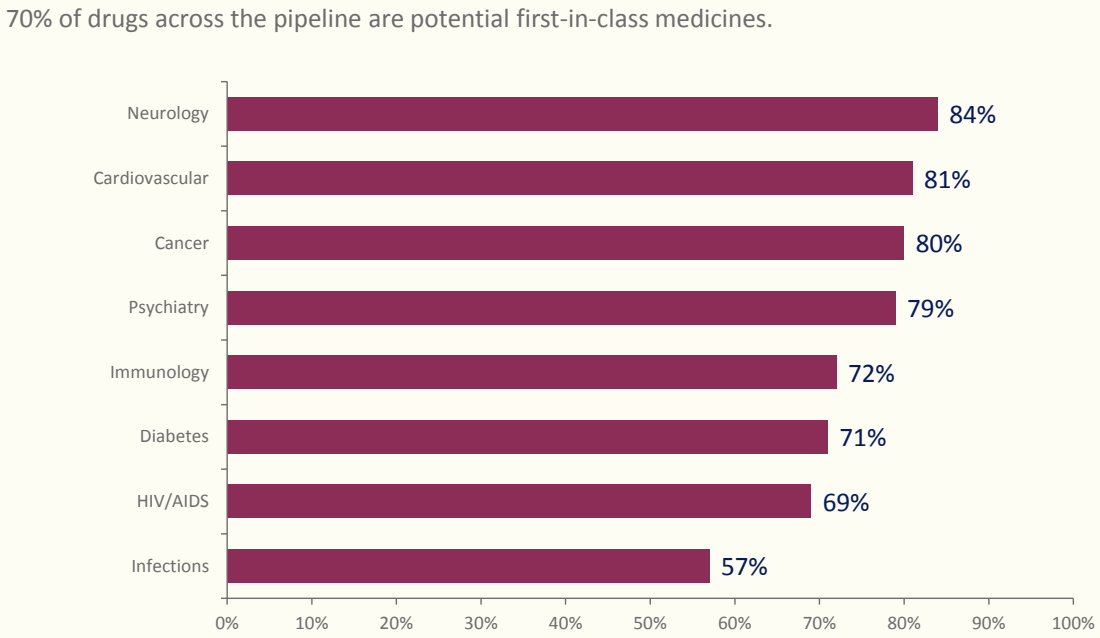


Because many of the 5,408 medicines in development are in trials for more than one indication, the total number of projects in development is close to 8,000.

*Defined as single products which are counted exactly once regardless of the number of indications pursued.

SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

Figure 17: Percentage of Potential First-In-Class Medicines in Selected Therapeutic Areas, 2011



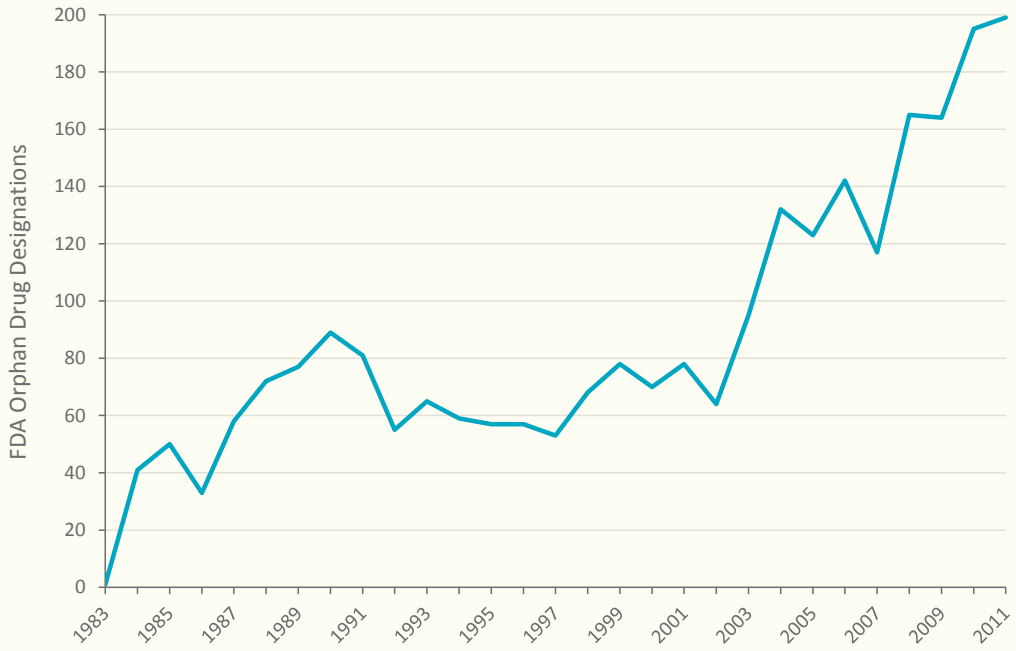
SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed January 2013).

The proportion of projects in development that could become first-in-class varies by therapeutic area but is particularly high in areas such as neurology (84%), cancer (80%), and psychiatry (79%).[6] (See Figure 17.) The high number of potential first-in-class drugs being researched in these areas likely reflects researchers' growing knowledge of the underpinnings of these disease areas and new opportunities for advances.

According to Analysis Group, biopharmaceutical companies are making significant progress in a number of key areas:[7]

- **Rare diseases.** There are nearly 7,000 rare diseases[8] — many of which are serious or life-threatening and have few treatment options. In 2011, 1,795 projects in development focused on rare diseases, which each affect fewer than 200,000 persons in the United States. The U.S. Food and Drug Administration (FDA) designations of orphan drugs in development have been increasing. In the past 10 years, an average of 140 drugs were designated as orphan drugs each year compared with 64 in the previous 10 years.[9]
- **Diseases that do not yet have approved treatments.** Scientists are increasingly developing medicines for diseases for which no therapies have been approved in the last 10 years and that have significant gaps in treatment options. For example, there are 61 medicines in development for amyotrophic lateral sclerosis or Lou Gehrig's disease, 41 for small cell lung cancer, 19 for sickle cell disease, and 158 for ovarian cancer.[10]
- **Medicines that are among the first to apply new scientific strategies to address disease.** New discoveries in basic science are leading to new therapeutic approaches that were never before possible. Among the potential new approaches under investigation today are:

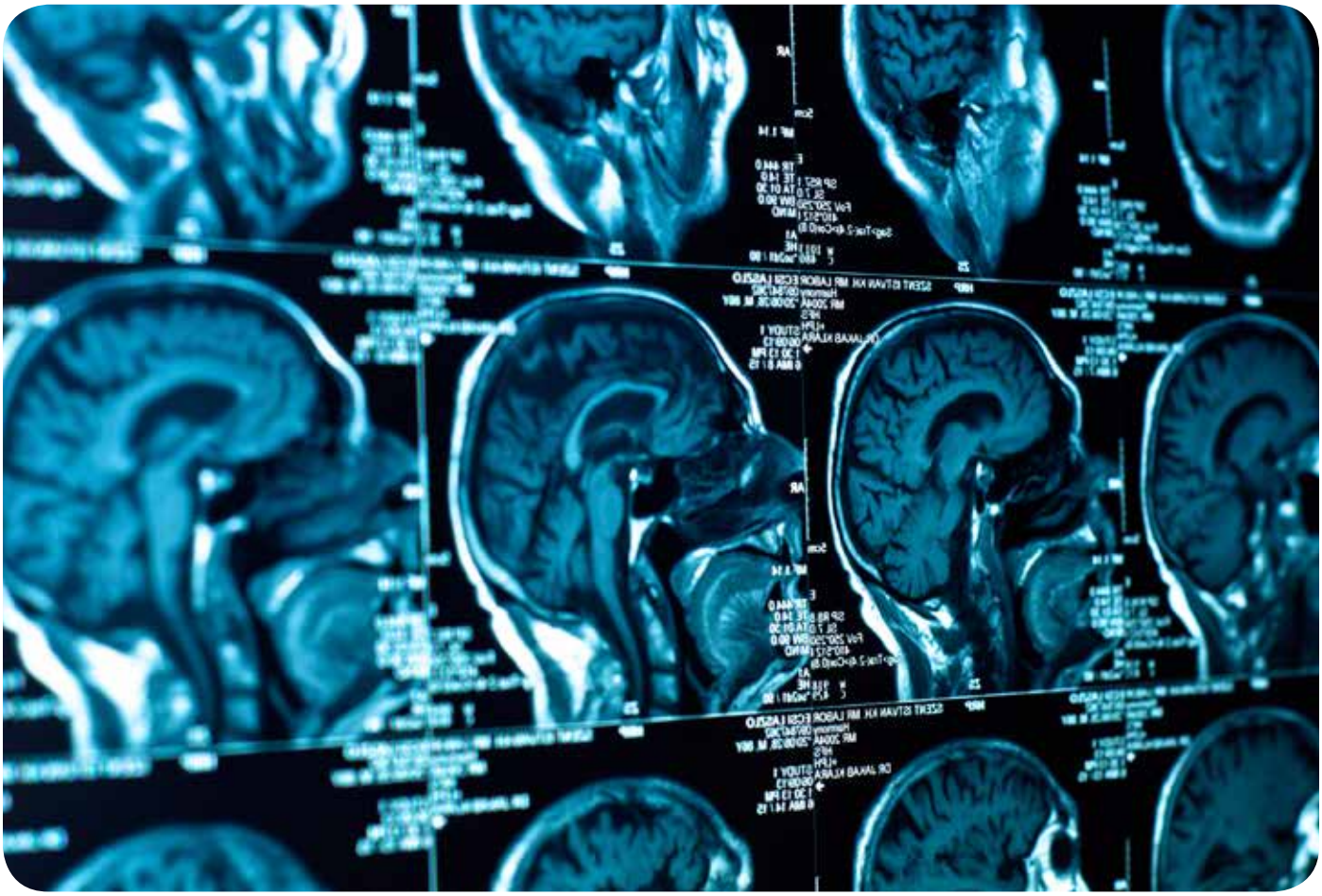
Figure 18: Number of Projects with Orphan Drug Designation by Year 1983–2011



SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

- **RNAi therapy.** While most drugs target proteins such as enzymes and cellular receptors, this new approach opens up opportunities to target RNA, which carries genetic information to create proteins in the cell. Antisense RNA interference (RNAi) therapy can help to silence harmful gene expression. In the past 20 years, this work has advanced from the laboratory bench to the bedside, and two RNAi therapies already have been approved. More than 127 RNAi projects are in the pipeline.[11]
- **Therapeutic cancer vaccines.** Unlike traditional vaccines, these new vaccines harness the power of the immune system to fight cancer rather than to prevent it. This idea first emerged in the late 1990s, and the first therapeutic cancer vaccine was approved in 2010. More than 20 therapeutic vaccines for cancer are in development.[12,13]

> *If you're a patient with a terrible disease, a serious cancer or something like that, I think you ought to take heart from what we are seeing.*[14]
>
> ► Janet Woodcock, M.D., Director of the U.S. Food and Drug Administration's Center for Drug Evaluation and Research



Our progress in understanding the specific pathways of disease has identified hundreds of new targets for potentially life-saving drugs that hold the potential to treat individual patients much more effectively. The result of this understanding is an emerging paradigm shift for the development of new medicines.[15]

► Mark McClellan, M.D., Ph.D., Engelberg Center for Health Care Reform, Brookings Institution, and Ellen Sigal, Ph.D., Friends of Cancer Research, 2012

New Horizons in Personalized Medicine

Personalized medicine presents a new set of tools to help diagnose and treat patients based on our growing understanding of the genetic and molecular basis of disease. This approach is becoming more widespread, particularly in the treatment of cancer, and it holds potential to prevent disease, find the correct treatment more quickly, prevent side effects, improve patients' quality of life, and treat disease more effectively. As the overall cost of health care continues to rise, personalized medicine could help to control costs by reducing unnecessary treatments and side effects.[16]

The role of personalized medicine is growing. According to the Personalized Medicine Coalition, there were 13 prominent examples of personalized medicines, treatments, and diagnostics available in 2006; by 2011, there were 72.[17] Likewise, a 2010 survey by the Tufts Center for the Study of Drug Development found that companies saw a roughly 75% increase in personalized medicine investment between 2005 and 2010 and expected to see an additional 53% increase from 2010 to 2015.[18] Of the companies surveyed, 94% of biopharmaceutical companies are investing in personalized medicine research, and 12% to 50% of the products in their pipelines are personalized medicines.[19]

> *The industry as a whole is committed to pushing strongly ahead ... Early indications show that development of personalized medicines is commanding more resources and fomenting more corresponding organization change than is generally appreciated outside the industry.*[20]
>
> ► Tufts Center for the Study of Drug Development, 2010

Spotlight on Medicines in the Pipeline

Treating a Dangerous Mutation in Infants

Hypophosphatasia is a rare inherited bone disease that is caused by a genetic mutation. The mutation results in low levels of an enzyme called alkaline phosphatase. This deficiency hinders the formation of bones and teeth and can result in substantial skeletal abnormalities. No medicine has been approved for this disease. A potential therapy in development would provide the enzyme necessary for proper bone growth in those with this devastating, rare disease.[21]

Addressing Difficult-to-Treat Symptoms of Schizophrenia

Schizophrenia is a severe and complex mental illness that impairs the patient mentally and emotionally. Although some medicines target symptoms like hallucinations and delusions, they are generally not able to improve other symptoms such as lack of motivation and interest in social activities. A new medicine in development could be the first in a new class that has the potential to target these difficult-to-treat symptoms by improving transmission of a chemical needed in the brain for proper communication between neurons.[22]

[1]Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

[2]Adis Insight. "R&D Insight Database." 19 February 2013.

[3]Adis Insight. Customized analysis for PhRMA based on R&D Insight Database. October 2011.

[4]Analysis Group, *Op. cit.*

[5]J. Lechleiter. "A Coming Renaissance in Pharmaceutical Research & Development?" *Forbes*, 28 January 2013. Available at www.forbes.com/sites/johnlechleiter/2013/01/28/a-coming-renaissance-in-pharmaceutical-research-development/ (accessed February 2013).

[6]Analysis Group, *Op. cit.*

[7]*Ibid.*

[8]National Institutes of Health, Office of Rare Diseases Research. "Rare Diseases Information." Available at http://rarediseases.info.nih.gov/Resources/Rare_Diseases_Information.aspx (accessed February 2013).

[9]Analysis Group, *Op. cit.*

[10]*Ibid.*

[11]*Ibid.*

[12]*Ibid.*

[13]T. Gryta. "Enlisting the Body to Fight Cancer." *Wall Street Journal*, 14 June 2011. Available at http://online.wsj.com/article/SB10001424052702304778304576377892911572686.html?mod=googlenews_wsj (accessed December 2012).

[14]J.D. Rockoff and R. Winslow. "Drug Makers Refill Parched Pipelines." *Wall Street Journal*, 11 July 2011. Available at http://online.wsj.com/article/SB10001424052702303499204576387423702555648.html (accessed January 2013).

[15]M. McClellan and E. Sigal. "Getting Drugs to Market Place Faster." The Hill's Congress Blog. *The Hill*, 20 April 2012. Available at http://thehill.com/blogs/congress-blog/healthcare/222771-getting-drugs-to-market-place-faster (accessed February 2013).

[16]Personalized Medicine Coalition. "The Case for Personalized Medicine: 3rd Edition." Washington, DC: PMC, October 2011. Available at www.personalizedmedicinecoalition.org/sites/default/files/files/Case_for_PM_3rd_edition.pdf (accessed February 2013).

[17]Personalized Medicine Coalition. "Personalized Medicine by the Numbers." Washington, DC: PMC: October 2011. Available at www.personalizedmedicinecoalition.org/sites/default/files/files/PM_by_the_Numbers.pdf (accessed February 2013).

[18]Tufts Center for the Study of Drug Development. "Personalized Medicine Is Playing a Growing Role in Development Pipelines." *Impact Report*. 2010; 12(6).

[19]*Ibid.*

[20]*Ibid.*

[21]Pharmaceutical Research and Manufacturers of America. "The Biopharmaceutical Pipeline: Evolving Science, Hope for Patients." Washington DC, PhRMA: 17 January 2013. Available at http://phrma.org/sites/default/files/2435/phrmapipelinereportfinal11713.pdf (accessed February 2013).

