IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, vs. APOTEX INC. and APOTEX CORP., Defendants.	Case No. 15-cv-61631-JIC/BSS

PLAINTIFFS AMGEN INC.'S AND AMGEN MANUFACTURING LIMITED'S MOTION FOR PRELIMINARY INJUNCTION AND INCORPORATED MEMORANDUM OF LAW

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

RULES

OTHER AUTHORITIES

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (together, "Amgen"), pursuant to this Court's October 13, 2015 Order Setting Briefing Schedule [D.E. 41] and Fed. R. Civ. P. 65, respectfully move for a preliminary injunction against Apotex Inc. and Apotex Corp. (together, "Apotex"), and submit this incorporated memorandum of law in support thereof.

PRELIMINARY STATEMENT

Amgen seeks a preliminary injunction to restrain Apotex from any commercial marketing of a "biosimilar" copy of Amgen's NEULASTA® (pegfilgrastim) product until Apotex complies with Federal law by giving Amgen proper notice. That notice must be given at least 180 days before the first commercial marketing of Apotex's product, and may not be given until the product is licensed by the Food and Drug Administration. Apotex refuses to provide that notice.

Apotex has applied to FDA for approval of a "biosimilar" version of Amgen's NEULASTA®, a medication that helps the body fight infection during chemotherapy. "Biosimilars" are like generic drugs, but instead of being copies of so-called "small molecules," biosimilars are instead similar to "biological products," which are themselves complex medicines made from living cells. Apotex submitted its application under the federal biosimilars statute, the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA"), Pub. L. No. 111-148, 124 Stat. 119 (2010). Before 2010, FDA licensed biological products only under the traditional pathway of 42 U.S.C. § 262(a), which typically requires three phases of clinical trials to prove safety and efficacy. The BPCIA created an abbreviated regulatory pathway, codified in 42 U.S.C. § 262(k), for approval of a biological product as "biosimilar to" a "reference product" that has itself already been licensed by FDA under the traditional regulatory pathway. Apotex sought FDA approval under the abbreviated pathway by referencing NEULASTA®. In the vocabulary of the BPCIA, Amgen Inc. is the Reference Product Sponsor (or, "RPS") and Apotex Inc. is the "subsection (k) applicant" (or, "Applicant"). *See* 42 U.S.C. § 262(*l*)(1)(A).

Congress enacted the BPCIA as part of the Affordable Care Act, because it was "the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established." BPCIA, Pub. L. No. 111-148, § 7001(b), 124 Stat. at 804. Prior to the BPCIA, innovators enjoyed permanent and exclusive rights to their clinical trial data and FDA license. In creating the abbreviated regulatory pathway, Congress advanced the public's interest in price competition in part by diminishing these innovators' rights. After an innovator's product has been licensed for four years, biosimilar applicants can now "reference" the innovator's

license pursuant to the BPCIA, and thereby rely on the innovator's prior demonstration of safety and efficacy rather than generate its own clinical trial data, as was traditionally required. After the innovator's product has been licensed for twelve years, and with the benefit of further data accumulated and reported to FDA from the innovator's post-approval experience, FDA may approve the biosimilar product based on this new statutory "referencing" authority. Licensure through the abbreviated biosimilar pathway saves the Applicant significant time, risk, and expense, and lets the Applicant enter a market with established demand for the product.

On the other side of the balance, Congress protected the public's interest in fostering innovation—the purpose of patents—by establishing a mechanism by which the RPS receives information, notice, and a period of time to assess and act on its patent rights, without imposing on the courts for emergency relief to prevent actual injury from patent infringement. Accordingly, the BPCIA has two phases, each directed at the orderly resolution of patent disputes. The "early" phase starts when FDA accepts the Applicant's Biologics License Application (or "aBLA") for review. The Applicant is to provide its aBLA to the RPS along with information about how its proposed product is manufactured. Based on this disclosure, the RPS identifies relevant patents, and the parties exchange detailed contentions about infringement, validity, and enforceability. *See* 42 U.S.C. § 262(*l*)(2)-(3). The parties then create a list of patents for litigation, either by agreement or by a blind exchange of previously identified patents, *see id.* §§ 262(*l*)(4), (5), and an "Immediate patent infringement action" under 42 U.S.C. § 262(*l*)(6) is filed. Apotex and Amgen engaged in the first phase of patent-dispute resolution under 42 U.S.C. § 262(*l*)(2) through (4), and this lawsuit is a paragraph (*l*)(6) lawsuit.

The second phase of the BPCIA process starts when FDA licenses the biosimilar product for commercial marketing. In this later phase, the BPCIA protects the value of patents, including those that may not have become part of the paragraph (*l*)(6) lawsuit, as well as those that are newly issued or licensed after the first phase commences, by preserving the status quo during a limited statutory period. This period occurs between FDA licensure of the biosimilar and its first commercial availability. During that defined statutory window of 180 days, the RPS may seek further discovery as is needed and injunctive relief to maintain the status quo after that 180-day window has closed and until the court finally resolves any patent issues. To that end, 42 U.S.C. § 262(*l*)(8)(A)—the provision at issue on this motion—states as follows:

> *Notice of Commercial Marketing.* –The subsection (k) applicant [here, Apotex] shall provide notice to the reference product sponsor [here, Amgen] not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).

Paragraph (*l*)(8)(B) authorizes the RPS to commence preliminary injunction proceedings "After receiving the notice under subparagraph (A) and before such date of the first commercial marketing of such biological product." And paragraph (*l*)(8)(C) provides for further, expedited discovery if the RPS seeks a preliminary injunction.

Apotex purported to give Amgen notice of commercial marketing on April 17, 2015. Notably, because FDA had not approved Apotex's aBLA at that time—indeed, it still has not done so—there was no "product licensed" when Apotex gave notice. Whether an Applicant could give notice before FDA approval was a question then being litigated in a separate lawsuit between Amgen and another company, Sandoz. Apotex gambled that the Federal Circuit would hold that notice of commercial marketing could be given before FDA approval. Apotex lost that bet. In July, the Federal Circuit held that a biosimilar applicant "may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen Inc.* v. *Sandoz Inc.*, 794 F.3d 1347, 1358 (Fed. Cir. 2015) (emphasis added). Apotex's April notice was ineffective.

Rather than agreeing to give notice after any FDA approval, Apotex now argues that it need not give notice at all, because giving notice is not mandatory. But that argument is foreclosed by the statute and by the same Federal Circuit case. The statute uses the verb "shall," which usually denotes a mandatory obligation. 42 U.S.C. § 262(*l*)(8)(A). And the Federal Circuit squarely rejected the notion that notice is optional: "A question exists, however, concerning whether the 'shall' provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." 794 F.3d at 1359. Apotex argues that it is exempt from this mandatory obligation because it has, so far, complied with the provisions of the BPCIA, specifically because it provided Amgen with a copy of its aBLA, *see* 42 U.S.C. § 262(*l*)(2)(A). Apotex seeks to distinguish itself from Sandoz, which did not provide the information called for by paragraph (*l*)(2)(A). But Apotex's compliance with paragraph (*l*)(2)(A) does not excuse it from the notice-of-commercial-marketing provision in paragraph (*l*)(8)(A). The Federal Circuit said so explicitly: "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (*l*)." *Amgen*, 794 F.3d at 1360. Apotex nevertheless refuses to provide notice under paragraph (*l*)(8)(A).

This is Amgen's motion for a preliminary injunction to compel Apotex to comply with the statute by forbidding Apotex from commencing commercial marketing of its biosimilar product until it has given Amgen at least 180 days' notice of first commercial marketing if, and after, FDA licenses its product.

The parties have cooperated to streamline this motion for the Court, stipulating to the elements of the preliminary-injunction test other than likelihood of success on the merits. What remains, then, is a question of law: Is Amgen likely to succeed in showing that under 42 U.S.C. § 262(*l*)(8)(A), if FDA approves Apotex's aBLA, Apotex must then give Amgen at least 180 days' notice before first commercial marketing of that biosimilar product? For the reasons set forth below, Amgen respectfully submits that such pre-marketing notice is required, and respectfully requests that the Court enter an injunction prohibiting Apotex from any commercial marketing of its biosimilar pegfilgrastim product until it has complied with that requirement.

STATEMENT OF FACTS

Amgen draws these facts from Apotex's Answer to Amgen's Complaint, from public records, and from the accompanying declarations of Robert Azelby, Vice President and General Manager Oncology at Amgen Inc., and Nicholas Groombridge, Amgen's counsel.

Amgen's NEULASTA® (pegfilgrastim) Product

Amgen Inc. discovers, develops, manufactures, and sells innovative therapeutic products based on advances in molecular biology, recombinant DNA technology, and chemistry. (Complaint ¶ 1; Answer ¶ 1.) Amgen Manufacturing Limited manufactures and sells biologic medicines for treating diseases in humans. (Complaint ¶ 2; Answer ¶ 2.)

Amgen's NEULASTA® (pegfilgrastim) is a recombinantly produced protein that stimulates the production of neutrophils, a type of white blood cell. It is used to counteract neutropenia, a neutrophil deficiency that makes a person highly susceptible to life-threatening infections and is a common side effect of certain chemotherapeutic drugs. (Complaint ¶¶ 38-39; Answer ¶¶ 38-39; Azelby Decl. ¶¶ 4-5.)

In 2002, Amgen obtained regulatory approval for NEULASTA® under the traditional biologics regulatory pathway, 42 U.S.C. § 262(a). To do so, Amgen demonstrated to FDA that NEULASTA® "is safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). Amgen Inc. is the owner of the FDA license for NEULASTA®. (Groombridge Decl. ¶ 9 & Ex. G.)

The value of the biological license for NEULASTA® to Amgen, to would-be Applicants and to society is the direct result of significant investments by Amgen. That is not unusual. Developing innovative pharmaceutical products requires enormous amounts of time, human resources, and money. The average cost to develop a new drug (including the cost of failures) exceeds $1 billion. (Groombridge Decl. ¶ 7 & Ex. H.)

As the BPCIA recognizes, Amgen and other innovative biopharmaceutical companies seek to protect their investments through patenting its inventions. Amgen is asserting two patents here—U.S. Patent Nos. 8,952,138 and 5,824,784—that are directed to pegfilgrastim and to methods of making recombinant proteins like pegfilgrastim.

Apotex's aBLA for Biosimilar Pegfilgrastim

Apotex Inc. develops, manufactures, and sells pharmaceuticals, including generic medicines. (Answer ¶ 3.) Apotex Corp. markets pharmaceuticals in the United States, including generic medicines. (Answer ¶ 4.)

Apotex filed an aBLA under the BPCIA's abbreviated pathway, 42 U.S.C. § 262(k), seeking approval of its biosimilar pegfilgrastim product, designating Amgen's NEULASTA® as the reference product. (Complaint ¶¶ 41-42; Answer ¶¶ 41-42, 44.) Amgen Inc. is therefore the Reference Product Sponsor with respect to Apotex's aBLA. (Groombridge Decl. ¶ 2 & Ex. A.) On December 16, 2014, Apotex notified Amgen that FDA had accepted Apotex's aBLA for review. (Complaint ¶ 46; Answer ¶ 46.) FDA has not yet approved Apotex's aBLA. As set forth in the parties' joint motion to set a briefing schedule, "Apotex asserts that FDA's decision regarding Apotex's aBLA could be issued at any time," and Apotex has agreed to refrain from commercial marketing of its product through only a date certain agreed to in connection with this motion. DE 37 at 2, 3.

The Parties' Exchanges of Information Pursuant to the BPCIA

The BPCIA established a patent-dispute-resolution regime that includes amendments to Titles 28, 35, and 42 of the United States Code. The BPCIA made submission of an aBLA an artificial act of patent infringement, allowing infringement suits to be filed before FDA approval and before marketing of the biosimilar product. *See* 35 U.S.C. § 271(e)(2)(C), (e)(4). And the BPCIA "established a unique and elaborate process for information exchange between the biosimilar applicant and the RPS to resolve patent disputes." *Amgen*, 794 F.3d at 1352. That process is embodied in 42 U.S.C. § 262(*l*), "Patents." Until quite recently, Amgen and Apotex

had followed that process faithfully. Apotex's refusal to continue to do so is the reason for this motion.

The BPCIA has two phases, each targeted at orderly resolution of patent disputes. The first phase begins (and began here) with FDA's acceptance of the Applicant's aBLA for review. Within 20 days after FDA notifies a biosimilar Applicant that it has accepted the Applicant's aBLA for review, the Applicant gives the RPS a copy of its aBLA 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)(A); *Amgen*, 794 F.3d at 1352. FDA accepted Apotex's aBLA for its biosimilar pegfilgrastim product on December 15, 2014. Apotex notified Amgen the next day, and thereafter provided its aBLA to Amgen. Apotex did not provide any additional manufacturing information, but Amgen has no basis to contend any such additional manufacturing information existed, and agrees for purposes of this motion that Apotex satisfied paragraph (*l*)(2)(A). Next follows a sequential exchange of "lists of patents for which" the parties "believe a claim of patent infringement could reasonably be asserted by the RPS, as well as their respective positions on infringement, validity, and enforceability of those patents." *Amgen*, 794 F.3d at 1352. The RPS initiates the exchange with a patent list in accordance with 42 U.S.C. § 262(*l*)(3)(A). The Applicant "may" respond with its own list of additional patents that could be infringed, but must provide—"shall provide" —for each listed patent either a statement that it will remain off the market until the patent expires or, on a claim-by-claim basis, a detailed statement of its factual and legal basis for believing that the patent is invalid, unenforceable, or not infringed. 42 U.S.C. § 262(*l*)(3)(B). Finally, the RPS then "shall provide," for the disputed patents, a detailed statement that each patent will be infringed and a response to the Applicant's invalidity and unenforceability contentions. 42 U.S.C. § 262(*l*)(3)(C).

Apotex and Amgen engaged in the exchanges described in paragraph (*l*)(3). The exchange was complete by June 16, 2015. (Complaint ¶¶ 48-50; Answer ¶¶ 48-50.)

The next step in this first phase of the BPCIA is for the parties to attempt to agree, under paragraph (*l*)(4), on which of the patents listed pursuant to paragraph (*l*)(3), if any, should be included in an immediate patent-infringement action and, failing agreement, to follow a dispute-resolution procedure under paragraph (*l*)(5) to identify those patents. Either way, once the parties have arrived at the list of patents on which suit will be brought, the RPS is then directed to bring an "Immediate patent infringement action" on each of the listed patents within 30 days.

42 U.S.C. § 262(*l*)(6). The Applicant must provide the complaint to FDA, which must publish it in the Federal Register. *Id.*

Apotex and Amgen agreed that Amgen would file suit under paragraph (*l*)(6) on two patents, U.S. Patent Nos. 8,952,138 and 5,824,784. (Complaint ¶ 51; Answer ¶ 51.) Amgen did so on August 8, 2015. This is that lawsuit.

Further Steps Under the BPCIA and Pre-Marketing Notice

The RPS's obligation to identify patents does not end with the exchange of patent lists pursuant to paragraph (*l*)(3) or with the filing of an immediate patent litigation under 262(*l*)(6). Instead, if a patent is newly issued to, or exclusively licensed by, the RPS after it has provided its paragraph (*l*)(3)(A) list, the RPS must supplement that list within 30 days. *See* 42 U.S.C. § 262(*l*)(7). Within 30 days thereafter, the Applicant "shall provide" the RPS with a statement in accordance with paragraph (*l*)(3)(B), providing "for each listed patent either a statement that it will remain off the market until the patent expires or, on a claim-by-claim basis, a detailed statement of its factual and legal basis for believing that the patent is invalid, unenforceable, or not infringed." *See* 42 U.S.C. § 262(*l*)(3)(B), (7).

These newly issued or licensed patents, along with patents that were initially listed under paragraph (*l*)(3) but not listed for inclusion in the paragraph (*l*)(6) lawsuit, then become subject to 42 U.S.C. § 262(*l*)(8), entitled "Notice of commercial marketing and preliminary injunction." That paragraph contains the requirement of pre-marketing notice, the provision at issue on this motion, 42 U.S.C. § 262(*l*)(8)(A).

The second phase of the BPCIA's orderly resolution of patent disputes starts at FDA approval of the Applicant's biosimilar product. FDA licensure of the biosimilar product authorizes the Applicant to commercially market the biosimilar in the United States. It also triggers the Applicant's obligation to give the RPS at least 180 days' advanced notice of the date of the first commercial marketing of the licensed biosimilar product. *See* 42 U.S.C. § 262(*l*)(8)(A). As the Federal Circuit stated, "Subsection 262(*l*) also provides that the Applicant give notice of commercial marketing to the RPS at least 180 days prior to commercial marketing of its product licensed under subsection (k), which then allows the RPS a period of time to seek a preliminary injunction based on patents that the parties initially identified during information exchange but were not selected for the immediate infringement action, as well as any newly issued or licensed patents." *Amgen*, 794 F.3d at 1352. Paragraph (*l*)(8) provides:

> (8) Notice of commercial marketing and preliminary injunction
>
> (A) Notice of commercial marketing
>
> The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).
>
> (B) Preliminary injunction
>
> After receiving the notice under subparagraph (A) and before such date of the first commercial marketing of such biological product, the reference product sponsor may seek a preliminary injunction prohibiting the subsection (k) 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 that is—
>
> > (i) included in the list provided by the reference product sponsor under paragraph (3)(A) or in the list provided by the subsection (k) applicant under paragraph (3)(B); and
> >
> > (ii) not included, as applicable, on—
> >
> > > (I) the list of patents described in paragraph (4); or
> > >
> > > (II) the lists of patents described in paragraph (5)(B).

42 U.S.C. § 262(*l*)(8)(A), (B). "The purpose of paragraph (*l*)(8)(A) is clear: requiring notice of commercial marketing be given to allow the RPS a period of time to assess and act upon its patent rights." *Amgen*, 794 F.3d at 1360.

On April 17, 2015, Apotex purported to provide notice of commercial marketing to Amgen. (Groombridge Decl. ¶ 2 & Ex. A.) Amgen responded on May 8, 2015, asserting that paragraph (*l*)(8)(A) notice cannot be given until FDA approves the Applicant's aBLA, among other things because the statute refers to "the biological product licensed under subsection (k)," and there is no product licensed prior to FDA approval. (*Id.* at ¶ 3 & Ex. B.)

Limitations on Declaratory Judgments

The BPCIA borrows from the Hatch-Waxman Act and prohibits gaming the system by placing limits on "any" actions for declaratory judgments with respect to patents that do not make the list, pursuant to either paragraph (*l*)(4) or (*l*)(5), for the immediate patent infringement action under paragraph (*l*)(6), plus later-issued or -licensed patents under paragraph (*l*)(7). That

prohibition ends when the Applicant gives at least 180 days' advance notice of first commercial marketing of the licensed biosimilar product. Thus, paragraph (*l*)(9) provides:

> (9) Limitation on declaratory judgment action
>
> (A) Subsection (k) application provided—If a subsection (k) applicant provides the application and information required under paragraph (2)(A), neither the reference product sponsor nor the subsection (k) applicant may, prior to the date notice is received under paragraph (8)(A), bring any action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of paragraph (8)(B).

Deferring the availability of declaratory judgment actions until the Applicant provides the notice of commercial marketing benefits both the Applicant and the RPS by ensuring that both parties earnestly engage in the first phase of the BPCIA's patent-resolution process. If the Applicant fails to complete a required action, the statute maintains the bar to declaratory judgments for the Applicant but lifts it with respect to the RPS:

> (B) Subsequent failure to act by subsection (k) applicant—If a subsection (k) applicant fails to complete an action required of the subsection (k) applicant under paragraph (3)(B)(ii), paragraph (5), paragraph (6)(C)(i), paragraph (7), or paragraph (8)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent included in the list described in paragraph (3)(A), including as provided under paragraph (7).
>
> (C) Subsection (k) application not provided—If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.

42 U.S.C. § 262(*l*)(9)(B), (C).

The *Amgen* v. *Sandoz* Case

The *Amgen* v. *Sandoz* decision from the Federal Circuit provides more than controlling precedent here. It also provides context to explain some of Apotex's actions. A brief overview of the case is therefore warranted:

Sandoz sought (and eventually received) FDA approval to market a biosimilar version of Amgen's NEUPOGEN® (filgrastim), a biological product that has similarity to the pegfilgrastim

product at issue here.[1] On July 8, 2014, Sandoz notified Amgen that it had filed an aBLA for its filgrastim product, that it believed the application would be approved in the first half of 2015, and that Sandoz "intended to launch its biosimilar product immediately upon FDA approval." *Amgen*, 794 F.3d at 1352-53. Sandoz deemed that to be notice under paragraph (*l*)(8)(A) even though FDA had not yet approved its aBLA. Further, Sandoz informed Amgen that Sandoz had chosen not to provide its aBLA and manufacturing information as contemplated by paragraph (*l*)(2)(A).

Amgen sued Sandoz in the Northern District of California for patent infringement, and sought a preliminary injunction to compel Sandoz to provide the aBLA and manufacturing information called for by paragraph (*l*)(2)(A) and to compel Sandoz to provide at least 180 days' notice of first commercial marketing after, but only after, FDA approval of Sandoz's application.

While the motion was pending in the district court, on March 6, 2015, FDA approved Sandoz's aBLA. That day, Sandoz again provided 180 days' notice of commercial marketing, maintaining that its July 2014 notice had been effective but nevertheless giving "a 'further notice of commercial marketing' to Amgen on the date of FDA approval." *Id.* at 1353.

The district court denied Amgen's motion, finding that neither provision of the aBLA and manufacturing information under paragraph (*l*)(2)(A) nor pre-marketing notice under paragraph (*l*)(8)(A) is mandatory, and that Sandoz had thus complied with the BPCIA.

Amgen appealed. Under the four-factor test for injunctive relief, the Federal Circuit granted Amgen's motion for an injunction pending appeal, and enjoined Sandoz from "marketing, selling, offering for sale, or importing into the United States its FDA-approved ZARXIO® biosimilar product until this Court resolves the appeal." (Groombridge Decl. ¶ 6 & Ex. E.) *See also Amgen*, 794 F.3d at 1362.

After receiving full briefing and hearing oral argument, the Federal Circuit affirmed in part and reversed in part. Judge Lourie wrote the Panel opinion, but was joined in different parts of that opinion by Judges Newman and Chen, who each dissented in part as well.

Regarding paragraph (*l*)(2)(A), Judges Lourie and Chen held that the Applicant is not required to provide its aBLA and manufacturing information, and that if it fails to do so, the

[1] Apotex has also submitted an aBLA seeking FDA approval of its own biosimilar filgrastim product. That product is the subject of a second lawsuit that Amgen has commenced against Apotex in this District, Case No. 15-62081, filed on October 2, 2015.

RPS's sole remedy is to commence a declaratory judgment action under paragraph (*l*)(9)(C) or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii). *See Amgen*, 794 F.3d at 1354-56. From this, Judge Newman dissented, and would have held that providing the aBLA and manufacturing information is mandatory. *Id.* at 1364 (Newman, J., dissenting in part).

Turning to 180 days' notice under paragraph (*l*)(8)(A)—the provision at issue here—the Panel unanimously held that to be effective, notice may be given only after FDA approval:

> We therefore conclude that, under paragraph (*l*)(8)(A), a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product. The district court thus erred in holding that a notice of commercial marketing under paragraph (*l*)(8)(A) may effectively be given before the biological product is licensed, and we therefore reverse its conclusion relating to its interpretation of § 262(*l*)(8)(A) and the date when Sandoz may market its product.

Id. at 1358 (majority opinion). The Panel then considered the impact of that decision on the facts of the case before it. Judges Lourie and Newman held that the requirement of notice under paragraph (*l*)(8)(A) is mandatory: "A question exists, however, concerning whether the "shall" provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." *Id.* at 1359. They extended the injunction pending appeal until only September 2, 2015, exactly 180 days after Sandoz gave post-FDA-approval notice of commercial marketing.

Judge Chen dissented in this part, and would have held that because Sandoz did not provide its aBLA and manufacturing information under paragraph (*l*)(2)(A), none of the subsequent provisions, including paragraph (*l*)(8)(A), applied to the dispute between Amgen and Sandoz: when "the (k) applicant fails to comply with (*l*)(2), the provisions in (*l*)(3)-(*l*)(8) cease to matter." *Id.* at 1367 (Chen, J., dissenting in part).

Each of Amgen and Sandoz petitioned the Federal Circuit to re-hear, en banc, the aspects of the opinion on which the other prevailed. The Federal Circuit denied those petitions today. (Groombridge Decl. ¶ 11 & Ex. I.)

Apotex's Newfound Position Regarding Notice Under Paragraph (*l*)(8)(A)

The Federal Circuit's decision in *Amgen* renders Apotex's April 17, 2015 notice of commercial marketing ineffective, because that notice was given before FDA approval of Apotex's application. The Federal Circuit held that an Applicant "may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen*, 794 F.3d at 1359.

On August 24, 2015, Apotex's counsel wrote to Amgen's counsel to assert that, under *Amgen* v. *Sandoz*, Apotex believed that it was not required to give 180 days' notice under paragraph (*l*)(8)(A), because Apotex—unlike Sandoz—had provided its aBLA under paragraph (*l*)(2)(A). Apotex asserted that "because Apotex followed the pathway and provided Amgen with its application and manufacturing information, providing a notice of commercial marketing is not mandatory." (Groombridge Decl. Ex. D.)

This Motion for a Preliminary Injunction

By this motion, Amgen seeks a preliminary injunction restraining Apotex from commercial marketing of its biosimilar pegfilgrastim product on any license issuing from its pending aBLA until it provides 180 days' notice after FDA approval of that product. The parties agree that whether Amgen is likely to succeed in showing that the BPCIA requires Apotex to give that notice is a question of law. And the parties have stipulated, to the fullest extent possible, to the other elements of the test for preliminary injunctive relief. (*See* Groombridge Decl. ¶ 7 & Ex. F.)

Irreparable Harm: The parties stipulated that "Solely for the purposes of Amgen's motion for a preliminary injunction, Apotex will not dispute that Amgen would be irreparably harmed if Apotex were to commence commercial marketing of its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. § 262(*l*)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing." (Groombridge Decl. Ex. F.)

Balance of Hardships: The parties stipulated that "because the question of whether Apotex is required to provide notice under 42 U.S.C. § 262(*l*)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing is a matter of statutory interpretation, the parties agree that, if the Court finds in favor of Amgen regarding likelihood of [success on] the merits, the balance of hardships favors Amgen." *Id.*

The Public Interest: The parties stipulated that "[b]ecause the public interest favors compliance with federal statutes as properly interpreted, Apotex agrees that should the Court find in favor of Amgen regarding likelihood of [success on] the merits, it will not dispute that the public interest favors the issuance of an injunction barring Apotex from commercially marketing its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. § 262(*l*)(8)(A)

after FDA approval of the product and at least 180 days prior to commencing such commercial marketing." *Id.*

The parties further stipulated to a briefing schedule for this motion, and Apotex agreed to refrain from commercial marketing until a date certain (assuming FDA approval) to give the Court time to consider this motion. (Groombridge Decl. ¶ 8 & DE 38, DE40.)

ARGUMENT

Amgen is entitled to a preliminary injunction if it demonstrates (1) a substantial likelihood of success on the merits; (2) that it will suffer irreparable injury unless the injunction issues; (3) that the threatened injury to Amgen outweighs the threatened harm the injunction may cause to Apotex; and (4) that the injunction will not disserve the public interest. *Bryan* v. *Hall Chem. Co.*, 993 F.2d 831, 835 (11th Cir. 1993); *see also Winter* v. *Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008); *Aevoe Corp.* v. *AE Tech Co.*, 727 F.3d 1375, 1381 (Fed. Cir. 2013).

I. Likelihood of Success on the Merits: The BPCIA Requires Apotex to Provide At Least 180 Days' Notice of Commercial Marketing After FDA Approval

The parties agree that the sole likelihood-of-success issue here is a question of law: does the BPCIA require Apotex to provide Amgen with at least 180 days' notice of the first commercial marketing of its biosimilar pegfilgrastim product after FDA approves Apotex's aBLA? The statute itself answers that question in the affirmative, as does the Federal Circuit's decision in *Amgen Inc.* v. *Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015).

A. The BPCIA Provides That Apotex Must Give 180 Days' Notice

"[A]ll statutory construction cases . . . begin with the language of the statute." *Momenta Pharms., Inc.* v. *Amphastar Pharms., Inc.*, 686 F.3d 1348, 1353-54 (Fed. Cir. 2012). "The 'first step in interpreting a statute is to determine whether the language at issue has a plain and unambiguous meaning with regard to the particular dispute in the case.'" *Id.* at 1354 (*quoting Robinson* v. *Shell Oil Co.*, 519 U.S. 337, 340 (1997)); *see also Intellectual Ventures II LLC* v. *JPMorgan Chase & Co.*, 781 F.3d 1372, 1375-77 (Fed. Cir. 2015).

Paragraph (*l*)(8)(A) is clear: "The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." 42 U.S.C. § 262(*l*)(8)(A) (emphasis added). The verb "shall" presumptively signals a statutory requirement. *See, e.g.*, *Nat'l Ass'n of Home Builders* v. *Defenders of Wildlife*, 551 U.S. 644, 661-62 (2007); *Lopez* v.

Davis, 531 U.S. 230, 241 (2001); *Lexecon, Inc.* v. *Milberg Weiss Bershad Hynes & Lerach*, 523 U.S. 26, 35 (1998); Antonin Scalia & Bryan A. Garner, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 114 (2012) ("[W]hen the word *shall* can reasonably read as mandatory, it ought to be so read."). Nothing in the statute suggests that "shall" in subsection (*l*)(8)(A) is anything but a mandatory command.

Paragraph (*l*)(9)(A) further confirms that an Applicant must give pre-marketing notice under paragraph (*l*)(8)(A). That paragraph provides the "Limitation on declaratory judgment action[s]" where, as here, the Applicant provides its aBLA and manufacturing information to the RPS under paragraph (*l*)(2)(A). Its prohibition ends only when the Applicant gives notice under paragraph (*l*)(8)(A), explicitly contemplating that such notice will be given:

> If a subsection (k) applicant provides the application and information required under paragraph (2)(A), neither the reference product sponsor nor the subsection (k) applicant may, prior to the date notice is received under paragraph (8)(A), bring any action under section 2201 of Title 28, for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of paragraph (8)(B).

42 U.S.C. § 262(*l*)(9)(A).

B. Requiring Notice Accords With the Statutory Purpose, While Rendering Notice Optional Frustrates That Purpose

The Federal Circuit, in a unanimous portion of its opinion, recognized the importance of the notice under paragraph (*l*)(8)(A). That notice "allows the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction from the court." *Amgen*, 794 F.3d at 1358. The Federal Circuit rejected the idea that notice could be given before FDA approval, because pre-approval notice would leave the RPS "to guess the scope of the approved license and when commercial marketing would actually begin." *Id.* On the other hand, requiring notice to be given after FDA approval "crystallize[s]" the controversy for the court and avoids needless litigation:

> We believe that Congress intended the notice to follow licensure, at which time the product, its therapeutic uses, and its manufacturing processes are fixed. When a subsection (k) applicant files its aBLA, it likely does not know for certain when, or if, it will obtain FDA licensure. The FDA could request changes to the product during the review process, or it could approve some but not all sought-for uses. Giving notice after FDA licensure, once the scope of the approved license is known and the marketing of the proposed biosimilar product is imminent, allows

> the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction from the court.
>
> Requiring that a product be licensed before notice of commercial marketing ensures the existence of a fully crystallized controversy regarding the need for injunctive relief. It provides a defined statutory window during which the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product.

Id. Apotex's position is directly at odds with these statutory purposes. If Apotex were correct and an Applicant could, at its whim, eliminate the notice period by "choosing" not to provide notice under paragraph (*l*)(8)(A), then the "RPS would be left to guess . . . when commercial marketing would actually begin," *id.*, and would have to monitor public sources even to find out when FDA approves the Applicant's aBLA, would have to sprint to court to seek a temporary restraining order just to secure time to seek a preliminary injunction, and would present the court far less than a "fully crystallized controversy" and deprive the court of the "defined statutory window" in which to "fairly assess the parties' rights prior to the launch of the biosimilar product." *Id.* Instead of an ordered, timed process, the result would be chaos, and the careful balance represented by paragraph (*l*)(8)(A) would topple in the Applicant's favor.

C. *Amgen* Confirms That Notice Is Required

For these reasons, the Federal Circuit held in *Amgen* v. *Sandoz* that notice under paragraph (*l*)(8)(A) is mandatory. It did so explicitly, rejecting Sandoz's argument that notice is optional: "A question exists . . . concerning whether the 'shall' provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." *Id.* at 1359.

That holding forecloses Apotex's argument. Apotex therefore argues that the Federal Circuit did not mean what it said, and that it actually held that notice is required only where an Applicant—like Sandoz, but not like Apotex—fails to provide the RPS with a copy of its aBLA and manufacturing information under paragraph (*l*)(2)(A). Thus, in its August 24, 2015 letter, Apotex plucked these words out of the middle of a sentence in the Federal Circuit's opinion: " . . . paragraph (*l*)(9)(B) specifies the consequence for a subsequent failure to comply with paragraph (*l*)(8)(A) after the applicant has complied with paragraph (*l*)(2)(A)," thus suggesting that Apotex need not comply with paragraph (*l*)(8)(A) and that Amgen's only remedy is to seek a declaratory judgment under paragraph (*l*)(9)(B). (Groombridge Decl. Ex. D at 1, *quoting* 794 F.3d at 1359.)

But the Federal Circuit's holding that "paragraph (*l*)(8)(A) is mandatory" contains no exception for Applicants who comply with paragraph (*l*)(2)(A), and in fact the court clearly held that "Paragraph (*l*)(8)(A) is a standalone notice provision," and that "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (l)." *Amgen*, 794 F.3d at 1359-60. Thus, Apotex's provision of the disclosures called for by paragraph (*l*)(2)(A) does not drive the outcome here; Apotex must still give notice under paragraph (*l*)(8)(A) once FDA approves its aBLA. Amgen is entitled to enforce that obligation, just as the Federal Circuit enforced it against Sandoz in granting an injunction pending appeal under Fed. R. App. P. 8A and then extending that injunction until September 2, 2015, precisely 180 days after Sandoz provided post-FDA-approval notice of commercial marketing under paragraph (*l*)(8)(A). (Groombridge Decl. ¶ 6 & Ex. E; *see also Amgen*, 794 F.3d at 1360.)

Nor does paragraph (*l*)(9)(B) change the analysis. Paragraph (*l*)(9)(B) is a prohibition on the Applicant seeking a declaratory judgment. As regards the provision of notice under paragraph (*l*)(8)(A), however, paragraph (*l*)(9)(B) offers the RPS no remedy at all because the RPS may seek a declaratory judgment whether or not the Applicant timely provides notice. That is, the Applicant's timely provision of notice under paragraph (*l*)(8)(A) lets both the Applicant and the RPS commence declaratory judgment actions under paragraph (*l*)(9)(A). On the other hand, if the Applicant "fails to complete an action required of" it under paragraph (*l*)(8)(A), then the prohibition against declaratory judgments persists for the Applicant but is lifted for the RPS by paragraph (*l*)(9)(B). Either way, the RPS is permitted to bring a declaratory judgment action.

Apotex also cited to Judge Chen's dissent. (*See* Groombridge Decl. Ex. D.) Judge Chen's and Judge Lourie's disagreement is principally about whether an Applicant that refuses to provide its aBLA and manufacturing information—like Sandoz but not like Apotex—is excused from providing notice of commercial marketing. Judge Chen viewed the provisions of paragraphs (*l*)(2) through (*l*)(8) as an "integrated litigation management process," with all of the steps in paragraphs (*l*)(3) through (*l*)(8) "contingent on the (k) applicant's performance of the first 'shall' step in (*l*)(2)." *Amgen*, 794 F.3d at 1367 (Chen, J., dissenting in part). To Judge Chen, once an Applicant like Sandoz "fails to comply with (*l*)(2)," "the provisions in (*l*)(3)-(*l*)(8) cease to matter." *Id.*

Judge Lourie disagreed and, specifically addressing the facts of Sandoz's refusal to provide its aBLA and manufacturing information, concluded that "where, as here, a subsection

(k) applicant completely fails to provide its aBLA and manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (*l*)(8)(A) is mandatory. Sandoz therefore may not market Zarxio before 180 days from March 6, 2015 [the date Sandoz gave post-FDA-approval notice], *i.e.* September 2, 2015." *Id.* at 1360 (majority opinion).