[22]Analysis Group, *Op. cit.*

6 Looking Ahead

Looking Ahead

Despite an extremely promising scientific landscape and ongoing positive impact of the biopharmaceutical sector on patients, the health care system, and the economy, the biopharmaceutical industry faces growing challenges.

Higher Hurdles

Changing Science

The drug development process is becoming more costly and complex. In part, this is due to today's need for medicines to treat increasingly challenging and costly chronic diseases, such as arthritis, cancer, diabetes, and neurodegenerative disorders. Scientific opportunities are leading researchers to focus on increasingly complex diseases and new approaches such as personalized medicine. This sophisticated science requires equally sophisticated tools, technologies, and expertise.

Regulatory Environment

Today's regulatory environment requires complex and extensive research to establish the safety and effectiveness of new medicines and an ever-growing amount of information on each new medicine. This typically means that companies must sponsor clinical trials with large numbers of participants. Patient recruitment and retention in clinical trials are continuing challenges.

International Competition

Many countries are now focusing on building an innovative biomedical sector because they recognize its benefits for their economies and their patients — posing a challenge to U.S. leadership in biomedical research. They are forming industry clusters, often in partnership with regional governments. They are also helping to grow their knowledge-based economies through strategies such as building research and development (R&D) infrastructure; emphasizing science, technology, engineering, and math (STEM) education; ensuring access to financial capital; and building and retaining a skilled workforce.[1] For example:

- **Singapore** invested significantly in R&D infrastructure, most famously by creating the Biopolis Research Park. More than 30 companies have located to Biopolis, including many well-known multinational companies.[2]
- **China** has increased R&D investment by 10% each year over the last decade for a total investment of $154 billion — second only to the United States. China also has established programs and incentives to attract talented scientists and foreign investment.[3]

Meeting Challenges

America's biopharmaceutical companies are adapting and seeking creative solutions to meet these growing economic, scientific, business, regulatory, and policy challenges. For example, companies are working to make the clinical trials process as efficient as possible and are focusing on diseases with the greatest unmet needs. They are developing partnerships and unique collaborations to expand the capacity to address complex disease targets. Companies are also working with the U.S. Food and Drug Administration, the National Institutes of Health, and related research agencies

to advance regulatory science and to foster the integration of emerging data and innovation into the development and review of new medicines.

These responses, combined with positive, forward-looking public policies that sustain a market-based system and incentives for innovators, such as strong intellectual property protections, will help ensure America's continued role as the worldwide leader in biopharmaceutical research.

To foster innovation and the medical advances and economic impact that go with it, we must:

- Continue to advance regulatory science and foster the integration of emerging scientific data and innovative approaches into the development and review of new medicines more efficiently, promoting public health in areas such as biomarkers, pharmacogenomics, and rare and orphan drug development.
- Advance medical innovation policies as a solution to health-system problems. For example, to help realize the potential of medical innovation as a solution for improving patient outcomes and controlling rising health care costs, it is important to recognize across all policy areas that the full value of medical advances emerges over time, and to support the ability of physicians and patients to choose from the full range of medically appropriate treatment options.
- Support coverage and payment policies that foster the introduction and availability of new medical advances to America's patients.
- Support the development of STEM workers to increase the nation's ability to develop and manufacture tomorrow's new treatments and to compete globally.
- Support strong intellectual property rights and enforcement in the United States and abroad.
- Sustain U.S. global leadership in the biosciences through economic, trade, and related policies to promote a level playing field globally.

---

[1] Battelle Technology Partnership Practice. "The Biopharmaceutical Research and Development Enterprise: Growth Platforms for Economies Around the World." Washington, DC: Battelle Technology Partnership Practice, May 2012.

[2] *Ibid.*

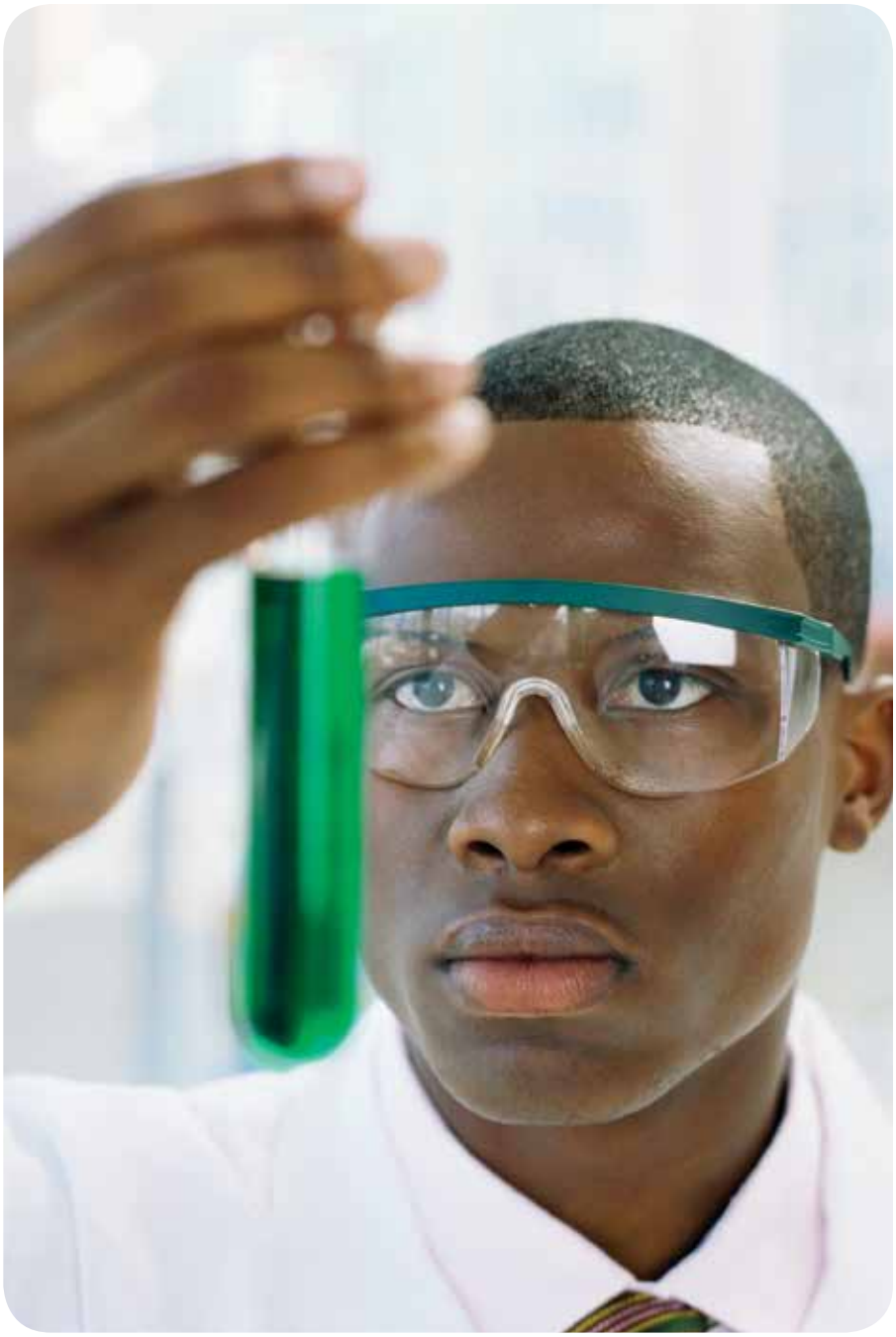
[3] *Ibid.*

Committed to Progress

The challenges facing the biopharmaceutical industry are many and substantial — complex scientific issues, an evolving regulatory environment, and stiff competition at home and abroad. But the scientific opportunities and the promise of medicines in the pipeline are remarkable. And the positive impact of the industry is far reaching.

The biopharmaceutical sector is meeting the challenges before it with innovative scientific work, creative approaches to building and sustaining the industry, and an unending commitment to saving lives and improving the health and quality of life of patients.

This commitment is reflected in the many advances that we have already seen across a wide spectrum of diseases that affect millions. And it brings many benefits such as good jobs and economic investment to communities and states across the nation. The future holds great promise for continued advancements, and with sustained support for innovation, the U.S. biopharmaceutical sector will continue to lead the world.



Appendix

PhRMA

RESEARCH • PROGRESS • HOPE

PhRMA: Who We Are

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading biopharmaceutical companies, which are committed to discovering and developing medicines that save and improve lives. The work of the biopharmaceutical research sector brings hope to millions of patients, allowing them to live longer, healthier lives, while helping to manage health care costs. PhRMA member companies have invested more than $500 billion in research and development into medical innovations since 2000, and an estimated $48.5 billion in 2012 alone. This investment also helps drive the industry's significant contributions to the U.S. economy, including the generation of hundreds of thousands of American jobs and vital support for local communities.

Our Mission

PhRMA's mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies. To accomplish this mission, PhRMA is dedicated to achieving these goals in Washington, D.C., the states, and the world:

- Broad patient access to safe and effective medicines through a free market, without price controls
- Strong intellectual property incentives
- Transparent, efficient regulation and a free flow of information to patients

To learn more about PhRMA, go to www.PhRMA.org/about.

PhRMA Member Companies

Full Members & Research Associate Members

Members & Subsidiaries

AbbVie, Inc.
North Chicago, IL

Alkermes plc
Waltham, MA

Amgen Inc.
Thousand Oaks, CA

Astellas Pharma US, Inc.
Northbrook, IL

AstraZeneca Pharmaceuticals LP
Wilmington, DE

Bausch + Lomb
Rochester, NY

Bayer
Wayne, NJ

Biogen Idec Inc.
Weston, MA

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT

Bristol-Myers Squibb Company
New York, NY

Celgene Corporation
Summit, NJ

Cubist Pharmaceuticals, Inc.
Lexington, MA

Daiichi Sankyo, Inc.
Parsippany, NJ

Dendreon Corporation
Seattle, WA

Eisai Inc.
Woodcliff Lake, NJ

EMD Serono
Rockland, MA

Endo Pharmaceuticals, Inc.
Chadds Ford, PA

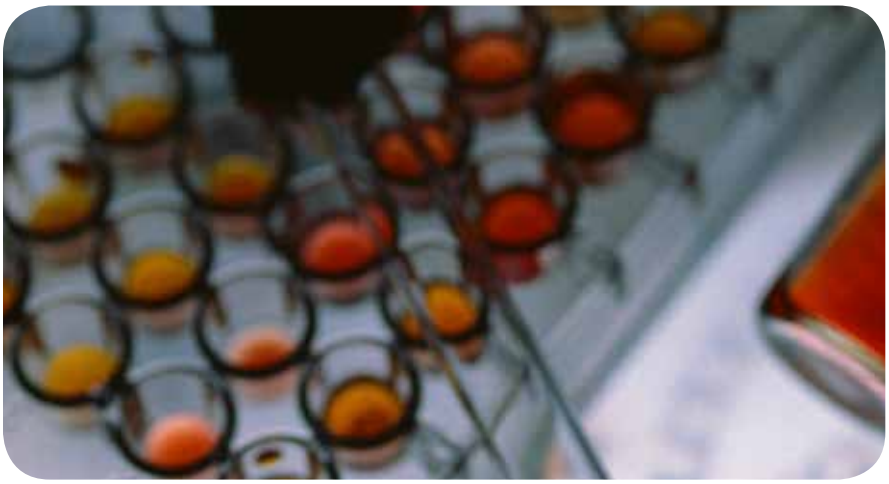
GlaxoSmithKline
Research Triangle Park, NC

Johnson & Johnson
New Brunswick, NJ

Eli Lilly and Company
Indianapolis, IN

Lundbeck Inc.
Deerfield, IL

Merck & Co., Inc.
Whitehouse Station, NJ
Merck Human Health Division
Merck Research Laboratories
Merck Vaccine Division



Novartis Pharmaceuticals Corporation
East Hanover, NJ

Novo Nordisk Inc.
Princeton, NJ

Otsuka America Pharmaceutical
Princeton, NJ
- *Otsuka America Pharmaceutical, Inc. (OAPI)*
- *Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)*
- *Otsuka Maryland Medicinal Laboratories, Inc. (OMML)*

Pfizer Inc.
New York, NY

Purdue Pharma L.P.
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Gaithersburg, MD

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Deerfield, IL

Research Associate Members

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San Diego, CA

Auxilium Pharmaceuticals, Inc.
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BioMarin Pharmaceutical Inc.
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King of Prussia, PA

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Shionogi Inc.
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Bethesda, MD

Theravance, Inc.
South San Francisco, CA

Vifor Pharma
Basking Ridge, NJ

VIVUS Inc.
Mountain View, CA

XOMA Corporation
Berkeley, CA

PhRMA Annual Membership Survey

Definition of Terms

Research and Development Expenditure Definitions

R&D Expenditures: Expenditures within PhRMA member companies' U.S. and/or foreign research laboratories plus research and development (R&D) funds contracted or granted to commercial laboratories, private practitioners, consultants, educational and nonprofit research institutions, manufacturing and other companies, or other research-performing organizations located inside/outside of the U.S. Includes basic and applied research, as well as developmental activities carried on or supported in the pharmaceutical, biological, chemical, medical, and related sciences, including psychology and psychiatry, if the purpose of such activities is concerned ultimately with the utilization of scientific principles in understanding diseases or in improving health. Includes the total cost incurred for all pharmaceutical R&D activities, including salaries, materials, supplies used, and a fair share of overhead, as well as the cost of developing quality control. However, it does not include the cost of routine quality control activities, capital expenditures, or any costs incurred for drug or medical R&D conducted under a grant or contract for other companies or organizations.

Domestic R&D: Expenditures within the United States by all PhRMA member companies.

R&D Abroad: Expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies is excluded.

Prehuman/Preclinical Testing: From synthesis to first testing in humans.

Phase 1/2/3 Clinical Testing: From first testing in designated phase to first testing in subsequent phase.

Approval Phase: From New Drug Application (NDA)/Biologic License Application (BLA) submission to NDA/BLA decision.

Phase 4 Clinical Testing: Any post-marketing R&D activities performed.

Uncategorized: Represents data for which detailed classifications were unavailable.