The converse is not true, however. The Panel majority did not hold or even imply that an Applicant like Apotex that provides its aBLA and any manufacturing information is excused from providing pre-marketing notice. On the contrary, the Panel held that "Paragraph (*l*)(8)(A) is a standalone notice provision," and that "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (*l*)." *Id.* at 1359-60.

That decision makes complete sense given the purpose of the BPCIA. As the unanimous Federal Circuit panel concluded, requiring notice of commercial marketing after FDA approval "provides a defined statutory window during which the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product." *Id.* at 1358. That goal is not altered, and the importance of that defined window is not lessened, because an Applicant like Apotex provides its aBLA and any manufacturing information. The provision of that information allows for the exchange of infringement, validity, and enforceability contentions under paragraph (*l*)(3), but it does not protect the RPS or the court from the crush of a hectic preliminary injunction motion and a temporary restraining order in the days following FDA approval. Rather, that protection comes from the 180-day window called for by paragraph (*l*)(8)(A). That is why the Federal Circuit majority held that notice of commercial marketing is mandatory under that provision.

That decision controls here. This Court should therefore hold that Amgen has a "substantial likelihood"—indeed, it has more than a substantial likelihood—of prevailing on its claim that notice under paragraph (*l*)(8)(A) is mandatory.

II. Irreparable Harm: Apotex's Premature Entry Into the Market Would Irreparably Harm Amgen, as Apotex Concedes

Premature entry by a generic challenger causes price erosion and works irreparable harm. The cases so holding are legion. *See, e.g.*, *Abbott Labs.* v. *Sandoz Inc.*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008); *Sanofi-Synthelabo* v. *Apotex, Inc.*, 470 F.3d 1368, 1381 (Fed. Cir. 2006). Indeed, in the dispute between Amgen and Sandoz, the Federal Circuit inherently recognized that Sandoz's premature entry into the short-acting filgrastim market would irreparably harm Amgen,

as a showing of irreparable harm is one of the requirements for an injunction pending appeal under Federal Rule of Appellate Procedure 8, and the Federal Circuit granted Amgen's motion for a Rule 8 injunction. (Groombridge Decl. ¶ 6 & Ex. E.)

Here, Robert Azelby, Amgen's Vice President and General Manager Oncology, has testified that Apotex's premature entry into the long-acting filgrastim market will severely and permanently harm Amgen through price erosion. (Azebly Decl. ¶ 12.) He testified: "Amgen currently manufactures and supplies NEULASTA® to meet the entire United States demand for long-acting filgrastim, and is prepared to continue to do so. There is no significant un-met medical need for pegfilgrastim." (*Id.* at ¶ 11.) Sales of Apotex's biosimilar pegfilgrastim product would therefore necessarily erode Amgen's sales. (*Id.*) If, as expected, Apotex prices its product below Amgen's price for NEULASTA®, Amgen could be forced to lower its prices to maintain its market share. (*Id.* at ¶ 12.) Because of Medicare reimbursement formulas, as Mr. Azelby explains, Amgen would not be able to restore its prices if Apotex were later found to have prematurely and wrongly entered the market. The erosion of prices would be permanent. (*Id.*)

Notably, Apotex has stipulated that Amgen would be irreparably harmed if Apotex were to enter the long-acting pegfilgrastim market without providing Amgen the at-least-180 days' notice of paragraph (*l*)(8)(A). Case law permits the parties to stipulate to this aspect of the test for injunctive relief, subject to the Court's independent review to ensure that the stipulation is not collusive. *See WIT Wälchli Innovation Techs.* v. *Westrick*, 12-CIV-20072, 2012 U.S. Dist. LEXIS 7933, at *10 (S.D. Fla. Jan. 24, 2012) (Cohn, J.). The case law recognizing irreparable harm in the context of premature entry by a generic manufacturer (and, in the case of *Amgen v. Sandoz*, a biosimilar manufacturer) supports the parties' stipulation here.

III. Balance of Hardships: The Threatened Injury to Amgen From the Denial of an Injunction Exceeds the Injury to Apotex If One Is Granted, As Apotex Concedes

In deciding whether to issue a preliminary injunction, courts balance the threatened injury to the movant if no preliminary injunction is issued against the threat to the non-movant of an injunction. *See Bryan*, 993 F.2d at 836. The threat to Amgen of the denial of an injunction dovetails with the irreparable harm Amgen faces and that Mr. Azelby explains. And here, too, Apotex has stipulated, agreeing that the balance of hardships favors Amgen if the Court finds that Amgen is likely to succeed on the merits of its claim. *See WIT Wälchli Innovation Techs.*, 2012 U.S. Dist. LEXIS 7933, at *10.

IV. Public Interest: The Public's Interest Is Served By Assuring That Parties Comply With Federal Law

Amgen spent significant amounts of money to develop and obtain the biological license for NEULASTA®. The prescribing information for NEULASTA® reports "seven randomized clinical trials" from which safety data are drawn. (Azelby Decl. ¶ 2; http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf at § 6.1.) In addition to clinical development and clinical trials, Amgen also incurred the expense and effort to obtain and maintain regulatory approval for facilities to manufacture NEULASTA®. (Groombridge Decl. Ex G.) The public interest supports—indeed, it depends on—innovators like Amgen making such investments. There is therefore a strong public interest in encouraging investment in drug development, and ensuring that the BPCIA protects innovators and further ensuring that parties follow the law serves the public interest. That interest is not outweighed by the fact that a biosimilar may enter the market and sell its product at a lower price.

In this regard, Apotex has stipulated that if the Court finds that Amgen is likely to succeed on the merits, it will not challenge that the public interest is best served by an injunction.

V. Amgen Should Have to Post at Most a Nominal Bond

Amgen respectfully submits that either no bond, or at most a nominal bond, be required to secure any injunction. The Court has wide discretion in setting a bond amount, including requiring "no security at all." *BellSouth Telecomms., Inc.* v. *MCImetro Access Transmission Servs.*, 425 F.3d 964, 971 (11th Cir. 2005). A bond is generally not required where the party seeking the injunction has a high probability of succeeding on the merits of the claim. *See, e.g.*, *Univ. Books & Videos, Inc.* v. *Metro. Dade Cnty.*, 33 F. Supp. 2d 1364, 1374 (S.D. Fla. 1999). And the bond requirement may be waived if not requested or if no evidence is presented that a party will suffer damages from the issuance of an injunction. *Tancogne* v. *Tomjai Enters. Corp.*, 408 F. Supp. 2d 1237, 1252 (S.D. Fla. 2005). Apotex, as the party seeking security, would bear the burden of demonstrating "a rational basis for the amount of the proposed bond." *Cont'l Group, Inc.* v. *KW Prop. Mgmt., LLC*, Case No. 09-60202, 2009 U.S. Dist. LEXIS 101448, at *19 (S.D. Fla. Oct. 30, 2009) (*quoting Int'l Equity Investments, Inc. v. Opportunity Equity Partners, Ltd.*, 441 F. Supp. 2d 552, 556 (S.D.N.Y. 2006)). Moreover, if the Court agrees with Amgen, then Apotex will be required to refrain from commercial marketing only for as long as Congress required Apotex and all Applicants to do so under the BPCIA. Just as the Federal

Circuit, after full briefing on the issue, held that Amgen should not have to post any bond to secure an injunction while Sandoz complied with paragraph (*l*)(8)(A), this Court should hold that no bond, or at most a nominal bond, is required

CONCLUSION

Amgen respectfully requests that the Court enter a preliminary injunction as set forth in Amgen's accompanying proposed order, specifically enjoining Apotex and those acting in concert with it from any commercial marketing of its biosimilar pegfilgrastim product, including selling that product or offering it for sale for use in the United States, until Apotex gives Amgen proper notice, at least 180 days before first commercial marketing but not before its pegfilgrastim biosimilar product is licensed by FDA, and the 180-day notice period is exhausted.

Dated: October 16, 2015

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on October 16, 2015, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to counsel and that a true and correct copy was served via electronic mail on all counsel of parties of record.

By: */s/ John F. O'Sullivan*____
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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiff, v. APOTEX INC. and APOTEX CORP., Defendant.	Case No. 0:15-CV-61631-JIC/BSS

DECLARATION OF ROBERT AZELBY IN SUPPORT OF AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION

I, Robert Azelby, declare and state as follows:

1. I am Vice President and General Manager Oncology at Amgen Inc. ("Amgen"). I submit this declaration in support of Amgen's Motion for a Preliminary Injunction against Apotex Inc. and Apotex Corp. ("Apotex"). I am personally knowledgeable about the matters set forth in this Declaration and, if called upon to do so, I could and would competently testify to the following facts, below:

Amgen's Neulasta® Product

2. Amgen's Neulasta® (pegfilgrastim) is approved by FDA for use in treating cancer patients receiving myelosuppressive chemotherapy. The current prescriber information for Neulasta® can be found at http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf.

3. In my role as Vice President and General Manager Oncology at Amgen, my responsibilities include the sales and marketing of Amgen oncology business unit products and services in the United States. I am therefore familiar with Neulasta®, the channels through

which it is sold and paid for, the patients it serves, how it is used by health care providers, and considerations that influence purchasing decisions. The sales force that sells Neulasta® reports indirectly through to me in my role as Vice President and General Manager Oncology.

4. The active ingredient in Amgen's Neulasta® is pegfilgrastim, a recombinantly expressed, 175-amino acid form of a protein known as human granulocyte-colony stimulating factor ("G-CSF") conjugated to a 20 kD monomethoxypolyethylene glycol (m-PEG) at the N-terminus of the G-CSF.

5. Neulasta® is indicated to decrease the incidence of infection in patients receiving myelosuppressive anti-cancer drugs. By binding to specific receptors on the surface of certain types of cells, Neulasta® 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. Neulasta® counteracts neutropenia.

6. The availability of Neulasta® 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.

7. Neulasta® is a highly successful product. It has achieved "blockbuster" status, an industry term used to denote products with over $1 Billion in total sales, and has become incorporated into the standard of care for cancer patients receiving certain myelosuppressive chemotherapy regimens. While Amgen does not publicly report the precise profitability of Neulasta®, the contribution margins on Neulasta® are significant.

Apotex's Proposed Entry Into the Long-Acting Filgrastim Market

8. In the United States, Amgen's Neulasta® does not currently face direct competition from any other long-acting filgrastim product. There are short-acting filgrastim products, including Amgen's Neupogen®, Teva's Granix®, and Sandoz's Zarxio®, but there is currently no long-acting treatment for neutropenia other than Amgen's Neulasta®.

9. I am aware that Apotex has applied for FDA approval of a biosimilar version of Neulasta®, which I am told it will call Pelgraz upon FDA approval. I also understand that Amgen asserts in this lawsuit that Apotex is required by law to provide Amgen with at least 180 days' notice, after FDA approval and before the first commercial marketing of its biosimilar pegfilgrastim product.

Price Erosion From Apotex's Entry Into the Long-Acting Filgrastim Market

10. I believe that Apotex's premature entry into the long-acting filgrastim market will severely and permanently harm Amgen. The harm to Amgen may include not only lost sales, but permanent erosion of Amgen's prices.

11. Amgen currently manufactures and supplies Neulasta® to meet the entire United States demand for long-acting filgrastim, and is prepared to continue to do so. There is no significant un-met medical need for pegfilgrastim. Sales of Apotex's Pelgraz will therefore come at the expense of Amgen's Neulasta® sales, and possibly also Amgen's Neupogen® sales.

12. I would expect Apotex to price its product below Amgen's prices for Neulasta®. Customers of filgrastim products are fairly price-sensitive. To maintain market share, Amgen could be forced to lower its prices to compete with Apotex. If Apotex were thereafter enjoined from the market as a result of a preliminary or permanent injunction in a patent lawsuit, it would be very difficult if not impossible for Amgen to simply raise its prices back to what they were

before competition with Apotex's Pelgraz. Amgen would face significant resistance from its customers if it sought to restore its previous pricing. Because of the way that Medicare reimbursement formulas and timing operate, any price increase could lead to a greater cost for our products than doctors would be receiving in reimbursement. If that were to occur, healthcare providers may be reluctant to prescribe Neulasta® to patients in need, fostering animosity towards Amgen.

13. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed the 15th day of October, 2015, at Thousand Oaks, California.

Robert Azelby

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiff, v. APOTEX INC. and APOTEX CORP., Defendant.	Case No. 0:15-CV-61631-JIC/BSS

DECLARATION OF NICHOLAS GROOMBRIDGE IN SUPPORT OF AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION

I, Nicholas Groombridge, declare and state as follows:

1. I am a member of the law firm of Paul, Weiss, Rifkind, Wharton & Garrison LLP, counsel for Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (together, "Amgen") in this action. I make this declaration to place before the Court certain documents in support of Amgen's motion for a preliminary injunction.

Relevant Correspondence Between the Parties

2. On April 17, 2015, W. Blake Coblentz, counsel for Defendants Apotex Inc. and Apotex Corp. wrote a letter to me, in my capacity as counsel for Amgen, stating as follows: "Pursuant to 42 U.S.C. § 262(l)(8)(A), Apotex Inc. and Apotex Corp. (collectively,"Apotex") hereby provide Notice of Commercial Marketing to Reference Product Sponsor, Amgen Inc. ("Amgen"), for Apotex's Pegfilgrastim Product described in its section 351(k) application, BLA No. 761026. Nothing in this letter constitutes a waiver of Apotex's rights under 42 U.S.C. § 262." I attach a true and correct copy of that letter hereto as Exhibit A.

3. On May 8, 2015, I responded to Mr. Coblentz, asserting that because FDA had not yet approved Apotex's Biologics License Application ("aBLA") for its pegfilgrastim product, Apotex's April 17 letter does not constitute effective notice under 42 U.S.C. § 262(*l*)(8)(A). I attach a true and correct copy of that letter hereto as Exhibit B.

4. On July 29, 2015, after the Federal Circuit issued its decision in *Amgen, Inc.* v. *Sandoz, Inc.*, 794 F.3d 1347 (Fed. Cir. 2015), I wrote to Mr. Coblentz to reiterate Amgen's assertion that Apotex's April 17, 2015 purported notice of commercial marketing was ineffective because it was provided prior to FDA approval of Apotex's aBLA, and to request confirmation that Apotex will provide legally effective notice of commercial marketing after it receives FDA approval for its pegfilgrastim product. I attach a true and correct copy of that letter hereto as Exhibit C.

5. On August 24, 2015, Mr. Coblentz responded to my July 29, 2015 letter, asserting Apotex's position that "providing a notice of commercial marketing is not mandatory" and citing passages of the *Amgen* v. *Sandoz* decision that Apotex contends support its position. I attach a true and correct copy of that letter hereto as Exhibit D.

The Federal Circuit's Injunction Pending Appeal

6. While the *Amgen* v. *Sandoz* case was on appeal, Amgen moved for an injunction pending appeal pursuant to Fed. R. App. P. 8(a). On May 5, 2015, the Federal Circuit granted that motion, ordering that Sandoz, Inc. be enjoined "from marketing, selling, offering for sale, or importing into the United States its FDA-approved ZARXIO® biosimilar product until this Court resolves the appeal." I attach a true and correct copy of that order hereto as Exhibit E.

The Parties' Stipulations In Connection With This Motion

7. In connection with Amgen's motion for a preliminary injunction, the parties reached a stipulation regarding the irreparable harm, balance of hardships, and public interest injunction factors. I attach a true and correct copy of that stipulation hereto as Exhibit F.

8. The parties also reached a stipulation regarding a proposed briefing schedule, and regarding a date certain before which Apotex will not commercially manufacture, use, offer to sell or sell within the United States or import into the United States its biosimilar pegfilgrastim product. In order to preserve the confidentiality of that date, which is commercially sensitive, the Court granted the parties' joint motion to seal that stipulation. *See* DE 40.

FDA Approval of NEULASTA®

9. The Amgen product at issue in this lawsuit is NEULASTA® (pegfilgrastim). FDA approved NEULASTA® in 2002, and Amgen, Inc. is the owner of the license for NEULASTA®, as identified on FDA's public website. *See* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/125031_0000_NeulastaTOC.cfm. I attach a true and correct copy of a printout of this web page as Exhibit G.

The Cost of Drug Development

10. Published texts have calculated that the cost of developing a new medicine and bringing it to market exceeds $1 billion, including the cost of failures. I attach as Exhibit H a true and correct copy of a study entitled "The R&D Cost of a New Medicine," by Jorge Mestre-Ferrandiz, Jon Sussex, and Adrian Towse, which at Table 2.2 collects the costs estimated by several such studies from the past thirty years.

The Federal Circuit's Denial of the Parties' Petitions for Rehearing *En Banc*

11. Each of Amgen and Sandoz petitioned the full Federal Circuit to re-hear en banc aspects of the panel's decision in the *Amgen* v. *Sandoz* case. The Federal Circuit denied both petitions today. I attach a true and correct copy of the order denying those petitions as Exhibit I.

12. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed the 16th day of October, 2015, at New York, New York.

Nicholas Groombridge

EXHIBIT A

COZEN O'CONNOR

April 17, 2015

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Re: Letter Regarding Notice of Commercial Marketing Under 42 U.S.C. § 262(l)(8)(A) for Apotex's Pegfilgrastim Product

Dear Nick:

Pursuant to 42 U.S.C. § 262(l)(8)(A), Apotex Inc. and Apotex Corp. (collectively, "Apotex") hereby provide Notice of Commercial Marketing to Reference Product Sponsor, Amgen Inc. ("Amgen"), for Apotex's Pegfilgrastim Product described in its section 351(k) application, BLA No. 761026.

Nothing in this letter constitutes a waiver of Apotex's rights under 42 U.S.C. § 262.

Sincerely,

COZEN O'CONNOR

W. Blake Coblentz

cc: Kerry McTigue

EXHIBIT B

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VIA EMAIL

May 8, 2015

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Dear Blake:

This is in response to your letter of April 17, 2015, purporting to provide Notice of Commercial Marketing, pursuant to 42 U.S.C. § 262(l)(8)(A), for Apotex's Pegfilgrastim Product described in its application under 42 U.S.C. § 262(k), BLA No. 761026. As Apotex's Pegfilgrastim Product is not yet licensed by the FDA, Apotex's April 17 letter does not constitute effective notice under § 262(l)(8)(A).[1] Nor can

[1] To the extent that Apotex is relying on the district court decision in *Amgen,Inc. v. Sandoz, Inc.*, 14-cv-4741-RS (N.D. Cal., Mar. 19, 2015), Apotex should be aware that the decision is currently the subject of an appeal pending before the Federal Circuit. In addition, that district court decision is squarely in conflict with an earlier decision

Apotex's purported notice be effective *nunc pro tunc* upon eventual licensure of Apotex's Pegfilgrastim Product by the FDA.

Subsection 262(l)(A) provides that "the subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." (emphasis added). Whereas other sections of the BPCIA refer to "the biological product that is the subject of the subsection (k) application" (*see e.g.*, §§ 262(l)(3)(A)(i); (l)(3)(B)(i); (l)(3)(B)(ii)(I); (l)(3)(C)), section (l)(8)(A) refers to the "biological product licensed." As Apotex's Pegfilgrastim Product is yet to be licensed, Apotex's purported notice is ineffective.

Amgen expressly reserves all rights in the event that Apotex attempts to act in reliance on its ineffective notice of commercial marketing. In order to avoid any misunderstanding going forward, we ask you to let us know whether Apotex will provide 180 day notice of first commercial marketing on or after licensure of its Pegfilgrastim Product, or, alternatively, whether it will attempt to rely on the purported notice embodied in your April 17 letter.

Sincerely yours,

/s/ Nicholas Groombridge

Nicholas Groombridge

CC: Kimberlin Morley, Esq.

---

of the same district court, *Sandoz, Inc. v. Amgen, Inc.*, No. C-13-2904 MMC, 2013 WL 6000069 (N.D. Cal. Nov 12, 2013).

EXHIBIT C

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VIA EMAIL

July 29, 2015

W. Blake Coblentz
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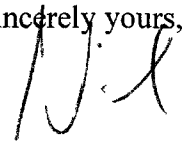
Dear Blake:

As you know from our prior correspondence, it is Amgen's view that the purported notice of commercial marketing provided by Apotex on April 17, 2015 is legally ineffective because it was provided prior to the approval of Apotex's Pegfilgrastim product by the U.S. Food and Drug Administration. The recent decision in *Amgen v. Sandoz*, No. 2015-1499, 2015 WL 4430108 (Fed. Cir. Jul. 21, 2015) confirms that Amgen's view is correct. In that case, the Federal Circuit held that "a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen*, 2015 WL 4430108, at *9 (emphasis added).

Accordingly, we request confirmation that Apotex will provide legally effective notice of commercial marketing pursuant to 42 U.S.C. Section 262(*l*)(8)(A) after it receives FDA approval for Apotex's Pegfilgrastim Product described in BLA No.

761026, and at least 180 days before Apotex begins commercial marketing of that product.

Sincerely yours,



Nicholas Groombridge

CC: Kimberlin Morley, Esq.

EXHIBIT D

COZEN O'CONNOR

August 24, 2015

W. Blake Coblentz
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Direct Fax 202-640-5916
wcoblentz@cozen.com

VIA EMAIL & UPS

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Dear Nick:

We write in response to your July 29, 2015 letter. We understand that it is your position that Apotex's notice of commercial marketing provided on April 17, 2015 is legally ineffective based on the recent *Amgen v. Sandoz* Federal Circuit decision.

As to your request for confirmation that Apotex will provide notice of commercial marketing pursuant to 42 U.S.C. § 262(l)(8)(A) after it receives FDA approval, because Apotex followed the pathway and provided Amgen with its application and manufacturing information, providing a notice of commercial marketing is not mandatory. Indeed, the majority opinion in *Amgen v. Sandoz* specifically recognizes that 42 U.S.C. § 262(l)(9)(B) "specifies the consequence for a subsequent failure to comply with (l)(8)(A) *after the applicant has complied* with paragraph (l)(2)(A) . . . ." *Amgen v. Sandoz*, No. 2015 WL 4430108, at *10 (emphasis in original). Moreover, Judge Chen, in his dissenting opinion, confirms that the plain language of 42 U.S.C. § 262(l)(9)(B) provides that if a (k) applicant complies with the requirements of 42 U.S.C. § 262(l)(2) – (l)(7), the RPS has authorization to immediately file suit on any patent it listed under 42 U.S.C. § 262(l)(3). *Amgen*, 2015 WL 4430108, at *21.

Sincerely,

COZEN O'CONNOR

W. Blake Coblentz

cc: Kerry McTigue

EXHIBIT E

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED,
Plaintiffs-Appellants

v.

SANDOZ INC.,
Defendant-Appellee

2015-1499

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-04741-RS, Judge Richard Seeborg.

ON MOTION

PER CURIAM.

O R D E R

Amgen Inc. et al. move for an injunction "preventing Sandoz [Inc.] from marketing, selling, offering for sale, or importing into the United States its FDA-approved ZARXIO® biosimilar product until this Court resolves the appeal." Sandoz opposes.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The motion is granted, effective immediately.

(2) The parties are directed to respond concerning what amount of a bond, if any, should be posted for each day that the injunction is in place. Sandoz shall file, within seven days of this order, a document not to exceed 10 pages explaining what amount of bond should be posted. Amgen shall file, within seven days of Sandoz's filing, a response not to exceed 10 pages. The bond amount will be determined by subsequent order of the court.

FOR THE COURT

/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk of Court

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

Case No. 15-cv-61631-JIC/BSS

AMGEN INC. and AMGEN MANUFACTURING LIMITED,

Plaintiffs,

vs.

APOTEX INC. and APOTEX CORP.,

Defendants.

JOINT STIPULATION REGARDING AMGEN'S MOTION FOR PRELIMINARY INJUNCTION

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively "Amgen") and Defendants Apotex Inc. and Apotex Corp. (collectively "Apotex") hereby stipulate and agree as follows:

WHEREAS Apotex is seeking licensure of a pegfilgrastim product by the U.S. Food and Drug Administration ("FDA") as a biosimilar pursuant to 42 U.S.C. § 262(k);

WHEREAS, Apotex plans to market its biosimilar pegfilgrastim product immediately upon gaining licensure from the FDA;

WHEREAS the parties have a dispute regarding the requirements and interpretation of 42 U.S.C. § 262(l)(8)(A);

WHEREAS Amgen intends to move, pursuant to Fed. R. Civ. P. 65, for a preliminary injunction enjoining Apotex from commercializing Apotex's biosimilar pegfilgrastim product unless and until Apotex provides notice of commercial marketing in accordance with the requirements of 42 U.S.C. § 262(l)(8)(A) as interpreted by Amgen;

WHEREAS the resolution of Amgen's motion for a preliminary injunction will require that the Court interpret 42 U.S.C. § 262(l)(8)(A) and statutory construction is an issue of law;

WHEREAS, because the parties recognize that Amgen's motion for a preliminary injunction must be denied if Amgen is unable to show that it is likely to succeed in demonstrating that, under the correct interpretation of 42 U.S.C. § 262(l)(8)(A), Apotex has failed to provide effective notice; and

WHEREAS the parties wish to expedite resolution of Amgen's motion for a preliminary injunction and minimize litigation costs and the use of judicial resources;

NOW THEREFORE it is hereby stipulated by and among the parties to this action through their counsel, that:

1. Solely for the purposes of Amgen's motion for a preliminary injunction, Apotex will not dispute that Amgen would be irreparably harmed if Apotex were to commence commercial marketing of its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. § 262(l)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing;
2. Regarding the balance of the hardships relevant to the issuance or non-issuance of a preliminary injunction to prevent Apotex from commercially marketing its biosimilar pegfilgrastim product, because the question of whether Apotex is required to provide notice under 42 U.S.C. § 262(l)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing is a matter of statutory interpretation, the parties

agree that, if the Court finds in favor of Amgen regarding likelihood of the merits, the balance of hardships favors Amgen.

3. Because the public interest favors compliance with federal statutes as properly interpreted, Apotex agrees that should the Court find in favor of Amgen regarding likelihood of the merits, it will not dispute that the public interest favors the issuance of an injunction barring Apotex from commercially marketing its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. §262(l)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing.

4. This stipulation, and the matters hereby stipulated to, shall be applicable solely to the resolution of Amgen's motion for a preliminary injunction (and any appeal of the ruling on that motion).

AGREED AND STIPULATED TO:

Date: September 25, 2015

By:
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Catherine Nyarady
Eric Allen Stone
Jennifer Gordon
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Attorneys for Apotex Inc. and Apotex Corp.

EXHIBIT G

Drug Approval Package

Neulasta (Pegfilgrastim) Injection
Company: Amgen, Inc.
Application No.: 125031
Approval Date: 1/31/2002

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Medical Review(s)
  Part 1 (PDF)
  Part 2 (PDF)
  Part 3 (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
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EXHIBIT H

THE R&D COST OF A NEW MEDICINE

Jorge Mestre-Ferrandiz,
Jon Sussex and Adrian Towse
Office of Health Economics

OHE Research
Office of Health Economics

THE R&D COST OF A NEW MEDICINE

JORGE MESTRE-FERRANDIZ,
JON SUSSEX AND ADRIAN TOWSE

DECEMBER 2012

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This publication has undergone a rigorous peer review by the independent OHE Editorial Board and other experts in the field. The views expressed are those of the authors and do not necessarily represent those of the OHE.

ABOUT THE AUTHORS

Dr Jorge Mestre-Ferrandiz is Director of Consulting at the Office of Health Economics. His research interests include pharmaceutical pricing and reimbursement systems worldwide, the economics of the pharmaceutical industry, the economics of innovation and incentives for encouraging medical R&D.

Jon Sussex is Deputy Director at the Office of Health Economics. His areas of expertise include health care expenditure; efficiency, competition and incentives in health care systems; the role of the private sector in publicly funded health care; and the economic regulation of the pharmaceutical industry.

Prof Adrian Towse is Director of the Office of Health Economics. His current research includes the use of "risk-sharing" arrangements between health care payers and pharmaceutical companies, including value-based pricing approaches; the economics of pharmacogenetics for health care payers and the pharmaceutical industry; economic issues that affect both R&D for and access to treatments for diseases prevalent in the developing world; the economics of medical negligence; and measuring productivity in health care.

ACKNOWLEDGEMENTS

This work was partially funded by an unrestricted research grant from AstraZeneca. We also would like to thank CMRI for allowing us to access their data. We are grateful to Prof Pedro-Pita Barros, Universidade Nova de Lisboa; Prof Martin Buxton, Brunel University; Prof Patricia Danzon, University of Pennsylvania; and Dr Nancy Mattison, The Mattison Group, for comments on an earlier draft.

CONTENTS

LIST OF ILLUSTRATIONS AND TABLES

EXECUTIVE SUMMARY

Introduction and Context

How much it costs to research and develop a successful new medicine has been an important policy issue at least since the 1960s. Cost estimates matter not just because of intellectual curiosity or for industry understanding of its performance, but because they are a key aspect of the international debate about the reasonableness of pharmaceutical prices and the magnitude of the long-term investments involved.

Debate continues about whether the R&D productivity of the biopharmaceutical industry has fallen. Calculations based on annual rates of R&D spending and the number of new molecular (chemical or biological) entities launched suggest a declining trend in R&D productivity. But it takes a long time to develop a new drug, so comparing current R&D spending levels with the current number of new approvals is an inaccurate measure of R&D productivity, at best.

Mean Research and Development Costs in the Literature

Published estimates of the mean (average) cost of researching and developing a successful new medicine suggest an increase in cost over the last decade—from the estimate of US$802m by DiMasi et al (2003) at 2000 prices (US$1,031m at 2011 prices) to the estimate by Paul et al (2010) of US$1,867m at 2011 prices. In this study, we present a new estimate, US$1,506m at 2011 prices, which lies within this range. Our analysis explores how these costs have been evolving and for what reasons.

Mean estimates of R&D costs per new medicine, and in particular drawing conclusions based on comparisons between estimates, should be treated with caution because of important differences in the studies, particularly in the use of different databases of drugs. Moreover, important differences exist across subgroups of drugs—for instance, by therapeutic area, by firm size and by compound origin.

Key Components of R&D Costs

Four main variables determine the capitalised cost of a new drug estimate: out-of-pocket costs, success rates, development times and the cost of capital. Given the long timescales required to develop a new drug and the associated risks, we need to allow for both failures and the cost of capital to compute the total cost of a new successful drug, i.e. not just the out-of-pocket costs. Capitalised cost is the standard accounting treatment for long-term investments. This recognises the fact that investors require a return on research that reflects alternative potential uses of their investment.

Out-of-pocket costs: Out-of-pocket development costs, before adjusting for failures, appear to have increased over time since the first DiMasi et al (1991) article. The most recent estimates, by Paul et al (2010) and Adams and Brantner (2010), are very similar for out-of-pocket development costs (from Phase I through III) at around US$215-220m in 2011 US$. The studies are less consistent in their estimates of the magnitude of the cost of the different clinical trial phases.

Success rates: The most recent estimates of probability of success for Phase I, Phase II and Phase III are between 49% and 75%, 30% and 48%, and 50% and 71%, respectively. Overall, the cumulative clinical success rate appears to have decreased over time. Pammolli, Magazzini and

Riccaboni (2011) find significant decreases in success rates, especially in Phase II and Phase III. But analyses by DiMasi and colleagues since the early 1990s suggest that success rates across the different phases have changed little.

Development times: Overall development time (Phases I–III) appears to have remained relatively constant over time, at around 6.5 years (75–79 months) on average. Phase III trials tend to be the longest development phase, although the most recent work suggests that development times for Phases II and III now are similar.

Cost of capital: The long timescales of pharmaceutical R&D mean that the cost of capital has a major impact on the final cost per successful NME. The estimated cost per successful drug is highly sensitive to the cost of capital applied. The more recent studies use a real annual cost of capital of 11%, up from the 9% used by DiMasi et al (1991).

Our New Cost Estimate

In this study, we present a new estimate for mean R&D costs per new successful drug based on previously unpublished information collected by CMRI in confidential surveys. Our fully capitalised R&D cost estimate per new medicine is US$1,506m at US$ 2011 prices (i.e. US$1.5 b). Time costs, i.e. cost of capital, represent 33% of total cost. Our new estimate lies within the range of other recently reported estimates.

Our overall probability of success is lower than those reported by DiMasi et al (2003) and Paul et al (2010). Development times in our study are similar to those reported by DiMasi et al (2003) and Paul et al (2010). Total out-of-pocket costs are very similar to those in Paul et al (2010) and slightly lower than those in DiMasi et al (2003).

Mean Costs May Hide Important Differences

Published estimates that refer to the mean cost of R&D per new medicine are just that—averages. The literature has shown that the costs of R&D vary with the subgroup of drugs included in the analysis. The most important factors affecting costs are: therapeutic area, firm size, and whether the molecule is a "traditional" chemical compound or a biologic.

Therapeutic area: R&D costs vary substantially across therapeutic area because of considerable variation in three key variables: success rates, development times and out-of-pocket costs.

The most recent analyses suggest that the most expensive therapeutic areas in terms of drug R&D costs are neurology, respiratory and oncology. This is because drugs in these categories experience lower success rates and longer development times. By comparison, anti-parasitics and drugs to treat HIV/AIDS have the lowest R&D costs because of higher success rates and shorter development times.

Self-originated versus licensed-in: Most of the published calculations of R&D costs to date focus on self-originated new compounds because comprehensive data for licensed-in/acquired compounds are very difficult to collect. However, an increasing proportion of drugs are now licensed in and clinical success rates for such drugs are higher than for self-originated drugs. Greater success may be the results of a "screening effect" for licensed-in compounds: many of the

licensed-in drugs are acquired after Phase I or Phase II testing has been conducted by the licensor and, thus, already have been shown to be promising candidates before being included in the acquiring company's development portfolio.

This difference also is apparent during early research, i.e. externally-sourced projects are significantly more likely to reach clinical testing than internal projects, perhaps for similar reasons. Indeed, some expectation of success would be necessary for a company to license or acquire any drug candidate.

Firm size: An important variable explored in the literature is the effect of firm size on R&D productivity and whether R&D costs per approved drug vary with firm size. For such analyses, papers focusing on self-originated compounds might produce biased results because the sample for small firms with successful self-originated drugs would be too small to be meaningful.

Results of research on the impact of firm size on R&D productivity and R&D costs are mixed. The evidence from the 1990s and early- to mid-2000s seems to suggest that size matters: multiple tangible and intangible assets are associated with fully integrated organisations, where core capacities can be important across diseases. It remains unclear, however, whether R&D productivity is greater for smaller companies than for traditional "big pharma".

Biopharmaceuticals: To address the problem of limited evidence on biological medicines, DiMasi and Grabowski (2007b) expanded their biotech sample from DiMasi et al (2003) with project level and aggregate annual expenditure data from a biotech firm. They found that the overall clinical success rate for biotech products is 30.2%, which is higher than the 21.5% estimate for traditional pharmaceutical products reported by DiMasi et al (2003). Total clinical and approval time is 8% longer for biopharmaceuticals, with nearly all the difference being in Phase I.

Capitalisation increases biopharma costs relative to traditional R&D costs because of the longer development timeline and a slightly higher cost of capital. To account for the latter, DiMasi and Grabowski (2007b) use an 11.5% cost of capital for biologics compared to 11% for other medicines. Comparisons between biologics and other pharmaceuticals based on this one study, however, should be viewed with caution because the sample size for biologics still is small.

Drivers of Trends in R&D Costs

The key drivers of the main components of R&D costs present three sets of issues grouped around out-of-pocket costs, failure/success rates and development times.

Drivers of out-of-pocket costs: A key element of R&D cost is the cost of clinical trials, which is affected by the cost per patient and the number of patients required to collect sufficient data. The complexity of clinical trials has increased over time, also increasing their costs. Two trends, however, appear to be helping to control trial costs. First, outsourcing to clinical research organisations (CROs) appears to increase the efficiency of running trials. Second, locating trials in emerging markets (Africa, Asia, Eastern Europe, Latin America and the Middle East) can reduce costs, both because local costs are lower and because patient recruitment may be faster. Nevertheless, although more clinical trials are being conducted in emerging markets, especially

Phase III trials, the majority of clinical trials still are conducted in the US and Western Europe, for reasons related to regulatory conditions, relevant expertise and infrastructure.

Drivers of failure rates: Failure rates appear to have increased over time and have fluctuated across stages of development. This may be the result of a combination of reasons. First, regulators are becoming more risk averse and may be more reluctant to approve some drugs. Second, R&D is directed towards tougher challenges that require drugs with novel mechanisms of action and for which clinical endpoints may be less clear cut. Third, within companies, projects may advance prematurely, for various reasons, to the later stages of clinical development and then fail in Phase III.

Other changes have been identified that could counter increased failure rates. These include better preclinical screening that ensures earlier project termination; integrating HTA earlier in the process to encourage earlier decisions about discontinuing projects for commercial reasons; and developing biomarkers and companion diagnostics that can lead to personalised or stratified medicine, with greater prospects for success. Alliances between companies, increasingly common, also may increase success rates.

In the short run, however, important technological challenges, especially for personalised/stratified medicines, may actually lead to higher failure rates and costs as science advances and while companies learn how to better develop biomarkers and companion diagnostics. It might take some time for biomarkers and diagnostics to be used efficiently, but "learning by doing" could drive a more efficient R&D process in the long run.

Drivers of development times: A number of factors affecting development times have been identified. First, regulators may be more risk averse, leading to increased regulatory stringency and longer regulatory reviews. Second, companies are directing efforts towards areas that are intrinsically associated with very long clinical development times. Third, clinical trials are becoming increasingly complex and, as a result, take longer to complete. Fourth, trade offs may be occurring between time and success rate—for example, longer Phase II development times that allow for additional scrutiny before deciding whether to advance to the next phase might produce higher success rates in Phase III. A better use of biomarkers might reduce overall development times by enabling pre-identification of patients with a high response rate and/or low probability of an adverse drug reaction.

A new drug development paradigm? A number of alternatives have been put forward to try to make the R&D process more efficient and affordable. The key suggestions include focusing on the earlier phases to reduce technical uncertainties before undertaking the more expensive trials in the later development stages and allowing for greater flexibility.

Conclusions

Mean estimates of R&D costs per successful drug are useful in providing an overall picture, but should be treated with caution. Important cost differences exist across therapeutic areas, firm sizes and compound origins. In addition, many of the cost estimates in the literature focus on self-originated new compounds and exclude licensed-in compounds and compounds that have been discovered and/or developed via alliances or deals between companies, which are

increasingly common. Other cost estimates do not differentiate at all between self-originated and licensed-in compounds, making it difficult to gauge their accuracy. These issues should be factored in when drawing conclusions about R&D costs.

With these caveats in mind, it does appear that R&D costs per new successful medicine are increasing. The reasons for the increase in R&D costs are multiple—from higher cash outlays to higher costs of capital and higher attrition rates throughout the clinical trials process.

Technological challenges are driving these cost increases in part; today's targeted diseases currently are more complex than diseases targeted decades ago, producing a negative impact on R&D costs. In addition, as we move towards personalised/stratified medicine, the need to identify the appropriate patient population more narrowly increases. Some examples already exist of new medicines being developed alongside companion diagnostics that target very specific patient subpopulations; this can increase the R&D costs in the short run as companies adapt to this new environment. In the long run, however, this "learning by doing" has the potential to make the R&D process more efficient.

Companies sometimes may advance projects prematurely through the R&D process when more time and resource invested at an earlier stage could prevent an ultimately unsuccessful and more expensive Phase III. Companies continue to work to improve the efficiency of R&D decisions by addressing those factors within their control—e.g. greater scrutiny in the early R&D stages, integrating health economics earlier in the process, and moving some trials to less expensive locations and/or using CROs to manage clinical trials. Biopharmaceutical companies also are trying to address the more complex scientific challenges through alliances with other companies and by working in collaboration with a range of other stakeholders. This allows both risks and rewards to be shared, rather than being borne by one party alone.

The R&D costs identified in our study are driven by a combination of factors, including changes in technology and decisions taken by companies and regulators. Whether the current drug development paradigm needs revising and—if so, how—is clearly an important policy issue that merits further investigation.

INTRODUCTION AND CONTEXT

Key Points

How much it costs to research and develop a successful new medicine has been an important policy issue at least since the 1960s[1]. Cost estimates matter not just because of intellectual curiosity or for industry understanding of its performance, but because they are a key aspect of the international debate about the reasonableness of pharmaceutical prices and the magnitude of the long-term investments involved.

Debate continues about whether the R&D productivity of the biopharmaceutical industry has fallen. Calculations based on annual rates of R&D spending and the number of new molecular (chemical or biological) entities launched suggest a declining trend in R&D productivity. But it takes a long time to develop a new drug, so comparing current R&D spending levels with the current number of new approvals is an inaccurate measure of R&D productivity, at best.

Published estimates of the mean (average) cost of researching and developing a successful new medicine suggest an increased over the last decade—from the estimate of US$802m by DiMasi et al (2003) at 2000 prices (US$1,031m at 2011 prices) to the estimate by Paul et al (2010) of US$1,867m at 2011 prices. In this study, we present a new estimate, US$1,506m (at 2011 prices), which lies within this range. Our analysis explores how these costs have been evolving and for what reasons.

Mean estimates of R&D costs per new medicine and, in particular, drawing conclusions based on comparisons between estimates, should be treated with caution because of important differences in the studies, particularly in the use of different databases of drugs. Moreover, important differences exist across subgroups of drugs—for instance, by therapeutic area, by firm size and by compound origin.

An important international policy debate continues about how much it costs to research and develop a successful new drug (NME[2]), be it chemical or biological. It is important to understand how much a new medicine costs to research and develop, identifying in particular the key drivers of changes in these costs over time, for at least two reasons:

1. To help understand the reasonableness, or otherwise, of the prices sought by producers of new medicines
2. Given R&D productivity challenges in recent years, companies must ensure that their R&D resources are spent optimally to maximise use of limited resources

Monitoring and understanding R&D cost drivers is important in devising optimal responses to change. These responses, however, need to come from both policy makers and biopharmaceutical companies. On the one hand, the pharmaceutical industry is highly regulated (R&D, marketing authorisation, pricing) so there is a need to explore what actions regulators can take to make R&D more efficient—without compromising safety and efficacy and still ensuring that new drugs provide value for money. On the other hand, companies need to take appropriate action to increase R&D productivity, in part by improving the ability to assess accurately the value of pursuing or discontinuing projects.

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[1] See, for example, Bogue (1965).

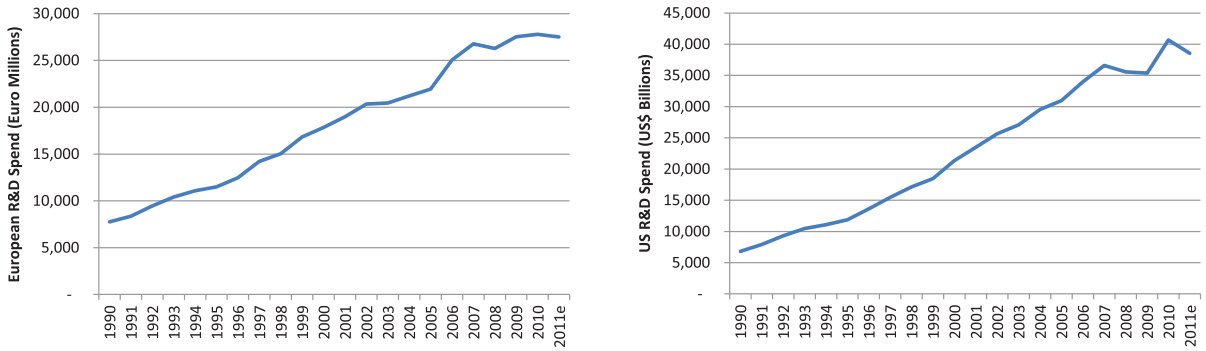
[2] Throughout the paper, we use the acronym "NME" (new molecular entity) to refer to a new product, whether chemical or biologic. Note that some other researchers instead use "NCE" (new chemical entity) and CMRI uses "NAS" (new active substance). See the Glossary for definitions of each term.

With this as context, the objective of this publication is to provide an up-to-date overview of the literature estimating drug R&D costs. In this study, R&D costs are the costs of researching, developing and gaining regulatory approval for a successful new medicine. As described in more detail in Figure 2.1, R&D costs include pre-discovery costs (or basic research), pre-clinical (or discovery) costs, clinical (or development) costs, and costs associated with regulatory review. Pre-discovery and pre-clinical stages are sometimes jointly referred to as "discovery research" (the "R" of "R&D"). Clinical (or "development") costs include Phase I, Phase II and Phase III costs (the "D" of "R&D"). R&D costs do not include Phase IV costs, studies done after marketing begins. We present some new observations on drug R&D costs, using previously unpublished evidence, and explore what we believe are the most important factors that are driving change in the key variables affecting costs.

Context: Setting the Scene

Debate continues about whether the R&D productivity of the pharmaceutical industry has decreased over time. The rationale of claiming it has decreased relies on comparing annual global pharmaceutical R&D spending (the "input") and the number of NMEs launched (the "output"). Figure 1.1 shows pharmaceutical R&D spending since 1990 in Europe and in the US (in euros and US dollars, respectively). Rates of growth have suffered some peaks and troughs over the last two decades and especially over the last few years. Indeed, R&D spending in the US and Europe fell in 2008 and may have fallen again in 2011, but the general trend is a rising one.

Figure 1.1. European and US R&D Spending



Source: EFPIA (2012)

While Figure 1.1 shows the evolution of the "input" variable, i.e. R&D spending, Table 1.1 shows one way of measuring R&D "output" in the pharmaceutical industry—the number of new chemical or biological entities launched in the same time period.

Table 1.1. Number of new chemical or biological entities (1990–2009)

Number	1990–1994	1995–1999	2000–2004	2005–2009
Total	215	207	162	146
Average per year	43	41	32	29

Source: EFPIA (2010a)

Table 1.2 breaks down the 2005–2009 figures to show new entities reaching world markets since 2005, year on year.

Table 1.2. Number of new chemical or biological entities (2005-2009)

Year	2005	2006	2007	2008	2009
Number	30	35	25	31	25

Source: EFPIA (2010a)

Wang and McAuslane (2012) find that the European Medicines Agency (EMA) approved 13 and 23 NMEs in 2010 and 2011, respectively, while the US Food and Drug Administration (FDA) approved 19 NMEs in 2010 and 32 in 2011.

The number of new entities launched has decreased from an average of 43 per year between 1990 and 1994 to around 30 or fewer per year over the last five years.

If we use this data to crudely analyse R&D productivity, we can argue there has been a decline in productivity; the input (R&D spending) is growing while the output (measured by the number of NMEs) is decreasing. However, as explained in greater detail later in this publication, it takes considerable time to research, develop and gain approval for an NME; hence, the outputs we observe during recent years are the result of R&D that was done 10–15 years ago. It is important that we do not focus solely on the static relationship between R&D spending and NME count as the basis for conclusions about whether productivity has increased or decreased. Whether the productivity of recent R&D spending has decreased will not be clear until we can count the number of new successful entities launched in the next five to ten years.

Closely related to the productivity discussion is another heavily debated issue about the pharmaceutical industry: how much it costs to develop a successful NME.

Taking a high-level view, and without looking at the details of each of the studies that estimate these costs, the costs of researching and developing a new drug appear to have increased significantly over the last decades. Indeed, Barker (2010) argues that "the current model for developing new drugs is becoming unaffordable" (page 357). The latest estimate places the cost of a successful drug, from the start of the R&D process to marketing approval, at around US$1.9b (Paul et al, 2010) in 2011 prices[3]. In 2003 these costs were estimated to be US$1.0b in 2011 prices (DiMasi et al, 2003), which itself was a large increase on an earlier estimate of US$451m in 2011 prices in the early 1990s (DiMasi et al, 1991).

Later in this publication we present our own new R&D costs estimate, based on our analysis of unpublished data collected by CMRI. Our estimate, US$1.5b in 2011 prices, lies within the US$1.0b–US$1.9b range. But, as argued in the next section, we need to be cautious when comparing the different estimates.

[3] Throughout the paper, we have updated all costs estimates to 2011 prices using the US GDP implicit price deflator.

Ideally, given that our main interest is to identify trends in real costs per successful NME, we would base this estimate on information from all successful NMEs over time. But such comprehensive information is not available. The various estimates that are available, moreover, use different databases, many of which cannot be compared as they contain confidential, project-specific information, and drugs of different vintages; conclusions based on comparisons across studies that use different databases should be treated with caution. To explore trends, we compare across studies that use similar databases and methodologies. This allows us to identify how the various elements that make up total R&D cost have been evolving over time.

The R&D cost per new medicine approved is indeed increasing. The reasons for the increase are multiple—from higher cash outlays to higher costs of capital and more expensive development phases in terms of out-of-pocket costs. Furthermore, success rates for clinical testing, legally required for a new drug to obtain a marketing authorisation, have been declining. We explore all of these factors in greater detail.

Although mean estimates of R&D costs per successful drug may provide a useful overall picture, they hide important cost differences that exist across therapeutic area, firm size, and compound origin. These issues should be factored in when drawing conclusions about R&D costs.

With respect to compound origin, many of the cost estimates in the literature focus on self-originated NMEs, i.e. they exclude licensed-in compounds and compounds that have been discovered and/or developed via alliances or agreements between companies. Alliances are becoming important in the biopharmaceutical market—not only between biotech and large pharmaceutical companies, but also between "big pharma" companies themselves. Where available, we compare costs for self-originated and licensed-in products.

This publication is organised as follows.

- Section 2 reports on mean cost estimates and discusses how key parameters have been evolving over time. For each parameter, we present the latest evidence and then discuss, where possible, it has have been evolving. We focus on four parameters, in this order: out-of-pocket costs, failure rates, time, and cost of capital. The last three components are relevant because costs are presented as capitalised value at launch, inclusive of failures.

- Section 3 presents unpublished new evidence on R&D costs, based on a number of CMRI surveys.

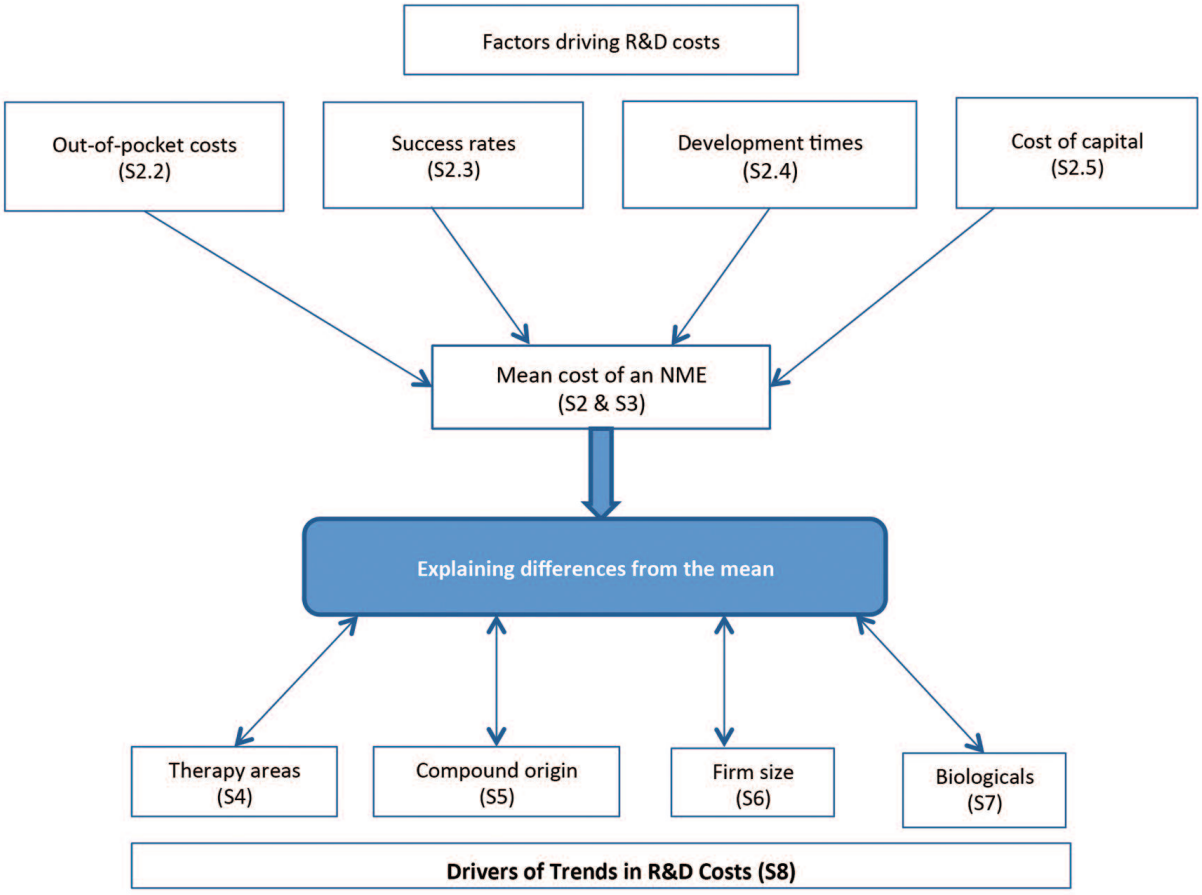
- Sections 4–7 discuss the factors that produce different R&D costs for different kinds of medicines and summarise the evidence as to how much these factors affect development costs.

    - Section 4 presents results quantifying differences across therapeutic areas.
    - Section 5 differentiates between self-generated and licensed-in compounds, and comments on the importance of alliances in drug development.
    - Section 6 takes into account whether and how firm size affects development costs.
    - Section 7 reports on estimates for "biotech" products ("biologicals") and how they compare with small molecules ("chemicals").

- Section 8 provides an overview of the key drivers of trends affecting the different components of drug development costs.
- Section 9 concludes.

Figure 1.2 shows the structure of the paper. The numbers in brackets indicate the relevant section of the paper.

Figure 1.2. Structure of the paper



THE COST OF A NEW MEDICINE—THE MEAN

Key Points

We identified eleven studies published since 1979 that estimate mean R&D costs of a successful NME. The most recent estimate is US$1.9b, a tenfold increase from the 1979 estimate of US$199m (both in 2011 prices).

We also provide a new cost estimate, based on CMRI data, of US$1.5b in 2011 prices. This estimate lies between the estimates by DiMasi et al (2003) and Paul et al (2010). Note that comparisons between different studies based on project-specific data are not straightforward because the studies often use different samples (specific drugs, drug vintages and companies). Most of the evidence focuses on clinical costs (i.e. the "D" of R&D), rather than pre-clinical or discovery (i.e. the "R" of "R&D"). This is because little, if any, project-specific evidence for the early research stages is available.

Four main variables determine the capitalised cost of a new drug estimate: out-of-pocket costs, success rates, development times and the cost of capital.

Out-of-pocket costs: Out-of-pocket development costs, before adjusting for failures, appear to have increased over time since the first DiMasi et al (1991) article. The most recent estimates, by Paul et al (2010) and Adams and Brantner (2010), are very similar for out-of-pocket development costs (i.e. from Phase I through Phase III) at around US$215-220m in 2011 US$. The studies are less consistent in their estimates of the magnitude of the cost of the different clinical trial phases.

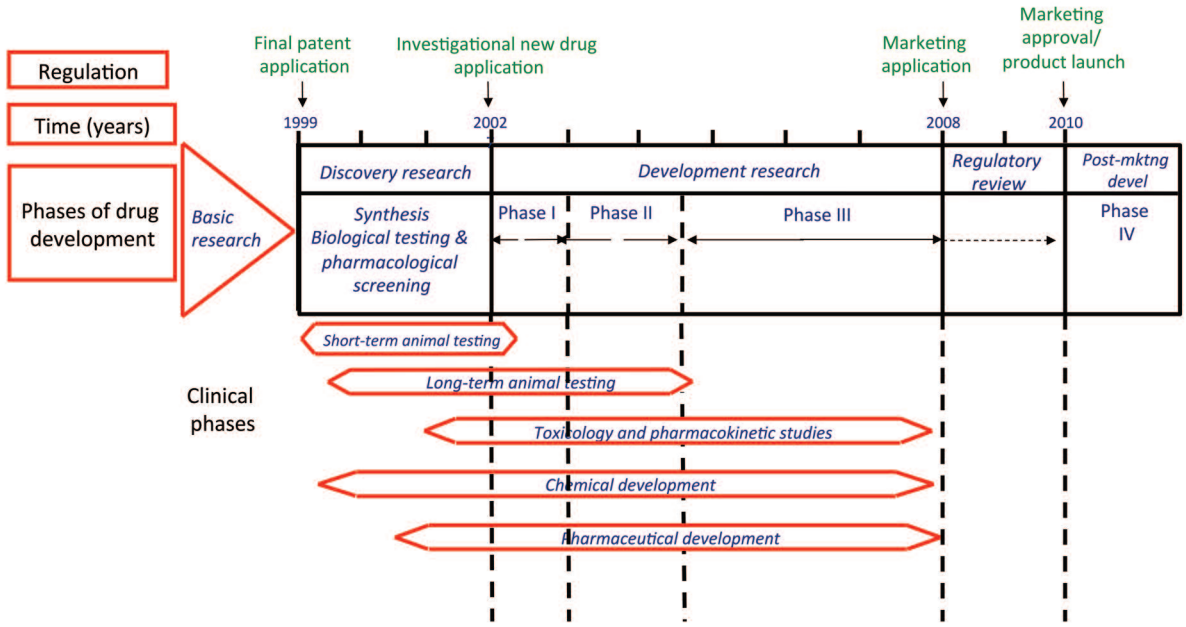
Success rates: The most recent estimates of probability of success for Phase I, Phase II and Phase III are between 49% and 75%, 30% and 48%, and 50% and 71%, respectively. Overall, the cumulative clinical success rate appears to have decreased over time. Pammolli, Magazzini and Riccaboni (2011) find significant decreases in success rates, especially in Phase II and Phase III. But analyses by DiMasi and colleagues since the early 1990s suggest that success rates across the different phases have changed little.

Development times: Overall development time (Phases I–III) appears to have remained relatively constant over time, at around 6.5 years (75–79 months) on average. Phase III trials tend to be the longest development phase, although the most recent work suggests that development times for Phases II and III now are similar.

Cost of capital: The long timescales of pharmaceutical R&D mean that the cost of capital has a major impact on the final cost per successful NME. The estimated cost per successful drug is highly sensitive to the cost of capital applied. The more recent studies use a real annual cost of capital of 11%, up from the 9% used by DiMasi et al (1991).

In this section we report on those papers that estimate the cost of a successful drug, i.e. one that is approved for marketing by a regulatory agency. We focus on the process from the start of discovery research to obtaining a marketing authorisation. Figure 2.1 shows this R&D process graphically.

Figure 2.1. The R&D process



Note: For definition of terms, see the Glossary
Source: Authors' adaptation from publicly available information

Broadly speaking, the R&D process can be divided into two parts: research and development. Research occurs at the early stages (under the heading "discovery research" in the graph). Discovery research sometimes is referred to as "pre-clinical research". There is an earlier stage, "basic research" (or "pre-discovery"), but only one paper provides cost estimates for this phase (Paul et al, 2010). "Development research" (or "clinical research") has three stages: Phase I, Phase II and Phase III.

After Phase III, companies submit their evidence for "regulatory review" to the relevant regulatory agencies (e.g. the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe). If successful, companies then may market the drug[4]; Phase IV research may occur in response to requirements or requests from the relevant authorities for more information about the drug, particularly in actual use, or be undertaken by the company for other reasons. This publication focuses on discovery research, development research, and regulatory review—but mainly on the development phases. Phase IV costs are not included as R&D costs.

Animal testing (included in Figure 2.1)—also known as "animal experimentation", "animal research", and "in vivo testing"—is the use of non-human animals in experiments. Currently, all new pharmaceuticals undergo rigorous animal testing. These safety tests, which provide crucial information for planning human trials, represent only a small proportion of the development process for a new medicine (Animal Research Info, nd). Safety testing begins early in the exploratory development of a potential drug with acute toxicity tests (short-term animal testing in Figure 2.1). Longer toxicity studies are used to support and inform long term clinical studies,

[4] Whether and how soon the drug actually appears on the market also will depend on any pricing and/or reimbursement determination that is required.

with the registration requirement of the drug in mind. These are usually 30-day studies, followed by six-month toxicity studies. As shown in Figure 2.1, drug candidate compounds continue to be tested on animals throughout the clinical trial process; data from human studies are used to inform and refine the animal studies so that they reveal more useful and accurate data. We do not specifically discuss costs of animal testing in this publication, as few studies provide specific cost information on them (see DiMasi et al, 1991 and 2003).

Before discussing existing estimates of the costs of an approved drug, it is important to highlight the difference across the studies. Comparing like to like is important in assessing trends accurately.

We identified eleven studies published since Hansen's seminal 1979 publication that estimate the mean cost of a successful NME[5]. Table 2.1 shows only the studies that use new evidence; we omit studies that reproduce evidence from previous studies. The table shows how these studies compare across the key issues that drive the estimations and summarises the data sources and cohorts of drugs used.

Broadly speaking, R&D cost estimates have used either aggregate data or project-level data. The first method uses industry-wide data and is based on estimating the economic relationship between past values of total research spending and new-drug approval rates. The second method uses data for individual projects collected by surveying pharmaceutical companies.

The cost estimates based on project-level data use different samples. Data differ in terms of drug vintage, i.e. time period when the drugs in the sample were first tested in humans or when they were approved; databases, i.e. the sample of drugs included and whether these were drawn from confidential surveys or publicly available; and the specific companies whose projects are included.

Most of the studies using project-specific data focus on development research (see Figure 2.1). The main reason for this is that estimates of the cost of "discovery research" are not project specific, so the studies that present an estimate for discovery (see Table 2.1) need to make assumptions on the allocation of discovery costs to particular medicines that are developed subsequently, as explained below.

Annex 1 contains the list of papers that have provided new evidence on any of the parameters or issues that drive R&D costs. Some papers provide evidence on all parameters, while others offer evidence on only a limited number. The data sources for the papers listed in Annex 1 are mentioned in the relevant parts of this publication.

The next sections discuss the key variables that drive R&D costs for new medicines: out-of-pocket costs, success/failure rates, timelines, and the cost of capital. Our interest lies in understanding the fully capitalised cost of a successful new drug, i.e. we want to include all the elements that determine the cost of a successful new drug. Capitalised cost, which is out-of-pocket cost corrected for the cost of capital, is the standard accounting method for long-term investments. It recognises that investors require a return on research investments that reflects

[5] Some papers have estimated the cost of developing new drugs under the auspices of what have become known as "product-development partnerships" (PDPs), especially for neglected diseases. The discussion of these estimates is beyond the scope of this publication; for more information, see GATB (2001) and MMV (2008).

Table 2.1. Comparison of models calculating mean R&D costs

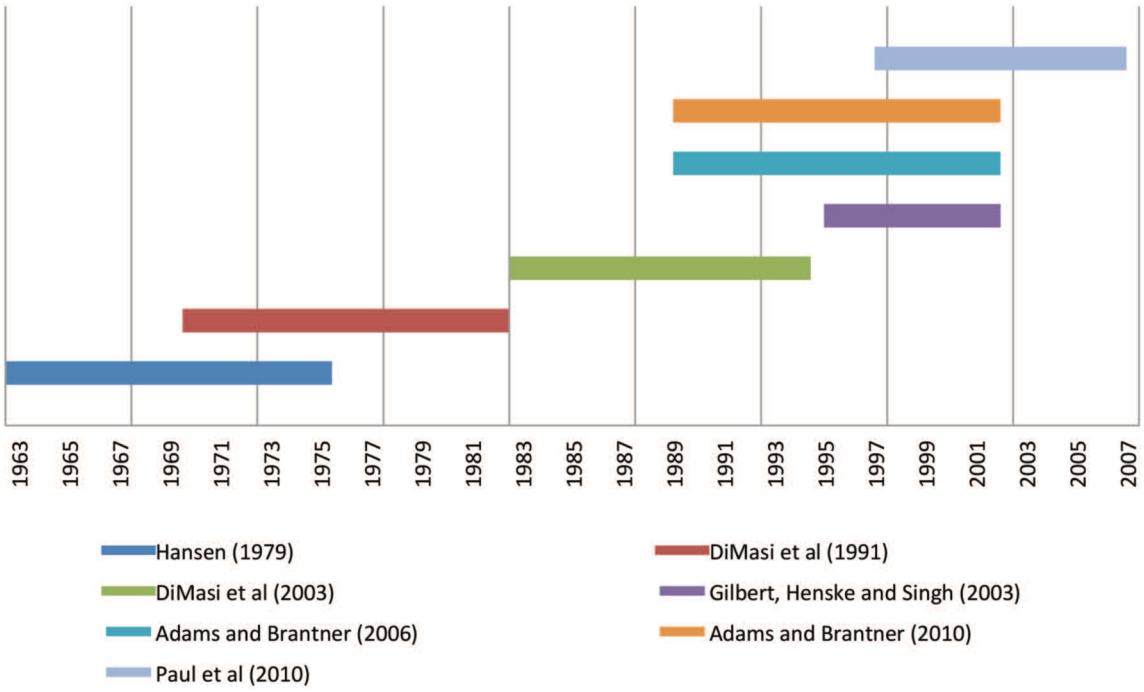
Publication	Sample of NMEs	Source of data			Cost of capital (real)	Discovery research included?	Geograph
		Success rates	Out-of-pocket costs	Development times			
Hansen, 1979	First tested in humans between 1963 and 1975	Confidential survey (14 US pharmaceutical companies)			8%	No	US
Wiggins, 1987	1970-1985	Industry-wide – Not project specific			8%	No	US
DiMasi et al, 1991	First tested in humans between 1970 and 1982	CSDD (full sample)	CSDD (subsample – n=93)	CSDD (full sample)	9%	Yes (estimated)	US
		12 US-owned pharmaceutical companies (firm proprietary)					
DiMasi et al, 2003	First tested in humans between 1983 and 1994	CSDD (full sample)	CSDD (subsample – n=68)	CSDD (full sample)	11%	Yes (estimated)	US
		10 pharmaceutical companies (firm proprietary)					
Gilbert, Henske and Singh, 2003	First tested in humans between 1995 and 2002[1]	Bain Economics model (1995-2002) – No details available			N/A	Yes	Seems global
Adams and Brantner, 2006	Drugs entering human clinical trials for the first time 1989-2002	PharmaProjects	DiMasi et al, 2003	PharmaProjects	11%	Use DiMasi et al (2003)	Global
Adams and Brantner, 2010	Drugs entering human clinical trials for the first time 1989-2002	Adams and Brantner, 2006	Standard & Poor's CompuStat Industrial file and Global Vantage Industrial Commercial file	Adams and Brantner, 2006	11%	No	Global
Paul et al, 2010	1997-2007[1]	Pharmaceutical Benchmarking Forum + Lilly internal data			11%	Yes	Global

[1] We are uncertain about this timeframe of both papers as they are not explicit about this. Note that all papers focus on self-originated NMEs.

potential alternative uses of that investment. So, the capitalised cost per drug approved increases out-of-pocket costs by the cost of capital for every year from the initial investment to approval (Paul et al, 2010). We also take society's perspective when calculating the cost of approved drugs, which means that the total cost of developing a new drug will be the same no matter who pays. This is important particularly for the discussion of tax treatment of R&D expenditures, as mentioned below.

Figure 2.2 shows the time periods for the different cohorts of medicines included in the studies that include cost data for individual projects.

Figure 2.2. Sample of NMEs: time period when first tested in humans



Note: How to read Figure 2.2: Hansen (1979) includes a sample of NMEs first tested in humans between 1963 and 1975; DiMasi et al (1991) between 1970 and 1982, and so on
Source: Table 2.1.

Based on Figure 2.2 above, we can infer that Hansen's paper looked at drug R&D costs during the early 1960s–mid-1970s, Wiggins (1987) and DiMasi (1991) during the 1970s and mid-1980s, DiMasi (2003) between the early 1980s and mid-1990s, Gilbert, Henske and Singh (2003) for the mid-1990s and early 2000s, and both the Adams and Brantner papers for the period between the late 1980s and early 2000s. Paul et al (2010) are not specific about the dates for their sample of NMEs; they say only that their database, from the Pharmaceutical Benchmarking Forum, integrates R&D productivity data from a group of large pharmaceutical firms, that it was started in 1997, and that the data reported include pipeline and productivity information through December 2007.

Table 2.2 summarises mean development costs presented in the various studies. All original estimates have been updated to US$ 2011 prices. Note that adjusting previous original estimates to 2011 prices does not mean that these estimates are an estimate of the cost per NME approved in 2011. The last row presents our new estimate based on unpublished CMRI data, discussed in detail in Section 3.

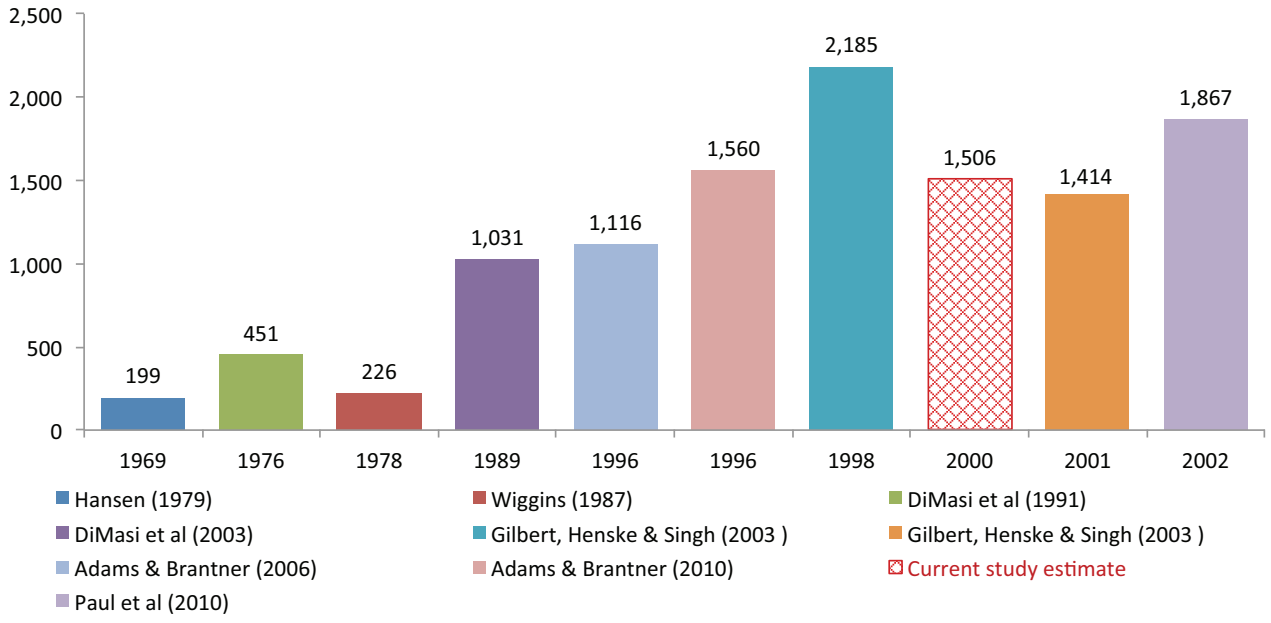
Table 2.2. Estimates of the full cost of bringing an NME to market (2011 US$m)

Source	US$m, 2011 prices
Hansen, 1979	199
Wiggins, 1987	226
DiMasi et al, 1991	451
OTA, 1993	625
Myers and Howe, 1997	664
DiMasi et al, 2003	1,031
Gilbert, Henske and Singh, 2003	(1995-2000) 1,414
	(2000-2002) 2,185
Adams and Branter, 2006	1,116
Adams and Branter, 2010	1,560
Paul et al, 2010	1,867
Mestre-Ferrandiz et al, 2012	1,506

Note: All values are adjusted to US$ 2011 prices using data for the US GDP implicit price deflator from the World Bank. The GDP implicit deflator shows the rate of price change in the economy as a whole, being the ratio of GDP in current local currency to GDP in constant local currency.