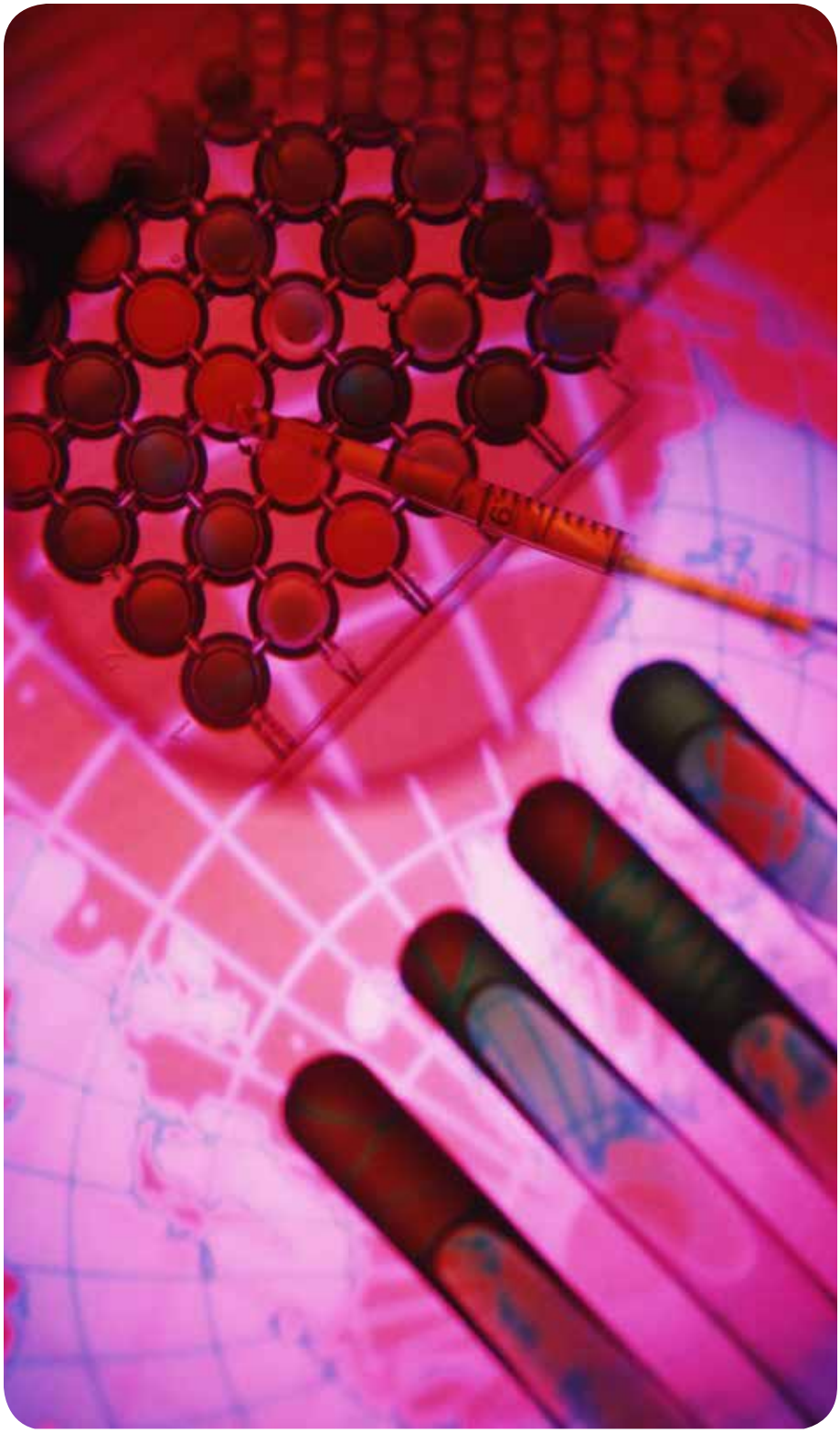
Sales Definitions

Sales: Product sales calculated as billed, free on board (FOB) plant or warehouse less cash discounts, Medicaid rebates, returns, and allowances. These include all marketing expenses except transportation costs. Also included is the sales value of products bought and resold without further processing or repackaging, as well as the dollar value of products made from the firm's own materials for other manufacturers' resale. Excluded are all royalty payments, interest, and other income.

Domestic Sales: Sales generated within the United States by all PhRMA member companies.

- **Private Sector:** Sales through regular marketing channels for end use other than by government agency administration or distribution.
- **Public Sector:** Sales or shipments made directly to federal, state, or local government agencies, hospitals, and clinics.

Sales Abroad: Sales generated outside the United States by U.S.-owned PhRMA member companies, and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded.



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Sales, PhRMA Member Companies

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7 Sales by Geographic Area: 2011 68

TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1975–2012

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2012**	$36,810.4	1.2%	$11,674.7	-4.9%	$48,485.1	-0.3%
2011	36,373.6	-10.6	12,271.4	22.4	48,645.0	-4.1
2010	40,688.1	15.1	10,021.7	-9.6	50,709.8	9.2
2009	35,356.0	-0.6	11,085.6	-6.1	46,441.6	-2.0
2008	35,571.1	-2.8	11,812.0	4.6	47,383.1	-1.1
2007	36,608.4	7.8	11,294.8	25.4	47,903.1	11.5
2006	33,967.9	9.7	9,005.6	1.3	42,973.5	7.8
2005	30,969.0	4.8	8,888.9	19.1	39,857.9	7.7
2004	29,555.5	9.2	7,462.6	1.0	37,018.1	7.4
2003	27,064.9	5.5	7,388.4	37.9	34,453.3	11.1
2002	25,655.1	9.2	5,357.2	-13.9	31,012.2	4.2
2001	23,502.0	10.0	6,220.6	33.3	29,772.7	14.4
2000	21,363.7	15.7	4,667.1	10.6	26,030.8	14.7
1999	18,471.1	7.4	4,219.6	9.9	22,690.7	8.2
1998	17,127.9	11.0	3,839.0	9.9	20,966.9	10.8
1997	15,466.0	13.9	3,492.1	6.5	18,958.1	12.4
1996	13,627.1	14.8	3,278.5	-1.6	16,905.6	11.2
1995	11,874.0	7.0	3,333.5	***	15,207.4	***
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
Average		**10.8%**		**12.2%**		**11.1%**

*R&D Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

**Estimated.

***R&D Abroad affected by merger and acquisition activity.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 2: R&D as a Percentage of Sales, PhRMA Member Companies: 1975–2012

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2012*	20.7%	16.4%
2011	19.4	15.9
2010	22.0	17.4
2009	19.5	16.8
2008	19.4	16.6
2007	19.8	17.5
2006	19.4	17.1
2005	18.6	16.9
2004	18.4	16.1**
2003	18.3	16.5**
2002	18.4	16.1
2001	18.0	16.7
2000	18.4	16.2
1999	18.2	15.5
1998	21.1	16.8
1997	21.6	17.1
1996	21.0	16.6
1995	20.8	16.7
1994	21.9	17.3
1993	21.6	17.0
1992	19.4	15.5
1991	17.9	14.6
1990	17.7	14.4
1989	18.4	14.8
1988	18.3	14.1
1987	17.4	13.4
1986	16.4	12.9
1985	16.3	12.9
1984	15.7	12.1
1983	15.9	11.8
1982	15.4	10.9
1981	14.8	10.0
1980	13.1	8.9
1979	12.5	8.6
1978	12.2	8.5
1977	12.4	9.0
1976	12.4	8.9
1975	12.7	9.0

*Estimated.

**Revised in 2007 to reflect updated data.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 3: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 2011

(dollar figures in millions)

R&D Expenditures for Human-use Pharmaceuticals	Dollars	Share
Domestic	$35,923.9	73.8%
Abroad*	$11,982.5	24.6%
Total Human-use R&D	**$47,906.4**	**98.5%**
R&D Expenditures for Veterinary-use Pharmaceuticals		
Domestic	$449.7	0.9%
Abroad*	$288.9	0.6%
Total Vet-use R&D	**$738.7**	**1.5%**
TOTAL R&D	**$48,645.0**	**100.0%**

*R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 4: R&D by Function, PhRMA Member Companies: 2011

(dollar figures in millions)

Function	Dollars	Share
Prehuman/Preclinical	$10,466.3	21.5%
Phase 1	4,211.0	8.7
Phase 2	6,096.4	12.5
Phase 3	17,392.9	35.8
Approval	4,033.4	8.3
Phase 4	4,760.9	9.8
Uncategorized	1,684.0	3.5
TOTAL R&D	**$48,645.0**	**100.0%**

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 5: R&D by Geographic Area,* PhRMA Member Companies: 2011

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$3.7	0.0%
South Africa	50.1	0.1
Other Africa	5.2	0.0
Americas		
United States	$36,373.6	74.8%
Canada	781.0	1.6
Mexico	114.6	0.2
Brazil	181.1	0.4
Argentina	101.1	0.2
Venezuela	5.3	0.0
Columbia	29.1	0.1
Chile	21.5	0.0
Peru	16.9	0.0
Other Latin America (Other South America, Central America, and all Caribbean nations)	77.6	0.2
Asia-Pacific		
Japan	$1,027.7	2.1%
China	327.6	0.7
India	48.7	0.1
Taiwan	38.7	0.1
South Korea	103.9	0.2
Other Asia-Pacific	272.3	0.6
Australia		
Australia and New Zealand	$274.7	0.6%
Europe		
France	$509.6	1.0%
Germany	659.2	1.4
Italy	190.6	0.4
Spain	230.7	0.5
United Kingdom	1,770.5	3.6
Other Western European	4,009.6	8.2
Czech Republic	50.6	0.1
Hungary	40.1	0.1
Poland	73.5	0.2
Turkey	48.2	0.1
Russia	73.3	0.2
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	538.7	1.1
Middle East		
Saudi Arabia	$7.3	0.0%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	74.8	0.2
Uncategorized	$513.6	1.1%
TOTAL R&D	**$48,645.00**	**100.0%**

*R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 6: Domestic Sales and Sales Abroad,* PhRMA Member Companies: 1975–2012

(dollar figures in millions)

Year	Domestic Sales	Annual Percentage Change	Sales Abroad*	Annual Percentage Change	Total Sales	Annual Percentage Change
2012**	$177,506.9	-3.9%	$117,293.1	10.0%	$294,800.0	1.2%
2011	187,870.7	3.7	117,138.5	23.1	305,009.2	10.4
2010	184,660.3	2.0	106,593.2	12.0	291,253.5	5.4
2009	181,116.8	-1.1	95,162.5	-7.5	276,279.3	-3.4
2008	183,167.2	-1.1	102,842.4	16.6	286,009.6	4.6
2007	185,209.2	4.2	88,213.4	14.8	273,422.6	7.4
2006	177,736.3	7.0	76,870.2	10.0	254,606.4	7.9
2005	166,155.5	3.4	69,881.0	0.1	236,036.5	2.4
2004***	160,751.0	8.6	69,806.9	14.6	230,557.9	10.3
2003***	148,038.6	6.4	60,914.4	13.4	208,953.0	8.4
2002	139,136.4	6.4	53,697.4	12.1	192,833.8	8.0
2001	130,715.9	12.8	47,886.9	5.9	178,602.8	10.9
2000	115,881.8	14.2	45,199.5	1.6	161,081.3	10.4
1999	101,461.8	24.8	44,496.6	2.7	145,958.4	17.1
1998	81,289.2	13.3	43,320.1	10.8	124,609.4	12.4
1997	71,761.9	10.8	39,086.2	6.1	110,848.1	9.1
1996	64,741.4	13.3	36,838.7	8.7	101,580.1	11.6
1995	57,145.5	12.6	33,893.5	****	91,039.0	****
1994	50,740.4	4.4	26,870.7	1.5	77,611.1	3.4
1993	48,590.9	1.0	26,467.3	2.8	75,058.2	1.7
1992	48,095.5	8.6	25,744.2	15.8	73,839.7	11.0
1991	44,304.5	15.1	22,231.1	12.1	66,535.6	14.1
1990	38,486.7	17.7	19,838.3	18.0	58,325.0	17.8
1989	32,706.6	14.4	16,817.9	-4.7	49,524.5	7.1
1988	28,582.6	10.4	17,649.3	17.1	46,231.9	12.9
1987	25,879.1	9.4	15,068.4	15.6	40,947.5	11.6
1986	23,658.8	14.1	13,030.5	19.9	36,689.3	16.1
1985	20,742.5	9.0	10,872.3	4.0	31,614.8	7.3
1984	19,026.1	13.2	10,450.9	0.4	29,477.0	8.3
1983	16,805.0	14.0	10,411.2	-2.4	27,216.2	7.1
1982	14,743.9	16.4	10,667.4	0.1	25,411.3	9.0
1981	12,665.0	7.4	10,658.3	1.4	23,323.3	4.6
1980	11,788.6	10.7	10,515.4	26.9	22,304.0	17.8
1979	10,651.3	11.2	8,287.8	21.0	18,939.1	15.3
1978	9,580.5	12.0	6,850.4	22.2	16,430.9	16.1
1977	8,550.4	7.5	5,605.0	10.2	14,155.4	8.6
1976	7,951.0	11.4	5,084.3	9.7	13,035.3	10.8
1975	7,135.7	10.3	4,633.3	19.1	11,769.0	13.6
Average		**9.4%**		**9.9%**		**9.4%**

*Sales Abroad includes sales generated outside the United States by U.S.-owned PhRMA member companies and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic sales, however, includes sales generated within the United States by all PhRMA member companies.
**Estimated.

***Revised in 2007 to reflect updated data.

****Sales abroad affected by merger and acquisition activity.

Note: Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

TABLE 7: Sales by Geographic Area,* PhRMA Member Companies: 2011

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$347.7	0.1%
South Africa	872.3	0.3
Other Africa	1,327.8	0.4
Americas		
United States	$187,870.7	61.6%
Canada	6,793.0	2.2
Mexico	2,576.9	0.8
Brazil	4,387.4	1.4
Argentina	873.9	0.3
Venezuela	1,323.2	0.4
Columbia	771.4	0.3
Chile	320.8	0.1
Peru	167.6	0.1
Other Latin America (Other South America, Central America, and all Caribbean nations)	1,449.8	0.5
Asia-Pacific		
Japan	$17,556.4	5.8%
China	3,391.2	1.1
India	1,635.0	0.5
Taiwan	1,152.2	0.4
South Korea	2,669.7	0.9
Other Asia-Pacific	2,003.6	0.7
Australia		
Australia and New Zealand	$4,008.7	1.3%
Europe		
France	$9,947.9	3.3%
Germany	8,127.0	2.7
Italy	6,761.6	2.2
Spain	5,976.2	2.0
United Kingdom	6,037.0	2.0
Other Western European	11,825.3	3.9
Czech Republic	687.2	0.2
Hungary	499.9	0.2
Poland	942.5	0.3
Turkey	1,518.4	0.5
Russia	1,816.9	0.6
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	5,576.4	1.8
Middle East		
Saudi Arabia	$716.3	0.2%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	1,268.8	0.4
Uncategorized	$1,808.3	0.6%
TOTAL SALES	**$305,009.2**	**100.0%**

*Sales abroad include expenditures outside the United States by U.S.-owned PhRMA member companies and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic sales, however, include sales generated within the United States by all PhRMA member companies.

Note: Total values may be affected by rounding.

SOURCE: *Pharmaceutical Research and Manufacturers of America*, PhRMA Annual Membership Survey, 2013.

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(continued from inside front cover)

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JULY 2013

EXHIBIT F

HEALTH ECONOMICS
Health Econ. **19**: 130–141 (2010)
Published online 26 February 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hec.1454

SPENDING ON NEW DRUG DEVELOPMENT[1]

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SUMMARY

This paper replicates DiMasi *et al.* (*J. Health Econ.* 2003; **22**: 151–185; *Drug Inf. J.* 2004; **38**: 211–223) estimates of expenditure on new drug development using publicly available data. The paper estimates that average expenditure on drugs in human clinical trials is around $27m per year, with $17m per year on drugs in Phase I, $34m on drugs in Phase II and $27m per year on drugs in Phase III of the human clinical trials. The paper's estimated expenditure on new drug development is somewhat greater than suggested by the survey results presented in DiMasi *et al.* (*J. Health Econ.* 2003; **22**: 151–185; *Drug Inf. J.* 2004; **38**: 211–223). The paper combines a 12-year panel of research and development expenditure for 183 publicly traded firms in the pharmaceutical industry with panel of drugs in human clinical trials for each firm over the same period. The paper estimates drug expenditure by estimating the relationship between research and development expenditure and the number of drugs in development for 1682 company/years (183 firms multiplied by the number of years for which we have financial and drug development information). The paper also estimates expenditure on drugs in various therapeutic categories. Copyright © 2009 John Wiley & Sons, Ltd.

Received 14 May 2007; Revised 24 November 2008; Accepted 5 January 2009

KEY WORDS: pharmaceuticals; drug development

1. INTRODUCTION

DiMasi *et al.* (2003, 2004) estimate the cost of new drug development for all drugs and for drugs in certain therapeutic categories, respectively. The authors estimate the average cost of new drug development to be $802m per new drug. This number has become a central part of the policy debates on numerous issues regarding the pharmaceutical industry including the Medicare Prescription Drug Act, drug importation, generic entry and vaccine development. Drug companies argue the high cost of drug development justifies the high prices paid by governments, insurers and customers. Given the importance of the $802m number to the debate it is important to know whether it is correct and what it means.

DiMasi *et al.* (2003) calculate the cost of new drug development with data from two sources. The authors survey 10 large pharmaceutical firms and ask those firms to report the expenditure in human clinical trials for 68 drugs chosen at random from the Tuft's drug development database called the CSDD. The authors then use information on average success rates and successful durations from the CSDD data to calculate the cost of bringing a new drug to market. Recently, Light and Warburton (2005) point out numerous problems with DiMasi *et al.* (2003). In particular, because 'cost data used

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[1]The authors are not aware of any potential conflicts that may bias their work. As far as the authors are aware, the study raises no ethical issues.

was proprietary and confidential, readers cannot know how each company collected its data, or what was counted as research costs, and no independent verification of the accuracy of the information is possible' (p. 1031). This paper provides an independent verification of the survey cost data by using an alternative publicly available data source on research and development expenditure. Adams and Brantner (2006) verify the second part of DiMasi *et al.* (2003) paper by using publicly available data to estimate success rates and average successful durations.