Figure 2.3 shows graphically how the estimates of mean R&D cost per NME differ across studies. Each bar represents one study, plotted at the middle of the time interval when projects in each study were first tested in humans. For example, projects included in Paul et al (2010) were first tested in humans between 1997 and 2007; the middle year is thus 2002. The hatched bar represents our new estimates based on CMRI data.

Figure 2.3. Mean R&D costs per successful NME by middle year of study data (2011 US$m)



Sources: Table 2.1 and Table 2.2

At an industry level, Wiggins (1987) computed a fully capitalised cost of a new chemical entity for the period 1970–1985 of US$226m (in 2011 prices). His method included a regression of the total number of NMEs that the FDA had approved between 1970 and 1985 on the estimated total NME-oriented research spending in previous years.

Studies using project-specific data build on Hansen's (1979) work, in particular the DiMasi et al papers of 1991 and 2003. Hansen used micro-level project data, collecting data on 67 products that entered clinical testing between 1963 and 1975 and were approved for marketing starting around 1970. Hansen estimated the cost to be US$199m (in 2011 prices).

The two DiMasi et al papers use the same methodology as Hansen (1979). They also use a consistent source of data, although as mentioned before they use a different cohort of NMEs. DiMasi et al (2003) estimate that the average out-of-pocket R&D cost per new drug is US$403m (in 2000 prices). Capitalising these costs to the point of marketing approval at a real annual cost of capital rate of 11% yields a total pre-approval cost estimate of US$802m in 2000 prices. In 2011 prices, the cost estimate is US$1.0b.

DiMasi et al (2003) build on earlier research conducted by the same authors (DiMasi et al, 1991). In both papers, they use micro-level data on the cost and timing of development obtained

through confidential surveys of pharmaceutical companies. Given the importance of these papers, we explain in some detail both the data and methodology used by these authors.

The DiMasi studies supplement the project level data with data from the Tufts Center for the Study of Drug Development (CSDD) database of investigational compounds. For their second paper, the authors use this database to randomly select compounds that were self-originated by the companies surveyed and first tested in humans during the period 1983–1994[6]. Surveys then were sent to 24 firms, some of which have since disappeared through mergers; although twelve companies replied to the survey, data from only ten companies were usable. These ten firms provided additional information on 76 compounds, but data on eight of those compounds were unusable. Hence, 68 compounds were chosen for the analysis of cost per phase. Clinical phase success probabilities are estimated from the data in the CSDD database of investigational drugs from which the survey sample was drawn.

Evidence presented by DiMasi et al (2003) on the costs of the discovery (i.e. pre-clinical) stages was based on aggregate data. In particular, aggregate level data at the firm level were used to impute costs per drug for R&D incurred prior to human testing. This is because, given the characteristics of such research, costs cannot be allocated to specific compounds.

Two recent papers (Adams and Brantner, 2006; Adams and Brantner, 2010) seek to replicate the DiMasi et al estimates using alternative data sources: PharmaProjects, for evidence on success rates and phase duration, and Standard & Poor's CompuStat Industrial file, for firms' R&D expenditures. Adams and Brantner thus try to solve the concern about much of the data being confidential, and so not available to other researchers for analysis, by using data that potentially could allow their research to be replicated. As a consequence, however, they do not have access to cost data at individual project level. Overall, their cost estimates tend to be somewhat higher than the DiMasi et al (2003) US$1.0b figure (2011 prices), albeit with wide variations across therapeutic areas and firms.

The Adams and Brantner (2006) data set includes all drugs that first entered one of the three phases of human clinical development somewhere in the world after 1989, which is the first year that PharmaProjects provides detailed and easily-accessible information on drug histories. While they have a larger sample of drugs than used in the DiMasi et al (2003) work, Adams and Brantner (2006) use the DiMasi et al (2003) estimates for R&D expenditures by phase. In general, PharmaProjects data show a higher probability that drugs will enter Phase III[7] and, thus, higher expected total costs for those drugs being tested. This is because expected cost per phase is the result of the product of out-of-pocket costs and probability of success. However, higher probability of success entails lower cost per successful molecule, other things constant.

Adams and Brantner (2006) estimate capitalised clinical costs per investigational compound of US$626m, at 2011 prices[8] (versus US$600m in DiMasi et al (2003), also at 2011 prices) and total capitalised cost per successful compound of US$1.1b at 2011 prices, using the same preclinical costs as DiMasi et al (2003).

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[6] For the DiMasi et al 1991 paper, compounds chosen were first tested in humans during the period 1970 to 1982.

[7] It seems that PharmaProjects does not report information on some drugs until they are in at least Phase II. Missing data in early trials may lead to upward biased estimates of transition probabilities. We are grateful to Prof Patricia Danzon for pointing this out.

[8] Adams and Brantner (2006) report their numbers in 2000 prices; we have converted them to 2011 prices using the US GDP implicit price deflator.

Adams and Brantner (2010) set out another independent test of DiMasi et al (2003) using a publicly available data source with R&D expenditures from 183 publicly traded firms (compared to the ten in DiMasi et al, 2003), which includes firms with both R&D expenditure information in the CompuStat database (see Danzon, Nicholson and Pereira, 2005) and drugs in the PharmaProjects data set. Specifically, Adams and Brantner (2010) combine data from two sources: Standard & Poor's CompuStat Industrial file and the Global Vantage Industrial Commercial file (also used by Danzon, Nicholson and Pereirs, 2005). These data sets provide information on publicly traded drug companies including net sales, employment and R&D expenditure. The data on drugs in development come from PharmaProjects (as in their 2006 paper). The two data sets overlap for the period 1989–2001 and are matched using the name of the pharmaceutical firm. The authors do not estimate pre-clinical expenditure.

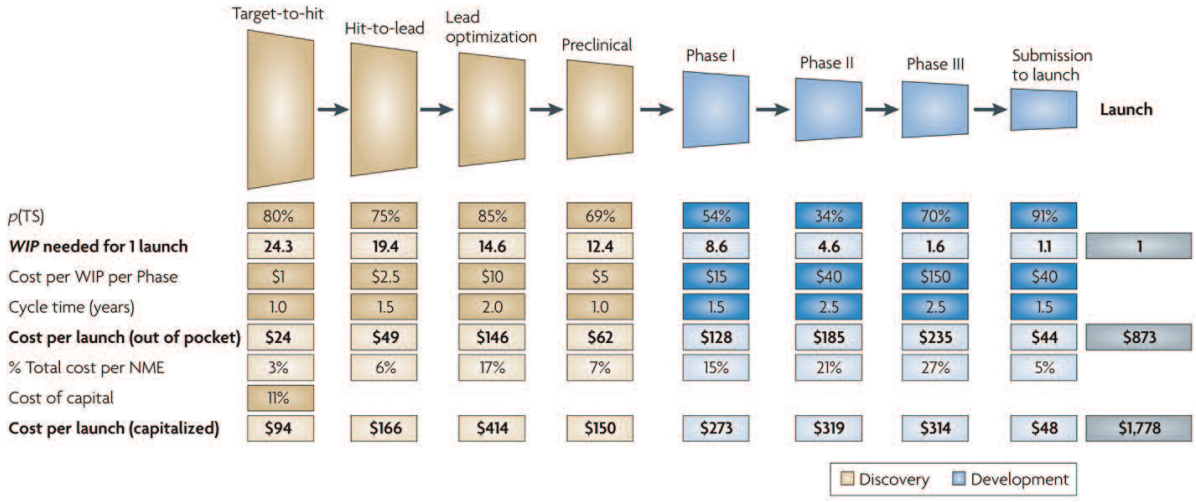
Adams and Brantner's 2010 results show expenditure higher than DiMasi et al (2003) for Phases I and II and lower for Phase III. Using the same durations and success rates as reported by Adams and Brantner (2006), Adams and Brantner (2010) estimate total R&D costs of US$1.6b in 2011 prices, which is higher than the previous estimates of DiMasi et al (2003) and Adams and Brantner (2006).

The work by Gilbert, Henske and Singh (2003) uses a model from Bain and Company to calculate total R&D costs. They split their sample into two overlapping time periods: 1995–2000 and 2000–2002. The cohort of projects used in this work is not specified, but appears to include medicines first tested in humans between 1995 and 2002. Gilbert, Henske and Singh (2003) calculate that the investment required for one successful drug approval is US$1.4b and US$2.2b, in 2011 prices[9], for the earlier and later time periods, respectively.

The most recent estimate can be found in Paul et al (2010), which uses another confidential database at project level. This paper uses R&D performance productivity data from 13 large pharmaceutical companies provided by the Pharmaceutical Benchmarking Forum as well as the internal data of the authors' employer, Eli Lilly and Company. Figure 2.4 shows the data used in their drug development model.

[9] Gilbert, Henske and Singh (2003) report their numbers in 2000 prices; we have converted them to 2011 prices using the US GDP implicit price deflator.

Figure 2.4. Analysis by Paul et al (2010)



	Target-to-hit	Hit-to-lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	Submission to launch	Launch
p(TS)	80%	75%	85%	69%	54%	34%	70%	91%	
***WIP* needed for 1 launch**	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1	1
Cost per WIP per Phase	$1	$2.5	$10	$5	$15	$40	$150	$40	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	
Cost per launch (out of pocket)	$24	$49	$146	$62	$128	$185	$235	$44	$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost of capital	11%								
Cost per launch (capitalized)	$94	$166	$414	$150	$273	$319	$314	$48	$1,778

Source: Paul et al (2010), in US$ 2008 prices

Paul et al suggest that the cost of developing a single NME stands at US$1.867bn (in 2011 prices). For the first time, this research provides a detailed analysis for the discovery stage—see the four left columns in Figure 2.4; the next four columns relate to the development stages. Based on the figures provided above, discovery out-of-pocket costs and discovery capitalised costs represent 32% of total out-of-pocket costs and 46% of total capitalised costs, respectively. Paul and colleagues note that their discovery costs are an underestimate, as earlier phases prior to target selection are excluded. Based on their analysis, only 8% of NMEs will successfully make it from point of candidate selection (i.e. moving from preclinical into Phase I) to approval. In DiMasi et al (2003), preclinical out-of-pocket costs represent 30% of total out-of-pocket costs and preclinical capitalised costs represent 41%. These shares are similar to those in Paul et al (2010).

The studies above differ in their endpoints, i.e. in whether they include the interval between regulatory approval, or licensing, and actual marketing or "launch". The DiMasi et al (2003) and Adams and Brantner (2006, 2010) studies consider expenditures up until regulatory approval. Paul et al (2010) and our calculation, based on CMRI data, includes expenditures from submission for approval to first launch, i.e. appearance on the market. Varying intervals of time may elapse between regulatory approval and actual marketing, particularly in countries that require pricing and reimbursement review and/or assent before marketing can commence (see EFPIA, 2010b). However, this amounts to a relatively small proportion of total R&D costs; for instance, in our analysis, only some US$35m, out of US$1.5b, is spent between submission and launch.

Note also that interpretations of variations in cost data between studies should be done with caution as costs are not completely exogenous. Costs are partly the result of strategic behaviour by the firms themselves and partly the result of technological change. Indeed, firms may choose a high-risk (high-cost)/high-return strategy or a low-risk (low-cost)/low-return strategy.

Policy Discussions around the Cost Estimates

A number of criticisms of the cost estimates discussed above have arisen, especially after the US$802m figure was published in 2003 by DiMasi et al. Below, we examine six papers, reports or books that have received widespread attention, highlighting their main criticisms and providing our views on them.

The first of the six, published in 2001 (Young and Surrusco, 2001), criticises the original DiMasi et al (1991) paper, although much of the criticism also would apply to DiMasi et al (2003). Young and Surrusco (2001) argue that the first analysis carried out by DiMasi et al (1991) is highly misleading, claiming in particular that it includes significant expenses that are tax deductible and also assumes unrealistic scenarios of risk. It cites a PhRMA estimate of US$500m, based on DiMasi et al. Young and Surrusco used a simpler measure than the one used by DiMasi and colleagues, also derived from data provided by the industry. The analysis divides the total number of drugs approved by total industry spending on R&D, allowing for some time lag. In particular, it allows for a seven-year lag between the start of R&D spending and FDA approval. For instance, using R&D spending between 1988 and 1994, and NMEs approved between 1994 and 2000, yields the highest pre-tax cost estimate per new drug of US$108m; after adjusting for the tax deductibility of R&D expenses, this is reduced to US$71m (all at 2000 prices). The lowest after-tax cost estimate, at US$57m (2000 prices), is achieved by dividing total R&D expenditure between 1984 and 1990 by the number of new drugs approved between 1990 and 1996. Young and Surrusco (2001) also estimate pre- and post-tax R&D spending per NME, similar to DiMasi et al (1991). The after-tax cash outlay calculated by DiMasi et al (1991) is roughly twice as high as the Young and Surrusco estimate (including all new drugs approved).

The Young and Surrusco (2001) report criticises the data and methodology used by DiMasi and colleagues, along the following lines: (1) the information provided in the surveys was not independently verified or checked for accuracy, (2) the analysis focuses only on the most expensive new drugs, not all new drugs, (3) the estimate includes the cost of all failed drugs and opportunity costs, i.e. the expense of investing in drug research rather than alternative types of investment, and (4) the calculations ignore the substantial tax deductions that companies are allowed in the US for R&D.

One of the most prominent critics of DiMasi et al (2003) is Angell (2004), whose focus has been on a number of issues relating to the pharmaceutical industry, not just drug development costs. For the purposes of this publication, however, we only refer to her comments on the DiMasi et al cost estimate. She argues that drug R&D costs are far lower than the US$802m estimate—in fact, well under US$100m. Angell has five main criticisms of the DiMasi et al work, some of which are very similar to those expressed by Young and Surrusco (2001) some years earlier.

1. The data come from companies directly and cannot be replicated by other researchers unless they have similar access to the companies
2. The estimates are based on only at a tiny handful of the most expensive drugs
3. Only self-originated compounds are included and these represent a small proportion of new drugs
4. Estimates should not be capitalised, given that companies are not investment houses and have no choice but to spend money on R&D
5. Estimates are pre-tax, so they do not reflect the fact that R&D expenses are deductible

Goozner (2004) also criticises the DiMasi et al estimate heavily. His focus is on the reasons DiMasi et al (2003) identify for the increase in the cost of clinical trials. Goozner argues that the publicly funded research institutes in the US are more efficient providers of clinical trial services than the private sector. If the DiMasi et al (2003) work "had factored out the half of the industry research that is more properly categorised as corporate waste" (page 246), he alleges, their number would have been in the US$115–240m region.

The issue around the confidential nature of the data used by DiMasi et al (2003) also was picked up in an exchange of papers between DiMasi, Hansen and Grabowski (2005a and 2005b) and Light and Warburton (2005a and 2005b) in the *Journal of Health Economics* in 2005. Light and Warburton outline what they consider six "serious sources of doubt about the validity and usefulness of the source data and methods used by DiMasi and colleagues" (Light and Warburton, 2005a, page 1031). These refer, among other items, to the fact that the data are based on confidential surveys and that it would be in the interest of pharmaceutical companies for cost estimates to be high(er). In their reply, DiMasi and colleagues state that they carried out numerous validations of their results using alternative data sources and analyses. The reliability of the data is supported by others, notably the US Congress's Office of Technology Assessment study, which states that "the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NMEs first tested in humans between 1970 and 1982" (OTA, 1993, page 66).

Light and Warburton (2011) argue that estimates of R&D costs are too high, focusing exclusively on DiMasi et al (2003) as "there is no more recent detailed study" (page 3). They do not comment on other work, such as Adams and Brantner (2006, 2010) and Paul et al (2010). Light and Warburton (2011) repeat most of the objections discussed above, adding that (1) the costs of the research component of R&D are unknown and highly variable, (2) clinical trials costs have been inflated in DiMasi et al (2003), and (3) development times have been exaggerated.

Light and Lexchin (2012) make criticisms similar to those noted above.

As mentioned in the Introduction, we take a societal perspective when thinking about the costs of R&D of new medicines. From a societal point of view, the total cost of developing a new drug will be the same no matter who pays—tax rebates affect who bears the costs, but not the total amount. For the firm, of course, tax rebates reduce the cost by shifting part of those costs to other taxpayers.

Moreover, as noted above, other recent studies that have either used publicly available information or have used different confidential data also agree that the DiMasi et al (2003) estimates were not overstated. It seems unlikely, then, that the data were unreliable.

To estimate the total cost per successful new drug emerging from R&D pipelines accurately, both the costs of lines of research that ultimately fail and the cost of capital must be included. Out-of-pocket costs are merely one part of the total cost. Capitalised costs are real costs. Investors require a return that reflects alternative potential uses of their investment. This capitalisation point is discussed later in the publication in detail.

The point about the decreasing importance of self-originated compounds relative to licensed-in compounds is valid, but has become so perhaps only recently as licensing-in has increased substantially. We discuss this later. Note that studies that use other databases, such as Adams and Brantner (2006, 2010) and Paul et al (2010) are not able to differentiate between self-originated and licensed-in compounds. As a result, these more recent estimates can be assumed to apply also to a wider universe of compounds, not just self-originated compounds.

Factors Affecting Development Costs

We now examine each of the four variables mentioned above: out-of-pocket costs, success rates, timelines and cost of capital. For each of these variables, we first provide the most recent evidence and then, where possible, explore how these variables have been evolving over time. Later on in the publication (Section 8), we explore which factors seem to be driving the evolution of these variables.

Out-of-Pocket Costs

Table 2.3 summarises the results obtained from the four studies that estimate out-of-pocket development costs (i.e. only for Phases I–III). Out-of-pocket development costs seem to have increased over time, especially relative to the 1991 DiMasi et al study.

Table 2.3. Out-of-pocket mean development costs (2011 US$m)

Source	Phase I	Phase II	Phase III	Total Phase I–Phase III	Cohort year
DiMasi et al, 1991	4	8	25	37	First tested in humans between 1970 and 1982
DiMasi et al, 2003	20	30	111	161	First tested in humans between 1983 and 1994
Paul et al, 2010	16	42	158	215	1997-2007[1]
Adams and Brantner, 2010	31	111	78	220	Drugs entering human clinical trials for the first time between 1989-2001

[1] We are uncertain about this timeframe as the paper is not explicit.

If we compare the 1991 and the 2010 figures (US$37m and between US$215m and US$220m, respectively), out-of-pocket development costs have increased nearly 500%—which implies an average cumulative increase in real terms of nearly 10% per year over the 19 years.

Paul et al (2010) and Adams and Brantner (2010) differ not in the total cost estimate, but also in the value of costs across phases. Adams and Brantner (2010) estimate significantly higher costs for Phase II than any of the other three studies in Table 2.4. Moreover, Adams and Brantner's work is the only one that estimates higher out-of-pocket costs for Phase II than for Phase III. The authors highlight this result—the reason they give is that their method may be misallocating expenditure to drugs in different stages of development, i.e. some costs that have been allocated to Phase II might actually have been spent in Phase I or III.

Success Rates

We have identified ten articles that provide evidence on success rates, although these differ in both methodology and data sets. Some of these papers do not use the results to estimate development costs. As mentioned above, only one paper provides detailed information on discovery (i.e. pre-clinical) success rates, namely Paul et al (2010). Figure 2.4 (above) shows the discovery success rates estimated by Paul et al (2010). Discovery is broken down into four steps: target-to-hit, hit-to-lead, lead optimisation, and pre-clinical. The overall probability of success—the product of the success rate for each step—for these four steps is 35%. Since this is the only estimate we have identified for discovery, it should be treated with caution.

Table 2.4 compares estimated clinical success rates. Note that the last column shows the overall clinical success rate, the product of the probabilities per stage. Comparisons across studies are not straightforward and should be viewed cautiously. For that reason, rather than comparing across all studies to explore the evolution of success rates, we focus on three sets of papers that use similar methodology and data sets: (1) Pammolli, Magazzini and Riccaboni (2011), (2) DiMasi et al (1991 and 2003), and (3) DiMasi et al (2010). We then comment briefly on the other papers.

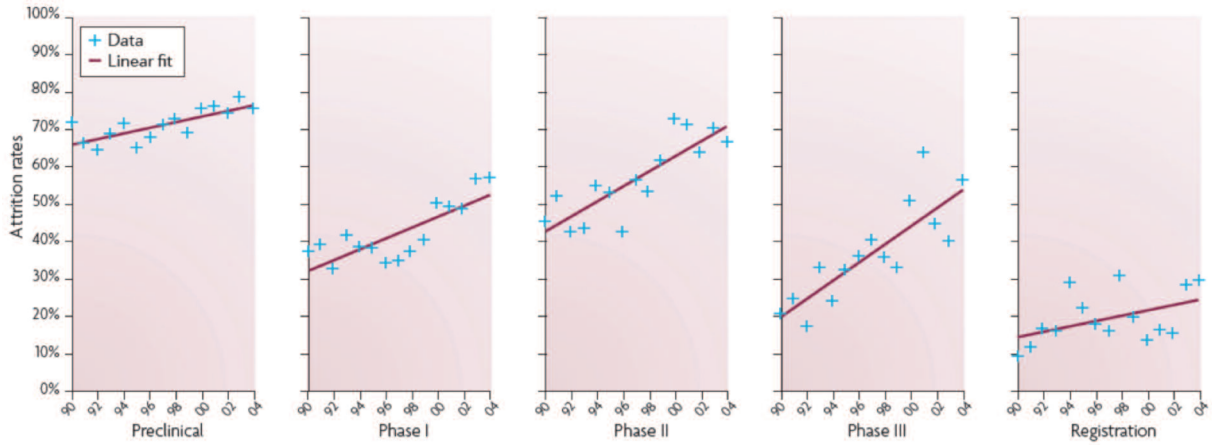
Table 2.4. Probability of success (percentages)

Source	Phase I	Phase II	Phase III	Cumulative probability of success (PI through PIII)[4]	Cohort year
DiMasi et al, 1991[1,3]	75	44.2	63.5	21.1	First tested in humans between 1970 and 1982
Gilbert, Henske and Singh, 2003 (1995-2000)	75	50	67	25.1	First tested in humans between 1995 and 20002
Gilbert, Henske and Singh, 2003 (2000-2002)	69	56	40	15.5	First tested in humans between 2000 and 20022
DiMasi et al, 2003[1,3]	71	44.2	68.5	21.5	First tested in humans between 1983 and 1994
Kola and Landis, 2004	60	38	55	12.5	First-in-man to registration drugs during 1991-2000
Abrantes-Metz, Adams and Metz, 2005	81	58	57	26.8	Entered one of the stages of the human clinical trials for the first time between 1989 and 2002
Adams and Brantner, 2006	100	74	46	34.0	Drugs entering human clinical trials for the first time between 1989-2002
Paul et al, 2010	54	34	70	12.9	1997-2007[2]
Adams and Brantner, 2010	75	48	71	25.6	Drugs entering human clinical trials for the first time between 1989-2002
DiMasi et al, 2010[3] (1993-2004)	65	40	64	16.6	First entered clinical testing between 1993 and 2004
DiMasi et al, 2010[3] (1993-1998)	67	41	63	17.3	First entered clinical testing between 1993 and 1998
DiMasi et al, 2010[3] (1999-2004)	64	39	66	16.5	First entered clinical testing between 1999 and 2004
Pammolli, Magazzini and Riccaboni, 2011[5]	68 – 49	58 – 30	80 – 50	31.6 – 7.4	Projects started between 1990 and 2004 in US, Europe and Japan

[1] These are what DiMasi calls "transition probabilities".
[2] We are uncertain about this timeframe as the paper is not explicit about this issue.
[3] Considering only self-originated compounds
[4] Calculated as the product of all three success probabilities for each study
[5] Pammolli, Magazzini and Riccaboni (2011) show the evolution of attrition rates across different phases between 1990 and 2004. In the table above, we report on the probability for 1990 and 2004, respectively. We calculate success rate as 1 minus attrition rate.

Pammolli, Magazzini and Riccaboni (2011) explore trends in attrition rates—the proportion of failures out of the total number of projects entering any given stage of R&D—for projects that entered clinical trials from 1990 to 2004 in the US, Europe and Japan. Figure 2.5, reproduced from their report, shows trends in attrition rates across five phases: preclinical, Phase I, Phase II, Phase III and registration. "Registration" in Figure 2.5 coincides with what we call "regulatory review" in Figure 2.1.

Figure 2.5. Trends in attrition rates



Source: Pammolli, Magazzini and Riccaboni (2011)

Figure 2.5 shows that attrition rates increased between 1990 and 2004 across all phases, but especially in Phase II and Phase III. Success rates have decreased accordingly.

Comparing DiMasi et al's 1991 and 2003 papers, the total probability of success in clinical stages increased very slightly from 21.1% in 1991 to 21.5% in 2003. They found a decrease in Phase I but an increase in Phase III, while the Phase II rate is constant (see Table 2.4).

DiMasi et al (2010) divide their sample into two periods: 1993-1998 and 1999-2004. Comparing these two periods, Phase I and Phase II success rates slightly decreased while the Phase III rate increased. The combined effect is that the overall success rate fell slightly between the two periods, from 17.3% to 16.5% (see Table 2.5).

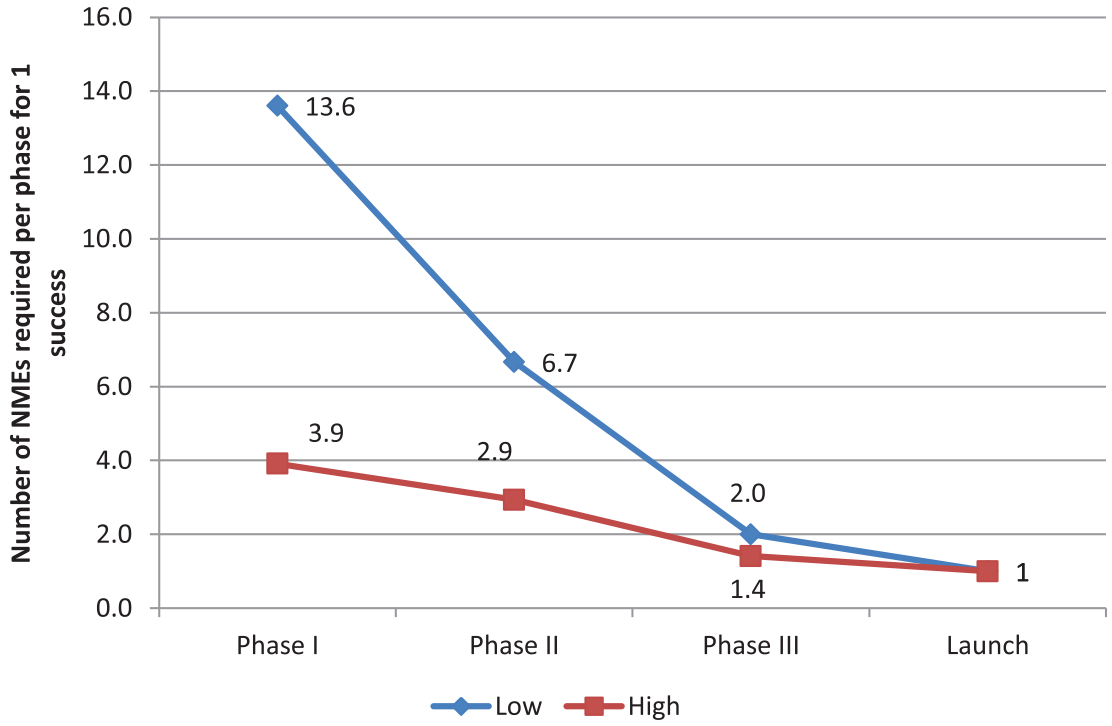
While DiMasi and colleagues find similar success rates over time, Pammolli, Magazzini and Riccaboni (2011) show very different results across time—in particular, a remarkable decrease in success rates for Phase II and Phase III between 1990 and 2004.

Relative to the probabilities reported by DiMasi et al (1991, 2003, 2010) and Pammolli, Magazzini and Riccaboni (2011), Adams and Brantner (2010) report slightly higher probabilities of success across the three phases. Probabilities found in Paul et al (2010) are within the range for Phases I and II (lower end) and slightly higher for Phase III.

Kola and Landis (2004) look at success rates for first testing in humans to drug approval during a ten year period (1991-2000) for ten large pharmaceutical companies based in the US and Europe. The acknowledgements in their paper suggest that the data come from the Pharmaceutical Benchmarking Forum, the same data source used by Paul et al (2010). Again, their probabilities of success are within our suggested range across the three phases.

In terms of absolute levels, and based on the most recent studies in Table 2.4, we could infer that the most recent estimates of probability of success for Phase I, Phase II and Phase III are between 49% and 75%, 30% and 48%, and 50% and 71%, respectively. Even the most recent studies show a wide range of success rates, which has important implications in terms of the number of projects that would be needed at each phase to ultimately produce one successful drug. Figure 2.6 shows the number of projects that would be required at Phase I, II and III under the low and high values of the ranges for probability of success just mentioned.

Figure 2.6. Number of NMEs required per phase for one successful NME, based on recent estimates for probability of success (high and low estimates)



Source: Authors' calculations based on Table 2.4

As shown in Figure 2.6, using the low estimate of success probabilities, 13.6 projects would be needed in Phase I to achieve one approved NME; this compares with 3.9 for the high estimate.

Attrition Rates: Reasons for Failure

Several articles in the published literature explore the reasons for failure and project discontinuation. Overall, the analyses support the view that commercial reasons have been increasingly important for discontinuing projects. Two earlier articles (DiMasi, 1995a and DiMasi, 2001) explore reasons for research termination, grouped in three major categories: safety ("human toxicity" or "animal toxicity"), efficacy ("activity too weak" or "lack of efficacy"), and economics ("commercial market too limited" or "insufficient return on investment"). This work shows that over time "economic" reasons became more prevalent and that compounds that failed for economic or efficacy reasons were terminated much more frequently later in clinical testing. Indeed, economic reasons were the most frequent reason for termination in late-stage clinical research.

More recent analysis (Kola and Landis, 2004) also shows that commercial, i.e. "economic", causes have become more important relative to more technical reasons such as adverse pharmacokinetics and bioavailability. Based on this research, Wilsdon, Attridge and Chambers (2008) argue that pressure is greater to terminate products that will not be differentiated in the market. Paul et al (2010) contend that the recent increase in the Phase III attrition rate especially is due primarily to the unprecedented nature of drug targets being pursued—more biologicals—as well as increasingly stringent safety standards being required for approval in most parts of the world.

Other researchers (Gordian et al, 2006) have explored Phase III trial failures reported from 1990 to 2002, focusing on small molecules only (i.e. excluding biologics) from large pharmaceutical companies. They found that a significant predictor of failure was whether drugs used a novel mechanism of action, with drugs using novel mechanisms failing more than twice as often in Phase III. Drugs that had both a novel mechanism and less objective endpoints failed 70% of the time; drugs with a validated mechanism and objective endpoints failed just 25% of the time. Gordian and colleagues defined an endpoint as objective if the clinical trial researchers could measure it with diagnostic tests whose results could be easily reproduced, or with scales that were both professionally measured and widely used; less-objective endpoints were defined as those that relied on less easily reproducible measurements, uncommonly used scales or self-reporting by patients. Gordian et al (2006) argue that the evidence overall shows that companies are not using Phase II trials as rigorously as they should to guide judgement as to whether to proceed to Phase III. They report learning of several examples where companies had pushed compounds through Phase III despite reservations by clinicians/statisticians based on Phase II results. It is possible, of course, that the results also reflect the trade off between the additional riskiness of novel mechanisms and treatments for diseases without well accepted endpoints, and the larger potential returns available from successful development of novel products to tackle untreated diseases.

Ma and Zemmel (2002) report a similar finding. They categorise drugs launched between 1991 and 2000 by the top 15 pharmaceutical companies as being either unprecedented/novel or "precedented". They conclude that novel approaches have a higher risk of failure, with an overall development survival rate of 5% compared to 8% for previously-used approaches.

Pammolli, Magazzini and Riccaboni (2011) also analyse reasons for the increase in attrition rates based on their sample of R&D projects. They calculate the potential pay-off for an R&D project as the product of the probability of market launch multiplied by the potential market value of the compound, yielding an "expected probability of success" (POS) for each project. Their results show that, since 2000, companies have been focusing more on high risk, high premium areas with a lower POS, such as:

1. Chronic diseases (Alzheimer's disease, diabetes, obesity, rheumatoid arthritis), compared to acute diseases. The average POS for chronic diseases is 6.9% compared to 8.8% for acute diseases
2. Potentially lethal diseases, mostly cancer and some infectious diseases, with an average POS of 5.5%, compared to 9.7% for non-lethal diseases

Some recent work (Puig-Peiró et al, 2012) also reinforces that commercial reasons are becoming more important in driving companies' decisions on which products to continue/discontinue. Based on a survey of four large biopharmaceutical companies, for the period 2005–2009, this

study also finds that the impact of portfolio prioritisation activities was the main commercial reason for discontinuation and its importance increased during the later years of the survey.

Development Times

We summarise the evidence on the evolution of development times in Table 2.5. Throughout this section we focus on Phase I–III times, included in several studies. Other phases, such as regulatory review, regulatory submission to market launch, and animal testing are not measured consistently.

Table 2.5. Development times (months)

Publication	Phase I	Phase II	Phase III	Total Phase I–Phase III	Cohort Study
DiMasi et al, 1991	16.2	22.5	29.9	68.6	First tested in humans between 1970 and 1982
DiMasi et al, 2003	21.6	25.7	30.5	77.8	First tested in humans between 1983 and 1994
Abrantes-Metz, Adams and Metz, 2005	19.7	25.1	41.4	86.2	Entered one of the stages of the human clinical trials for the first time between 1989 and 2002
Adams and Brantner, 2006	19	30	30	79	Drugs entering human clinical trials for the first time between 1989-2002
Keyhami, Diener-West and Powe, 2006	N/A			61.2	Drugs approved in the US between 1 January 1992 and 1 January 2002
Adams and Brantner, 2010	16.6	30.7	27.2	74.5	Drugs entering human clinical trials for the first time between 1989-2002
Paul et al, 2010	18	30	30	78	1997-2007[1]
Kaitin and DiMasi, 2011	N/A			78[2]	New product approvals in the US during 2000–2009

[1] We are uncertain about this timeframe as the paper is not explicit.

[2] Kaitin and DiMasi (2011) provide evidence for clinical phases in total without differentiating between phases. The 78 months refers to the subset of FDA-approved compounds between 2000 and 2009.

Overall, it seems that development times, Phases I–III, have remained relatively constant over time since the early 2000s, at around 75-79 months on average. Two studies are "outliers". Keyhami, Diener-West and Powe (2006) suggest distinctively shorter development times. Theirs was a retrospective study that examined development times for those drugs listed in the US *Federal Register*; 168 drugs approved between 1 January 1992 and 1 January 2002 met this eligibility criterion. The authors argue that it appears that the duration of total post-IND development time (which begins with Phase I) and regulatory review time both have decreased.

Moreover, clinical trial durations have not increased and appeared to be trending downward. Abrantes-Metz, Adams and Metz (2005), the other outlier, estimate total Phase I–Phase III development time to be around 86 months.

In the past, Phase III tended to take the longest time, but the most recent work seems to suggest that development times for Phases II and III are now similar.

Kaitin and DiMasi (2011) also provide duration times for approved drugs according to FDA's therapeutic rating and confirm that approval phase durations for priority-review drugs are shorter than for standard drugs: 0.8 versus 1.6 years for those drugs approved between 2005 and 2009. However, total clinical phase duration for these drugs is similar: 6.3 years and 6.5 years for priority and standard drugs, respectively.

Cost of Capital

The long timescales of pharmaceutical R&D mean that the cost of capital has a major impact on the final cost per NME as R&D costs, on average, are incurred many years before any revenue is earned to recover them. Approximately half of the total cost per NME estimated by DiMasi et al (2003) was due to the cost of capitalising R&D expenditures using their assumption of an 11% real annual cost of capital rate[10], i.e. US$399m out of US$802m (2000 prices).

The estimated cost per NME is highly sensitive to the cost of capital applied. DiMasi et al's (2003) sensitivity analysis implied that if the cost of capital were one percentage point higher or lower than 11%, then the cost per NME would rise or fall by approximately US$50m (year 2000 prices), respectively.

Two main issues arise with respect to the cost of capital invested in pharmaceutical R&D and are considered in turn in the following paragraphs. These are:

1. The magnitude of the cost of capital
2. Whether the cost of capital is assumed constant, or rather is assumed to fall as an R&D project progresses (if successful) through its various stages from discovery through development to launch—the so-called "staircase" approach.

The cost of capital should be measured as the expected return that is foregone, i.e. the return that would be expected from investing in an equally risky portfolio of other investments. Pharmaceutical R&D is predominantly (90% or more) financed by equity, rather than debt. The weighted average cost of capital (WACC) in this case is therefore very close to the cost of equity for pharmaceuticals.

[10] All cost of capital rates are real annual rates, unless otherwise specified.

According to the capital asset pricing model (CAPM)—see for example Brealey and Myers (2000)—the cost of equity depends on:

1. The estimated risk free cost of capital
2. The equity market risk premium and
3. The non-diversifiable risk of a particular investment—i.e. the risk that investors cannot manage by holding a broad portfolio of investments. In the CAPM this is referred to as the "beta".

All of these can only be measured by observation of historical data for capital markets, even though investments are inevitably forward looking. Empirical estimates of all three elements have varied over time. Table 2.6 lists the real annual costs of capital that have been used in major published studies of the cost of an NME.

Table 2.6. Cost of capital used in the literature

Publication	Real Annual Cost of Capital	Notes
Hansen, 1979	8%	For R&D expenditures in the 1960s and 1970s
Wiggins, 1987	8%	Used Hansen (1979) figure
DiMasi et al, 1991	9%	Based on a CAPM analysis by Grabowski and Vernon (1990) "for a representative sample of pharmaceutical firms for each of the years from the mid-1970s to the mid-1980s"
OTA, 1993	10% and 14% down to 10% "staircase"	10% = OTA's observed cost of capital for the pharmaceutical industry in "the early 1980s" (based on CAPM analysis) 14% to 10% "staircase" to test the effect of the risk-return staircase approach
DiMasi et al, 2003	11%	Based on CAPM analyses for "a representative group of pharmaceutical firms" at various points over the period 1985–2000
Adams and Brantner, 2006	11%	Used DiMasi et al (2003) figure
DiMasi and Grabowski, 2007b	11.5%	For biopharmaceutical firms specifically (i.e. not major pharmaceutical firms). Average real cost of capital estimated by the authors using a CAPM approach for years 1994, 2000 and 2004.
Vernon, Golec and DiMasi, 2009	14.36%	Fama-French based estimate. CAPM estimate for comparison was 11.02%.
Paul et al, 2010	11%	Used DiMasi et al (2003) figure

Table 2.6 shows that there has been an upward trend in the assumed cost of capital for pharmaceutical R&D. Early estimates of the cost of a NME were based on a real cost of capital estimated to be 8%, starting with Hansen in 1979; DiMasi et al used 11% in 2003. The 11.5% figure used by DiMasi et al in 2007 was specifically for producers of biologicals and so is not directly comparable with the other figures. The figure that stands out is the 14.36% estimated by Vernon, Golec and DiMasi et al (2009).

All but one of the studies in Table 2.6 has used a CAPM approach. The exception is Vernon, Golec and DiMasi's (2009) re-estimation of the DiMasi et al (2003) cost of an NME using a cost of capital for pharmaceutical companies estimated using the Fama-French model. The CAPM model assumes that the risk premium that investors will demand when investing in an industry, e.g. pharmaceuticals, is driven by a single factor: the extent of non-diversifiable risk, i.e. the extent to which returns to equity investment as a whole are correlated with returns in that particular industry. The extent of this correlation is known as the industry's "beta". The Fama-French model (see, for example, Fama and French, 1993) adds two further factors that appear to drive the cost of capital in an industry based on empirical observations even after controlling for beta: firstly, the stocks of small market capitalisation firms appear to yield higher rates of return than those of large market capitalisation firms (other things equal) and, secondly, rates of return for stocks with high ratios of book value to price per share appear to be higher than for firms with low ratios of book value of equity capital to market value of equity capital. Vernon, Golec and DiMasi (2009) estimate that whereas the CAPM estimate of the real annual cost of capital to the pharmaceutical sector is 11.02%, the estimate based on the Fama-French model would be considerably higher at 14.36%. They explain the higher estimate as follows:

> Why do our COC estimates from the Fama–French model exceed the CAPM estimates for pharmaceutical firms? We find that the pharmaceutical industry is exposed to more size-related risk than the average industry. For example, the average industry has a 0.39 size-factor loading, compared to 0.67 for the pharmaceutical industry. Note that size risk is not purely based on company size but rather on the types of risks often faced by small firms. Pharmaceutical R&D projects have very skewed payoffs, and this could account for their extra size risk, even though the firms themselves are not particularly small. (Vernon, Golec and DiMasi, 2009, np).

However, using data from a different period, Fama and French (1997) estimated that for the pharmaceutical industry the relationship between cost of capital and market size was negative rather than positive; as a result they found the cost of capital for the pharmaceutical industry to be significantly below the CAPM estimate. Clearly the Fama-French estimates are sensitive to the time period and data set used. We therefore focus in what follows on the more recent CAPM estimates, but also test the sensitivity of the cost of an NME to a higher cost of capital similar to the Fama-French model estimate by Vernon, Golec and DiMasi.

All of the studies referred to in Table 2.6 produced their main estimates of the cost of an NME using a single cost of capital for all phases of pharmaceutical R&D although the OTA also tested, as a sensitivity to its main estimate, the impact of using a staircase approach. Here, a higher cost of capital is assumed to apply to discovery and pre-clinical testing than to later phases of clinical trials. The rationale for the staircase approach is explained in Myers and Howe (1997); essentially it is that investors appear to require a higher rate of return earlier in the R&D process

to commit their capital. The cost of capital for biotechnology companies, heavily focused on discovery and early stage development, has in the past been observed to be higher than the cost of capital for more traditional pharmaceutical companies, which have investments through all stages of R&D up to regulatory approval.

However, there may be reasons for this observed difference in costs of capital other than how early in the R&D process investments are concentrated—such as investors' relative lack of experience with biotechs and market perceptions of the relative management capabilities of smaller, newer biotechs relative to larger, longer established pharmaceutical companies. Also, over time, the pharmaceutical "market for technology" is becoming better established (Pammolli and Riccaboni, 2001). This provides an exit route for investors in early stage R&D who, if they wish, can now more easily find a buyer to take over their R&D project at a fair price. Thus, risk for investors may be declining and the staircase, if it exists, may be becoming flatter over time.

The staircase approach remains controversial. In our view, the relevant concept is the ex-ante cost per capital of committing to investing in the whole R&D process. In our own cost-per-NME estimates set out in Section 3 of this publication, we therefore use a constant 11% cost of capital through all stages of R&D, and test as a sensitivity replacing that with a constant 14% cost of capital as estimated by Vernon, Golec and DiMasi (2009) using a Fama-French model rather than CAPM. We also model the impact of using a staircase cost of capital.

In summary, the estimated cost of an NME is highly sensitive to the assumed cost of capital. A range of empirical estimates have been used, predominantly based on the CAPM. Alternative estimates based on the Fama-French model are either considerably higher or lower than the CAPM approach. In the rest of this publication, we focus on the current consensus that the cost of capital is around 11% real per annum, but we allow for the uncertainty surrounding this by means of sensitivity analysis.

Sensitivity Analysis: Impact of Changing the Key Variables

Most of the papers that offer point estimates for drug development costs present some sensitivity analysis to understand the impact of altering the different key variables that drive overall costs. They do so both because their model is based on assumptions and because they need to ascertain which key parameters are driving the results. One such paper is DiMasi (2002), which undertakes significant sensitivity analysis based on the DiMasi et al (2003) data[11]. Two key variables are development times and success rates. For instance, decreasing development times and regulatory review times by 50% can lower total costs by US$235m per approved drug. Similarly, increasing the clinical approval success rate from approximately 20% (base case level was 21%) to 33%—a 65% increase—reduces total costs by US$221m. These estimates represent around a 50% reduction in costs from the original cost estimate of US$463m.

Overall, DiMasi argues that decreasing development and regulatory review by one quarter to one half of current levels, or increasing success rate from one in five to one in three, can have significant effects. Other more modest, but still substantial, gains can be achieved by making earlier decisions during clinical development to abandon drugs that are most likely to fail. Paul et al (2010) carry out an extensive simulation exercise to explore how variations from their

[11] Note that the DiMasi (2002) article was published while the DiMasi et al (2003) paper was in press.

baseline value affect the capitalised cost per launch. The simulation also is intended to provide recommendations on the key areas for improving R&D productivity. Attrition rates in clinical phases, especially Phases II and III, remain the most important determinant of overall R&D efficiency in the Paul et al (2010) analysis. For example, a decrease in the probability of success in Phase II from a baseline of 34% to 25% increases the cost per NME to US$2.3b, a 29% increase. A decrease in Phase III probability of success from the baseline of 70% to 60% increases cost per NME to US$1.56b. Combining these two lower probabilities of success yields a cost per NME of US$2.7b.

This study also looks at how "work in progress" (WIP)—the number of compounds required to gain approval for one NME—changes as attrition changes. For instance, if the probability of success in Phases II and III are 25% and 50%, respectively, approximately 16 compounds must enter Phase I to achieve one successful NME.

Paul et al (2010) show that development times for Phase II and Phase III are important. For example, reducing either Phase II or Phase III development times by 50%, from 2.5 to 1.25 years, would reduce the cost per NME by about US$200m, which is similar to the DiMasi et al (2003) estimates.

The authors argue that while such reductions are unrealistic in magnitude, modest reductions still will have an impact.

A NEW ESTIMATE FOR DRUG DEVELOPMENT COSTS: OUR ANALYSIS

Key Points

In this study, we present a new estimate for mean R&D costs per NME based on previously unpublished information collected by CMRI in confidential surveys. Our fully capitalised R&D cost estimate per new medicine is US$1.5b in US$ 2011 prices. Time costs, i.e. cost of capital, represent 33% of total cost. Our new estimate lies within the range of other recently reported estimates.

Our overall probability of success estimates for Phase I, Phase II and Phase III are lower than those reported by DiMasi et al (2003) and Paul et al (2010).

Overall, our study and those by DiMasi et al (2003) and Paul et al (2010) report similar development times. For Phase I, our data report the longest development times, but we report slightly shorter times for Phase III. Phase II development times from the CMRI data fall between those reported by DiMasi et al (2003) and Paul et al (2010).

Total out-of-pockets costs for Phases I, II and III are very similar in our study and that of Paul et al (2010) (around US$230m at 2011 prices) and slightly lower than found by DiMasi et al (2003). Our out-of-pocket cost estimate lies between the other two estimates for Phase III. For Phase I and Phase II, our estimates are the highest.

We also carried out some sensitivity analysis by, among other things, altering our base case assumptions by plus and minus 10% as well as using a 14% cost of capital and a declining staircase cost of capital. Cost of capital and success rates have the greatest impact on the resulting cost estimates.

The analysis we present in this publication is based on information generated by different projects undertaken by CMRI[12] obtained through confidential surveys of pharmaceutical companies. The evidence on expenditure per stage of development comes from CMRI's 2002 Resource Metrics Pilot Programme under which 16 global pharmaceutical companies provided resource data at project, rather than at corporate, level[13]. Success rates and development times data come from CMRI's Industry Success Rates 2003 and Global R&D Performance Metrics, respectively. The data for all three CMRI sources are from the same sample of companies. This is similar to the approach used by DiMasi et al (2003) where a sample of projects is used to estimate project-specific costs.

In the 2002 CMRI Resource Metrics Pilot Programme, companies provided project level data on 217 projects (209 unique molecules). At this level, resource-use data were collected on both person hours and external costs for milestone intervals, i.e. different R&D stages, further subdivided by function. Although all projects for all compounds were eligible for inclusion, for our purpose of calculating the cost of a new medicine, we only focus on what CMRI terms "new active substances"[14] and omit line extension projects[15].

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[12] For more information on CMRI, please see the Glossary.

[13] Using 2002 pharmaceutical sales from IMS (2004) to measure firm size, firms responding to the survey included three from the top 10 companies, five from the top 20, and two from the top 30; the remaining six were outside the top 30.

[14] A new active substance has been defined as a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a "prescription only" medicine. We consistently use the acronym "NME" in this publication to refer to such substances to avoid confusion.

[15] The CMRI programme collected resource data at project level. Where multiple projects were supplied for the same compound (NME), the project that was farthest along in development at the end of 2002 was defined as the lead project. All other projects were classified as either parallel development projects or line extension projects although, for the purpose of this publication, lead and parallel development projects have been grouped. Parallel development projects are projects where clinical development was started before the first-ever compound launch worldwide. We cannot differentiate from the CMRI database between lead and parallel development projects. Line extension projects are all projects where clinical development was started following the first-ever compound launch worldwide.

To be included in the analysis, each project must fulfil the following criteria:

1. Have a start and end date for the interval
2. Have person hours and external expenditure for the complete interval
3. Have an interval duration that is not negative and not zero

Total expenditure per project was collected for key intervals (described below) completed between 1998 and 2002. The data used in this publication illustrate five key aspects of each interval:

1. Duration of interval[16]
2. Person hours allocated during the interval
3. External expenditure during the interval
4. Proportion of expenditure allocated externally during the interval
5. Total expenditure during the interval

Throughout the analysis, a specific interval is represented by a single group of projects. The figures represent the resources applied between the date of the start of the interval and the end of the interval. Some costs, therefore, may not relate directly to activities occurring during that interval, as there may be some pre-payment or start-up costs for activities due to occur in the next interval, or payment of invoices relating to activities occurring in the last interval or, as a corollary, some costs may be recorded as occurring during the preceding or following interval.

Following data cleaning, it was possible to include 97 projects in the analysis presented in this publication. Projects were excluded from the calculations primarily because of poor or insufficient data—e.g. data were supplied for the calendar year instead of for the completed milestone interval, or either total person hours or total external cost was missing.

Given the time required to take one molecule through the entire R&D process, it has not been practical to follow a cohort of molecules from start to finish. Hence, the R&D process has been broken down into sequential intervals in order to analyse the data on projects active in each interval. A project with resource data for a successful completion of one interval may have been terminated in a subsequent interval. But it is possible for data to have been provided for multiple intervals for the same project. This methodology contrasts with previous research described in Section 2, above, where researchers were able to follow successful products throughout the entire drug development process.

In order to calculate the cost per interval for each project, companies were requested by CMRI to submit data for internal and external expenditures. Regarding internal expenditure, companies submitted data on internal expenditure (A), on the number of full-time equivalent employees[17] (B) and the hours they were assumed to be available (C), which were used to calculate "internal expenditure per person hour" (D) using the following formula:

$$D = A / (C*B)$$

[16] As mentioned before, we use CMRI's Industry Success Rates 2003 and Global R&D Performance Metrics on interval duration for our calculations.

[17] A part-time employee is pro-rated as a fraction of a full-time employee (FTE). For instance, someone employed to work three days a week is a 0.6 of an FTE.

In the absence of more disaggregated data, we assume that expenditure per person hour is the same across functions and through the different stages of R&D. In order to calculate total expenditure per project per interval, person hours (E) associated with key intervals were converted into a calculated internal expenditure using the internal expenditure per person hour (D). The internal expenditure is then summed with the external expenditure (F) to provide the total expenditure (G):

$$G = (E*D) + F$$

Companies were asked by CMRI to provide all resource data in their home country currency. CMRI then converted to US$ using OECD average 2002 exchange rates[18]. We converted all resource data to 2011 US$ prices.

Development times[19] and success rates come from the CMRI R&D development times database. It contains information on over 1,600 new active substances that have been in active development at some stage during the preceding nine years.

CMRI defines six key milestones, giving rise to the following six key intervals:

Interval 1. Pre-first toxicity dose
Interval 2. First toxicity dose to first human dose
Interval 3. First human dose to first patient dose
Interval 4. First patient dose to first pivotal dose
Interval 5. First pivotal dose to first core submission
Interval 6. First core submission to first core launch

The milestone "first toxicity dose" is reached when the first dose is given in the first animal toxicity study required to support administration to a human. This is a key milestone that indicates that the preclinical programme is now active. This implies that the first of our intervals, "pre-first toxicity dose", refers to the "discovery" stage. Milestone "first human dose" is when the dose is administered for the first time to a human in any country. As illustrated in Figure 3.1, the decision to administer the active substance to humans, which is based on a preclinical safety assessment, is taken before our interval three ("first human dose to first patient dose").

The "first patient dose" milestone is reached when the active substance for the relevant project is administered to patients for a specific indication with the intention of treating for that indication. The date for the "first pivotal dose" is the date when the first dose is given to the first patient in the first pivotal safety and efficacy trial. This is the date of the first dose in the first large-scale clinical study necessary to support registration in one of the core markets[20]. This normally will be a consequence of the company making the "launch decision", i.e. to conduct the large-scale clinical safety and efficacy studies necessary to support registration. It may occur before interval four is completed if sufficient data are available for the "launch decision" to be made. For many companies, the launch decision will be the most important decision in financial terms since it represents a major commitment of resources.

[18] Exchange rates per US$ used in the conversion: 1.061 euros; 0.671 British pounds; 7.884 Danish krone; 125.3 Japanese yen

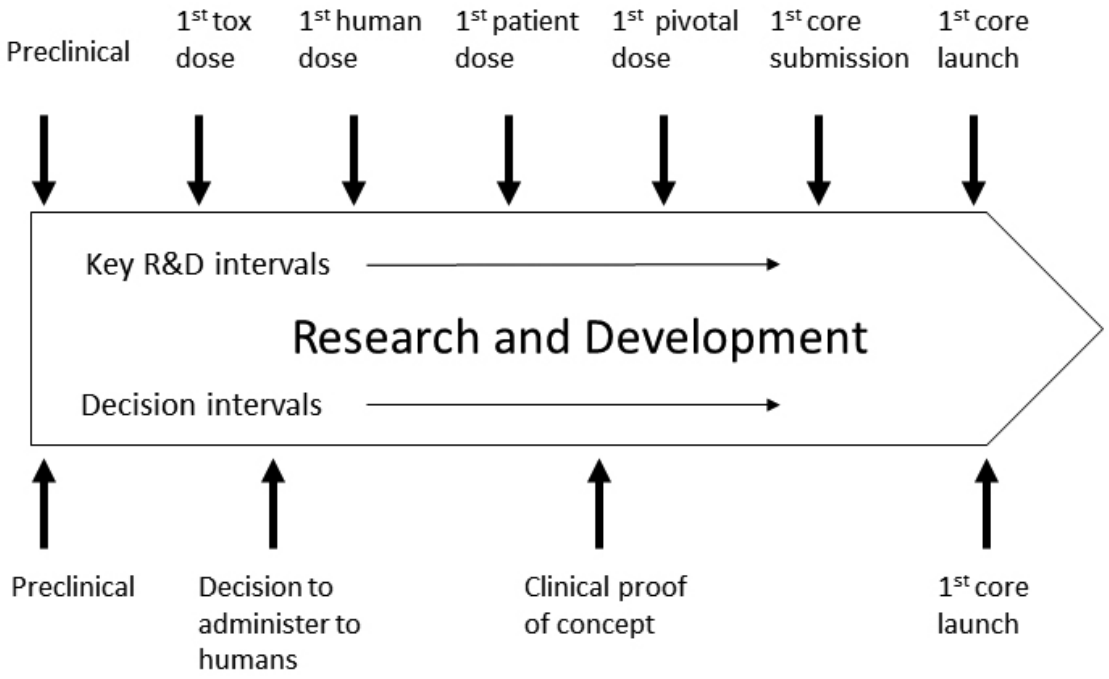
[19] Note that CMRI uses the term "cycle" times, rather than "development" times, but it is the same concept.

[20] The eight core countries are Canada, France, Germany, Italy, Japan, Spain, UK and the US

"Decision based intervals" are illustrated in the lower part of Figure 3.1. "Clinical proof of concept" occurs when definitive clinical evidence has been gathered to support a recommendation to continue the development of the active substance. This takes place within our fourth interval.

The "first submission" milestone is achieved when the first-ever regulatory dossier is submitted to apply for a license to market the compound for this project. The country where this application is made does not have to be one of the eight core markets. If submissions were made to multiple countries, companies would list all countries where a dossier was submitted on this date. The "first core submission" occurs when the first submission is made in any one of the core markets, which can coincide with the date of the milestone "first submission". The milestone "first core launch" is reached when the product is marketed for the first time in any of the core markets.

Figure 3.1. Milestones and intervals used in CMRI's programmes

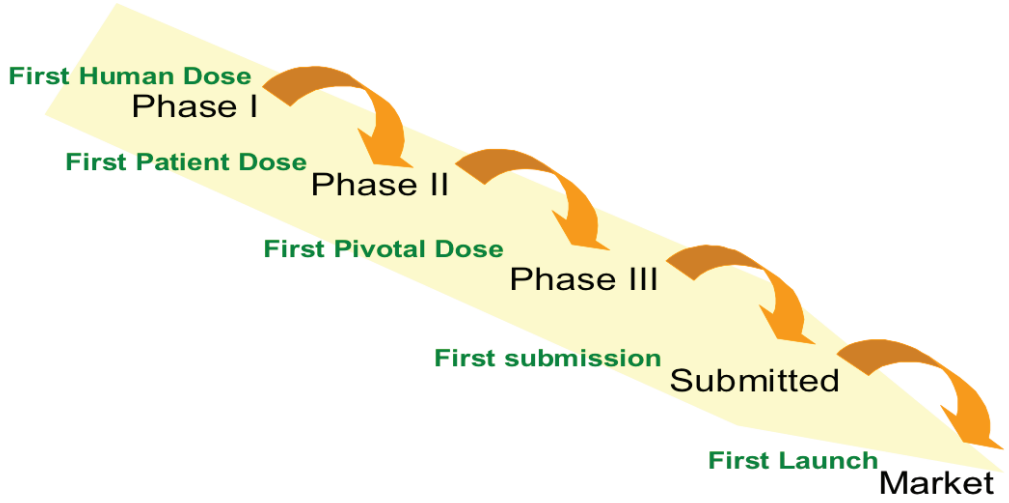


All in all, we have six key R&D milestones, giving rise to six intervals. As mentioned above, the first of the intervals considered in the CMRI database corresponds to the "discovery" stage, the second to "preclinical", and the third–fifth intervals to the clinical stages. The last stage refers to the approval process.

Figure 3.2 illustrates how these milestones relate to clinical Phases I, II and III.

Phase I trials start when the milestone "first human dose" is reached, while Phase II trials take place during our Interval 4—first patient dose to first pivotal dose. Finally, Phase III clinical trials start after our milestone "first pivotal dose" is reached.

Figure 3.2. Relating CMRI's milestones to "standard" clinical phases



Data and Methods

Table 3.1 summarises the data used to estimate the mean cost for Intervals 2–6. Interval 1, pre-first toxicity dose, is not included in Table 3.1 because many costs associated with discovery cannot be attributed to specific compounds. Hence, Interval 1 expenditure was omitted, and instead was estimated using data from the 16 survey participants that was provided in the CMRI Corporate Resource survey. Drug discovery expenditure for 2002 was summed and then divided by the total number of compounds for this cohort of companies that reached Interval 2, first toxicity dose, in 2002 using data as provided in the 2002 CMRI Performance Metrics Programme. Although this is not project-specific data, it does take into account the cost of attrition at this early stage. Later on we provide an estimate of the hypothetical spending required at this stage to launch one successful NME[21].

Note that the number of observations in Table 3.1 (last column) sum to 77. The other 20 of the total of 97 projects mentioned in section 3.1 are for the first interval (pre-first toxicity dose) only; no project-specific information is available for them and hence they are not included in Table 3.1.

As shown in Table 3.1, the most expensive interval by far is from milestone "first pivotal dose" to "first core submission" (Interval 5). This is consistent with the previous literature, which shows that Phase III trials, which usually are large in scale, are the most expensive. Moreover, the mean cost per investigational drug entering a phase increases from one clinical phase to the next. Note that for the five intervals in Table 3.1, the mean is higher than the median. This implies that the distributions of costs is skewed.

[21] In this Section all cost figures are reported in 2011 US$.

Table 3.1. Summary of the data on cost per interval (2011 US$m)

Interval	Mean (US$m)	Median (US$m)	Maximum (US$m)	Minimum (US$m)	Standard deviation	Number of obs.
2 — 1st toxicity dose to 1st human dose	6.5	5.0	27.0	0.1	5.4	41
3 — 1st human dose to 1st patient dose	16.0	10.6	42.5	3.1	10.0	18
4 —1st patient dose to 1st pivotal dose	53.9	24.6	139.7	10.8	51.1	6
5 — 1st pivotal dose to 1st core submission	129.3	90.3	282.1	7.0	103.1	5
6 — 1st core submission to 1st core launch	29.0	21.0	72.5	0.9	25.8	7

Source: CMRI

The approach used in this study to estimate the cost of R&D for a new medicine is different from the approach used by DiMasi et al (2003) in that we calculate the cost of the hypothetical number of compounds in each interval required to ultimately achieve one successful medicine. Our analysis must start, then, by answering the following question: How many compounds are required in Interval 2 to launch one medicine?[22] In this calculation, we take into account the success rates illustrated in Table 3.2. DiMasi et al (2003), in comparison, start by calculating the expected cost (the product of mean cost and probability of success) for each phase. Once they capitalise these costs to take into account the cost of capital, they use the overall probability of success (product of the different probabilities of success per phase) to calculate the total cost per successful medicine.

We have calculated success rates using CMRI Industry Success Rates 2003. All NMEs in this analysis entered at least one clinical development phase during 1997 to 1999. Each NME is tracked until it reaches the next milestone in the development process or is terminated. NMEs are only considered to be terminated when all projects relating to that NME are terminated. In our base case, NMEs whose fate is unknown at the end of 2002 are excluded from the calculation as follows:

Current success rate = [(NMEs progressed) / (NMEs entered phase – NMEs of unknown fate)] * 100.

Table 3.2 summarises the data used to calculate success rates for each Interval, excluding Interval 1 (see above).

[22] Recall that for our first interval (pre-1st tox) we use aggregated data.

Table 3.2. Success rates by interval

	2 — 1st tox dose to 1st human dose	3 — 1st human dose to 1st patient dose	4 — 1st patient dose to 1st pivotal dose	5 — 1st pivotal dose to 1st core submission	6 — 1st core submission to 1st core launch
Current success rate %	70%	63%	31%	63%	87%
Number of observations	437	320	234	112	68

Source: CMRI

Taking into account the success rates illustrated in Table 3.2, the overall probability of success is equal to 7% (=0.70*0.63*0.31*0.63*0.87).

Table 3.3 shows the data used to calculate the time it takes from the start of the interval to the first core launch.

Table 3.3. Development times by interval

Time in years (no. of obs.)	1 — Pre-1st tox dose	2 — 1st tox dose to 1st human dose	3 — 1st human dose to 1st patient dose	4 — 1st patient dose to 1st pivotal dose	5 — 1st pivotal dose to 1st core submission	6 — 1st core submission to 1st core launch
From interval start to first core launch	11.5 (25)	7.6 (287)	6.8 (158)	5.5 (40)	3.3 (29)	0.9 (20)
From interval mid-point to core launch	9.6 (25)	7.2 (287)	6.2 (158)	4.4 (40)	2.1 (29)	0.5 (20)

Source: CMRI

Table 3.3 shows that the total R&D process for a new medicine takes, on average, 11.5 years. This is less than the time obtained by DiMasi et al (2003), which is 148 months (12.3 years). However, as noted above, our calculations include a period that DiMasi et al (2003) do not: the time between the licensing approval decision and actual marketing of the drug ("launch"). In some cases, this time period is negligible—days or weeks. However, in cases where a price and reimbursement determination must be made before marketing can commence, this period can be a few months to more than a year, and varies by country[23].

[23] For more information on the time taken for pricing and reimbursement decisions, see EFPIA (2010b).

Given the long timeframe, as discussed earlier, we must capitalise the costs incurred in each interval up to the point of launch. We assume that costs are distributed uniformly over each interval, so we calculate the capitalised cost from the mid-point of the interval to the first core launch, rather than from the time from the interval start to the core launch. We have used 11% as our central estimate of the relevant real annual cost of capital, as this is the most recent published estimate available. But given the uncertainty around the cost of capital, and its importance to the cost of an NME, we have conducted sensitivity analysis to investigate the impact of other plausible rates. The results of this sensitivity analysis are shown below and in Annex 2.

Results

Table 3.4 presents the hypothetical out-of-pocket spending needed for one successful medicine.

Table 3.4. Hypothetical out-of-pocket spending needed for one successful medicine (2011 US$m)

Interval	Mean spending per stage (US$m)	Probability of leaving stage	No. of compounds needed for one success	Hypothetical spending (US$m)
1 — Pre-1st toxicity dose	—	—	—	76.5
2 — 1st toxicity dose to 1st human dose	6.5	0.70	13.3	86.8
3 — 1st human dose to 1st patient dose	16.0	0.63	9.3	149.5
4 — 1st patient dose to 1st pivotal dose	53.9	0.31	5.9	316.9
5 — 1st pivotal dose to 1st core submission	129.3	0.63	1.8	235.9
6 — 1st core submission to 1st core launch	29.0	0.87	1.1	33.3
Total	**234.6**			**899.0**

Source: Authors' calculations based on CMRI data

Before we discuss in detail the methodology used to obtain the "hypothetical spend" in the far right column of Table 3.4, recall that the number in Table 3.4 for our first interval, US$76.5m, has been calculated using aggregated data. Also note that although in Table 3.1 we present both the mean and the median, for the purpose of our calculations here we use the mean only.

Table 3.4 shows that 13.3 compounds are needed in Interval 2 to ultimately produce one successful medicine. This number is obtained by dividing 1.0 by the overall probability of success, i.e. taking into account the probabilities of success for the different intervals. The hypothetical spending for Interval 2 is calculated by multiplying the mean spending in this stage, US$6.5m, by the number of compounds needed in this interval for one successful medicine, 13.3. The number of compounds needed in the next interval then is calculated by multiplying 13.3 by the probability that these molecules leave the stage, i.e. 0.70. This multiplication yields 9.3 compounds. Again, the hypothetical spending in this interval will be the result of multiplying 9.3 by US$16.0m (mean spending in this interval). The same methodology is then applied to the remaining intervals.

Taking into account success rates and mean spending per interval, Table 3.4 shows that a company needs to spend US$87m in Interval 2 to ultimately launch a new medicine, US$150m in Interval 3, and so on. Summing up these hypothetical expenditures, the hypothetical out-of-pocket cost of developing a new medicine is US$899m. Note that Interval 4 now becomes the most expensive interval. This is partially because a molecule that has reached this stage has a relatively low probability of successfully proceeding to the next stage, compared to the other intervals.

These calculations do not yet take into account the cost of capital. Table 3.5 shows the calculations when the costs for each interval are capitalised up to the date of launch.

Table 3.5. Capitalised cost per successful medicine (2011 US$m)

Interval	Hypothetical spending (US$m)	Time from interval mid-point to 1st core launch (years)	Baseline cost of capital	Capitalised spending per successful med (US$m)
1 — Pre-1 toxicity dose	86.1	9.6	11%	207.4
2 — 1st toxicity dose to 1st human dose	97.6	7.2	11%	184.1
3 — 1st human dose to 1st patient dose	168.1	6.2	11%	284.0
4 — 1st patient dose to 1st pivotal dose	356.3	4.4	11%	501.6
5 — 1st pivotal dose to 1st core submission	265.3	2.1	11%	293.8
6 — 1st core submission to 1st core launch	37.3	0.5	11%	34.9
Total	**1,010.6**			**1,506**

Source: Authors' calculations based on CMRI data

Summing across all intervals, we estimate that the out-of-pocket cost estimate per approved medicine is US$1.0b, while our fully capitalised cost estimate is US$1.5b in 2011 prices. Time costs therefore represent 33% of total cost.

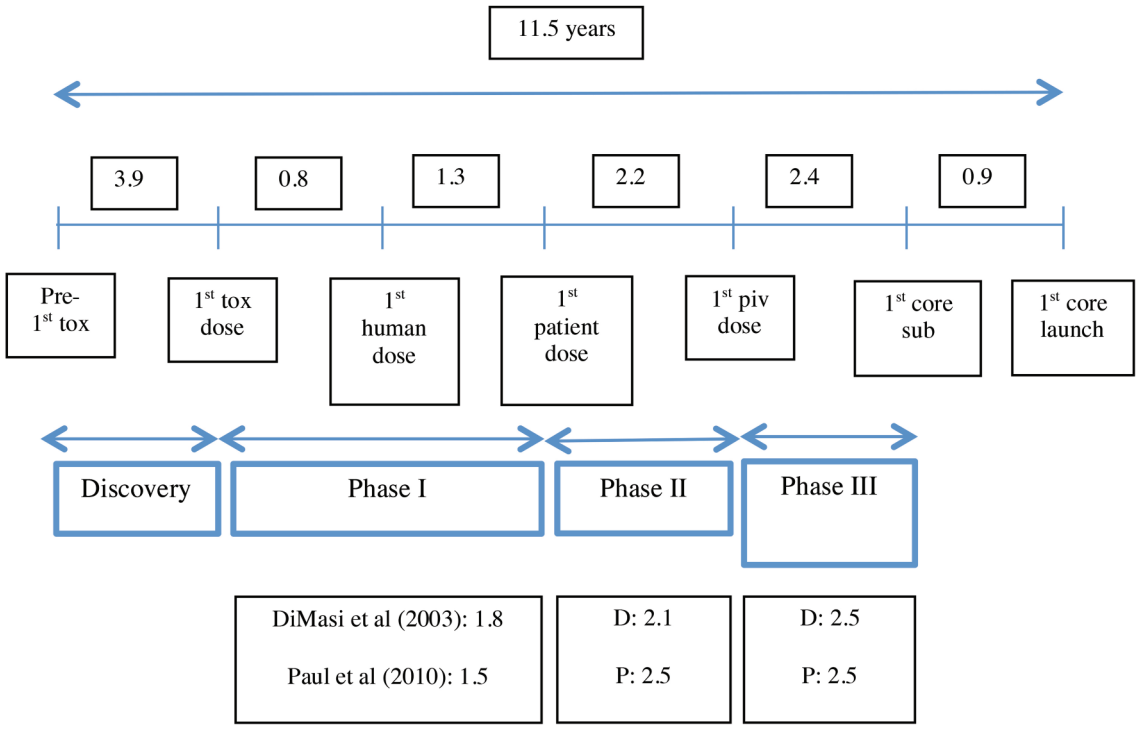
Comparing Our Analysis with the Published Analyses

Below, we explore how the key variables of the CMRI data that we use compare with the most recent articles, in particular with DiMasi et al (2003) and Paul et al (2010). We have selected these two articles as comparators because they most often are cited in policy discussions and they also are based on original data. As outlined above, CMRI defines the R&D stages somewhat differently than the others. Throughout this subsection, we compare by phase by combining Intervals 2 (first toxicity dose to first human dose) and 3 (first human dose to first patient dose) of the CMRI data into Phase I, treating Interval 4 (first patient dose to first pivotal dose) as Phase II, and Interval 5 (first pivotal dose to first core submission) as Phase III.