By comparing aggregate annual expenditure on research and development across firms and over time to the number of drugs in human clinical trials for each firm and each year, we can determine the 'marginal expenditure' on an additional drug in development. If Drug Firm A spends an additional $50m in 1992 relative to 1991 but in 1992 Drug Firm A has two additional drugs in development we argue this provides an estimate of average annual expenditure by Drug Firm A, i.e. $25m per drug per year. Similarly, if Drug Firm B spends $100m more than Drug Firm A in 1992 but Drug Firm B has an additional four drugs in development in 1992, then we estimate drug expenditure to be $25m per drug per year. Note that this is an estimate of the correlation between expenditure and the number of drugs in development. We are not attempting to estimate the impact of an additional dollar of expenditure on the number of drugs in development or the impact of additional drug on the amount of expenditure.

There are a number of advantages to this approach. First, we are using publicly available data so our results can be verified by other researchers. Second, we are using data from 183 publicly traded firms rather than 10 firms selected by the study's authors. Our selection criteria is that the firms have research and development expenditure information in the CompuStat data base, be in the pharmaceutical industry (see Danzon *et al.*, 2004) and have drugs in the Pharmaprojects data set (see Adams and Brantner, 2006). These firms range in size from 100 employees to almost 180 000 employees with sales ranging from $2m annually to almost $45b annually. Third, we are using contemporaneous reports of research and development expenditure where the reports are scrutinized by both the market and the SEC. In their comment on DiMasi *et al.* (2003), Light and Warburton (2005) argue that

> considering the clear interest of pharmaceutical companies in higher (rather than lower) estimates of drug development costs, and sampled firms' likely awareness of the intended use of the survey data, it is not unlikely that companies would deliberately and systematically overstate costs in their survey responses (p. 1031).

We argue that such biases are less likely here given the large number of firms and the checks on the reports including audits.

Of course there are also serious concerns about the approach we use here. First, the data are aggregate research and development expenditure. Those not only include expenditure on drugs in human clinical trials but also include development expenditure on drugs yet to reach trials. To identify the amount spent in human clinical trials we must infer the information from cross sectional and time-series variation in expenditure that is associated with variation in the number of drugs in development. Such variation may lead to spurious estimates. For example, if one firm specializes in anti-infective drugs and we compare the specialty firm's expenditure on anti-infective drugs to that of a firm that has just one or two anti-infective drugs, we may estimate that expenditure on the extra drug as being small. This low estimate may be due savings from specialization rather than an accurate measure of the cost of adding another anti-infective drug.

Second, we are estimating changes for the 'marginal drug', which may be more expensive than the average drug.[2] The relationship between expenditure on the marginal drug and expenditure on the average drug depends on what assumption the reader is willing to make regarding how expenditure per

[2]Thanks to Eric Durbin for pointing this out.

DOI: 10.1002/hec

drug changes with the number of drugs. If expenditure per drug is constant then the marginal and the average are the same. On the other hand, if expenditure per drug is increasing with the number of drugs in development then marginal expenditure will be higher than average expenditure. A number of papers suggest that there may be economies of scale or scope in drug development (Cockburn and Henderson, 1996, 2001; Danzon *et al*., 2004). If there are economies of scale then we would expect marginal expenditure to be less than average expenditure.[3] Note that marginal expenditure may be a more useful measure for determining the incentive effects of policy changes.

Third, we use Pharmaprojects' definition of a 'drug development project' and assign the drug to the 'originator'. In general, this definition corresponds to a new patented molecular entity. In the main part of the analysis we drop drugs that are new formulations of existing drugs (i.e. an extended release version of an existing drug). The analysis does not account for the fact that the drug development project is part of a joint venture (and thus expenditure is spread across multiple firms) or is being developed by an altogether different firm (and our method is assigning the drug project to the wrong firm).[4] Such mis-measurement may bias our estimates downward. It should be noted that our counts of drugs in the different phases are measuring the development associated with the originating firm.

In order to have a number that is comparable to DiMasi *et al*.'s (2003) average expenditure over the sample period, we control for differences between firms and differences over time. We attempt to control for some cross-sectional variation by conditioning on net sales. If for example, larger firms spend more on drug development projects than smaller firms then net sales should control for this variation. Similarly, if firms are spending more on drug development projects at the end of the period than at the beginning then our controls for time will provide a better sense of the average expenditure per project during the period. Note that identification of spending per drugs is coming to some extent from the fact that larger firms have more drugs and that there are more drugs over time in the database. The controls attempt to separately identify the effect of having another drug in human clinical trials from the effect of being large or later in time.

DiMasi *et al*. (2003) uses a similar approach to verify their own estimates. The authors use firm level R&D expenditure reported by PhRMA and estimate lagged expenditure on firm level counts of approved drugs. The authors estimate average expenditure per approved drug to be between $354m and $558m. These numbers are similar to their estimate of $403m using the survey data. Other researchers have simply divided aggregate R&D expenditure by the total number of approvals per year. The concern with these approaches is that less than one in four drugs in human clinical trials actually make it to the market and the process can take between 6 and 12 years with substantial variation across drugs (Adams and Brantner, 2003).

The rest of the paper proceeds as follows. Section 2 discusses the data used in this study and provides some background information on new drug development. Section 3 presents the results. Section 4 concludes.

2. DATA AND BACKGROUND

This paper combines data from two data sources. Information on each firm's research and development expenditure comes from the Standard Poor's CompuStat Industrial file and Global Vantage Industrial Commercial file used by Danzon *et al*. (2004).[5] This data set provides financial information on publicly traded drug companies including net sales, employment and expenditure on research and development.

[3]To the extent one is concerned that large firms may have lower (or higher) expenditure per drug than smaller firms, some of this variation is accounted for in the analysis through conditioning on sales revenue.
[4]Danzon *et al*. (2005) analyze joint ventures.
[5]All monetary values are in 1999 dollars using the domestic manufacturing Producer Price Index.

DOI: 10.1002/hec

Table I. Firm/year summary statistics

Variable	Obs	Mean	Median	Std. Dev.	Max
Number of drugs	2245	4	2	6	45
R&D expenditure ($m)	1682	264	37	551	4678
Net sales ($m)	1701	2355	110	5438	44 611
Employees ('000)	1537	11	1	25	179

Information on drugs in development comes from a Pharmaprojects data set used by Adams and Brantner (2006) and Abrantes-Metz *et al*. (2005). This data set uses public information to track drugs through the development process, providing information on the length of time in different phase as well as when and if drugs completed a development phase. The two data sets overlap for the years 1989–2001. The data sets are matched using the name of the pharmaceutical firm.[6] Pharmaprojects updates its information on the firms developing each drug after a merger, so we used text searches of the database and searches of a related data set called the Manufacturing Index to determine the ownership of drugs over time.[7]

According to Danzon *et al*. (2004) there are 383 firms in their original data. Once we match these firms to firms in the Pharmaprojects data we are left with 183 firms. It is not clear exactly why there are firms that do not match. The two data sets do not exactly overlap in time and that may explain some of it. Another explanation is that the Pharmaprojects does not capture name changes or mergers among smaller firms (see footnote 7). Table I presents some basic summary statistics for this sample of firm/year combinations. Table I shows there are an average of four drugs in development for each firm for each year 1989–2001. Note this measure is not a very good measure of the stock of drugs in development because we only observe drugs entering one of the stages of human clinical trials after 1989. In the average firm/year $264m is spent on research and development, $2355m is made in sales and there are 11 000 employees. Note that medians are substantially lower than the means suggesting that the distributions are all skewed toward zero.

Figures 1–3 present the distribution of the number of drugs in human clinical trials per firm/year, the amount of R&D expenditure per firm/year, and a scatter plot of the two, respectively. The first two figures show that the distributions of drugs and expenditures are heavily skewed to zero. The third figure seems to show a positive correlation between the amount of R&D expenditure per firm per year and the number of drugs in development per firm per year.

Figure 4 presents a summary of the research and development process for new drugs. The first stage of drug discovery is commonly called 'preclinical development'. In this stage pharmaceutical firms analyze thousands of drugs to determine whether one may have an affect on a disease or condition. As candidates are discovered these drugs are tested on animals to determine whether the drug may be safe and effective in human beings. It is estimated that drugs spend over 4 years in preclinical testing. DiMasi *et al*. (2003) do not have direct survey information on preclinical expenditure because pharmaceutical firms do not track preclinical expenditure by particular drug candidates. Given this and given that the Pharmaprojects data are based on public information and are not very reliable regarding drugs in preclinical development, we do not estimate expenditure on preclinical development.

After preclinical development the sponsoring firm applies for an investigation new drug application (IND) with the FDA in order to test the candidate in humans.[8] There are three steps to human clinical

[6]This matching was done by hand in order for it to be as accurate as possible.
[7]This was done for all mergers involving firms in the Forbes' top 20 of pharmaceutical industry over the period as well as any other major mergers in the pharmaceutical industry.
[8]If the firm wants to eventually market the drug in the US the firm must apply for an IND prior to undertaking human trials. That said, there are exceptions.

DOI: 10.1002/hec

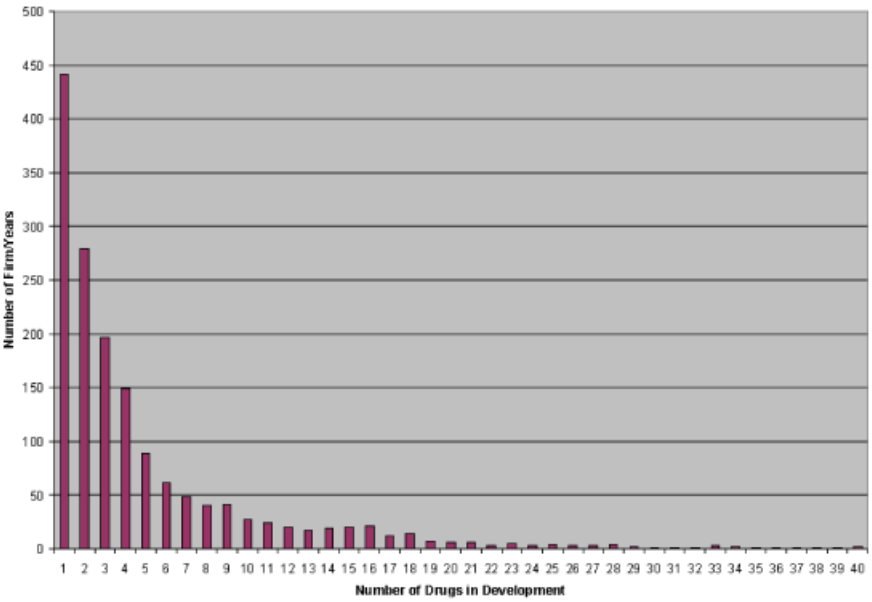

Figure 1. Drugs in development

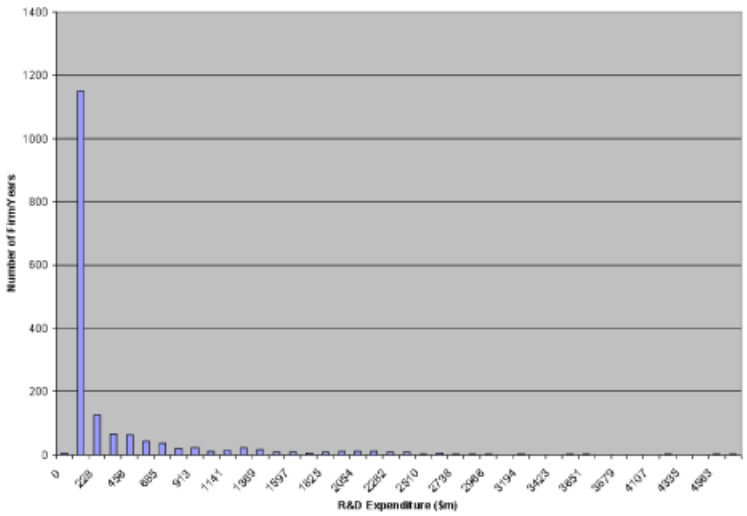

Figure 2. Annual R&D expenditure

trials. In Phase I, the drug is tested for safety on a small group (e.g. 20) of healthy volunteers. Phase II tests concentrate on safety but the test is on a larger group of patients with the condition (e.g. 200). Phase III are the large efficacy trials with upwards of 3,000 patients participating. Once the trials are completed the results of all three stages are presented to the FDA in the form of a new drug application (NDA).

Table II presents some basic summary statistics on the drugs owned by the firms in the sample. The first set of three rows show the mean length in months of successful durations. The second set of three

DOI: 10.1002/hec

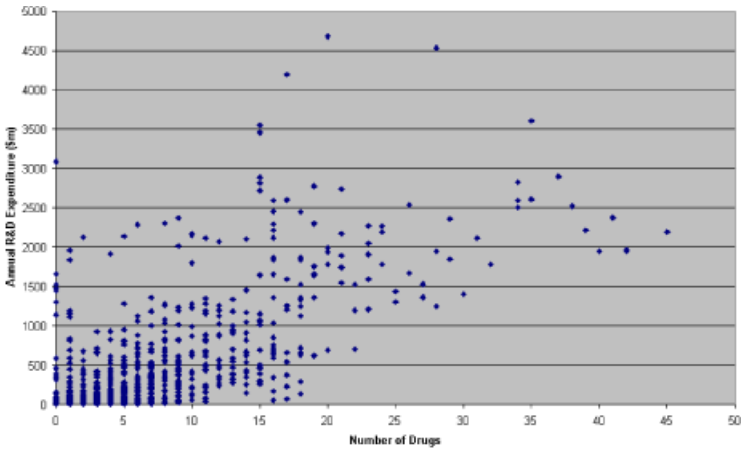

Figure 3. R&D expenditure by drugs in development

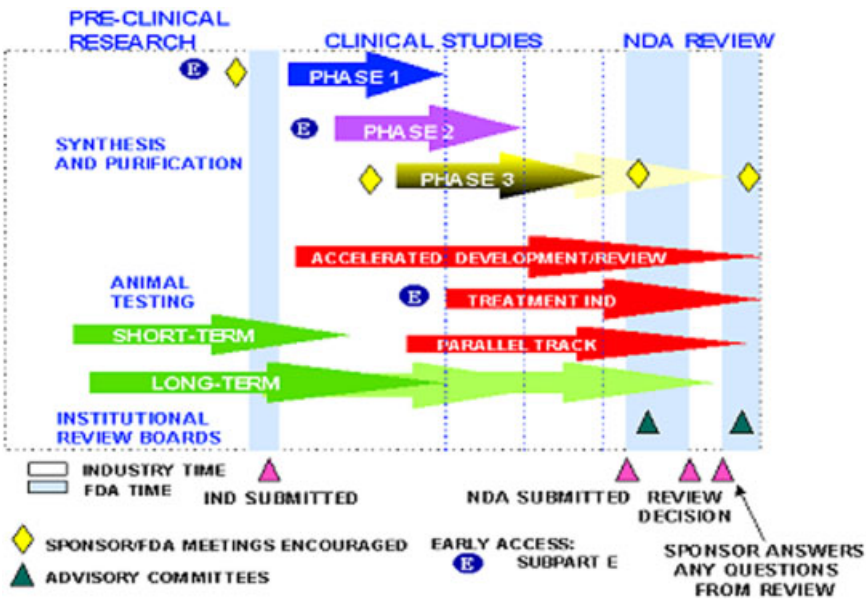

Figure 4. CDER chart of the development process

Table II. Summary statistics for drugs

	Obs	Mean
Duration (months)		
Phase I	235	16.58
Phase II	144	30.65
Phase III	130	27.15
Success (frequency)		
Phase I	314	0.75
Phase II	302	0.48
Phase III	184	0.71

DOI: 10.1002/hec

rows shows the frequency with which drugs successfully complete the phase. The table shows that these drugs seem to be fairly representative (see Adams and Brantner, 2006; DiMasi *et al*., 2003). Successful durations vary by a month or two and success rates vary by a few percentage points of those reported in Adams and Brantner (2006).