In terms of success rates, for Phase I (Intervals 2 and 3) the probabilities of success that we use for our estimate, 44% (0.70*0.63=), is below the DiMasi et al (2003) and Paul et al (2010) probabilities, which are 71% and 54%, respectively. For Phase II (Interval 4), our probability of success, at 31%, is also lower than the probabilities reported by DiMasi et al (2003) and Paul et al (2010), which were 44% and 34%, respectively. For Phase III (Interval 5) our success probability is again the lowest, at 63%; the highest one is reported by Paul et al (2010) at 70%; DiMasi et al (2003) report a Phase III success rate of 68.5%.

Based on the information provided in Table 3.5 and the CMRI 11.5-year R&D time, Figure 3.3 shows development times for our six intervals.

Figure 3.3. Interval times in years, CMRI data



Key: D = DiMasi et al (2003); P = Paul et al (2010)
Note: Not drawn to scale

The three studies included in Figure 3.3 report similar development times for Phases I–III: CMRI at 6.7 years, with DiMasi et al (2003) and Paul et al (2010) both at 6.5 years. For Phase I, however, CMRI data report the longest development times at 2.1 years, while for Phase III, they report slightly lower times—2.4 years versus 2.5 for both DiMasi et al and Paul et al. Phase II development time for CMRI data, 2.2 years, falls between DiMasi et al at 2.1 years and Paul et al at 2.5 years.

Table 3.6 compares out-of-pocket costs across the three data sources for Phases I, II and III only and shows that total out-of-pockets costs are very similar between our study and Paul et al (2010) at around US$210m in 2011 prices, but both are somewhat higher than found by DiMasi et al (2003). Our out-of-pocket cost estimate lies between the other two estimates for Phase III. For Phase I and Phase II, our estimates are the highest.

Table 3.6. Out-of-pocket costs for Phases I–III (2011 US$m)

Phase	DiMasi et al (2003)	Paul et al (2010)	CMRI
Phase I	20	16	23
Phase II	30	42	54
Phase III	111	158	129
Total Phases I–III	161	215	206

Sensitivity Analysis

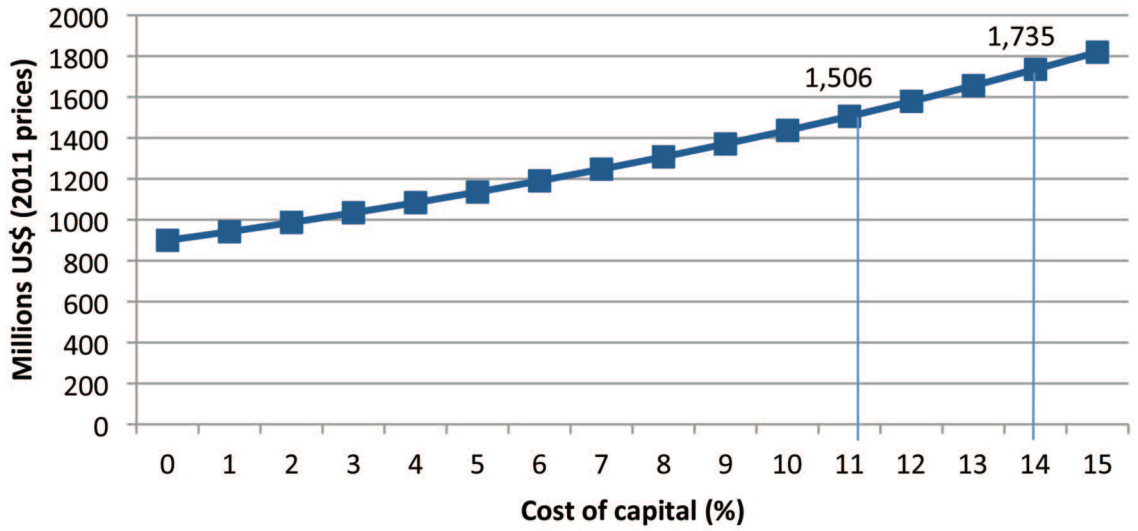
We undertook sensitivity analysis for several of the key parameters that underlie the cost estimates: cost of capital, success rates and duration of intervals. Annex 2 shows the detailed calculations. We report here only on the analysis of the cost of capital and then summarise the results, highlighting those parameters with the greater impact.

Figure 3.4 shows how total capitalised costs would vary as the cost of capital varies, all other factors remaining constant. Increasing the cost of capital from 11% to 14% (as used in Vernon, Golec and DiMasi, 2009) would increase the capitalised total cost of a new medicine by US$230m from US$1,506m to US$1,735m (all in 2011 prices). If the cost of capital were taken to be zero, the total cost of a new medicine would be the US$899m, as reported in Table 3.4.

We also estimate the cost of developing a new medicine using the Myers and Howe (1997) staircase approach. These authors appear to be suggesting a cost of capital of 15.1% for discovery, 10.2% for preclinical testing, and 9% for Phase I trials onwards. Recall that our first interval can be considered to be “discovery”, our second interval “preclinical”, and Intervals 3-5 “clinical”. Using these figures, we calculate the capitalised cost of a new medicine at US$1,502m, which is practically the same as our base case result of US$1,506m.

Table 3.7 summarises the effects of altering the other key parameters by ±10%: out-of-pocket costs, success rates and interval duration. The cost estimates are most sensitive to the success rates.

Figure 3.4. Capitalised total cost per successful medicine by cost of capital (2011 US$m)



Source: Authors' calculations based on CMRI data

Table 3.7. Sensitivity analysis: effect on our base case cost estimate per new medicine

	Out-of-pocket costs	Success rates	Interval duration
Base case + 10%	+ 10%	- 22%	+ 6%
Base case - 10%	- 10%	+ 36%	- 13%

To summarise, in this section we have provided a new cost estimate per new medicine: US$1.5b in 2011 prices. This estimate is based on unpublished data from various CMRI databases. Our estimate lies between the DiMasi (2003) et al and the Paul et al (2010) numbers—US$1.0b and US$1.9b, respectively, in 2011 prices. This new estimate supports the view that drug development costs have been increasing over the last decade—although it is uncertain by exactly how much. It must be noted, however, that the main limitation of our new estimate is the small number of projects used to calculate out-of-pocket costs for the last three intervals.

THERAPEUTIC AREAS

Key Points

R&D costs vary substantially by therapeutic area. This is because of considerable variation across therapeutic areas in three key variables: success rates, development cycle times and out-of-pocket costs.

The most recent analyses suggest that the most expensive therapeutic areas in terms of drug R&D costs are neurology, respiratory and oncology. This is because drugs in these categories experience lower success rates and longer development times. By comparison, anti-parasitics and drugs to treat HIV/AIDS have the lowest R&D costs because of higher success rates and shorter development times.

Most papers that analyse R&D costs emphasise that one of the key issues responsible for differing cost estimates is therapeutic area, i.e. R&D cost per successful new medicine varies by therapeutic area. Below, we review those papers that have looked at development by therapeutic area. As before, we report on the latest evidence available in terms of the absolute values of the key variables, and were possible, we highlight how these variables have been evolving over time. Note that the published papers do not always include the same therapeutic areas.

Success Rates

We have identified several papers that show success rates by therapeutic area. Two papers, DiMasi (2001) and DiMasi et al (2010), use a similar database but different drug cohorts. This allows us to use these two papers to show how success rates for a number of therapeutic areas have evolved over time. Note that these papers report overall probability of success, rather than success by clinical phase.

DiMasi (2001) looks at the development histories of 671 NMEs for which survey firms had filed a first IND from 1981 to 1992; 508 were self-originated medicines and 163 were acquired from other companies. DiMasi et al (2010) updates clinical success rates for investigational compounds that entered clinical testing between 1993 and 2004 for the 50 largest pharmaceutical firms (2006 sales). Comparing success rates from DiMasi et al (2010) to DiMasi's earlier research (DiMasi, 2001), we note that the therapeutic area analgesic/anaesthetic is no longer reported and GI/metabolism is reported as a single therapeutic area, as is antineoplastic/immunologic.

Table 4.1 presents how current and the highest possible, or "maximum", success rates compare in both articles, taking into account the sample size (n) and the approved and open NMEs in five of the largest therapeutic classes by sample size. "Current success rate" is defined as the ratio of approved molecules to total number of molecules (column "n" in Table 4.1); maximum success rate assumes that all open compounds eventually will be approved.

Several points are important. First, the 828 NMEs included in the sample in the 2010 article is more than double the 363 NMEs in the 2001 paper—but, in the 2010 study, proportionately fewer of the NMEs have been approved and a higher number are still in development. This is why current success rates shown in Table 4.1 for the 2010 article are substantially lower for the five selected therapeutic classes—indeed, current success rates are very low for most of them (even equal to or lower than 5%). However, should all molecules still in development prove to be

successful (probably too optimistic), the maximum possible success rates are sometimes higher in 2010 than in 2001, and sometimes lower, with important differences across therapeutic areas.

Table 4.1. Success rates for selected therapeutic area—DiMasi (2001) versus DiMasi et al (2010)

Therapeutic area	n		Approved NMEs		Open NMEs		Current success rate		Maximum success rate	
	2001	2010	2001	2010	2001	2010	2001	2010	2001	2010
Anti-infective	57 (16%)	122 (15%)	16	19	3	14	28%	16%	33%	27%
Antineoplastic/ Immunologic	51 (14%)	254 (31%)	8	18	6	75	16%	7%	27%	37%
CV	120 (33%)	134 (16%)	21	4	6	24	18%	3%	23%	21%
CNS	110 (30%)	235 (28%)	16	9	14	40	15%	4%	27%	21%
GI/Metabolism	15 (4%)	120 (14%)	3	4	2	28	20%	3%	33%	27%
Respiratory	25 (7%)	83 (10%)	3	4	0	15	12%	5%	12%	23%
Total of selected classes	**363**	**828**	**65 (18%)**	**54 (7%)**	**9 (8%)**	**168 (20%)**				

Key: CV = cardiovascular; CNS = central nervous system; GI = gastrointestinal
Source: DiMasi (2001) and DiMasi et al (2010)

Second, note the change in relative importance, in terms of sample size, of the therapeutic classes reported above. Antineoplastic/immunologic is now the most important class with 31% of all NMEs (whether successful or not, or still in development). NMEs for CNS represent around 30% of all NMEs in both samples.

Third, success rates by therapeutic area offer some insights into success rate variations. The paper by DiMasi and colleagues published in 2004 (DiMasi et al, 2004) focused on comparing four therapeutic areas (analgesic/anaesthetic, anti-infective, CV, CNS) with the "average" using the same database as the DiMasi et al 2003 paper. These four areas represent 65% of the total sample of 68 compounds. The authors find similar an overall success rate for analgesics/anaesthetics and anti-infectives at 24.6% and 24.9%, respectively, and for CV and CNS at 18.4% and 18.0%, respectively.

By clinical phase, DiMasi et al (2004) show that both anti-infectives and analgesics/anaesthetics enjoy a relatively high success rate for Phase II (37.7% and 34.8%, respectively), while CV (26%) and CNS (24.6%) are below average. In their previous study, NMEs for anti-infectives and CV achieved above-average success rates entering Phase II, while the success rate for NSAIDs was similar to the average.

Success rates for compounds entering Phase III are above the 68.5% average only for analgesics/anaesthetics (78.3%). The success rate for anti-infectives, CV and CNS are 65.2%, 67.9% and 61%, respectively. In their previous work, anti-infectives, CV and NSAIDs exceeded the 64.5% success rate, while NMEs in the neuropharmacology therapeutic area were less successful than average.

In summary, anti-infectives are relatively more likely to reach Phase III, reflecting the low percentage of anti-infective failures in Phase II and the relatively high clinical approval for the class. Conversely, a relatively small percentage of CV drugs make it to Phase III, which is linked to the high share of class failures occurring in Phase II and low overall clinical approval rates.

Kola and Landis (2004) also calculate success rates by therapeutic area. They analyse drugs during a ten year period (1991–2000) for ten large pharmaceutical companies. They calculate an average success rate from first-in-human to registration of 11%; or, in aggregate, only one in nine compounds makes it through development and is approved in Europe and/or the US. Again, clear differences arise across therapeutic areas. The highest success rate is for CV, at 20% (similar to estimates in earlier DiMasi work), while success rates for oncology and CNS are much lower, at around 5–8%. Stark differences in success rates for similar therapeutic areas also are evident in the earlier articles authored by DiMasi and in Kola and Landis. One example is CNS: DiMasi (2001) reports a success rate of 14.5% while the Kola and Landis estimate is 7–8%.

Kola and Landis argue that the vast majority of attrition takes place in Phase IIb (specifically designed to study efficacy) and Phase III. But even at registration the failure rate is 23%, with oncology suffering a particularly high attrition rate of 30% at this stage. Approximately 45% of all compounds that enter Phase III fail, and in some therapeutic areas, such as oncology, the failure rate is as high as 59%. Kola and Landis argue that this failure rate is far too high, given the testing that must be completed to reach it. Approximately 62% of all compounds entering Phase II fail—and again this is higher in oncology (more than 70%).

Adams and Brantner (2006) also estimate success rates, measured as the probability of market entry, by therapeutic area and clinical phase, as shown in Table 4.2. There are considerable differences across therapeutic areas, with an overall probability of success ranging from 3% for respiratory drugs (with a very low entry probability for approval, indicating a high failure rate in Phase III) to a relatively higher overall success rate for anti-parasitics. One result consistent across disorders and primary indication is that entry probabilities decrease significantly from Phase II to approval, reflecting an increase in failure rates as the drug moves through the development process.

Osborne et al (2011) investigate industry-sponsored clinical trials (Phases I–III) for HIV that were conducted within the US between January 1998 and June 2008. The source of their data is the national database at ClinicalTrials.gov[24]. Their sample is composed of 66 drugs; 11 reached

[24] A service of the US National Institutes of Health begun in 1997, ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical trials conducted in the United States and around the world. It provides information about a trial's purpose, who may participate, and locations.

Table 4.2. Probability of market entry

Disorder		Entry probability (%)			Cumulative[1]
	n	Phase II	Phase III	Approval	
Blood	163	60	57	25	9%
Cardiovascular	280	69	4	22	6%
Dermatological	122	8	44	29	11%
Genitourinary	12	92	5	37	20%
HIV/AIDS	108	75	50	36	14%
Cancer	68	78	46	20	7%
Musculoskeletal	134	73	41	22	7%
Neurological	192	73	47	22	8%
Anti-parasitic	20	100	67	53	36%
Respiratory	165	68	31	16	3%
Sensory	53	88	60	40	21%
Primary Indication					
Alzheimer's disease	46	65	46	25	7%
Rheumatoid arthritis	51	91	33	23	7%
Asthma	74	81	36	26	8%
Breast cancer	54	96	58	44	24%
HIV/AIDS	89	83	56	44	20%

[1] The product of three probabilities
Source: Adams and Brantner (2006)

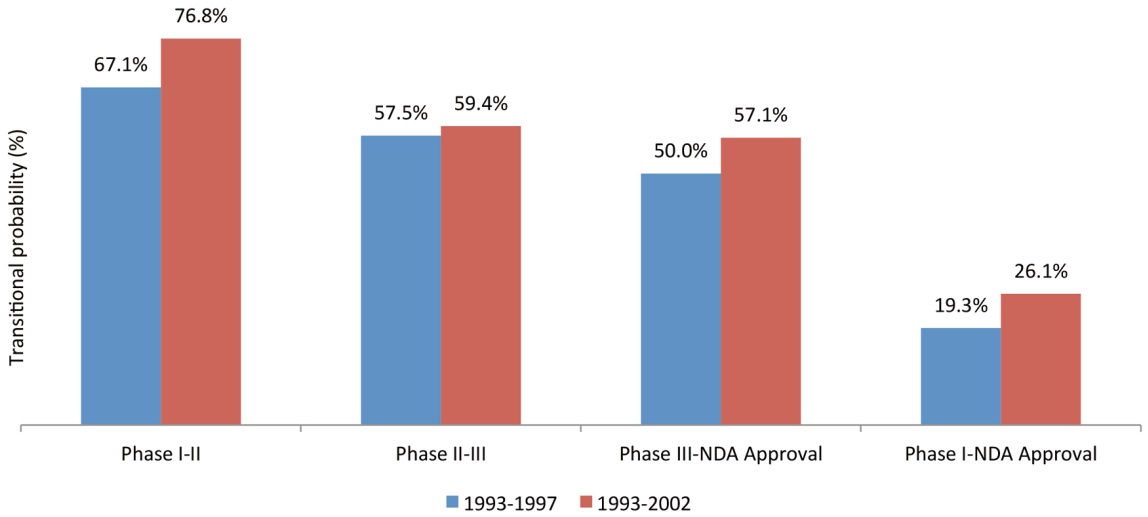
approval, which implies a 16.7% overall success rate. This success rate is similar to the success rates estimated by Adams and Brantner (2006).

A paper by DiMasi and Grabowski (2007a) explores in detail the economics of new oncology drug development, and provides data on duration and risks for them. The authors use a variety of sources, including the CSDD database and public sources.

For success rates, DiMasi and Grabowski (2007a) investigate data on the pipeline of 20 large pharmaceutical companies, analysing 838 drugs that entered clinical testing for the first time anywhere in the world from 1993–2002, 175 (21%) of which were being investigated for oncology indications. One of the important results presented in this paper is that oncology drugs tend to be studied for more indications than for other drugs: 57% of oncology drugs were tested for more than one indication (46% for other drugs) and 32% of oncology drugs were tested for at least four indications (9% for other drugs).

The authors also break up the sample into two time periods: the full sample for 1993–2002 and a 1993–1997 subsample. Figure 4.1 shows the transition probabilities for investigational oncology drugs for these two periods. One of the main findings is that 50% of oncology drugs entering Phase III fail, although there is an improvement over time at each stage. Moreover, one in five oncology drugs that entered the pipeline during 1993–1997 eventually will attain marketing approval, while one in four would do so in the longer 1993–2002 period.

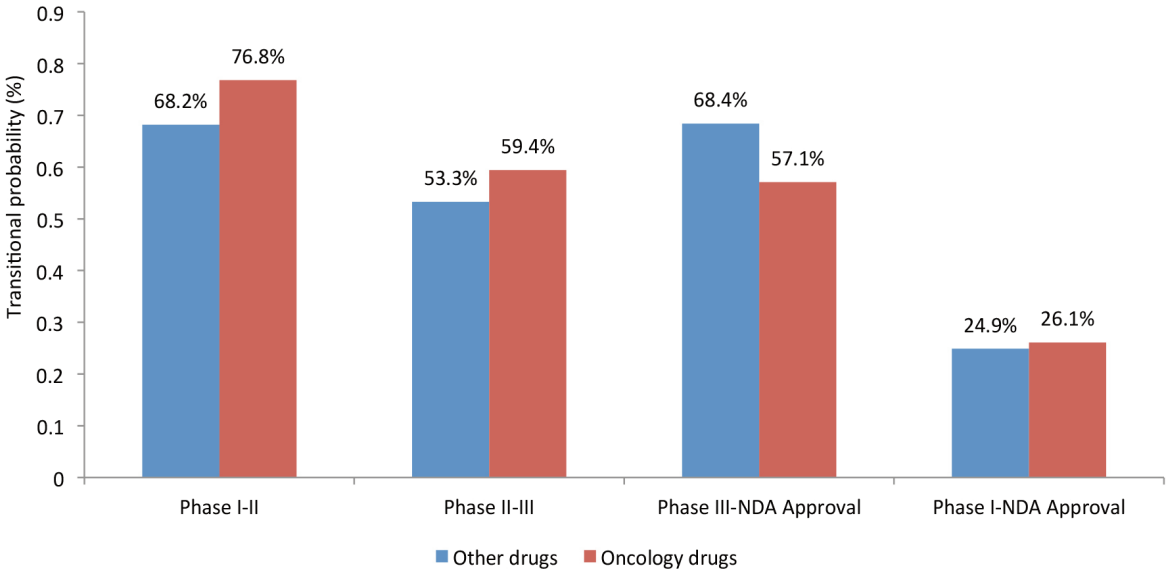
Figure 4.1. Clinical phase transition probabilities for oncology compounds



Source: DiMasi and Grabowski (2007a)

The authors also compare how oncology drugs fare versus all other drugs, as a group. Figure 4.2 shows their results. Oncology drugs have a higher likelihood of progressing to later stages of clinical testing—but their success rate for expensive Phase III testing is notably lower. Consequently, the overall approval success rate is similar for oncology and other medicines.

Figure 4.2. Transition probabilities: oncology versus other drugs, 1993 – 2002



Source: DiMasi and Grabowski (2007a)

Parker and Kohler (2010) explore clinical success rates for drugs used to treat moderate to severe Crohn's disease that were in Phase I–III clinical studies between January 1998 and June 2008. They find, based on data from ClinicalTrials.gov, that the cumulative success rate for the 37 drugs included in their sample was 18%.

Again using the ClinicalTrials.gov database, Parker, Zhang and Buckstein (2011) estimate an overall clinical success rate of 8% for drugs for non-Hodgkin's lymphoma that initiated a Phase I trial in the US between January 1998 and June 2008. Two drugs included in their sample gained approval after Phase II trials; including these two drugs as successful increases the overall success rate to about 11%.

Jayasundara, Keystone and Parker (2012) compute success rates for drugs (both biologics and small molecules) for patients with moderate to severe rheumatoid arthritis. ClinicalTrials.gov was their main source of data. They find a 16% cumulative success rate for the 69 drugs that were included in the study, and that were included in a Phase I, Phase II or Phase III trial in the US between December 1998 and March 2011. Jayasundara, Keystone and Parker (2012) also find a higher overall success rate for biologics (31%) in this indication compared to small-molecule drugs.

To summarise, neurology and respiratory are the two therapeutic areas with the lowest success rates, true since the early 2000s. However, success rates for CV appear to have decreased over time; the more recent evidence suggests CV also is one of the therapeutic areas with lower success rates. Success rates for oncologic drugs are particularly low relative to other therapeutic classes in Phase III. Conversely, success rates for anti-parasitics, analgesics/anaesthetics and drugs for HIV/AIDS are among the highest.

Development Times

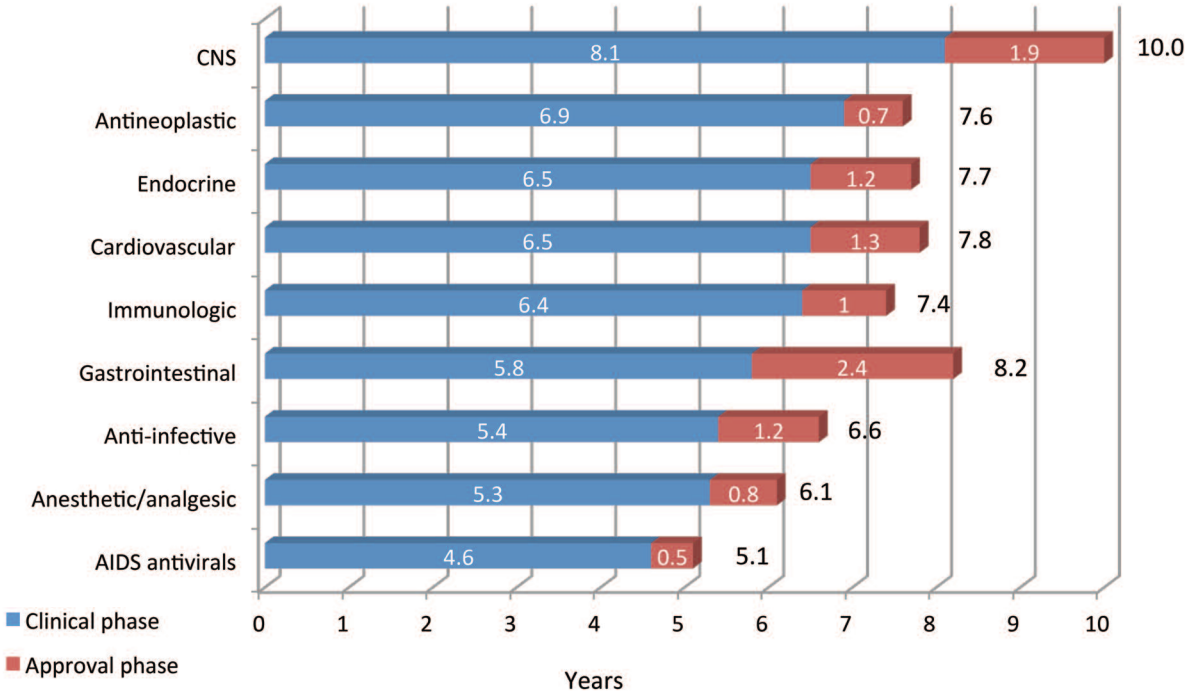
The most recent paper looking at development times for specific therapeutic area is that by Kaitin and DiMasi (2011), which looks at drugs approved between 2005 and 2009. Figure 4.3 shows these results.

Figure 4.3 shows substantial variability in mean duration—for instance, the mean clinical phase was 76% longer for the drug class that moved most slowly (CNS) as compared with the one that moved fastest (AIDS antivirals).

Kaitin and DiMasi (2011) also examined durations for orphan drugs, although not by therapeutic area as the numbers were too small to disaggregate. They show that the mean approval phase time between 2000 and 2009 was six months shorter for orphan drugs than for non-orphan drugs. As the authors point out, this is expected as orphan drugs receive priority status from the FDA proportionately more often than non-orphan drugs. Clinical phase durations, however, are often comparable to or longer than those for non-orphan drugs.

Using earlier work based on similar databases (DiMasi et al, 2004), we can compare the evolution of development times for CNS, CV and anti-infectives, as these three areas are included in both papers. The more recent evidence (Kaitin and DiMasi, 2011) shows higher development times for the three areas in both the clinical phase and approval phase: for CNS up from 114.6 months to 120.0 months; for anti-infectives up from 63.0 months to 79.2 months; and for CV up from 82.0 months to 93.6 months.

Figure 4.3. Mean clinical and approval phase times for approved NMEs by therapeutic class, 2005–2009



Note: The anti-infective group does not include AIDS antivirals
Source: Kaitin and DiMasi (2011)

Adams and Brantner (2006) divide their analysis by disorder and by primary indication. Table 4.3 shows their results for duration of clinical phases. Several points are worth mentioning. The shortest phase, by far, is Phase I. Moreover, somewhat surprisingly, the duration of Phase II trials for most disorders and primary indications tends to be longer than for Phase III. Drugs for HIV/AIDS have had the shortest Phase III and overall durations. The authors argue that this shows how regulatory policy may affect development costs, as sponsors have been allowed to file NDAs for almost all AIDS drugs without completing large-scale human clinical trials.

Table 4.4 shows differences in clinical and regulatory times between oncology and other drugs from DiMasi and Grabowski (2007a). The authors do not disaggregate "other" drugs by therapeutic area. FDA review times were shorter for oncology drugs by six months, but the clinical phases took, on average, 1.5 years longer. The authors postulate reasons to explain these differences, such as difficulties in recruiting patients and longer times needed to establish effect on survival.

To summarise, development times tend to be longest for neurology, respiratory and cancer drugs, especially in the clinical phases, and are shortest for anti-parasitics, analgesics/anaesthetics and drugs for HIV/AIDS, as the result of shorter development times for both the clinical and approval phases.

Table 4.3. Durations by disorder and primary indication

Disorder	Number	Duration (months)			
	n	Phase I	Phase II	Phase III	Total
Blood	163	18	32	33	83
Cardiovascular	280	14	35	30	79
Dermatological	122	13	29	24	66
Genitourinary	120	21	28	25	74
HIV/AIDS	108	19	23	19	61
Cancer	681	21	30	29	80
Musculoskeletal	134	19	39	30	88
Neurological	192	20	39	32	91
Anti-parasitic	20	18	33	13	64
Respiratory	165	18	30	36	84
Sensory	53	11	44	30	85
Primary Indication	**n**	**Phase I**	**Phase II**	**Phase III**	**Total**
Alzheimer's disease	46	17	37	18	72
Rheumatoid arthritis	51	18	36	39	93
Asthma	74	18	33	31	82
Breast cancer	54	17	37	37	91
HIV/AIDS	89	22	22	19	63

Note: The authors do not report standard deviations, so we cannot conclude whether the differences are statistically significant.
Source: Adams and Brantner (2006)

Table 4.4. Development and regulatory approval times: oncologic versus other drugs

Therap class	Approval Phase	Clinical Phase	Total
Other drugs	21.6	75.6	97.2
Oncology Drugs	15.6	93.6	109.2

Source: DiMasi and Grabowski (2007a)

Overall R&D Costs

Some of the papers that explore differences across therapeutic area in detail also estimate total R&D costs, which are driven by the estimates for the key variables outlined in the previous sections. Some of the papers cited above do not attempt to calculate overall development costs, but focus only on success rates and/or development times. Indeed, as mentioned throughout this publication, one of the most difficult variables for which to obtain data is out-of-pocket costs at the project/clinical phase level.

DiMasi et al (2004) calculate average clinical period cost per approved new drug by therapeutic class (see Table 4.5). Note that pre-clinical costs are not included.

Table 4.5. Average clinical period cost per approved new drug by therapeutic class (2011 US$m)

Therap class	Out-of-pocket	Time	Total
CNS	351	326	677
Anti-infective	465	167	632
All	*362*	*236*	*599*
CV	356	235	591
Analgesic/anaesthetic	324	158	482

Source: Adapted from DiMasi et al (2004)

Analgesic/anaesthetic, CV and CNS drugs have below average out-of-pocket costs per approved drug at 11%, 2% and 3% below average, respectively. At the same time, out-of-pocket costs are 28% above the average for anti-infectives. When time costs are included, capitalised costs per approved analgesic/anaesthetic are even farther below average (20%), but well above average for CNS and anti-infective drugs. Capitalised costs for an approved new drug for CV use are close to the average.

The first study to calculate development costs by therapeutic area, by DiMasi et al (1995), finds an increase over time in clinical cost per approved new drug across all the therapeutic areas included in the analysis.

Adams and Brantner (2006) also estimate total costs by disorder and primary indication, as shown in Table 4.6. The observed differences in development costs are due primarily to differences in success rates and durations, not out-of-pocket spending by disorder or primary indication.

In contrast with DiMasi et al (1995), Adams and Brantner (2006) found that HIV drugs had quite high clinical costs and anti-infectives as a whole have somewhat higher than average expected capitalised clinical costs. Another issue is that a sizeable proportion of HIV drug development costs shifted from pre-approval clinical trials to required post-approval studies—and so will not be captured as development costs.

Table 4.6. Costs for new drugs by disorder and primary indication

Disorder	Cost (2011 US$m)
Blood	1,164
Cardiovascular	1,140
Dermatological	870
Genitourinary	816
HIV/AIDS	694
Cancer	1,339
Musculoskeletal	1,216
Neurological	1,306
Anti-parasitic	583
Respiratory	1,457
Sensory	833
Primary Indication	
Alzheimer's disease	1,161
Rheumatoid arthritis	1,203
Asthma	951
Breast cancer	784
HIV/AIDS	616

Note: All values are adjusted to 2011 dollars using the US GDP implicit price deflator from the World Bank
Source: Adams and Brantner (2006)

In summary, the most recent published analyses (DiMasi et al, 2004; Kola and Landis, 2004; Adams and Brantner, 2006; DiMasi and Grabowski, 2007a; DiMasi et al, 2010; Kaitin and DiMasi, 2011) suggest the following.

1. Neurology is currently one of the most "expensive" therapeutic areas, i.e. total capitalised costs are higher for NMEs in this area. This is due to both low success rates and high development times. Out-of-pocket costs, however, tend to be similar to other therapeutic areas.

2. The other two expensive areas are respiratory and cancer/oncology. The evidence is consistent in that success rates for respiratory drugs are among the lowest, while development times seem to be in the top range. In terms of oncology drugs, the earlier evidence shows success rates for these to be among the lowest, a finding later reinforced by DiMasi and Grabowski (2007a), especially for Phase III trials. Overall approval success rates, however, seem to be similar for oncology drugs versus other drugs. Development times for oncology drugs are higher than other therapeutic areas, especially in the clinical stages.

3. In terms of lower-cost therapeutic areas, the evidence suggests that R&D costs for HIV/AIDS and anti-parasitic drugs are the lowest at around US$600m-$700m in 2011 US$. For both anti-parasitics and drugs for HIV/AIDS, this is the result of having relatively high cumulative probabilities of success in clinical phases and lower total development times.

As discussed earlier and in more detail in Section 8, there might be good reasons for these differences across therapeutic areas; for instance, some areas are fast-tracked (e.g. HIV drugs) and some are more difficult to study and have less well-defined endpoints (e.g. autoimmune diseases and oncology).

COMPOUND ORIGIN: SELF-ORIGINATED VERSUS LICENSED-IN

Key Points

Most of the published calculations of R&D costs to date focus on self-originated new compounds because comprehensive data for licensed-in/acquired compounds are very difficult to collect. However, an increasing proportion of drugs are being licensed in by companies.

Clinical success rates tend to be higher for drugs that are licensed in than for self-originated drugs. Greater success may be the results of a "screening effect" for licensed-in compounds: many of the licensed-in drugs are acquired after Phase I or Phase II testing has been conducted by the licensor and, thus, already have been shown to be promising candidates before being included in the acquiring company's development portfolio.

This difference also is apparent during early research, i.e. externally-sourced projects are significantly more likely to reach clinical testing than internal projects, perhaps for similar reasons. Indeed, some expectation of success would be necessary for a company to license or acquire any drug candidate.

Most of the published work to date that calculates development costs focuses on self-originated NMEs. The main reason is the lack of data for licensed-in projects; it is usually very difficult, if not impossible, to apportion development costs for these projects between the specific companies. Moreover, when one project is transferred to another company, it rarely is possible to track down the details (especially out-of-pocket costs) of that project from the original company. However, an increasing percentage, and now the majority, of drugs are licensed and involve at least two firms. Most of the more recent articles estimating the cost of developing a successful new drug mention this issue but either (1) still use only self-originated drugs for their cost estimates or (2) cannot distinguish in their databases whether particular medicines are self-originated or have been licensed in.

Some studies, however, do compare the probability of success of self-originated and licensed-in drugs. The most recent study is DiMasi et al (2010). Table 5.1, reproduced from their paper, shows a higher probability of success for licensed-in compounds. The authors give two reasons for this: (1) licensed-in compounds have generally gone through some screening or testing prior to licensing and have been shown to be promising candidates, and (2) it is likely that many of these licensed-in drugs were acquired after some clinical testing had been done on them. The same authors used similar arguments in their earlier research (DiMasi et al, 1994; DiMasi, 1995a; DiMasi, 2001). The authors also comment that licensed-in drugs could be acquired at any phase—but they do not have data on when they were licensed in.

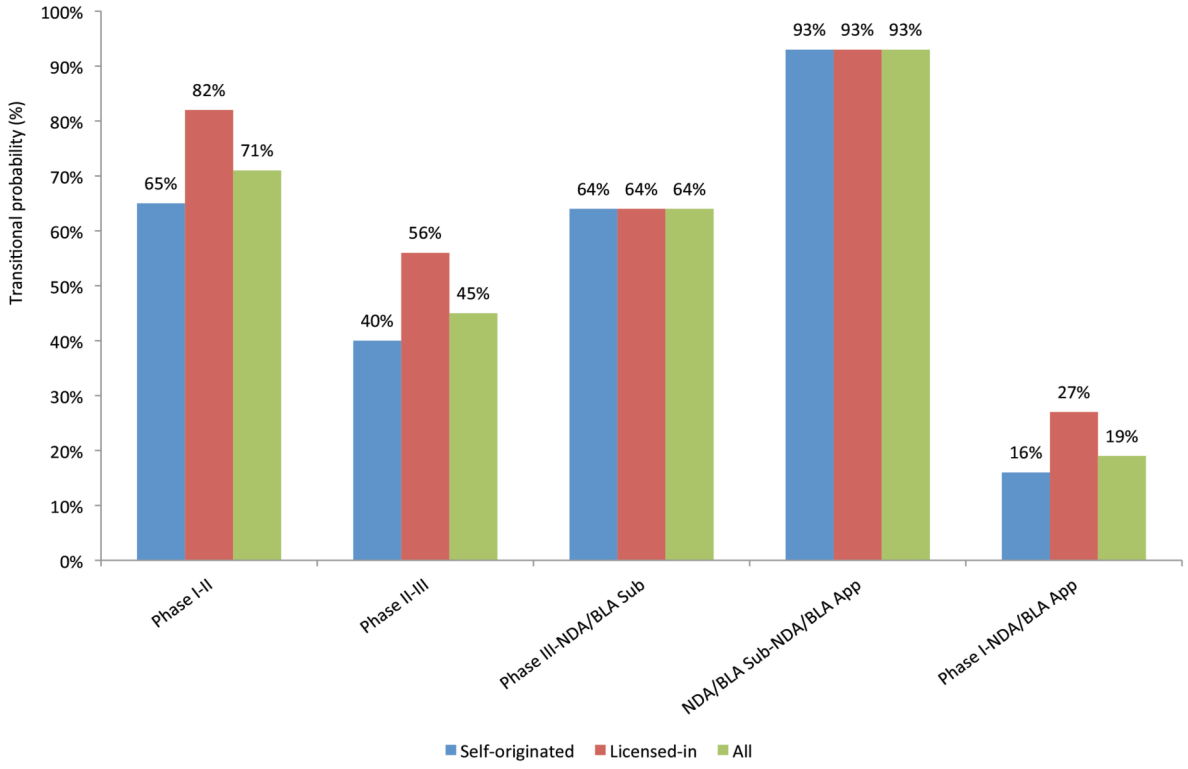
DiMasi et al (2010) also compare transition probabilities, as reported in Figure 5.1. They estimate a higher overall clinical approval success rate for licensed-in versus self-originated drugs: 27% versus 16%. However, the two groups of medicines had identical success rates for both Phase III (64%) and regulatory review (93%). Higher overall clinical approval success rate implies, other things constant, lower total R&D costs per approved drug; for instance, and using the results from DiMasi et al (2003), the R&D cost per approved drug with the higher 27% success rate would fall to US$640m (2003 prices), assuming other things stay constant, as compared with the original estimate of US$802m, which corresponds with the 21.5% success rate.

Table 5.1. Current and maximum-possible success rates by source of molecule for compounds first tested in humans from 1993 to 2004

Molecule source	n	Approved molecules	Open molecules[1]	Percentage completed (%)[1]	Current success rate (%)[1]	Maximum possible success rate (%)[2]
1993-2004						
Self-originated	1,225	87	239	80.5	7.1	26.6
Licensed-in	412	41	141	65.8	10.0	44.2
Licensed-out	101	10	42	58.4	9.9	51.5
All	**1,738**	**138**	**422**	**75.7**	**7.9**	**32.2**
1993-1998						
Self-originated	584	64	48	91.8	11.0	19.2
Licensed-in	180	32	30	83.3	17.8	34.4
Licensed-out	57	9	21	63.2	15.8	52.6
All	**821**	**105**	**99**	**87.9**	**12.8**	**24.8**

[1] Through June 2009.
[2] Assumes that all open compounds will eventually be approved.
Note: Current success rate is defined as the ratio of approved molecules to total number of molecules (column "n" in Table 5.1); maximum-possible success rate assumes that all open compounds eventually will be approved
Source: DiMasi et al (2010)

Figure 5.1. Phase transition probabilities and clinical approval success probabilities by source of compound, for compounds first tested in humans from 1993 to 2004



Key: BLA = biologics license application; NDA = new drug application
Source: DiMasi et al (2010)

Gilbert, Henske and Singh (2003) explore differences between self-originated and licensed-in drugs for earlier time periods than DiMasi et al (2010). They argue that licensing-in has been become more attractive but, as a result, price competition for the licensing-in of compounds has sharpened. They claim that the average expected return on investment for the acquirer for Phase III licensing-in dropped from 12% in the years 1995-2000 to about 6% in the early 2000s. Decreasing success rates of Phase III trials also has been important in driving down expected returns from licensed-in compounds. Gilbert, Henske and Singh find that in-licensing productivity has declined: for the 1995–2000 period they calculate that a US$0.7b investment (including royalties) was required for one successful drug launch for licensed-in compounds that were already in Phase III; this increased to US$1.1b for the 2000–2002 period. Increase in the investment required and lower expected returns echoes the two issues mentioned above: increased competition for licensing-in of compounds and falling Phase III success rates.

Adams and Brantner (2006, 2010) also raise this important issue, but their data do not allow them to classify drugs as licensed-in or self-originated.

Phlippen and Vermeersch (2008) analyse the portfolios of the 20 highest R&D-spending firms in 2005, focusing on 1,328 newly announced research projects in the preclinical stage, which is earlier than in the analyses described above. Success is defined as a project reaching Phase I by January 2007; failure is defined as project cancellation or no information about the project for four or more years. A project is classified as “unknown” if no information is available for one to three years. Phlippen and Vermeersch found that externally-sourced projects are significantly more likely to reach clinical testing than internal projects.

Overall, the evidence supports the view that licensed-in compounds tend to enjoy higher clinical success rates, partly as a result of the screening effect that takes place before such compounds are licensed. For pre-clinical stages, the evidence also supports the finding that externally-sourced projects are significantly more likely to reach clinical testing than internal projects.

FIRM SIZE

Key Points

An important variable explored in the literature is the effect of firm size on R&D productivity and whether R&D costs per approved drug vary with firm size. For such analyses, papers focusing on self-originated compounds might produce biased results because the sample for small firms with successful self-originated drugs would be too small to be meaningful.

Results of research on the impact of firm size on R&D productivity and R&D costs are mixed. The evidence from the 1990s and early- to mid-2000s seems to suggest that size matters: multiple tangible and intangible assets are associated with fully integrated organisations, where core capacities can be important across diseases. It remains unclear, however, whether R&D productivity is greater for smaller companies than for traditional "big pharma".

An important variable explored in the literature is whether firm size affects R&D productivity and R&D costs per approved drug. However, ensuring that all drug costs are captured has meant that the focus of most research has been on self-originated drugs; we expect small firms to be under-represented because too few will have taken self-originated drugs through to approval. Moreover, the drugs that small firms choose to develop in-house, rather than out-license to larger firms, are likely to be drugs with relatively low development costs anyhow, such as orphan drugs and other niche drugs. Thus, any comparison of R&D costs between small and large firms is likely to be biased by unmeasured product selection bias. Taking this into consideration, results in terms of the impact of firm size on R&D productivity and drug development costs are mixed.

Analyses in the mid-1990s by DiMasi (1995a) and DiMasi, Grabowski and Vernon (1995) suggested that, at that time, the smallest firms[25] had higher total capitalised costs per approved drug. They had lower clinical development times and costs than larger firms, but much higher preclinical costs, which dominated the overall cost estimates. DiMasi, Grabowski and Vernon (1995) suggested that this evidence supported the view that there exist economies of scale in pharmaceutical R&D and that these are concentrated in the preclinical or discovery phase. This fits with Henderson and Cockburn (1996), which finds support for the proposition of programme-level economies at the discovery stage.

Abrantes-Metz, Adams and Metz (2005) compare development times and success rates between what they define as "big pharma", i.e. firms in the top ten by revenue in 2001, and "non-big pharma", i.e. all other companies. They find that the overall success rate for "big pharma" of 25.2% is slightly lower across the three clinical phases, relative to the 26.3% success rate for the full sample, and lower for Phases I and II compared to "non-big pharma". However, the success rate in Phase III is notably higher for "big pharma" relative to "non-big pharma": 69% versus 54%, respectively. Development (Phase I–III) times for successful drugs are substantially shorter for "big pharma" than for "non-big pharma"—76.2 months versus 87.8 months.

Munos (2009) explores FDA approvals of NMEs and NBEs (new biological entities). He finds that the share of NMEs approved that is accounted for by "large" pharmaceutical companies has declined from around 75% in 1995 to around 35% in 2008. Large pharmaceutical companies are defined as one of the "top" 15 drug companies (criterion not specified), or their predecessors,

[25] Firm size was measured by pharmaceutical sales.

and joint ventures; all other companies, including biotechnology companies, are categorised as "small" pharmaceutical companies. He shows that the share of NMEs approved that were accounted for by biotech and small pharmaceutical companies trebled, from 23% to nearly 70%, over the same period. He finds evidence to support the argument that small companies outperformed their larger competitors and expects smaller companies' share of NMEs to stabilise at around 50%. This, he argues, has been driven by two factors: (1) the rise in the number of small companies producing NMEs—up from 78 to 145 during the 1980s and 1990s, facilitated by venture capital funding for the biotech boom and (2) the emergence of new, more productive companies has meant that the mean annual NME output of small companies has increased from 0.04 to 0.12 per company since 1995.

Munos argues that the hypotheses to test in the future are (1) whether the NME output of small companies will increase as they become more enmeshed in innovation networks, (2) whether large companies are making more detailed investigations into fundamental science, and (3) whether heightened safety concerns by regulators affect large and small companies differently, as small firms are more likely to be developing orphan drugs and/or drugs likely to gain priority review due to unmet medical need. Overall, Munos views individual small companies as a less reliable source for NMEs than larger companies, but "collectively they produce more, for less" (Munos, 2009, page 965).

In summary, then, results of research on the effect of R&D productivity are mixed. The evidence from the 1990s and early 2000s does suggest that size matters; multiple tangible and intangible assets associated with fully integrated organisations provide core capacities important across diseases (Henderson, Orsenigo and Pisano, 1997; Pammolli and Riccaboni, 2000 and 2001; Henderson and Cockburn, 1996; Cockburn and Henderson, 1994). This is also supported by Garnier (2008), who argues that benefits from greater size include providing critical mass for global clinical development and acquiring crucial technology platforms. In Garnier's view, the potential way forward is "not to break up pharma giants into smaller companies, but to return power to scientists by reorganising R&D into small, highly focused groups headed by people who are leaders in their scientific fields and can guide and inspire their teams to achieve greatness" (Garnier, 2008, page 70).

BIOLOGICS AND BIOPHARMACEUTICALS

Key Points

To address the problem of limited evidence on biologic medicines, DiMasi and Grabowski (2007b) expanded their biotech sample from DiMasi et al (2003) with project level and aggregate annual expenditure data from a biotech firm. They found that the overall clinical success rate for biotech products is 30.2%, which is higher than the 21.5% estimate for traditional pharmaceutical products reported by DiMasi et al (2003). Total clinical plus approval time is 8% longer for biopharmaceuticals than for traditional pharmaceuticals, with nearly all the difference being in Phase I.

Capitalisation increases biopharma costs relative to traditional pharma costs because of the longer development timeline and a slightly higher cost of capital. To account for the latter, DiMasi and Grabowski (2007b) use an 11.5% cost of capital for biologics compared with 11% for other medicines. Comparisons between biologics and other pharmaceuticals based on this one study, however, should be treated with caution because the sample size for biologics still is small.

DiMasi and Grabowski (2007b) performed the first detailed analysis of R&D costs for biologic medicines. They use two data sources for their analysis: the sample from DiMasi et al (2003) and project level and aggregate annual expenditure data from a biotechnology firm for drugs that entered clinical testing from 1990 to 2003. In total, there are four biologics from three companies from the earlier study and 13 compounds from the biotechnology firm. The focus is on recombinant proteins (9) and monoclonal antibodies (8).

Using the same methods as the DiMasi et al (2003) paper, DiMasi and Grabowski (2007b) estimate average clinical period phase costs at US$189m in 2011 prices[26]. Relative to the DiMasi et al (2003) results, the mean total out-of-pocket costs for the clinical phases are 14% higher for biologic compounds than for non-biologics. Multiplying mean costs per phase by the probability of entering each phase (100% for Phase I, 83.7% for Phase II and 47.1% for Phase III) yields the expected clinical out-of-pocket cost per investigational biopharmaceutical compound of US$124m in 2011 prices.

DiMasi and Grabowski (2007b) use the same method as DiMasi et al (2003) to estimate preclinical costs: they multiply the estimated clinical phase cost per investigational molecule by a ratio of preclinical to clinical expenditures obtained by applying an appropriate lag that associates preclinical expenditures with clinical expenditures incurred some time later; this recognises that pre-clinical R&D expenditures occur years prior to the associated clinical testing costs. DiMasi and Grabowski (2007b) estimate that clinical-period phase costs account for 65% of total out-of-pocket costs, which yields an out-of-pocket preclinical cost per investigational molecule of US$68.3m in 2011 prices. As DiMasi and Grabowski (2007b) estimate that the probability of entering the preclinical phase is 100%, the expected out-of-pocket preclinical cost is also equal to US$68.3m. Thus, the total out-of-pocket cost, preclinical and clinical, per investigational biopharmaceutical compound is US$257.3m (US$189m + US$68.3m) in 2011 prices and the total expected out-of-pocket costs are US$192.3m (US$124m + US$68.3m).

[26] Figures in DiMasi and Graboswki (2007b) are in 2005 prices. We have converted all figures to 2011 prices.

The overall clinical success rate for biological products is estimated to be 30.2%, higher than the 21.5% estimated for other pharmaceutical products in DiMasi et al (2003); out-of-pocket (non-capitalised) clinical costs per approved new biopharmaceutical drug equals US$412m in 2011 prices—the result of dividing the expected clinical cost (US$124m) by the overall clinical success rate. Out-of-pocket preclinical costs per approved molecule are US$226m, at 2011 prices, calculated similarly to clinical costs.

In terms of development times, total clinical plus approval time is 8% longer for biopharmaceuticals than for other pharmaceuticals, with nearly all the difference accounted for by Phase I.

In order to calculate capitalised costs, DiMasi and Grabowski use an 11.5% cost of capital for biopharmaceuticals compared with 11% for other medicines. Table 7.1 shows the results for capitalised costs per investigational biopharmaceutical.

Table 7.1. Capitalised costs per investigational biopharmaceutical compound (2011 US$m)

Phase	Expected out-of-pocket cost ($)	Phase length (months)	Start of phase to approval (months)	End of phase to approval	Expected capitalised cost
Preclinical	68.3	52	149.7	97.7	211.6
Phase I	36.8	19.5	97.7	78.2	81.8
Phase II	36.0	29.3	78.2	48.9	64.2
Phase III	51.6	32.9	48.9	16	69.5
Total					**427.2**

Note: Figures reported in DiMasi and Grabowski (2007b) are in 2005 prices. We have converted all figures to 2011 prices.
Source: DiMasi and Grabowski (2007b)

Preclinical capitalised cost per investigational molecule is obtained by spreading the US$68.3m out-of-pocket cost per investigational molecule, determined above, over an estimated 52-month preclinical period and then capitalising forward to the date of marketing approval at a 11.5% real annual discount rate. Based on this methodology, total R&D costs per approved biopharmaceutical product are US$1.4b in 2011 prices. Tables 7.2 and 7.3 show how out-of-pocket costs and capitalised costs compare for biotech and pharmaceutical products. The data for pharmaceutical—non-biologic—products are based on DiMasi et al (2003); note that DiMasi and Grabowski (2007b) update the estimated costs in DiMasi et al (2003) to 2005 prices, using the GDP deflator.

Table 7.2. Pre-approval out-of-pocket outlays per approved new molecule (2011 US$m)

Phase	Biologics	Pharma (non-biologics)
Preclinical	226	155
Clinical	412	360
Total	**637**	**515**

Note: Figures reported in DiMasi and Grabowski (2007b) are in 2005 prices. We have converted all figures to 2011 prices.
Source: DiMasi and Grabowski (2007b)

As shown above, out-of-pocket costs for pharmaceutical products are significantly lower than for biologics—46%, 14% and 24% higher for preclinical, clinical and total, respectively. Table 7.3 shows capitalised costs.

Table 7.3. Pre-approval capitalised cost per approved new molecule (2011 US$m))

Phase	Biologics	Pharma (non-biologics)
Preclinical	701	429
Clinical	714	596
Total	**1,415**	**1,025**

Source: DiMasi and Grabowski (2007b)

Likewise for capitalised costs, biologics costs are higher than estimates for non-biologic pharmaceuticals. The authors point out that capitalisation increases the cost of biologics relative to pharmaceuticals because of the longer development timeline and a slightly higher cost of capital.

The authors conclude that the estimates for biologics are higher than found in their previous study (2003). However, DiMasi and Grabowski themselves caution that their analyses may be imprecise for a number of reasons: (1) the data for biologic products are of a more recent vintage than the pharmaceutical products that were included in the 2003 study, (2) the sample size is small for calculating mean phase costs, (3) non-biologic product costs may not have changed to the same extent in recent years as they did earlier, and (4) the biologics and non-biologics in the study are concentrated in different therapeutic classes, which may affect costs, a factor that the authors considered important enough to examine in a subsequent paper (DiMasi and Grabowski, 2007a).

In summary, little evidence exists about how great the differences may be in R&D costs for biologics versus "traditional" pharmaceutical products. With caveats, the recent evidence provided by DiMasi and Grabowski (2007b) suggests that total capitalised R&D costs for biologic medicines are higher than for other pharmaceuticals.

DRIVERS OF TRENDS IN R&D COSTS

Key Points

The key drivers of the main components of R&D costs present three sets of issues grouped around out-of-pocket costs, failure/success rates and development times.

Drivers of out-of-pocket costs: A key element of R&D cost is the cost of clinical trials, which is affected by the cost per patient and the number of patients required to collect sufficient data. The complexity of clinical trials has increased over time, also increasing their costs. Two trends, however, appear to be helping to control trial costs. First, outsourcing to clinical research organisations (CROs) appears to increase the efficiency of running trials. Second, locating trials in emerging markets (Africa, Asia, Eastern Europe, Latin America and the Middle East) can reduce costs, both because local costs are lower and because patient recruitment may be faster. Nevertheless, although more clinical trials are being conducted in emerging markets, especially Phase III trials, the majority of clinical trials still are conducted in the US and Western Europe, for reasons related to regulatory conditions, relevant expertise and infrastructure.

Drivers of failure rates: Failure rates appear to have increased over time and have fluctuated across stages of development. This may be the result of a combination of reasons. First, regulators are becoming more risk averse and may be more reluctant to approve some drugs. Second, R&D is directed towards tougher challenges that require drugs with novel mechanisms of action and for which clinical endpoints may be less clear cut. Third, within companies, projects may advance prematurely, for various reasons, to the later stages of clinical development and then fail in Phase III.

Other changes have been identified that could counter increased failure rates. These include better preclinical screening that allows earlier project termination; integrating HTA earlier in the process to encourage earlier decisions about discontinuing projects for commercial reasons; and developing biomarkers and companion diagnostics that can lead to personalised/stratified medicines, with greater prospects for success. Alliances between companies, increasingly common, also may increase success rates.

In the short run, however, important technological challenges, especially for stratified medicines, may actually lead to higher failure rates and costs as science advances and while companies learn how to develop biomarkers and companion diagnostics better. It might take some time for biomarkers and diagnostics to be used efficiently, but “learning by doing” could drive a more efficient R&D process in the long run.

Drivers of development times: A number of factors affecting development times have been identified. First, regulators may be more risk averse, leading to increased regulatory stringency and longer regulatory reviews. Second, companies are directing efforts towards areas that are intrinsically associated with very long clinical development times. Third, clinical trials are becoming increasingly complex and, as a result, take longer to complete. Fourth, trade-offs may be occurring between time and success rate—for example, longer Phase II development times that allow for additional scrutiny before deciding whether to advance to the next phase might produce higher success rates in Phase III. A better use of biomarkers might reduce overall development times by enabling pre-identification of patients with a high response rate and/or low probability of an adverse drug reaction.

A new drug development paradigm? A number of alternatives have been put forward to try to make the R&D process more efficient and affordable. The key suggestions include focusing on earlier phases to reduce technical uncertainties before undertaking the more expensive trials in later development stages and to allow for greater flexibility.

This section focuses on the drivers of trends over time for the key components of R&D costs: out-of-pocket costs, failure/success rates, and time. Some drivers will affect more than one component, as outlined below.

Drivers of Out-of-Pocket Costs

A key set of factors determining out-of-pocket costs relates to the costs of performing clinical trials. Costs have increased with a rise in per-patient costs, the number of patients in clinical trials, and the complexity of clinical trials. Two trends that may help control costs are outsourcing trial management to CROs and performing some clinical trials in emerging markets.

Research published in 2006 showed that the cost per patient of running a Phase III clinical study for a new pharmaceutical exceeded US$28,700, on average. Phase II trials were comparatively cheaper, with average per-patient cost of just over US$21,300. Phase I trials were less expensive at US$17,300 per patient[27] (CEI, 2006).

In addition, the average number of patients included in clinical trials approved by the FDA has doubled in recent years (CSDD, 2008). Scannell et al (2012) also provide examples of increases in the average number of patients per trial. The increases in part are in response to more demanding data requirements from regulators, linked in turn to regulators being more risk averse, discussed below.

The complexity of clinical trials has increased for both regulatory and market reasons. This includes more frequent testing of active compounds against placebo, where ethically possible. The increasing HTA requirements of many public and private third party payers means that pharmacoeconomic, market-oriented variables are more often included in clinical studies to help demonstrate cost effectiveness. Mattison (2009) offers some estimates of this impact, based on a survey. Her results show that all of the 16 companies surveyed estimate that the overall HTA environment has increased development costs[28]: nine of the 16 companies believe this has increased costs by up to 10%, five by 10–25%, and two by 25–50%.

Two factors may help control the costs of clinical trials: outsourcing the management of clinical trials to specialist clinical research organisations (CROs) and locating trials in emerging markets. Hu et al (2007) find that the proportion of drug discovery and development expenditures that was outsourced increased from 10% in 1997 to 41% in 2009; other research suggests that CROs played a substantial role in 64% of Phase I–III trials in 2003 versus 28% in 1993 (Shuchman, 2007). The evidence suggests that most of the revenue growth for CROs is coming from trials for Phases III–IV, with growth rates of around 17%; revenues for earlier-phase trials are growing at around 18% (Mansell, 2007). Mansell (2007) cites an analysis by CSDD from 2006 that shows that one of the advantages of using CROs is increased overall efficiency in running clinical

[27] The original source quoted the numbers in 2006 prices; we have converted them to 2011 prices, using the GDP implicit price deflator.

[28] The period over which this increase applies is undefined.

trials. This ultimately reduced out-of-pocket costs because projects with high CRO involvement stayed closer to schedule. On average, projects with high CRO involvement were filed more than 30 days nearer to the projected submission date. Overall, although CRO-managed trials tended to be larger, they were completed more quickly, especially during the study close-out period.

With respect to the location of clinical trials, many observers have discussed the increasing role of emerging markets as sites for global trials. We have explored the geographic distribution of the clinical trials included in the ClinicalTrials.gov database to get a sense of siting. As of early August 2012, the distribution of trials across the world, as reported on ClinicalTrials.gov, was as shown in Table 8.1.

Table 8.1. Distribution of trials included on ClinicalTrials.gov (August 2012)

Geographic location	Number of trials	Share of total number
US	63,044	48%
Europe	34,632	27%
Canada	9,887	8%
East Asia	10,730	8%
Middle East	5,243	4%
South America	4,342	3%
Pacific	3,642	3%
Africa	2,888	2%
North Asia	2,381	2%
South Asia	2,320	2%
Japan	2,407	2%
Southeast Asia	2,571	2%
Mexico	1,679	1%
Central America	1,742	1%
Total number of trials	**130,356**	

Note: Studies with multiple locations are included in each region containing locations, so the sum of number of trials per location (147,508) is higher than the total number of trials (130,356)
Source: NLM (2012)

Table 8.1 shows that the majority of trials included in the database still are located in the US and Europe; within Europe, 83% of trials are located in Western Europe and the remaining 17% in Eastern Europe. Clearly, the share of trials done in emerging markets, at 28%, is important (the total minus the US, Europe, Canada and Japan).

Cockburn et al (2010), using information from ClinicalTrials.gov, found that Phase I and Phase II sites for industry-sponsored trials are primarily in North America and Western Europe, but Eastern European countries account for a significant share of Phase II trials. Emerging regions (Africa, Asia, Eastern Europe, Latin America and the Middle East) are most often the sites for

Phase III studies, which require larger numbers of patients that occur outside North America and Western Europe. For industry-sponsored Phase II and III sites, Cockburn et al (2010) find a steady decline in the North American share, from 61% in 2003 to 51% in 2008, and an increase in the total share for emerging economies from 13% to 22%. The tentative conclusion is that some regional specialisation in early versus late stage trials seems to be occurring, but that other factors are in play as well, such as trial costs, intellectual property protection and medical infrastructure.

Mansell (2007) reports on the results of the Jefferies CRO survey of March 2007: in 2006–2007, 60% of clinical development dollars allocated to patient access was spent within the US; it was projected that 60% would be spent outside the US by 2010, with shifts primarily to China and India. Based on Table 8.1, and subject to caveats about the data contained in the ClinicalTrials.gov database, trials in the US still represent nearly 50% of all trials. According to Mansell (2007), India's share of global trials increased from 1.5% in 2006 to 5% in 2008 and was expected to reach 15% by 2011. The numbers provided by Mansell (2007) do not match the percentages for India in Table 8.1; we believe that the main reason for this is the use of different sources. However, the overall trend is supported by more recent research, although the exact percentage of trials estimated as being carried out in any particular country varies.

The key reason for this apparent clinical trial globalisation is that sites in emerging markets offer cost savings; e.g. Wilsdon, Attridge and Chambers (2008) argue that India and China can offer costs savings of 67–90% and 50–60%, respectively, compared to the US—and these locales also can offer better access to patients, including faster enrolment rates, important subpopulations, and treatment-naïve patients. Wilsdon, Attridge and Chambers (2008) also find, echoing Cockburn et al (2010), that the share of emerging markets appears to be higher for Phase III, the most expensive trials, and lower for earlier stages. This could have a large effect on out-of-pocket drug developments costs.

Bailey, Cruickshank and Sharma (2009) also argue that emerging markets are attractive for some trials because Phase III trials can be completed faster, meaning that drugs reach the market sooner, and costs are lower. China, India and Russia in particular offer adequate and improving infrastructure, including the requisite pool of scientific talent.

Garnier (2008) agrees that siting clinical trials in emerging markets can reduce waste and improve the quality of decision making. He argues that by switching 50% of its Phase II and III trials from high-cost locations (the US and Western Europe) to India and South America, a mid-size pharmaceutical company with 60,000 patients in clinical trials could save US$600m annually. As an example of cost differences, he notes a top-notch academic centre in India charges US$1,500-2,500 per patient case report while a second-rate centre in the US charges US$20,000, a tenfold difference.

Despite the potential cost advantages of using emerging markets for clinical trials, however, the vast majority of trials still are done in the US and Western countries. Many factors affect decisions about where to conduct clinical trials, such as the location of key partners, internal facilities and future product launches. The US and other Western countries still rank high on these dimensions and are somewhat lower risk than emerging markets. For instance, and as

shown by Bailey, Cruickshank and Sharma (2009), the US, the UK and Germany still are more attractive than emerging countries in terms of the regulatory environment, relevant expertise and infrastructure; the primary disincentives identified for siting trials in countries such as Russia, India and China are weak IP protection and various forms of government intervention, including a tax on clinical trials.

Drivers of Failure Rates

As highlighted above, failure rates seem to have increased over time, although the evidence is somewhat mixed. A number of factors help explain this trend. First, regulators are becoming more risk averse, which may produce more stringent regulatory regimes that ultimately affect the likelihood of a medicine being authorised for market. As noted by Scannell et al (2012), the availability of safe and effective drugs to treat a given disease may raise the regulatory bar for other drugs for the same indication.

Second, industry R&D is now directed towards tougher scientific challenges where finding successful new treatments is inherently more difficult. Pammolli, Magazzini and Riccaboni (2011) argue that the perceived decline in R&D productivity in pharmaceuticals over the past two decades is associated with an increasing concentration of R&D investment in areas where risk of failure is high. For example, they identify an increasing focus on developing treatments for chronic and degenerative diseases, which require longer and more expensive testing than acute diseases. At the same time, treatments for the "easy" targets have been found, leaving only the poorly understood and more complex targets, such as autoimmune diseases and genitourinary conditions. If, as a result, companies must search for drugs that have both a novel mechanism of action and less clear cut endpoints, then the impact on success rates will be negative. A stronger focus on more complex and sophisticated medicines already is evident. For example, biologics represented 12% of global industry sales in 2001, growing to 19% in 2006; recent projections put the 2011 share at around 30%.

Scannell et al (2012) offer an alternative view of the "low hanging fruit" argument. They maintain that the fruit that already has been picked reduces the value of the fruit that remains on the tree because it is now more difficult to show benefits relative to existing treatments than before.

Third, failure rates may increase artificially in the later phases for a number of reasons. For example, Gordian et al (2003) speculate that companies may advance some projects into Phase III prematurely and failure of those projects then is attributed to that phase. Moreover, commercial success is increasingly affected by regulation of medicines pricing and reimbursement, which often requires demonstrating an advance over the standard of care. Products that ultimately are unable to do that, but progress through development anyhow, would fail in the later phases, increasing those failure rates but not affecting rates in the earlier phases.

At the same time, actions that may help reduce R&D costs overall may increase failure rates at earlier stages—i.e. by terminating projects earlier and ensuring that only products most likely to succeed are continued—in a sense making companies more risk averse. This might include, for instance, better preclinical screening and additional scrutiny of higher-risk compounds. Commercial factors are increasingly important in decisions about terminating projects.

Integrating HTA into R&D decision making as early as possible may allow companies to discontinue projects for commercial reasons earlier in the R&D process. In a survey of 40 companies, DiMasi, Caglarcan and Wood-Armany (2001) found that pharmacoeconomic analyses are being initiated early in clinical development. The survey showed that this is influencing clinical trial design, especially in the selection of comparator compounds, and other key decisions during the development process including whether to continue clinical testing on individual drugs. Mattison (2009) finds that HTA may be first considered as early as before proof of concept.

The overall impact of HTA on the cost of drug development is not clear. Collecting additional data from clinical trials likely adds to development costs; but earlier discontinuation of products that are not likely to be commercially successful could reduce them.

Commercial considerations appear to be increasingly important, compared to technical reasons, in decisions about continuing projects. Companies aim to address technical issues as early as possible in the drug development process, to manage time and expenditure. However, a decline in the frequency of technical grounds as the reason for R&D project determination might be due to termination of projects for commercial reasons before the technical issues become apparent.

Thus, two main factors appear to drive decisions on projects. The shift towards more complex therapeutic area implies that technical reasons still are, and will continue to be, important drivers of project discontinuation decisions and failure rates. Companies also appear to be integrating commercial assessments into the process earlier to help avoid continuing projects with little chance of commercial success. The balance between these two factors remains an empirical issue; it will differ across, and perhaps within, companies depending on the disease areas targeted and internal R&D management processes.

In future, genomics may have a powerful impact on development times, development costs and success rates. Companies may be better able to control success rates throughout the development process with advances that allow personalised/stratified medicine. For example, the development and use of biomarkers and companion diagnostics can help determine which patients are most likely to benefit from a specific treatment. Eventually, genomics may provide a far better understanding of how the human body works at the molecular level. The use of molecular diagnostics, for example, could accelerate the R&D process for treatments when a biomarker or other genetic characteristic allowing for patient stratification is ascertained at an early stage of treatment development (Garau et al, 2012). Although genomic-based approaches initially may increase development times and costs, in the long run "individualised medicine" could decrease out-of-pocket development costs and development times while increasing success rates.

Personalised medicine might reduce Phase II and Phase III attrition rates in two key ways. First, target selection may improve; as discussed earlier, validated targets have higher success rates than more novel targets. Patient stratification in oncology clinical trials, for example, could reduce attrition rates particularly in Phases II–III (Walker and Newell, 2009). Second, personalised medicine allows routine pursuit of early proof of concept (POC) studies, especially in Phase I, for which biomarkers and surrogate endpoints often can be employed.

Increased efficiencies also can be achieved via improvements in science, such as combinatorial chemistry, high-throughput screening (HTS) and genomics, thus reducing attrition.

Alliances and networks are another development that may positively affect success rates in the longer term. As noted above, greater collaboration across the various R&D stages is occurring between and within industry, academia, regulators, governments and health care providers. Public and private medical research is increasingly synergistic and complementary (HERG, OHE and RAND, 2008, and Mestre-Ferrandiz and Sussex, 2009). Partnering and collaborative ventures allow all stakeholders, whether publicly- or privately-funded, to access disease knowledge communities. Some observers also argue that the move to a more virtual R&D process with significant outsourcing can maximise flexibility and better manage development risk. These trends have the potential to improve success rates in the medium term as companies benefit from synergies; it may create some delays in the short term, however, as companies learn how to collaborate effectively.

Finally, as the evidence in Section 5 suggests, licensing-in can reduce attrition rates, even at early stages of the R&D process. Boschwitz et al (2005) note that the value of early-stage deals is rising as late-stage deal costs seem to have stabilised. This fits with the observed trend for alliances and deals to occur earlier because of rising and more intense competition among pharmaceutical companies to fill pipelines at later stages of development. (See, e.g. Mudhar, 2006; van Brunt, 2005; and Aghazadeh et al, 2005). In contrast to the assertions of Boschwitz et al (2005), however, increasing competition appears to be inflating the price of later-stage deals, as Gilbert, Henske and Singh (2003) suggest. Danzon, Nicholson and Pereira (2005) analyse productivity in pharmaceutical and biotech R&D and show that alliances take place in all phases—I, II and III. This study does not provide evidence on the proportion of deals per phase, however, or suggest whether that has changed over time. While pharmaceutical companies are increasingly looking for licensing-in deals, it is uncertain whether the number of smaller firms willing to license-out to pharmaceutical companies is increasing, decreasing or remains unchanged.

Drivers of Development Times

Several factors affecting development times have been identified. First, regulators appear to be more risk averse, increasing the stringency of regulation and regulatory review. However, regulators do continue to attempt to address this issue, in some cases with very forward-looking initiatives. In the US, for example, the FDA launched its Critical Path Initiative (CPI) in 2004, to "drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured" (FDA, 2011, np.). In 2006, the FDA released its Critical Path Opportunities List of 76 tangible examples where new scientific discoveries—in fields like genomics, imaging, and informatics—could be applied during development to improve the accuracy of tests that predict the safety and efficacy of potential medical products (FDA, 2011).

In Europe, the EMA in 2011 launched its Road Map to 2015, which describes three priority areas for the Agency's work, one of them under the heading "facilitating access to medicines" (EMA, 2011a). This includes "stimulating the development of medicines for areas of unmet medical need, neglected diseases and rare diseases, and for all types of medicines for veterinary use" and "facilitating new approaches to medicine development" (EMA, 2011a, page 5). This reflects EMA's recognition of the importance of further developing the regulatory framework for new and emerging science, in particular with respect to benefit/risk evaluation, potential safety issues, and ethical and environmental considerations. EMA also intends to continue to review

the model for regulation of medicines in the EU, particularly with regard to the development of medicines and the benefit/risk balance.

Second, changing therapeutic targets also are affecting development times. As Kaitin and DiMasi (2011) show, companies are increasingly directing efforts towards areas that are intrinsically associated with very long clinical development times, such as CNS and antineoplastic drugs. This, in turn, is driven by markets, where only the truly novel new drug is likely to be treated favourably in pricing and reimbursement regimes.

Third, in terms of the duration of clinical trials, more complex clinical trial protocols are demanding more of both investigators and study volunteers. This has led not only to clinical trials of longer duration, but also to increased difficulty in recruiting and retaining patients (CSDD, 2008).

Emerging new technologies may spark a countertrend that eventually could shorten development times. As noted above, pharmacogenomics, including the use of biomarkers, has the potential to reduce development times by allowing far more accurate identification of patients with a high response rate and/or a low probability of an adverse drug reaction.