3. RESULTS

3.1. Mean expenditure estimates

Table III presents regression results for the amount of research and development expenditure on the number of drugs in human clinical trials. There are six regressions reported in the table. First are the basic regressions on the number of drugs in human clinical trials then on the number of drugs in each of the three phases of development. These regressions are then repeated adding measures of time and firm characteristics. All results report robust standard errors clustering on firm name. The number of drugs is the number of drugs in development for each firm/year combination. Note that 'new formulations' of existing drugs are not included in the count variable.[9] This is done in order to make the estimates closer to DiMasi *et al*. (2003) estimate for new molecular entities.[10] The variable time is simply the number of years from 1988. The variable 'sales' is the amount of net sales for each firm/year. The time and sales variables allow the analysis to capture changes in expenditure over the time period and across firms, where 'sales' is probably best thought of a measure of firm size.

Table III shows that average expenditure per drug in human clinical trials is between \$74m and \$27m per year.[11] Once we include controls for time and firm characteristics, the results suggest that the average expenditure on drugs across all three phases of development is approximately \$27m per year. This estimate is quite precise and is statistically different from zero at traditional levels. If sales are not accounted for then Phase I expenditure is estimated to be \$81m per year, \$68m for drugs in Phase II and \$77m for drugs in Phase III. Once time and sales are accounted for, these estimates fall to \$16m, \$34m and \$27m respectively.[12] The Phase II and III expenditures are estimated precisely and are statistically different from zero. The Phase I estimate is less precisely estimated and 0 lies within the traditional confidence interval.

How do these results compare to the estimates of expenditure in DiMasi *et al*. (2003)? We estimate the average annual expenditure on drugs in all three phases of human clinical trials is \$27m. If we take DiMasi *et al*. (2003) estimates of expenditure for each phase of \$15m, \$24m and \$86m for Phases I, II and III, respectively, and weight them proportionally to the time spent in development and the probability of being in each of the phases then we have the appropriate comparison.[13] This transformation gives an estimate of annual expenditure of \$21m.[14] Our estimate is higher than this transformed estimate from DiMasi *et al*. (2003) although \$21m lies within the 95% confidence interval.[15] To compare the expenditure by phase it is necessary to do another transformation. The numbers presented in DiMasi *et al*. (2003) are for the average drug over the length of the phase, while

[9]A new formulation may, for example, be an extended release version of an existing approved drug.
[10]Thanks to an anonymous referee for this suggestion. The estimates of expenditure per drug including formulations are lower than the estimates presented here. The last section suggests that this occurs because expenditure on new formulations is substantially lower than for other drugs.
[11]Most of the decrease seems to come from including the sales variable.
[12]Note that these results are most properly thought of as correlations between the number of drugs and the amount of expenditure. There has been no effort made to account for endogeniety in the joint decisions to increase expenditure and take more drugs into clinical trials.
[13]From DiMasi *et al*. (2003) the average durations are 12, 26 and 34 months, respectively.
[14]The average expenditure is $(12*15+0.71*26*24+0.31*34*86)/(12+26+34) = (180+443+906)/72 = 21$.
[15]\$21m does not lie within the 90% confidence interval. Although, this does not account for sampling error with the original DiMasi *et al*. (2003) estimate.

DOI: 10.1002/hec

Table III. R&D expenses OLS (robust standard errors)

	1	2	3	4	5	6
All phases	74.31**		74.86**		26.85**	
	(5.87)		(5.91)		(3.44)	
Phase I		80.72**		78.05**		16.78
		(18.61)		(18.61)		(10.35)
Phase II		68.01**		69.07**		33.59**
		(12.72)		(12.67)		(6.80)
Phase III		76.94**		80.08**		26.78**
		(23.90)		(24.07)		(11.08)
Time			−62.34**	−62.27**	−23.75**	−25.31**
			(10.88)	(13.08)	(5.91)	(6.76)
Time^2			4.32**	4.31**	2.09**	2.19**
			(0.83)	(0.97)	(0.46)	(0.53)
Sales					0.07**	0.07**
					(0.01)	(0.01)
Constant	−22.64	−21.49	147.19**	147.97**	19.87	23.16
	(20.88)	(21.00)	(31.04)	(36.18)	(17.20)	(17.69)
Observations	1682	1682	1682	1682	1682	1682
R^2	0.59	0.59	0.60	0.60	0.89	0.89

Standard errors are clustered on firm names. **Is statisically different from 0 at 1% level and *is at 5% level.

we have estimated expenditure for 1 year. If we use the phase durations presented in Table II we can estimate expenditure for the whole phase. This procedure gives 1.38∗17m = \$24m for Phase I, which is more than DiMasi *et al.* (2003) estimate of \$15m for Phase I. For Phase II the same method produces an estimate of \$86m, which is much higher than the DiMasi *et al.* (2003) estimate of \$24m. Finally, for Phase III this method gives an estimate of \$61m, which is less than the DiMasi *et al.* (2003) estimate of \$86m. For Phases I and III, the DiMasi *et al.* (2003) estimates lie within the 95% confidence interval around our estimates. However, there is no overlap between the confidence interval around the DiMasi *et al.* (2003) estimate of Phase II expenditure and the confidence interval around our estimate.

It is not clear what explains such a large discrepancy between our estimate of Phase II expenditure and DiMasi *et al.* (2003) estimate. One possibility and a more general concern is that our method may be misallocating expenditure to drugs in different stages of development. This may occur for two reasons. First, we assume that if a drug moves into a new phase in a particular year then the drug has been in that phase for the whole year. Still, given the expected difference in Phases II and III expenditure this assumption is more likely to lead to an underestimate of Phase III expenditure than an overestimate of Phase II expenditure. Second, the relationship between financial years and the years assigned in the data. Again, this may reduce the accuracy of the estimates but it is unlikely to bias the estimates. Another possibility is that there is under reporting of drugs in human clinical trials particularly in the earlier phases.[16]

As other work has shown, expenditure on research and development is increasing at a substantial rate. In fact, here we have it increasing at a parabolic rate although this is due to the particular functional form that is used in the estimation. The results also show that there is a strong relationship between sales and research and development expenditure with every \$1 in sales associated with an extra \$0.07 in R&D expenditure. Note also, adding sales to the regression substantially improves the model's ability to explain the data. The constant in this estimation cannot really be interpreted as we do not have a measure of the stock of drugs in development as of 1989. We are only able to observe new development starts in 1989 and later.

The baseline regression measures the average expenditure on new drugs by firm and year. It does not account for whether that average may be driven up by the large increase in R&D expenditure observed

[16]It is not clear exactly how such under reporting would bias the results and in what direction.

DOI: 10.1002/hec

during the period or by large expenditures by the larger pharmaceutical firms. Latter regressions add a parabolic time trend and a parameter ('sales') to capture variation across firms. The time trend estimates capture the large increase in expenditure that occurred during the period. The sales coefficient suggests that large firms, at least large firm/years, are associated with large expenditures per drug.[17] This variation across firms is also captured to some extent via the quantile regression analysis presented in the next section.[18] This analysis suggests larger firms spend more on clinical trials.

Note that the measured positive relationship between sales and expenditure may not be causal. Larger pharmaceutical firms may have different R&D strategies than smaller firms. For example, Big Pharma may run substantially more trials over different treatments, comparison groups, and populations compared with smaller firms. Such trials may put the firm in a better position to sell the drug internationally and in multiple domestic markets for different indications. Note also that these numbers do not measure expenditure by smaller non-publicly traded firms such as those funded by venture capital firms.

3.2. Quartile expenditure estimates

Table IV presents results from the 25, 50 and 75% quartile regressions. Comparing these results to the results from columns 5 and 6 in Table III we see that expenditure per drug per year is substantially less at the lower quartiles. At the bottom quartile, expenditure per new drug in development is around \$9m per year, with \$15m at the median and \$18m at the top quartile. All these numbers are estimated fairly precisely. These numbers compare to \$27m per year for the mean. Similarly, estimated expenditures per phase of development are substantially lower at the 25, 50 and 75% quartiles relative to the mean. The results suggest that the distribution of expenditure on drug development is quite skewed. These results suggest that a number of firms spend very large sums on drug development.

As before, we can transform our median estimates to compare with the median estimates presented in DiMasi *et al*. (2003). This procedure gives $1.38*14.60 = \$20$m for Phase I, which is more than DiMasi *et al*. (2003) estimate of \$14m for Phase I. For Phase II the same method produces an estimate of \$36m, which is much higher than the DiMasi *et al*. (2003) estimate of \$17m. Finally, for Phase III this method gives an estimate of \$30m, which is much less than the DiMasi *et al*. (2003) estimate of \$62m.

3.3. Implications for cost estimates

If we use the mean estimates for expenditure on drugs in development in place of the survey estimates used by DiMasi *et al*. (2003) we can recalculate the over all 'cost of drug development' or more accurately the net revenue needed to make investment in drug development profitable. Doing this calculation using the same durations and success rates as reported in Adams and Brantner (2006) we estimate new drug development cost to be \$1214m, which is much higher than the original estimate of \$802m or even the Adams and Brantner (2006) estimate of \$867m. These high estimates may be due to measurement of expenditure on the marginal drug rather than the average drug.[19] However, such an estimate may be more useful to policy makers as it is more likely to measure the impact of changes in

[17]The baseline analysis is measured at the firm/year level. This means that we are measuring the expenditure of the average firm/year on a drug rather than the expenditure on the average drug. If the average firm/year is large then our measure may be high because large firms happen to spend more on drugs. By adding a coefficient for firm size the measure can be adjusted to account for the variation in expenditure across firms. Note however, that if the average drug is developed in a large firm then these results may need to be adjusted either by adding back in the sales coefficient multiplied by the sales of the firm, which produces the average drug or by looking at the quartile estimates in the next section.

[18]Note that the coefficient estimate on sales is larger for the 75% quartile compared with the 50% quartile and the 25% quartile. That is, for drugs with larger expenditures there is a stronger relationship between the size of the firm and the size of the expenditures.

[19]Note also that these estimates are based on the very high Phase II expenditure estimates.

DOI: 10.1002/hec

Table IV. R&D expenses quantiles (standard errors)

	25%	25%	50%	50%	75%	75%
All phases	8.88**		14.60**		18.68**	
	(0.12)		(0.19)		(0.15)	
Phase I		7.65**		18.35**		18.31**
		(0.42)		(0.55)		(0.44)
Phase II		10.73**		13.98**		22.59**
		(0.36)		(0.46)		(0.39)
Phase III		7.84**		13.05**		15.45**
		(0.44)		(0.58)		(0.50)
Time	−2.48**	−2.56**	−3.58**	−3.52**	−4.46**	−4.09**
	(0.69)	(0.80)	(1.01)	(1.00)	(0.80)	(0.85)
Time^2	0.19**	0.19**	0.29**	0.29**	0.39**	0.36**
	(0.05)	(0.05)	(0.07)	(0.07)	(0.05)	(0.06)
Sales	0.07**	0.07**	0.08**	0.08**	0.10**	0.10**
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Constant	2.15	2.16	6.82*	6.54*	14.85**	13.81**
	(2.27)	(2.61)	(3.31)	(3.26)	(2.52)	(2.69)
Observations	1682	1682	1682	1682	1682	1682
Pseudo R^2	0.60	0.60	0.70	0.70	0.80	0.80

Standard errors are in parenthesis. **Refers to statistical significance from 0 at the 1% level, *at the 5% level.

policy on the development of new drugs. We could interpret these estimates as stating a firm would need expected net revenue of over $1 billion to develop one more drug for the market.[20]

3.4. Expenditure by therapy

DiMasi *et al.* (2004) presents estimates of drug development costs for a small number of major therapies. In attempt to replicate this work, Table V presents results similar to those presented in Table III but where the drug counts are by major therapeutic category. Table V presents the marginal cost of a drug by major therapy grouping. This number is estimated by counting the number of drugs in human clinical trials for each of the major categories presented.[21] Note, that we would not expect these numbers to be negative.[22] The table shows cardiovascular, dermatological, genitourinary, anticancer and neurological drugs all have more expenditure per drug in human clinical trials than the average drug. Note, however, only genitourinary drugs are estimated to be statistically different from the average at traditional levels. New formulations of existing drugs have substantially smaller expenditure in human clinical trials than the average drug. In fact, expenditure on new formulation is not estimated to be statistically different from zero, but is statistically different from the average. The reader may be surprised that biotech drugs are estimated to have less than average expenditure (although the estimate is not statistically different from the average). This may be due to imprecise measurement, or it may be due to the way these drugs are categorized in the data. That is, more important biological drugs may be categorized under their indication (anticancer or musculoskeletal) rather than as a product of the biotech industry.

Some of these results can be compared with the results presented in DiMasi *et al.* (2004). It should be noted, however, that in both this paper and the DiMasi *et al.* (2004) paper the sample sizes for individual therapeutic categories can be quite small. There are three categories in which both papers

[20]Thanks to Mark Duggan for his thoughts about the differences between marginal and average drugs.

[21]Note that we only include the larger therapeutic categories as smaller categories do not have enough drugs in human clinical trials for reliable estimates. Thanks to an anonymous referee for this suggestion. We have also estimated expenditure by therapy for each phase, but we do not include these results because of concern about the reliability of the estimates given the small number of drugs in each phase for each therapy.

[22]Therefore, the observed negative coefficients suggest that the model may be misspecified, although none of the negative coefficients are statistically significantly different from zero.

DOI: 10.1002/hec

Table V. R&D expenses OLS by therapy for all phases

	1		2		3	
	Coefficient	Robust SE	Coefficient	Robust SE	Coefficient	Robust SE
Cardiovascular	137.65**	26.28	141.48**	26.05	35.85*	17.75
Dermatological	254.60**	106.99	261.49*	104.54	99.71*	48.86
Formulations	−3.69	8.96	−6.28	8.42	4.01	3.45
Genitourinary	58.96	50.14	52.98	48.27	108.04**	41.06
Anti-infective	129.96**	35.87	130.07**	35.50	26.56	14.83
Anticancer	56.17*	27.82	52.25*	26.50	43.14**	15.78
Neurological	136.01**	29.25	139.13**	29.33	33.32*	16.03
Biotechnology	26.89	15.03	26.48	14.88	24.40**	6.75
Miscellaneous	−10.14	16.79	−9.31	16.24	2.81	5.08
Time			−63.53**	11.06	−22.89**	6.20
Time^2			4.60**	0.84	1.96**	0.49
Sales					0.07**	0.01
Constant	7.54	22.91	168.53**	34.66	25.67	17.71
Observations	1682		1682		1682	
R^2	0.65		0.66		0.90	

Standard errors are clustered on firm names. **Refers to statistical significance at the 1% level and *refers to the 5% level.

report results – cardiovascular, anti-infective and neurological/CNS.[23] For these three categories the expenditure estimates for drugs in any of the three phases of human clinical trials are $36m, $27m and $33m, respectively, where the estimate for cardiovascular drugs and neurological drugs are statistically significantly different from 0 at the 95% level and the estimate for anti-infective drugs is not. To compare these numbers to the numbers in DiMasi *et al*. (2004) we can make the same transformation as above to get estimates of $17m, $33m and $17m respectively.[24] While the magnitudes of the estimates do not differ that greatly, particularly for anti-infectives, the DiMasi *et al*. (2004) estimates are also located within the traditional confidence intervals of the estimates presented in Table V.

These results support the argument in Adams and Brantner (2006) that there is substantial variation in drug development costs by therapeutic category. On average annual expenditure by drug is $27m. However, for genitourinary drugs like Viagra, the expenditure number is four times higher. It is also higher for dermatological and cancer drugs. In contrast annual expenditure on new formulations of existing drugs is only a couple of million of dollars. Do therapeutic categories with high annual expenditures have high success rates and short durations to compensate? Not necessarily. Results presented in Adams and Brantner (2006) suggest genitourinary drugs do have very high success rates and relatively short durations. This means that their overall drug development costs may not be too different from 'the average drug'. However, cancer drugs have relatively low success rates and long durations making them much more expensive than the average drug (Adams and Brantner, 2006).

4. CONCLUSION

Recent criticism of the study by DiMasi *et al*. (2003) argues it is not possible to verify the results because the data are confidential. Further, Light and Warburton (2005) argue the sample of expenditure estimates may not be representative and may be biased upwards. This paper attempts to replicate DiMasi *et al*. (2003) expenditure estimates using publicly available data. By matching information on

[23]The last category may not overlap as the definition of CNS drugs in DiMasi *et al*. (2004) may not be the same as the definition of neurological drugs used in Pharmaprojects.

[24]The formula is the same as the one presented in footnote 14 where the expenditure estimates and the probabilities are from DiMasi *et al*. (2004) and the proportion of time in each phase is as for the original formula. Note that DiMasi *et al*. (2004) do not present duration by phase for individual therapeutic categories.

DOI: 10.1002/hec

drugs in development with research and development expenditure over the period 1989–2001 and across some 180 firms, we infer the additional annual expenditure on each new drug in development. Our results suggest expenditure on Phases I and II is higher than suggested by DiMasi *et al*. (2003) while expenditure on Phase III is lower. If we combine our estimates in this paper with estimates on success rates and durations from Adams and Brantner (2006) we find that the 'cost of drug development' (or the net revenue needed to make investment in new drugs profitable) is over $1 billion and higher than the DiMasi *et al*. (2003) estimate of $802m. As we are estimating expenditure on the *additional* drug we may be estimating the revenue needed to invest in the marginal rather than the average drug. While this may make our estimate higher, it may also make our estimate more useful when considering the consequences of policy changes such as price regulation. This paper also confirms results presented in Adams and Brantner (2006) that there is a substantial amount of variation in expenditure by therapeutic category.

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DOI: 10.1002/hec

EXHIBIT G

Pharma MedTech BusinessIntelligence

"The Pink Sheet" DAILY

Biosimilar Reimbursement Under The Sequester: The Lower The Price, The Bigger The Spread

[redacted] McCaughan Email the Author | View Full Issue

[redacted] Article # 14140806001 | Posted: August 8 2014 2:45 PM

Executive Summary

With its biosimilar application submitted to FDA, Novartis will likely become the first company to test the Medicare reimbursement formula for the new product class. The 2% sequester cut in Medicare may actually make that formula more attractive for biosimilars than the original law.

FDA finally has a biosimilar application to review.

On July 24, Novartis AG announced that it has a BLA for a version of Amgen's *Neupogen* (filgrastim) pending at FDA. It will thus set all kinds of precedents as the first biosimilar reviewed under the new 351(k) pathway (unless someone else has snuck an application in without announcing it, which seems unlikely).

Upon approval, it will also test a novel Medicare Part B reimbursement formula, intended to put biosimilars on a more equal footing when it comes to competing in that key segment. In an interview with "The Pink Sheet" DAILY, Mark McCamish, head of Global Biopharmaceutical and Oncology Injectables Development at Novartis' Sandoz Inc. subsidiary, highlighted that reimbursement formula as a key reason why the company opted to use the 351(k) route rather than file for a full BLA – as Teva Pharmaceutical Industries Ltd. did, getting approval in 2012 for its version of filgrastim ("Sandoz's Filgrastim Biosimilar Relies On Data Extrapolation" — *"The Pink Sheet" DAILY*, Jul. 24, 2014).

Related Articles:

Sandoz's Filgrastim Biosimilar Relies On Data Extrapolation
"The Pink Sheet" DAILY Jul. 24, 2014

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The Medicare reimbursement formula may in fact be even more attractive than intended, thanks to the 2% across-the-board payment cut in Medicare triggered by the sequester in 2013.

The sequester is nobody's idea of rational public policy. But it just might end up working in a manner that makes the "spread" on biosimilars larger than on innovator products, with the size of the "spread" collected by physicians actually increasing as the price of the biosimilar decreases.

Like most issues involving Medicare reimbursement, the explanation is convoluted – and like everything involving biosimilars, there is no precedent to cite yet to show how it actually works in the real world. But here is what we know:

Under Section 3139 of the Affordable Care Act, biosimilars approved by FDA under the 351(k) pathway will be reimbursed under Medicare Part B using a unique formula: average sales price plus 6% of the innovator's ASP (rather than 6% of the biosimilar ASP).

The intention was to assure that biosimilars would not be hampered by the paradoxical way that Part B pricing works. In general, a lower price in Part B means a smaller "spread" for physicians and therefore an incentive to choose higher priced products. So, if a product like Teva's *Granix* (tbo-filgrastim) is sold at an ASP of $80 versus Neupogen's $100, a physician would collect a spread of $4.80 for using Granix (6% of $80), compared to $6 for using Neupogen. And if Teva discounts even more steeply, the spread just gets smaller.

That obviously isn't much of an incentive for the doctor to choose the lower cost option.

Editor's Note

This story was contributed by The RPM Report. The RPM Report's FDA/CMS Summit for Biopharma Executives, convening Dec. 11-12 in Washington, D.C., features discussions on drug pricing, payer views on breakthrough drug prices, changes in the Medicare drug benefit, and how health insurance exchanges are impacting pharma. Learn more and register here

As written, the biosimilar law would mean that a physician choosing Novartis' 351(k) version of filgrastim would still collect a $6 spread, no matter what the ASP is. That would assure a level playing field.

The sequester, however, changes those formulas – and does so in a way that actually makes the biosimilar reimbursement more attractive than the innovator.

When the 2% payment cut took effect last year, CMS applied it both to the ASP and to the 6% spread. Thus, providers are receiving a net payment of ASP+4.3%. That by itself is a complicated calculation because the sequester only impacts the federal government's portion of the payment (80% of the charge); patients – or their supplemental insurance policies – pay the other 20%, and that is not reduced by the sequester. (The American College of Rheumatology explains the formula here .)

Thus, in this hypothetical examples, a provider using Neupogen at an ASP of $100 would receive a $4.30 spread. Granix at $80 ASP would be reimbursed at a total of $83.44 – still the smaller amount.

However, a 351(k) biosimilar priced at $80 would produce a total reimbursement of $84.62 – a spread of $4.62 that is a smidge higher than the $4.30 provided for the brand. And, in a hypothetical case of an even more deeply discounted biosimilar, say at $50, the spread actually goes up: the total reimbursement would be $55.10 in that instance.

All of this, of course, assumes that CMS agrees with this way of calculating the formula for biosimilars under the sequester. It also assumes the provider purchases the product at ASP; the real market is much more dynamic than that, and innovator companies will of course be testing different discounting models to maintain the most attractive reimbursement they can.

Still, it appears clear that the sequester in Medicare will have the unintended impact of making Part B payments more attractive for biosimilars than they would have been.

EXHIBIT H

US006162427A

United States Patent [19]

Baumann et al.

[11] **Patent Number: 6,162,427**

[45] **Date of Patent: *Dec. 19, 2000**

[54] **COMBINATION OF G-CSF WITH A CHEMOTHERAPEUTIC AGENT FOR STEM CELL MOBILIZATION**

[75] Inventors: **Matthias Baumann**, Karl-Ludwig-Strasse; **Peter-Paul Ochlich**, Wallonenstrasse, both of Germany

[73] Assignee: **Roche Diagnostics GmbH**, Mannheim, Germany

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/091,401**

[22] PCT Filed: **Dec. 12, 1996**

[86] PCT No.: **PCT/EP96/05568**

§ 371 Date: **Nov. 12, 1998**

§ 102(e) Date: **Nov. 12, 1998**

[87] PCT Pub. No.: **WO97/22359**

PCT Pub. Date: **Jun. 26, 1997**

[30] **Foreign Application Priority Data**

Dec. 20, 1995 [DE] Germany 195 49 232

[51] **Int. Cl.**[7] **A61K 38/19**; A61K 31/675

[52] **U.S. Cl.** **424/85.1**; 514/2; 514/8; 514/76; 514/54; 514/110; 514/114

[58] **Field of Search** 424/85.1; 514/2, 514/8, 76, 54, 110, 114

[56] **References Cited**

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[57] **ABSTRACT**

The invention relates to the use of G-CSF in combination with a chemotherapeutic agent (in particular, cyclophosphamide) to produce a pharmaceutical preparation for boosting the mobilization of hematopoietic stem cells from bone marrow in the treatment of diseases requiring peripheral stem cell transplantation. The claimed combination results in more efficient leukapheresis, e.g. before myeloblative or myelotoxic therapy.

7 Claims, No Drawings

COMBINATION OF G-CSF WITH A CHEMOTHERAPEUTIC AGENT FOR STEM CELL MOBILIZATION

The present invention relates to the novel use of G-CSF and a chemotherapeutic agent or a combination of chemotherapeutic agents to produce a pharmaceutical preparation for enhanced mobilization of hematopoietic stem cells in the treatment of diseases requiring peripheral stem cell transplantation as is the case, e.g., in high-dosage chemotherapy or bone marrow ablation by irradiation. In addition, the invention is directed to a pharmaceutical packaging unit containing G-CSF, chemotherapeutic agent(s) and informational instructions regarding the application of the G-CSF and the chemotherapeutic agent or the combination of chemotherapeutic agents for enhanced mobilization of hematopoietic stem cells prior to the onset of a corresponding therapy.

The use of high-dosage chemotherapy or bone marrow ablation by irradiation requires subsequent incorporation of hematopoietic stem cells into the patient, in which case recovery of such cells is required.

In the methods of peripheral stem cell recovery (e.g., in leukopheresis), the mobilization of bone marrow stem cells has a crucial influence on the efficiency of these methods. At present, 2–3 leukophereses are required for successful peripheral stem cell transplantation, resulting in considerable stress for the patients.

The success of treatment crucially depends on the mobilization of the bone marrow stem cells, the subsequent return of which permitting to achieve reconstitution of a functioning hematopoietic system.

Numerous substances capable of effecting such a mobilization are known, e.g., G-CSF (granulocyte colony stimulating factor).

Some chemotherapeutic agents are also known to possess the ability of mobilizing bone marrow stem cells (Richman et al., Blood, Vol. 47, No. 6. 1031 (1976)).

Various documents also describe the combination of G-CSF with other active substances. Thus, combined treatments using antibiotics are known from EP-A-0,648,501 and WO-A-95/28178. The U.S. Pat. No. 5,422,105 reports the combination with one or more antimicrobial substances such as antiviral, antifungal or antibacterial agents in order to enhance the effect of a CSF-1 therapy. In addition, there have been investigations on the use of G-CSF in association with high-dosage chemotherapies in autologous bone marrow transplantations (Lymphokine Cytokine Res. (1994), 13(6), 383–90; and Leukemia and Lymphoma (1995), 19(5–6), 479–84).

In other investigations related to bone marrow transplantations, Shirota et al. have determined that cyclophosphamide which is known as cytostatic agent facilitates the permeability of the endothelial barrier for stem cells (Exp. Hematol. 19, 369–373 (1991)).

As the required number of leukophereses is extremely stressing for the patient in the run-up to the treatment of particular diseases, e.g., in preparing a myeloablative or myelotoxic therapy, the invention was based on the object of achieving a superior yield of stem cells or a decrease in the number of leukophereses via enhanced mobilization of stem cells.

Surprisingly, it has now been found that an unexpectedly high stem cell concentration in blood can be achieved when administering G-CSF in combination with a chemotherapeutic agent (chemotherapeutic agents).

Therefore, the invention is directed to the use of G-CSF and a chemotherapeutic agent or a combination of chemotherapeutic agents to produce a pharmaceutical preparation for enhanced mobilization of hematopoietic stem cells in the treatment of diseases requiring peripheral stem cell transplantation, wherein G-CSF and the chemotherapeutic agent are present formulated in separate administration forms, so that they can be taken out separately and administered successively according to the optimum application regimen. According to the invention, it is preferred to apply the G-CSF prior to the onset of the administration of chemotherapeutic agents in order to enhance the mobilization of hematopoietic stem cells.

The combined use according to the invention of G-CSF and chemotherapeutic agent relates to all those diseases requiring recovery of stem cells from the blood for subsequent peripheral transplantation, particularly tumor diseases.

According to the present invention, G-CSF prepared using recombinant methods and variants thereof may be used. The term G-CSF or G-CSF variant according to the present invention encompasses all naturally occurring variants of G-CSF, as well as G-CSF proteins derived therefrom, modified by recombinant DNA technology, particularly fused proteins containing other protein sequences in addition to the G-CSF portion. Particularly preferred in this meaning is a G-CSF mutein having an N-terminal Met residue at position 1, which is suited for expression in prokaryotic cells. Similarly suitable is a recombinant G-CSF variant free of methionine which may be prepared according to WO-A-91/11520. The term "G-CSF variant" is understood to comprise those G-CSF molecules wherein one or more amino acids may be deleted or replaced by other amino acids, with the essential properties of G-CSF, particularly the ability to mobilize bone marrow cells, being largely retained. Suitable G-CSF muteins are described in EP-A-0,456,200, for example.

As chemotherapeutic agents in the meaning of the invention those therapeutic agents may be used which open the endothelial barrier, rendering it permeable for stem cells. Hereinbelow, chemotherapeutic agents are understood to be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells. Here, in particular, cytostatic agents or derivatives thereof from the following group of cytostatic agents may be mentioned: alkylating agents such as, e.g., cyclophosphamide, chlorambucil, melphalan, busulfan, N-mustard compounds, mustargen; metal complex cytostatic agents such as metal complexes of platinum, palladium or ruthenium; antimetabolites such as methotrexate, 5-fluorouracil, cytorabin; natural substances such as vinblastine, vincristine, vindesine, etc.; antibiotic agents such as dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, etc.; hormones and hormone antagonists such as diethylstilbestrol, testolactone, tamoxifen, aminoglutethimide, and other compounds such as, e.g., hydroxyurea or procarbacin, as well as corticoids such as prednisolone, with cyclophosphamide being particularly preferred.

G-CSF may be administered using standard administration forms, with injection solutions being preferred. Water is preferably used as injection medium which includes adjuvants common in injection solutions, such as stabilizers, solubilizers and buffers. For example, such adjuvants are tartrate and citrate buffers, ethanol, complexing agents such as ethylenediaminetetraacetic acid and the non-toxic salts thereof, high molecular weight polymers such as liquid polyethylene oxide for viscosity control. Liquid vehicles for injection solutions must be sterile and are preferably filled into ampoules.

The chemotherapeutic agents may be applied in liquid or solid form on the enteral or parenteral route. Here, the

standard administration forms such as tablets, capsules, coated tablets, syrups, solutions and suspensions are possible.

The dosage may depend on various factors such as mode of application, species, age, or individual condition. According to the invention, from 5 to 300 μg/kg/day of G-CSF sc. is applied. The administration of G-CSF is effected once per day over two to three days. The administration of chemotherapeutic agent(s) is initiated either immediately after the second or third G-CSF injection or on the fourth day. According to the invention, from 0.05–100 mg/kg/day of chemotherapeutic agent(s) is/are administered.

Surprisingly, it was determined that administration of G-CSF prior to opening of the endothelial barrier induced by chemotherapeutic agents significantly increases the stem cell mobilization and thus, can improve leukopheresis efficiency.

By administering G-CSF prior to administration of the chemotherapeutic agent(s), a massive granulopoiesis in the spleen and a substantial increase of the spleen weight could be observed which, according to Bungart et al., Brit. J. Haem. 76, 174–179, 1990, is attributable to the stem cell mobilization.

In addition, administration of G-CSF and a chemotherapeutic agent in the run-up to a, e.g., antitumor therapy offers the opportunity of recovering the stem cells mobilized in large amounts from the blood with higher efficiency (e.g., using leukopheresis), then performing the antitumor therapy using a cytostatic agent or irradiation and subsequently, conducting the peripheral stem cell transplantation.

The invention is also directed to a pharmaceutical packaging unit including at least three spatially separated components, the first component being a standard administration form of G-CSF, the second component representing a standard pharmaceutical administration form of a chemotherapeutic agent or a combination of chemotherapeutic agents, and the third component comprising informational instructions for the administration of G-CSF prior to administration of the chemotherapeutic agent (chemotherapeutic agents) for enhanced mobilization of hematopoietic stem cells.

Where G-CSF is administered in combination with, e.g., two chemotherapeutic agents, these chemotherapeutic agents may be formulated separately or together, so that the packaging unit consists of either three or four spatially separated components.

Without intending to be limiting, the invention will be illustrated in more detail in the following embodiment.

Embodiment

Using mice, the in vivo interactions between rh G-CSF and cyclophosphamide (CY) applications regarding the effects of various schemes of treatment on

the hematopoietic capacity of femoral cells,

the femoral bone marrow and spleen histologies, and

the leukocyte number (WBC) were examined.

The following test groups were examined:

G-CSF/CY group: G-CSF application was effected on three successive days prior to cyclophosphamide (CY) administration; the third injection was effected immediately before CY administration.

CY/G-CSF group: corresponding to the present clinical practice, G-CSF was applied beginning 24 hours after CY injection.

CY group: treatment was effected using CY alone.

Control group.

1. Materials

a) Animals

Female NMRI mice were purchased. Initially, their body weight was approximately between 26 and 28 g. The animals were fed on pellets and had ad libitum access to feed and drinking water.

They were kept separately at room temperature (23±1° C.) and a relative humidity of 55% (50–70%). The room air was exchanged approximately 10 times per hour. The day/night rhythm was held constant, with light/dark periods of 12 hours each, beginning at 6 a.m. A light intensity of about 60 lux was provided throughout the room during the light period. The health condition of the animals was recorded daily, and cleaning was effected at regular intervals. Categorizing of the animals into the individual test groups can be inferred from Table 1.

b) Reagents

Recombinant human (rh) G-CSF, cyclophosphamide

2. Methods

a) Peripheral Leukocyte Number (WBC)

The measurements were conducted using an analyzer. Under anesthesia, 25 μl of native whole blood was withdrawn from the postorbital plexus using heparinized glass capillaries, diluted with 3.75 ml of an isosmotic solution, and analyzed with respect to WBC.

b) Femoral Bone Marrow Cell Number (BMC)

After 4 weeks of treatment or after a two weeks period free of treatment, respectively, the femora of 5 animals (n=8, G-CSF/CY group) from the various test groups were collected. They were opened aseptically at the proximal and distal ends. Rinsing the bone marrow cavities with 1.5 ml of MEM (supplemented with penicillin/streptomycin and L-glutamine), the bone marrow cells were recovered using syringes equipped with adapters. Except for the G-CSF/CY test group wherein both femora of from 3 to 8 animals were analyzed, one femur of each animal was examined. The cells were counted in an autolyzer system.

c) CFU-C Test (Colony-Forming Units Culture)

The femoral bone marrow cell number was adjusted to 2.5×10^{-6} cells/ml in MEM (flow). 0.2 ml of this suspension was mixed with 0.5 ml of horse serum, 0.1 ml of thioglycerol (20 mM, diluted 1:4 with MEM), 1.0 ml of methylcellulose (2% in MEM), 0.6 ml of MEM (flow), and 0.1 ml of either additional medium or standardized stimulated mouse serum (1:200 dilution of serum, withdrawn 3 hours after ip. administration of 2.5 mg/kg lipopolysaccharide (LPS)) or 5 ng/ml rhG-CSF. The well-mixed semi-solid suspension was pipetted into Petri dishes 4 cm in diameter and incubated for 6 days at 37° C., 5% CO_2 and 95% r.h.. After addition of 0.5 ml of p-iodonitrotetrazolium violet solution (0.5 mg/ml PBS), the dishes were incubated for another 24 hours. The colonies were counted using a colony counter and standardized to 10^6 bone marrow cells.

d) Tissue Preparation and Histological Test

The animals were sacrificed on the day of final administration of the compounds, and spleen tissue as well as one femoral bone of each animal were fixed in 10% neutral-buffered formaldehyde solution. The bone samples were decalcified over two weeks in 5% formic acid, dissolved in formaldehyde/distilled water. Spleen and bones were stored routinely in paraffine, cut to 4 μm thickness, and stained with hematoxylin-eosin (HE), as well as with PAS. Bone marrow and spleen were semi-quantitatively evaluated with respect to cell quality, myelofibrosis and cellular necrosis using a light microscope.

e) Statistics

The various test groups were compared with control animals with respect to the end points of BMC, CFU-C response to G-CSF, CFU-C response to serum, and spleen weight. Repeated measurements of WBC (basis: 1, 2, 3, and 4 weeks) were transformed into an end point, based on the individual AUC approximation according to Zerbe et al., Biometrics 33, 653, 1992. Investigations for approximate normal distribution of WBC and spleen weight were analyzed according to the Welch T Test (Welch, Biometrika 34, 28, 1947) because a notable variance in the heterogeneity was observed. Due to the absence of an approximately normal distribution for the other end points, a permutational U test according to Mehta et al., CYTEL Software Corp. Turbo Version, Cambridge, U.S.A., 1992, was conducted. The method of multiple end point analysis was carried out for the end points of CFU-C, when administering G-CSF or serum, and the spleen weight. The end points after the period with no treatment (week 6) were analyzed for reversibility using a method according to Dunnett, JASA 50, 1096, 1955, which may be used for comparing with the controls. The calculations were performed using SAS, Version 6.10 (SAS/STAT: Changes and enhancements, Release 6.10, SAS Institute, 1994) and Statxact (Mehta et al., see above).

3. Results

a) Effects Regarding the Femoral Bone Marrow Cell Number (BMC)

The effects of various treatment regimens are included in Table 2. CY alone reduced the bone marrow cell number to about 60% of the control. Both combinations of CY and G-CSF reduced the number to about 30% of the control. Two weeks after the treatment was completed, however, the animals from the CY/G-CSF test group again showed increasing bone marrow cell numbers compared to the number immediately after treatment. At the end, they reached about 50% of the control. The other three test groups did not show any relevant changes during the follow-up period with no treatment.

b) Effects in the CFU-C Test

The response to serum of LPS-treated mice and to G-CSF was massively decreased in the CY group, compared to the bone marrow cells of the controls. A marked decrease was observed in G-CSF/CY treatment, while the CY/G-CSF test group showed increased colony formation in the presence of serum of LPS-treated mice and in the presence of G-CSF.

After a 2 weeks period with no treatment, the differences between both G-CSF groups and the controls became smaller. The proliferative response to serum of LPS-treated mice in the CY group showed after this period an extraordinary elevation compared to the marked decrease at the end of the treatment period.

c) Bone Marrow Histology

At the end of the treatment period: The granulopoietic cell density in the hematopoietically active areas of the femoral bone marrow markedly increased in both groups that had been treated with G-CSF and CY compared to the control animals and the CY test group (Table 3). The effect is particularly apparent in the G-CSF/CY test group. However, it can be seen that a clearly perceptible decrease of the hematopoietic areas as a result of fibrosis and ossification occurred in the various treatment groups. The CY group did not show any signs of increased granulopoiesis.

The stimulation of granulopoiesis due to administration of G-CSF prior to CY gave rise to all stages of maturity, whereas maturity stages were observed with less abundance upon administration of CY/G-CSF. The occurrence of single cell necroses was moderate in the G-CSF/CY and CY test groups and low in the CY/G-CSF group.

d) Effects on the Spleen

Histology at the end of treatment: Light microscopy of spleen tissue revealed a marked increase of granulopoietic cells after 4 weeks of treatment in both groups which had received G-CSF in combination with CY (Table 4). Granulopoiesis comprised all stages of granulopoietic cell maturation most markedly in the G-CSF/CY group. The granulopoietic cell proliferation in the CY/G-CSF group mainly consisted of myeloblastic cells, maturity stages were barely observable. The considerable increase of granulopoietic cells occurred in association with a considerable rearrangement of the spleen organic structure. Single cell necroses were observed in the G-CSF/CY group and to a lesser extent, in the animals of the CY/G-CSF test group. The spleen of animals that had been treated with CY alone showed a slight cellular decline in the follicles and the reticulum. During a 2 weeks period with no treatment, the changes returned to normal. In those groups, however, where G-CSF and CY had been administered, there were signs of a slightly increased hematopoietic stimulation in the form of elevated granulopoiesis, erythropoiesis and megakaryopoiesis.

e) Effects on Spleen Weight

An enormous increase (more than 3.3 fold of the control) was determined at the end of the treatment period in those animals that had been treated with G-CSF/CY (Table 5), and an 1.8 fold increase compared to the control was observed in the CY/G-CSF test group. There were no relevant effects on the spleen weight in the CY group.

f) WBC

Blood samples were taken prior to the first treatment and then once per week immediately before administering CY (or placebo). Thus, the blood samples in the G-CSF/CY test group were taken after the administration of G-CSF. Additional blood samples were collected at the end of the treatment period (after 4 weeks) and after the two weeks period with no treatment, respectively.

As is apparent from Table 6, there were no relevant differences in the WBC between the controls and the CY and CY/G-CSF groups.

During week 1, the G-CSF/CY test group showed a WBC slightly elevated above the upper limit of normal; during the following weeks 2, 3 and 4, there was a substantial WBC increase (from 7- to 8 fold of the control); complete reversal of this effect could be observed after the two weeks period with no treatment.

On the whole, it can be seen that the extent of osteomyelofibrosis and multifocal ossification after the treatment using G-CSF/CY was definitely higher compared to other methods. Furthermore, massive granulopoiesis and a substantial increase in spleen weight could be observed in this test group, emphasizing the increased stem cell mobilization.

The reduced CFU-C capacity of bone marrow cells after G-CSF/CY administration must be regarded as a result of an increased mobilization of progenitor cells into the blood. This is supported by the multiple end point analysis.

TABLE 1

Dosage and assignment of animals to test group		
Test groups	Weekly dosage during weeks 1 to 4	Number of animals per test group
G-CSF/CY group		
G-CSF administration sc. followed by	250 μg/kg on 3 successive days +	(n = 8)

TABLE 1-continued

Dosage and assignment of animals to test group

Test groups	Weekly dosage during weeks 1 to 4	Number of animals per test group
CY administration ip. (n = 16)	50 mg/kg immediately after G-CSF administration on the 3rd day	
CY/G-CSF group		
CY administration ip. after 24 hrs followed by G-CSF administration (n = 10)	50 mg/kg + 250 μg/kg on 3 successive days	(n = 5)
CY group		
ip. (n = 10)	50 mg/kg	(n = 5)
Control group		
(n = 10)	0.9% NaCl solution ip. and sc.	(n = 5)

After 6 weeks (2 weeks with no treatment) another examination was conducted in satellite groups.

TABLE 2

Bone marrow cell numbers (BMC) of mice after 4 weeks of treatment and after a 2 weeks period with no treatment († = animal died untimely)

Treatment group	BMC (× 10^6/femur) 4 weeks treatment	BMC (× 10^6/femur) After 2 weeks without treatment
Control	13.2	14.7
	†	15.9
	8.6	20.6
	21.3	18.1
	18	16.6
Median value	15.28	17.18
CY alone	13.6	12.7
	7.8	8.3
	13	6.1
	7.6	10.3
	2.9	9.9
Median value	8.98	9.46
G-CSF + CY	5.6	4.7
	7.4	9.5
	0.75	3.4
	2.1	0.48
	1.6	1.32
	7.8	2.2
	0.65	0.55
	1.2	0.72
Median value	3.39	2.86
CY + G-CSF	3.5	9.4
	3.5	7.4
	7.3	3.5
	7.9	9.1
	0.25	12.5
Median value	4.49	8.38

TABLE 3

Histopathological findings in bone marrow (femur)

	CY	G-CSF/CY	CY/G-CSF
After 4 weeks treatment			
Cellular decline	++	(+)	+/++
Fat cells	+/++	(+)	+

TABLE 3-continued

Histopathological findings in bone marrow (femur)

	CY	G-CSF/CY	CY/G-CSF
Hyperemia	—	—	+
Increased single cell necrosis	++	++	+
Stimulated granulopoiesis	±0	+++	++
Osteomyelofibrosis or multifocal ossification	1.5, +++	8/8, ++/+++	
After 2 weeks with no treatment			
Fat cells	(+)	(+)	(+)
Stimulated granulopoiesis	(+)	+/++	+/++
Osteomyelofibrosis or multifocal ossification	3/5, (+)/+	8/8, +++	3.5, +/++

(+) = minimal
+ = faint
++ = moderate
+++ = marked

TABLE 4

Histopathological findings in the spleen

	CY alone	G-CSF/CY	CY/G-CSF
State after 4 weeks treatment			
Cellular decline Follicle cells (lymphocytes)	+	—	—
Cellular decline Reticulum cells	+	—	—
Stimulated granulopoiesis	—	+++[1]	+/++[2]
Loss of follicle structure		+++	+/++
Increased single cell necrosis		++	(+)
After 2 weeks with no treatment			
Stimulated hematopoiesis	—	+	+

[1]All maturity stages
[2]Mainly myeloblastic cells

TABLE 5

Spleen weight († = animal died untimely)

Treatment group	Spleen weight (g) after 4 weeks treatment	Spleen weight (g) after 2 weeks with no treatment
Control	0.141	0.135
	†	0.090
	0.148	0.127
	0.410	0.133
	0.161	0.150
Median value	0.215	0.127
CY alone	0.107	0.183
	0.100	0.121
	0.174	0.235
	0.082	0.199
	0.189	0.133
Median value	0.130	0.174
G-CSF + CY	0.523	0.194
	0.448	0.248
	0.497	0.181
	0.477	0.262
	0.523	0.219

TABLE 5-continued

Spleen weight
(† = animal died untimely)

Treatment group	Spleen weight (g) after 4 weeks treatment	Spleen weight (g) after 2 weeks with no treatment
	0.492	0.261
	0.483	0.153
	0.486	0.273
Median value	0.491	0.224
CY + G-CSF	0.263	0.177
	0.218	0.228
	0.225	0.208
	0.324	0.218
	0.254	0.232
Median value	0.257	0.213

TABLE 6

Leukocyte number (WBC)
(† = animal died untimely)

Treatment group	Animal number	WBC (× $10^6/\mu l$) Time (weeks) 0	1	2	3	4	6
Control	1	5.6	5.2	9.4	3.3	6.6	—
	2	10	6.3	6.9	†	†	†
	3	7	4.8	7	3.4	6.8	—
	4	7.6	7.6	7.7	3.9	7.7	
	5	9.1	6	11	3.5	6.3	—
	6	8.4	5.1	9.5	6.2	7.5	4.5
	7	2.5	2.3	5.3	5	5.7	3
	8	9.5	7.3	12.2	8.5	13.7	7.8
	9	6.3	4.3	8.8	4.2	10.1	4.5
	10	6	5.9	8.5	5.9	8	6.4
Median value		7.20	5.48	8.63	4.88	8.04	5.24
CY alone	1	4.8	2.9	5	7.6	4	—
	2	9	7.1	5.3	2.7	2.8	—
	3	8.6	5.9	7.3	5.2	7	—
	4	6.3	4.8	6.3	6.1	4.8	—
	5	5.3	4.5	4.9	8.6	2.9	—
	6	6.4	5	5.1	6.7	4.1	3.6
	7	6.8	4.7	4.9	5	3.6	3.2
	8	5.6	5.7	4.8	4.1	3.7	4.6
	9	5.8	4.7	5.9	4.1	7.1	5.9
	10	9.4	6	7.1	4	2.8	5.9
Median value		6.80	5.13	5.66	5.41	4.28	4.64
G-CSF + CY	1	6.1	11.7	27.7	33.4	39.4	—
	2	6.8	12.4	46.5	43.7	30.5	—
	3	5.6	11.2	30.3	58.78	40.6	—
	4	4.3	11.7	35.3	51.4	40.7	—
	5	6.2	22.4	62.2	55.4	66.7	—
	6	6.2	12.6	49.2	84.2	85.4	—
	7	7.1	16.8	84.8	105.4	102.3	—
	8	8	18.6	82	117.6	70.1	—
	9	3	5.4	42.7	15.8	33.3	2.2
	10	4.6	18.2	62.8	69	33.2	3.9
	11	5.8	10.9	29.1	40	33.5	2.7
	12	5	12.7	43.8	51.9	28.1	6.4
	13	5.8	14.6	28.8	33.4	20	4.6
	14	6.2	10.2	50	36.8	45.4	3.6

TABLE 6-continued

Leukocyte number (WBC)
(† = animal died untimely)

Treatment group	Animal number	WBC (× $10^6/\mu l$) Time (weeks) 0	1	2	3	4	6
	15	8.6	20.2	30	36.2	25.3	5.2
	16	5.9	12.8	26.8	45.5	54.8	4.9
Median value		6.00	14.04	48.08	55.16	44.60	4.19
CY + G-CSF	1	6.7	6.1	6.9	9.5	12.68	—
	2	9.1	7.1	11.08	11.6	3.78	—
	3	9.1	11.1	4.5	9.6	5.9	—
	4	6.9	5.2	10.4	16.6	5	—
	5	6.3	3.9	7	#	11.6	—
	6	9.6	8.3	5	6.9	4.1	4.6
	7	6.6	6.3	8.6	7.1	7.5	4.2
	8	6.1	4.4	5.4	3.8	3.18	2.4
	9	10.3	7.6	4.8	4.2	6.2	3.7
	10	8.2	6.5	5.4	6.2	4.3	3.2
Median value		7.89	6.65	6.91	8.39	6.42	3.62

What is claimed is:

1. A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment, comprising administering to the patient a hematopoietic stem cell mobilizing-effective amount of G-CSF; and thereafter administering to the patient a disease treating-effective amount of at least one chemotherapeutic agent.

2. The method of claim **1**, wherein the disease is a tumor disease.

3. The method of claim **1**, wherein the G-CSF is recombinant G-CSF.

4. The method of claim **1**, wherein the at least one chemotherapeutic agent opens the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells.

5. The method of claim **1**, wherein the at least one chemotherapeutic agent is cyclophosphamide.

6. The method of claim **1**, wherein the G-CSF is administered once per day over 2–3 consecutive days, and the chemotherapeutic agent is administered immediately after the final administration of G-CSF, or on a fourth consecutive day.

7. A pharmaceutical kit, comprising

a first component comprising G-CSF;

a second component comprising at least one chemotherapeutic agent; and

a third component comprising instructions for the administration of the G-CSF prior to the onset of administration of the at least one chemotherapeutic agent.

* * * * *

EXHIBIT I

BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

FDA proposes the following goals contingent on the allocation of resources for each of the fiscal years 2013-2017 of at least the inflation-adjusted value of $20 million in non-user fee funds, plus collections of biosimilar user fees, to support the process for the review of biosimilar biological applications.

I. REVIEW PERFORMANCE GOALS

A. Biosimilar Biological Product Application Submissions and Resubmissions

B. Supplements with Clinical Data

C. Original Manufacturing Supplements

D. Goals Summary Tables

II. FIRST CYCLE REVIEW PERFORMANCE

A. Notification of Issues Identified during the Filing Review

B. Notification of Planned Review Timelines

III. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

A. Review Performance Goals – Biosimilar Biological Product Proprietary Names

IV. MAJOR DISPUTE RESOLUTION

A. Procedure

B. Performance goal

C. Conditions

V. CLINICAL HOLDS

A. Procedure

B. Performance goal

VI. SPECIAL PROTOCOL ASSESSMENT

A. Procedure

B. Performance goal

C. Reporting

VII. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

B. Scheduling Meetings

C. Meeting Minutes

D. Conditions

VIII. DEFINITIONS AND EXPLANATION OF TERMS

BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the authorization of the biosimilar biological product user fee program are summarized below.

I. REVIEW PERFORMANCE GOALS

A. Biosimilar Biological Product Application Submissions and Resubmissions

FY 2013

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2014

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2015

1. Review and act on 80 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 80 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2016

1. Review and act on 85 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 85 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2017

1. Review and act on 90 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 90 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

B. Supplements with Clinical Data

1. Review and act on 90 percent of original supplements with clinical data within 10 months of receipt.

2. Review and act on 90 percent of resubmitted supplements with clinical data within 6 months of receipt.

C. Original Manufacturing Supplements

1. Review and act on 90 percent of manufacturing supplements within 6 months of receipt.

D. Goals Summary Tables

Original and Resubmitted Applications and Supplements

SUBMISSION COHORT	PERFORMANCE GOAL				
	2013	**2014**	**2015**	**2016**	**2017**
Original Biosimilar Biological Product Application Submissions	70% in 10 months of the receipt date	70% in 10 months of the receipt date	80% in 10 months of the receipt date	85% in 10 months of the receipt date	90% in 10 months of the receipt date
Resubmitted Original Biosimilar Biological Product Applications	70% in 6 months of the receipt date	70% in 6 months of the receipt date	80% in 6 months of the receipt date	85% in 6 months of the receipt date	90% in 6 months of the receipt date

Original Supplements with Clinical Data	90% in 10 months of the receipt date
Resubmitted Supplements with Clinical Data	90% in 6 months of the receipt date
Manufacturing Supplements	90% in 6 months of the receipt date

II. FIRST CYCLE REVIEW PERFORMANCE

A. Notification of Issues Identified during the Filing Review

1. Performance Goal: For original biosimilar biological product applications and supplements with clinical data, FDA will report substantive review issues identified during the initial filing review to the applicant by letter, teleconference, facsimile, secure e-mail, or other expedient means.

2. The timeline for such communication will be within 74 calendar days from the date of FDA receipt of the original submission.

3. If no substantive review issues were identified during the filing review, FDA will so notify the applicant.

4. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.

5. FDA will notify the applicant of substantive review issues prior to the goal date for 90% of applications.

B. Notification of Planned Review Timelines

1. Performance Goal: For original biosimilar biological product applications and supplements with clinical data, FDA will inform the applicant of the planned timeline for review of the application. The information conveyed will include a target date for communication of feedback from the review division to the applicant regarding proposed labeling, postmarketing requirements, and postmarketing commitments the Agency will be requesting.

2. The planned review timeline will be included with the notification of issues identified during the filing review, within 74 calendar days from the date of FDA receipt of the original submission.

3. The planned review timelines will be consistent with the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMPs), taking into consideration the specific circumstances surrounding the individual biosimilar biological product application.

4. The planned review timeline will be based on the application as submitted.

5. FDA will inform the applicant of the planned review timeline for 90% of all applications and supplements with clinical data.

6. In the event FDA determines that significant deficiencies in the application preclude discussion of labeling, postmarketing requirements, or postmarketing commitments by the target date identified in the planned review timeline (e.g.,

failure to demonstrate a biosimilar biological product is highly similar to the reference product, significant safety concern(s), need for a new study(ies) or extensive re-analyses of existing data before approval), FDA will communicate this determination to the applicant in accordance with GRMPs and no later than the target date. In such cases the planned review timeline will be considered to have been met. Communication of FDA's determination may occur by letter, teleconference, facsimile, secure e-mail, or other expedient means.

7. To help expedite the development of biosimilar biological products, communication of the deficiencies identified in the application will generally occur through issuance of a discipline review (DR) letter(s) in advance of the planned target date for initiation of discussions regarding labeling, postmarketing requirements, and postmarketing commitments the Agency may request.

8. If the applicant submits a major amendment(s) (refer to Section VIII.B for additional information on major amendments) and the review division chooses to review such amendment(s) during that review cycle, the planned review timeline initially communicated (under Section II.B.1 and 2) will generally no longer be applicable. Consistent with the underlying principles articulated in the GRMP guidance, FDA's decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

    - If the review division determines that the major amendment will result in an extension of the biosimilar biological product review clock, the review division will communicate to the applicant at the time of the clock extension a new planned review timeline, including a new review timeline for communication of feedback on proposed labeling, postmarketing requirements, and any postmarketing commitments the Agency may request.

    - In the rare case where the review division determines that the major amendment will not result in an extension of the biosimilar biological product review clock, the review division may choose to retain the previously communicated planned review timeline or may communicate a new planned review timeline to the applicant.

    - The division will notify the applicant promptly of its decision regarding review of the major amendment(s) and whether the planned review timeline is still applicable.

III. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA will utilize user fees to implement various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design.

A. Review Performance Goals – Biosimilar Biological Product Proprietary Names

1. Proprietary names submitted during the biosimilar biological product development (BPD) phase

    a) Review 90% of proprietary name submissions filed within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

    b) If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

    c) If the proprietary name is found to be unacceptable, the above review performance goals also would apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

    d) A complete submission is required to begin the review clock.

2. Proprietary names submitted with biosimilar biological product application

    a) Review 90% of biosimilar biological product application proprietary name submissions filed within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

    b) A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (during the BPD phase) and has received tentative acceptance.

    c) If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

    d) If the proprietary name is found to be unacceptable, the above review performance goals apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

    e) A complete submission is required to begin the review clock.

IV. MAJOR DISPUTE RESOLUTION

A. Procedure: For procedural or scientific matters involving the review of biosimilar biological product applications and supplements (as defined in BsUFA) that cannot be resolved at the signatory authority level (including a request for reconsideration by the signatory authority after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal.

C. Conditions:

1. Sponsors should first try to resolve the procedural or scientific issue at the signatory authority level. If it cannot be resolved at that level, it should be appealed to the next higher organizational level (with a copy to the signatory authority) and then, if necessary, to the next higher organizational level.

2. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either grant or deny the appeal.

3. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

4. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the "response" should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

5. In these cases, once the required information is received by the Agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either deny or grant the appeal.

6. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

7. Note: If the Agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting to allow conformance with advisory committee administrative procedures.

V. CLINICAL HOLDS

A. Procedure: The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response.

B. Performance goal: 90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response.

VI. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

A. Procedure: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the Agency will evaluate certain protocols and related issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

1. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., are the clinical endpoints adequate to assess whether there are clinically meaningful differences between the proposed biosimilar biological product and the reference product).

2. Within 45 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

3. Protocols that qualify for this program include any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for comparative clinical trials that will form the primary basis for demonstrating that there are no clinically meaningful differences between the proposed biosimilar biological product and the reference product, and protocols for clinical trials intended to support a demonstration of interchangeability). For such protocols to qualify for this comprehensive protocol assessment, the sponsor must have had a BPD Type 2 or 3 Meeting, as defined in section VIII (F and G), below, with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.

4. If a protocol is reviewed under the process outlined above, and agreement with the Agency is reached on design, execution, and analyses, and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the Agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless

public health concerns unrecognized at the time of protocol assessment under this process are evident.

B. Performance goal:

For FY 2013, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2014, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2015, 80% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2016, 85% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2017, 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

C. Reporting: The Agency will track and report the number of original special protocol assessments and resubmissions per original special protocol assessment.

VII. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

1. **Procedure:** Within 14 calendar days of the Agency's receipt of a request and meeting package from industry for a BPD Type 1 Meeting, or within 21 calendar days of the Agency's receipt of a request and meeting package from industry for a Biosimilar Initial Advisory Meeting or a BPD Type 2, 3, or 4 Meeting, as defined in section VIII(D-H), below, CBER and CDER should notify the requester in writing of the date, time, place, and format (i.e., a scheduled face-to-face, teleconference, or videoconference) for the meeting, as well as expected Center participants.

2. **Performance Goal:** FDA will provide this notification within 14 days for 90 percent of BPD Type 1 Meeting requests and within 21 days for 90 percent of Biosimilar Initial Advisory Meeting and BPD Type 2, 3 and 4 Meeting requests.

B. Scheduling Meetings

1. **Procedure:** The meeting date should reflect the next available date on which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested.

a) Biosimilar Initial Advisory Meeting should occur within 90 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

b) BPD Type 1 Meetings should occur within 30 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

c) BPD Type 2 Meetings should occur within 75 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

d) BPD Type 3 Meetings should occur within 120 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

e) BPD Type 4 Meetings should occur within 60 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

2. **Performance goal:**

For FY 2013, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2014, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2015, 80% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2016, 85% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2017, 90% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

C. Meeting Minutes

1. **Procedure:** The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail.

2. **Performance Goal:** FDA will provide meeting minutes within 30 days of the date of the meeting for 90 percent of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings.

D. Conditions

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) and supporting documentation (i.e., the meeting package) should be submitted to the appropriate review division or office. The request should provide:

   a) A brief statement of the purpose of the meeting, the sponsor's proposal for the type of meeting, and the sponsor's proposal for a face-to-face meeting or a teleconference;

   b) A listing of the specific objectives/outcomes the requester expects from the meeting;

   c) A proposed agenda, including estimated times needed for each agenda item;

   d) A list of questions, grouped by discipline. For each question there should be a brief explanation of the context and purpose of the question.

   e) A listing of planned external attendees; and

   f) A listing of requested participants/disciplines representative(s) from the Center.

   g) Suggested dates and times (e.g., morning or afternoon) for the meeting that are within or beyond the appropriate time frame of the meeting type being requested.

2. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for BPD Type 2, 3 and 4 Meetings will be honored except in the most unusual circumstances.

   The Center may determine that a different type of meeting is more appropriate and it may grant a meeting of a different type than requested, which may require the payment of a biosimilar biological product development fee as described in section 744B of the Federal Food, Drug, and Cosmetic Act before the meeting will be provided. If a biosimilar biological product development fee is required under section 744B, and the sponsor does not pay the fee within the time frame required under section 744B, the meeting will be cancelled. If the sponsor pays the biosimilar biological product development fee after the meeting has been cancelled due to non-payment, the time frame described in section VII.A.1 will be calculated from the date on which FDA received the payment, not the date on which the sponsor originally submitted the meeting request.

Sponsors are encouraged to consult FDA to obtain further information on recommended meeting procedures.

3. FDA will develop and publish for comment draft guidance on Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings by end of second quarter of FY 2014.

VIII. DEFINITIONS AND EXPLANATION OF TERMS

A. The term "review and act on" means the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

B. Goal Date Extensions for Major Amendments

1. A major amendment to an original application, supplement with clinical data, or resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by three months.

2. A major amendment may include, for example, a major new clinical safety/efficacy study report; major re-analysis of previously submitted study(ies); submission of a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) not included in the original application; or significant amendment to a previously submitted REMS with ETASU. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

3. A major amendment to a manufacturing supplement submitted at any time during the review cycle may extend the goal date by two months.

4. Only one extension can be given per review cycle.

5. Consistent with the underlying principles articulated in the GRMP guidance, FDA's decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

C. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.

D. A Biosimilar Initial Advisory Meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service Act may be feasible for a particular product, and, if so, general advice on the expected content of the development program. Such term does not include any meeting that involves substantive review of summary data or full study reports.

E. A BPD Type 1 Meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (e.g. meeting to discuss clinical holds, dispute resolution meeting), a special protocol assessment meeting, or a meeting to address an important safety issue.

F. A BPD Type 2 Meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing biosimilar biological product development program. Such term includes substantive review of summary data, but does not include review of full study reports.

G. A BPD Type 3 Meeting is an in depth data review and advice meeting regarding an ongoing biosimilar biological product development program. Such term includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies, including design and analysis.

H. A BPD Type 4 Meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement submitted under 351(k) of the PHS Act.

JS 44 (Rev. 12/12) cand rev (1/15/13)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

Amgen Inc.
Amgen Manufacturing Limited

(b) County of Residence of First Listed Plaintiff Ventura, CA
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Vernon Winters
Sidley Austin LLP, 555 California Street 20th Floor
San Francisco CA 94018, 415-772-1200 (see attachment)

DEFENDANTS

Sandoz Inc.
Sandoz International GmbH
Sandoz GmbH

County of Residence of First Listed Defendant Mercer, NJ
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
28 U.S.C. ss. 1331, 1338(b)

Brief description of cause:
Patent infringement; unfair competition; conversion

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ❒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE Hon. Maxine M. Chesney DOCKET NUMBER 3:13-cv-02904-MMC

DATE
10/24/2014

SIGNATURE OF ATTORNEY OF RECORD
/s/ Vernon M. Winters

IX. DIVISIONAL ASSIGNMENT (Civil L.R. 3-2)

(Place an "X" in One Box Only) ☐ SAN FRANCISCO/OAKLAND ☐ SAN JOSE ☐ EUREKA

ATTACHMENT TO CIVIL COVER SHEET

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