Indeed, in several cases drugs already have been developed with companion diagnostics that identify which patients are likely to benefit most (see Garau et al, 2012, for examples). This trend, however, poses many new challenges. For instance, if a diagnostic is co-developed with the drug, then Phase II studies need to be designed to evaluate the candidate assays available, to select one, and then to perform analytic validation of the assay before launching the Phase III trial. Even if such R&D challenges are overcome, commercial challenges remain. For example, if this co-development initiative involves more than one company, pricing and reimbursement agencies will need to determine how to split the reward between the drug and the companion diagnostic. This already is raising serious issues as some payers are refusing to cover the diagnostic.

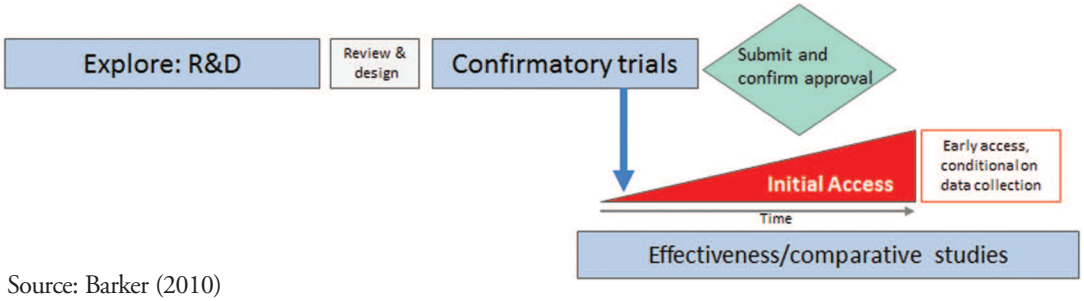
As discussed above, one recurrent theme in the past was that companies had not been using Phase II trials "rationally" and many projects taken into Phase III subsequently failed. As mentioned earlier, duration of Phase II trials has increased over time; perhaps this in part is because companies are being more diligent in their Phase II trials and using those results to making tougher decisions about whether to continue projects. Given the mixed evidence about the evolution of Phase III success rates, it is difficult to ascertain whether this is the case.

A New Drug Development Paradigm?

A key issue that dominates policy discussions around drug development is whether the current model (see Figure 2.1, above) is affordable. The preceding chapters have made clear the evidence that supports the contention that the cost of a successful new medicine has increased over the last decades. A number of options have been identified that change the current drug development paradigm to increase the productivity of R&D and reduce drug development costs. We now comment on two of these options, suggested by Barker (2010) and by Paul et al (2011). Barker's (2010) two main concerns regarding the current drug development paradigm are that (1) the model is too inflexible in process, timing and methods and (2) alignment and partnership

between stakeholders and innovators is lacking. He proposes a flexible blueprint for drug development, represented in Figure 8.1.

Figure 8.1. Proposed flexible blueprint



Source: Barker (2010)

Barker's approach relies on five key features.

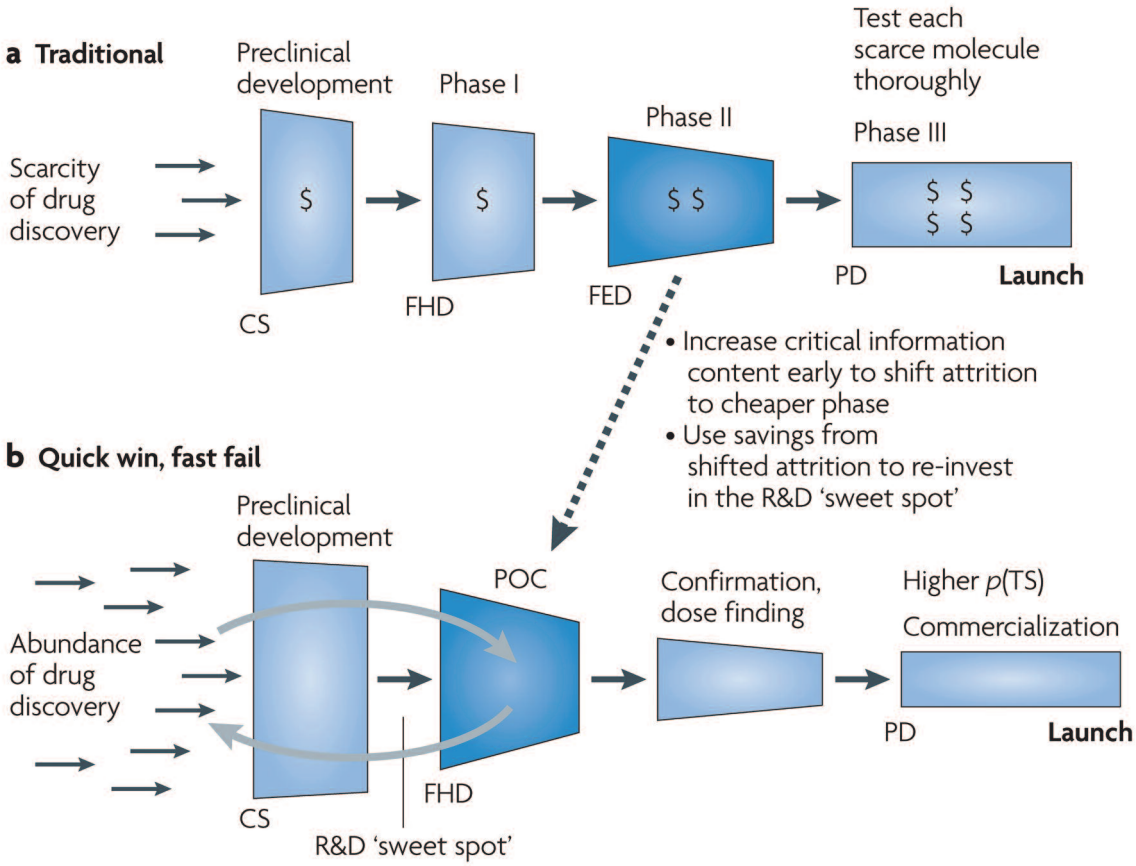
1. Division into two stages, exploratory and confirmatory trials, rather than Phases I-IV
2. A collaborative design step before the most expensive confirmatory trials are commissioned
3. Ability/need to customise the model for different benefit-risk/uncertainty profiles
4. Ability to allow early, controlled patient access to the medicine if justified by interim findings of confirmatory trials
5. Subject the drug to requirements for pharmacovigilance and pharmacoeconomic analysis before the full "green light" for wide access and long term reimbursement is granted

Collaboration among companies on trials and early research is key in the exploration stage. Before undertaking the confirmatory trials, which should be flexible in their design and analysis, the "review and design" step builds in collaboration among companies, regulators, HTA agencies and patient groups. The proposed model is designed to deliver the evidence required for both regulatory approval and value assessment.

Paul et al (2010) focus on making R&D efforts more iterative, shortening the R&D process and incorporating feedback loops across the different R&D stages. Figure 8.2 replicates their diagram comparing the more traditional R&D model with what they call the "quick win, fast fail" model. The Paul et al model requires redistribution of R&D investment from later stages to the "R&D sweet spot" which they believe resides prior to Phase II and is where heavy emphasis is placed on having sufficient discovery capacity and capability to assure selection of validated targets. The focus of the R&D sweet spot is the resolution of technical uncertainty early in development. One similarity between the Barker (2010) and Paul et al (2010) approaches is the focus on the earlier phases to reduce technical uncertainties before beginning the more expensive, later-stage trials.

A second similarity between the Barker (2010) and Paul et al (2010) approaches is the emphasis on flexibility during the R&D stages. This also has been termed "adaptive" or "flexible" trial design. The core concept is to use accumulating data to decide on how to modify aspects of the study mid-trial, in a pre-planned manner, and without undermining the validity or integrity of the study. Once results are obtained, companies could adjust the trial's key characteristics, such as sample size, allocation of treatments, addition or deletion of treatment arms, inclusion/exclusion criteria and combining trials or treatment phases.

Figure 8.2. "Quick win, fast fail" model



Notes: POC = proof of concept; p(Ts) = probability of success; CS = candidate selection; FED = first efficacy dose; FHD = first human dose; PD = product description
Source: Paul et al (2010)

SUMMARY AND CONCLUSIONS

Research shows that R&D costs per approved NME have been increasing over time. Although private pharmaceutical R&D spending is increasing in real terms, the number of NMEs approved each year is not. This implies that R&D productivity is falling if we measure "output" as the count of NMEs approved per year. Given the long timelines in drug development, however, focusing on this static relationship can be misleading and is of little use.

We have calculated a new cost estimate using unpublished data from various CMRI surveys. Our new estimate of the R&D cost per NME is US$1.5bn in 2011 prices, within the range of other recent estimates.

Four key variables drive total R&D costs per approved NME: success rates, development times, out-of-pocket costs, and cost of capital.

The evidence suggests that success rates have been falling, especially in Phase II and Phase III, although the evidence is not conclusive.

Development times in total for Phases I, II and III, on the other hand, have remained relatively constant over time, at around 75–79 months. Phase II and Phase III durations are now similar to one another; Phase III used to be considerably longer.

Out-of-pocket development costs appear to have increased in real terms over time. The most recent estimates show that out-of-pocket clinical costs (i.e. for Phases I–III) are now around US$220m in 2011 prices.

The long timescales of pharmaceutical R&D mean that the estimated cost per NME is highly sensitive to the cost of capital applied. The more recent analyses use a real annual cost of capital of 11%, up from 9% used in earlier work.

The evidence provided in this publication also shows important variations around the mean cost per NME for different types of medicines. First, significant differences are evident in the cost of R&D for new medicines across therapeutic areas. The most recent evidence suggests that neurology, respiratory and oncology are the most expensive areas. At the lower cost end are drugs for HIV/AIDS and anti-parasitics. The cost difference across therapeutic areas can be more than twofold.

Second, licensed-in compounds tend to be more successful than self-originated NMEs, both in the pre-clinical and clinical phases, probably due to a "screening effect". However, most of the published work to date that calculates R&D costs focuses on self-originated NMEs, due to a lack of data for licensed/acquired compounds.

Third, the evidence supports the idea that drugs with a more validated target and more objective endpoints are more successful than drugs with more novel mechanisms of action and less clear cut endpoints.

Fourth, although the available evidence is limited, total capitalised costs for biologicals appear to be higher than for other pharmaceuticals.

Mean estimates of R&D costs per successful drug should be treated with caution. While useful to provide an overall picture, cost differences around the mean are important.

The reasons for the increase in R&D costs are multiple. Technological challenges are one set of drivers of cost increases; diseases targeted currently are more complex than diseases targeted decades ago. In addition, as we move towards personalised/stratified medicine, patient recruitment will change as methods for identifying and recruiting the appropriate patient population also change. Some examples already exist of new medicines being developed alongside companion diagnostics that target very specific patient subpopulations; this can increase R&D costs in the short run as companies adapt to this new environment. In the long run, however, this "learning by doing" has the potential to make the R&D process more efficient.

Companies sometimes may advance projects through the R&D process prematurely when more time and resource invested at an earlier stage could prevent an ultimately unsuccessful and more expensive Phase III trial. Companies continue to work to improve the efficiency of R&D decisions by addressing those factors within their control—e.g. closer scrutiny in the early R&D stages, integrating health economics earlier in the process, and moving some trials to less expensive locations and/or using CROs to manage clinical trials. Biopharmaceutical companies also are trying to address the more complex scientific challenges through alliances with other companies and by working in collaboration with a range of stakeholders. This allows both risks and rewards to be shared, rather than being borne by one party alone.

The R&D costs identified in our study are driven by a combination of factors, including changes in technology and decisions taken by companies and regulators. Whether the current drug development paradigm needs revising and—if so, how—is clearly an important policy issue that merits further investigation.

Table A1. List of papers providing quantitative evidence

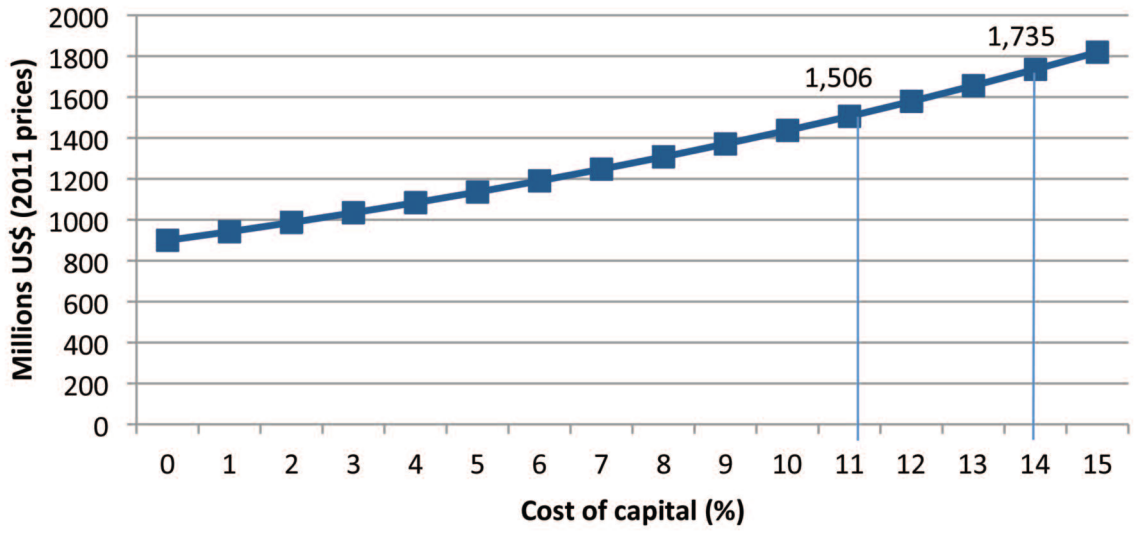
Publication	Mean development costs	Success rates	Development times	Out-of-pocket costs	Therapeutic area	Compound origin	Firm size	Biologicals
Hansen, 1979	X	X	X	X				
Wiggins, 1987	X							
DiMasi et al, 1991	X	X	X	X				
OTA, 1993								
DiMasi et al, 1994								
DiMasi et al, 1995					X		X	
DiMasi, 1995					X	X	X	
DiMasi, 2001					X	X		
DiMasi et al, 2003	X	X	X	X				
Gilbert, Henske and Singh, 2003	X	X	X			X		
Kola and Landis, 2004	X			X				
Abrantes-Metz, Adams and Metz, 2005	X					X		
Adams and Brantner, 2006	X	X	X		X			
Keyhami, Diener-West and Powe, 2006			X					
DiMasi and Grabowski, 2007a					X			
DiMasi and Grabowski, 2007b								X
Phlippen and Vermeersch, 2008						X		
Adams and Brantner, 2010	X		X					
Paul et al, 2010	X	X	X	X				
DiMasi et al, 2010		X				X		

ANNEX 2. SENSITIVITY ANALYSIS

We undertook sensitivity analysis for several of the key parameters that underlie our cost estimates based on the CMRI data: cost of capital, success rates and duration of intervals.

Figure A2.1 shows how total capitalised costs would vary as the cost of capital varies, all other factors remaining constant. As Figure A2.1 illustrates, total cost changes by about US$68m per one percentage point change in the neighbourhood of our base case cost of capital (11%). At a 14% cost of capital, used by Vernon, Golec and DiMasi (2009), the capitalised total cost of a new medicine is US$1.7b in 2011 prices.

Figure A2.1. Capitalised total cost per successful medicine by cost of capital (2011 US$m)



We also estimate the cost of developing a new medicine using the Myers and Howe (1997) staircase approach. These authors imply a cost of capital of 15.1% for discovery, 10.2% for preclinical testing, and 9% for Phase I trials onwards. Using these figures, we calculate that the capitalised cost of a new medicine is US$1.502m (US$1.5b), which is essentially the same as our base case result of US$1,506m.

We now calculate the effect of altering success rates. As explained in Section 4, base case success rates exclude those projects with unknown fate. However, by assuming that either all unknown NMEs will be progressed or terminated, we can obtain "maximum" and "minimum" success rates respectively. Taking this into account, we thus have:

- Maximum success rate = [(NMEs progressed + NMEs of unknown fate) / NMEs entered phase] * 100 and
- Minimum success rate = [NMEs progressed / NMEs entered phase] * 100.

Table A2.1 shows how current success rates compare to these two additional rates.

Table A2.1. Current, maximum and minimum success rates

Interval	Current success rate	Maximum success rate	Minimum success rate
3 — 1st human dose to 1st patient dose	63%	66%	58%
4 — 1st patient dose to 1st pivotal dose	31%	44%	25%
5 — 1st pivotal dose to 1st core submission	63%	71%	49%
6 — 1st core submission to 1st core launch	87%	90%	66%
Overall	7%	**13%**	**3%**

Note: The maximum and minimum success rate for Interval 3, first toxicity dose to first human dose, is the same, 70%.

The overall probability of success under maximum success rates increases from 7% to 13%, while under minimum success rates, the overall probability decreases to 3%.

Using the different success rates, we can calculate a "maximum" and "minimum" cost of a new medicine (Table A2.2).

Table A2.2. Capitalised cost of a successful medicine under current, maximum and minimum success rates (cost of capital = 11%; US$ 2011 prices)

Interval	Current success rate (US$m)	Maximum success rate (US$m)	Minimum success rate (US$m)
2 — 1st toxicity dose to 1st human dose[1]	184.1	106.2	420.2
3 — 1st human dose to 1st patient dose	284.0	163.8	648.3
4 — 1st patient dose to 1st pivotal dose	501.6	303.2	1054.2
5 — 1st pivotal dose to 1st core submission	293.8	252.0	497.9
6 — 1st core submission to 1st core launch	34.9	33.7	46.0
Total	**1,506**	**1,066.2**	**2,874.0**

[1] As noted in Table A2.1, the success rate for the interval "1st tox dose to 1st human dose" is unchanged for "current", "maximum" and "minimum" success rates. However, with maximum and minimum success rates, the number of compounds needed in this interval to achieve one successful compound will be lower and higher, respectively, relative to "current" success rates, so the capitalised cost for this interval will change.

Using our maximum success rates decreases the cost of a new medicine by nearly 30%, while using our minimum rates nearly doubles our base-case estimate.

We now quantify the impact of altering success rates by changing the success rates of each interval. Table A2.3 shows how results change when we change each success rate by one percentage point up and down. For example, the probability of success for the Interval 3 increases from 63% to 64%.

Altering probabilities by one percentage point up and down for each interval decreases and increases the cost of a successful medicine by US$73m and US$80m, respectively. Hence, a higher success rate has a somewhat smaller impact (quantitatively) on total cost than does a correspondingly lower success rate. When success rates increase by one percentage point, the total cost of a new medicine is 4.9% less than our base case result; decreasing success rates by one percentage point yields a total cost 5.3% higher than our base case estimate.

As illustrated in Table A2.3, the biggest difference arises in Interval 4, where the impact is around ±US$29m, while the smallest impact is in the last interval (well below US$1m).

Table A2.3. Capitalised cost of a successful NME altering success rates by ±1% (cost of capital = 11%; 2011 prices)

Interval	"Current" success rate (US$m)	Current plus 1p.p. (US$m	Current minus 1p.p. (US$m)
2— 1st tox dose to 1st human dose	184.1	168.4	201.6
3 — 1st human dose to 1st patient dose	284.0	263.6	306.5
4 — 1st patient dose to 1st pivotal dose	501.6	472.9	532.8
5 — 1st pivotal dose to 1st core submission	293.8	285.9	302.0
6 — 1st core submission to 1st core launch	34.9	34.5	35.3
Total	**1,506**	**1,432.7**	**1,585.6**

Table A2.4 illustrates the effects of altering success rates by ±10%; for example, the success rate for Internal 2 increases from 70% to 77%.

Table A2.4. Effects of altering current success rates by ±10%

Interval	Current success rate	Capitalised cost (US$m)	Current +10%	Capitalised cost (US$m)	Current -10%	Capitalised cost (US$m)
2 — 1st tox dose to 1st human dose	70%	184.1	77%	114.3	63%	311.7
3 — 1st human dose to 1st patient dose	63%	284.0	69%	194.0	57%	432.9
4 — 1st patient dose to 1st pivotal dose	31%	501.6	34%	376.9	28%	688.1
5 — 1st pivotal dose to 1st core submission	63%	293.8	69%	242.8	57%	362.7
6 — 1st core submission to 1st core launch	87%	34.9	6%	1.7	8%	8.8
Total	7%	**1,506**	12%	**1,167.0**	4%	**2,041.5**

When success rates for each individual interval increase by 10%, the total cost of a successful medicine decreases by US$339m to US$1.2b. This implies a 22% reduction in the cost estimate. Alternatively, when success rates decrease by 10%, the impact is higher, given that the difference from our base case cost is US$536m, yielding a total cost of US$2.0b. This is equivalent to a 36% increase. Again, the greatest impact is for Interval 4, closely followed by Interval 3.

Finally, we also carry out sensitivity analysis for cycle times. For this purpose, we alter the time from midpoint of the interval to first core launch by ±10% for each interval. Table A2.5 illustrates the effect of increasing and decreasing cycle times.

Table A2.5. Sensitivity analysis for cycle times (2011 prices)

Interval	Time from interval mid-point to 1st core launch (years)	Capitalised cost (US$m)	Current +10%	Capitalised cost (US$m)	Current -10%	Capitalised cost (US$m)
1 — Pre-first toxicity dose	9.6	207.4	10.5	229.1	8.6	160.6
2 — 1st tox dose to 1st human dose	7.2	184.1	7.9	198.4	6.5	151.8
3 — 1st human dose to 1st patient dose	6.2	284.0	6.8	302.8	5.5	240.9
4 — 1st patient dose to 1st pivotal dose	4.4	501.6	4.8	525.2	4.0	445.8
5 — 1st pivotal dose to 1st core submission	2.1	293.8	2.3	300.3	1.9	277.7
6 — 1st core submission to 1st core launch	0.5	34.9	0.5	35.0	0.4	34.5
Total		**1,506**		**1,590.9**		**1,311.2**

As Table A2.5 shows, if we increase the overall time taken to develop and launch a new medicine by 10% (from 11.5 to 12.7 years), the capitalised cost of a new drug increases by US$85m (6%) to US$1.6b. A decrease of 10% in the overall cycle time has a quantitatively greater impact, given that the capitalised cost decreases by US$195m (13%), from US$1.5b to US$1.3b.

Table A2.6 summarises the effects of altering two key parameters (success rates and interval duration) by 10%.

Table A2.6. Sensitivity analysis: effect on our base case cost estimate per new medicine

	Success rates	Interval duration
Base case +10%	- 22%	+ 6%
Base case -10%	+ 36%	- 13%

GLOSSARY

BLA: Biologics license application. The BLA is a request to the FDA for permission to market a biologic product in the US.

CMRI: CMRI, acquired by Thomson Reuters in 2006, began researching issues in R&D in the early 1980s as the Centre for Medicines Research (CMR). It maintains various databases of drugs/biologics and biopharmaceutical industry activities.

CSDD: The Tufts University Center for the Study of Drug Development has been studying public policy issues surrounding drug development and the biopharmaceutical industries since the mid-1970s. It maintains an extensive database of investigational compounds/biologics.

Discovery: In the discovery phase, researchers select a target, such as a gene or protein, then search for a molecule or compound that may act on the target to alter the disease. The phase also includes early safety and efficacy tests undertaken in computational models, cells and animals. It is sometimes referred to as "pre-clinical testing".

Development costs: Costs associated with Phase I, Phase II and Phase III clinical trials

EMA: European Medicines Agency. The EMA is a decentralised agency of the European Union, located in London. It is responsible for the scientific evaluation of medicines developed by biopharmaceutical companies for use in the European Union.

FDA: Food and Drug Administration. The FDA, part of the US Department of Health and Human Services, is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, and veterinary products.

IND: Investigational new drug. When a company requests permission from the FDA to allow research in humans to begin for a new compound, it submits an IND application. The FDA reviews the application for safety to assure that human research subjects will not be subjected to unreasonable risk. The candidate drug then usually enters a Phase I clinical trial.

Licensed-in drugs: These are compounds that have been licensed or otherwise acquired from outside the company at some point in the development cycle.

NAS: New active substance. An NAS is defined as a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a "prescription only" medicine. See "NME".

NBE: New biological entity. An NBE is a drug that contains no biological substance that has been approved before. See "NME".

NCE: New chemical entity. An NCE is a drug that contains no active molecule that has been approved before. See "NME".

NDA: New drug application. The NDA is the vehicle through which the drug sponsor formally proposes that the FDA approve a new pharmaceutical for sale and marketing in the US.

NME: New molecular entity. Includes both new chemical entities (NCEs) and new biological entities (NBEs). We use this term consistently throughout the paper to minimise confusion and do not use "NCE", "NAS" or "NBE".

Out-of-pocket cost: This is the cash outlay required for the development costs to produce a new drug. It does not include the cost of capital.

Phase I clinical trials: First tests of the candidate medicine in humans. Studies are conducted with about 20 to 100 health volunteers.

Phase II clinical trials: Evaluate the candidate medicine's efficacy in about 100 to 500 patients with the targeted disease.

Phase III clinical trials: Studies of the candidate medicine in about 1,000 to 5,000 patients with the targeted disease to generate data about safety, efficacy and the overall benefit-risk profile of the medicine.

Phase IV, post-marketing, or post-approval studies: Phase IV studies delineate additional information, which may include the treatment's risks, benefits, and optimal use. These studies take place after the drug has been approved/licensed and is available on the market. They are not part of the R&D process and are not included in development cost or time calculations.

Pre-clinical testing: See "Discovery".

Pre-discovery: Basic research within a company focused on a particular disease/disease group that is intended to advance understanding of the disease as a prelude to the discovery phase.

R&D costs: Research and development costs. R&D costs include pre-discovery costs (or basic research), pre-clinical (or discovery) costs, clinical (or development) costs, and costs associated with regulatory review. Pre-discovery and pre-clinical stages are sometimes jointly referred to as "discovery research" (the "R" of "R&D"). Clinical (or "development") costs include Phase I, Phase II and Phase III costs (the "D" of "R&D"). R&D costs do not include Phase IV costs.

Self-originated drugs: These are compounds that have been discovered and developed by a single company, not licensed or otherwise acquired from outside the company.

REFERENCES

Abrantes-Metz, R., Adams, C. and Metz, A. (2005) Pharmaceutical development phases: A duration analysis. *Journal of Pharmaceutical Finance, Economics and Policy.* 14(4), 19-41.

Adams, C. and Brantner, V. (2006) Estimating the cost of new drug development: Is it really $802 million? *Health Affairs.* 25(2), 420-428.

Adams, C. and Brantner, V. (2010) Spending on new drug development. *Health Economics.* 19(2), 130-141.

Aghazadeh, B. et al. (2005) Know the R&D enemy: The key to fighting attrition. *In Vivo.* 23(1), 1-6.

Angell, M. (2004) *The truth about the drug companies. How they deceive us and what to do about it.* New York: Random House.

Animal Research Info. (nd) *Safety & testing.* Available at: http://www.animalresearch.info/en/drug-development/safety-testing/ [Accessed 25 September 2012].

Bailey, W., Cruickshank, C. and Sharma, N. (2009) Make your move: Taking clinical trials to the best location. *Executive Agenda.* Chicago: AT Kearney. Available at: http://www.atkearney.com/health/ideas-insights/article/-/asset_publisher/LCcgOeS4t85g/content/make-your-move/10192 [Accessed 21 September 2012].

Barker, R. (2010) A flexible blueprint for the future of drug development. *Lancet.* 375(9712), 357-359.

Bogue, J.Y. (1965) Research and safety in the development of medicines. *In* Teeling-Smith, G. ed. *Science, industry and the state: Office of Health Economics symposium.* Oxford: Pergamon Press Ltd. 53-70. Available at: http://ohematerials.org/archives/1960s/1965-69/ [Accessed 21 September 2012].

Boschwitz, J. et al. (2005) Making licensing pay. *In Vivo.* 23(5), 43-47.

Brealey, R. and Myers, S. (2000) *Principles of corporate finance.* London: McGraw-Hill.

CEI (Cutting Edge Information). (2006) *Phase 3 clinical trial costs exceed $26,000 per patient.* Press release. 12 October. Available at: http://www.prnewswire.com/news-releases/phase-3-clinical-trial-costs-exceed-26000-per-patient-56447427.html [Accessed 25 September 2012].

Cockburn, I. et al. (2010) *Dissecting the globalization of clinical investigations.* Presentation at OHE lunchtime seminar. 12 May. London: Office of Health Economics.

Cockburn, I. and Henderson, R. (1994) Racing to invest? The dynamics of competition in ethical drug discovery. *Journal of Economics and Management Strategy.* 3(3), 481-519.

CSDD (Tufts Center for the Study of Drug Development). (2008) *Growing complexity of clinical trials increases burden on investigators and volunteers.* Press Release. 15 January. Boston: Tufts Center for the Study of Drug Development.

Danzon, P., Nicholson, S. and Pereira, N. (2005) Productivity in pharmaceutical-biotechnology R&D: The role of experiences and alliances. *Journal of Health Economics.* 24(5), 317-339.

DiMasi, J. (1995a) Commentary: Success rates for new drugs entering clinical testing in the US. *Clinical Pharmacology and Therapeutics.* 58(1), 1-14.

DiMasi, J. (1995b) Trends in drug development costs, times and risks. *Drug Information Journal.* 29, 375-384.

DiMasi, J. (2001) Risks in new drug development: Approval success rates for investigational drugs. *Clinical Pharmacology and Therapeutics.* 69(5), 297-307.

DiMasi, J. (2002) The value of improving the productivity of the drug development process: Faster times and better decisions. *Pharmacoeconomics.* 20(Suppl. 3), 1-10.

DiMasi, J. et al. (1991) Cost of innovation in the pharmaceutical industry. *Journal of Health Economics.* 10(2), 107-152.

DiMasi, J. et al. (1995) R&D Costs for new drugs by therapeutic category. A study of the US pharmaceutical industry. *Pharmacoeconomics.* 7(2), 152-169.

DiMasi, J. et al. (2003) The price of innovation: New estimates of drug development costs. *Journal of Health Economics.* 22(2), 151-185.

DiMasi, J., et al. (2010) Trends in risks associated with new drug development: Success rates for investigational drugs. *Clinical Pharmacology and Therapeutics.* 87(3), 272-277.

DiMasi, J. and Grabowski, H. (2007a) Economics of new oncology drug development. *Journal of Clinical Oncology.* 25(2), 209-216.

DiMasi, J. and Grabowski, H. (2007b) The cost of biopharmaceutical R&D: Is biotech different? *Managerial and Decision Economics.* 28(4-5), 285-291.

DiMasi, J., Caglarcan, E. and Wood-Armany, M. (2001) Emerging role of pharmacoeconomics in the research and development decision-making process. *Pharmacoeconomics.* 19(7), 753-766.

DiMasi, J., Grabowski, H. and Vernon, J. (1995) R&D costs, innovative output and firm size in the pharmaceutical industry. *International Journal of the Economics of Business.* 2(2), 201-219.

DiMasi, J., Grabowski, H. and Vernon, J. (2004) R&D costs and returns by therapeutic category. *Drug Information Journal.* 38(3), 211-223.

DiMasi, J., Hansen, R. and Grabowski, H. (2005a) Reply: Extraordinary claims require extraordinary evidence. *Journal of Health Economics.* 24(5), 1034-1044.

DiMasi, J., Hansen, R. and Grabowski, H. (2005b) Reply: Setting the record straight on setting the record straight. Response to the Light and Warburton rejoinder. *Journal of Health Economics.* 24(5), 1049-1053.

EFPIA (European Federation of Pharmaceutical Industries and Associations). (2010a) *The pharmaceutical industry in figures.* Brussels: European Federation of Pharmaceutical Industries and Associations.

EFPIA (European Federation of Pharmaceutical Industries and Associations). (2010b) *Patients W.A.I.T. Indicator.* Brussels: European Federation of Pharmaceutical Industries and Associations.

EFPIA (European Federation of Pharmaceutical Industries and Associations). (2012) *The pharmaceutical industry in figures.* Brussels: European Federation of Pharmaceutical Industries and Associations.

EMA (European Medicines Agency). (2011a) *Road map to 2015: The Agency's contribution to science, medicines and health.* London: European Medicines Agency.

EMA (European Medicines Agency). (2011b) *Implementing the European Medicines Agency's road map to 2015: The Agency's contribution to science, medicines and health.* London: European Medicines Agency.

Fama, E. and French, K. (1993) Common risk factors in the returns on stocks and bonds. *Journal of Financial Economics.* 33(1), 3-56.

Fama, E. and French, K. (1997) Industry costs of equity. *Journal of Financial Economics.* 43(2), 153-193.

FDA (US Food and Drug Administration, Department of Health and Human Services). (2011) *Science and research: FDA's Critical Path Initiative.* Available at: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm [Accessed 24 September 2012].

Garau, M. et al. (2012) *Can and should value based pricing be applied to molecular diagnostics?* OHE Research Paper 12/03. London: Office of Health Economics.

Garnier, J.P. (2008) Rebuilding the R&D engine in big pharma. *Harvard Business Review.* 86(5), 69-76.

GATB (Global Alliance for TB Drug Development). (2001) *The Economics of TB drug development.* New York: Global Alliance for TB Drug Development.

Gilbert, J., Henske, P. and Singh, A. (2003) Rebuilding big pharma's business model. *In Vivo.* 21(10), 1-10.

Goozner, M. (2004) *The $800 million pill. The truth behind the cost of new drugs.* Berkeley: University of California Press.

Gordian, M. et al. (2006) Why products fail in Phase III. *In Vivo.* 24(4), 49-57.

Hansen, R. (1979) The pharmaceutical development process: Estimates of development costs and times and the effect of proposed regulatory changes. *In* Chien, R.A. ed. *Issues in pharmaceutical economics.* Lexington, MA: D.C. Heath and Company. 151-191.

Henderson, R. and Cockburn, I. (1996) Scale and scope and spillovers: The determinants of research productivity in drug discovery. *RAND Journal of Economics.* 27(1), 32-59.

Henderson, R., Orsenigo, L. and Pisano, G. (1997) The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional and organisational change. *In* Mowery, D. and Nelson, R. eds. *Sources of industrial leadership. Studies of seven countries.* Cambridge: University of Cambridge Press. 267-311.

HERG, OHE and RAND (Health Economics Research Group, Office of Health Economics and RAND Europe). (2008) *Medical research: What's it worth? Estimating the economic benefits from medical research in the UK.* London: UK Evaluation Forum.

Hu, M. et al. (2007) *The innovation gap in pharmaceutical drug discovery & new models for R&D success.* Evanston, IL: Kellogg School of Management. Available at: http://www.kellogg.northwestern.edu/academic/biotech/faculty/articles/NewRDModel.pdf [Accessed 21 September 2012].

IMS. (2004) *World review executive 2002.* London: IMS.

Jayasundara, K., Keystone, E. and Parker, J. (2012) Risk of failure of a clinical drug trial in patients with moderate to severe rheumatoid arthritis. *The Journal of Rheumatology.* 39(11), 1-5.

Kaitin, K. and DiMasi, J. (2011) Pharmaceutical innovation in the 21st Century: New drug approvals in the first decade, 2000-2009. *Clinical Pharmacology and Therapeutics.* 89(2), 183-188.

Keyhami, S., Diener-West, M. and Powe, N. (2006) Are development times for pharmaceuticals increasing or decreasing? *Health Affairs.* 25(2), 461-468.

Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery.* 3(8), 711-715.

Light, D. and Lexchin, J. (2012) Pharmaceutical research and development: What do we get for all that money? *British Medical Journal.* 344, e4348.

Light, D. and Warburton, R. (2005a) Extraordinary claims require extraordinary evidence. *Journal of Health Economics.* 24(5), 1030-1033.

Light, D. and Warburton, R. (2005b) Discussion: Setting the record straight in the reply by DiMasi, Hansen and Grabowski. *Journal of Health Economics.* 24(5), 1045-1048.

Light, D. and Warburton, R. (2011) Demythologizing the high costs of pharmaceutical research. *BioSocieties.* 6(1), 34-50.

Ma, P. and Zemmel, R. (2002) Value of novelty? *Nature Reviews Drug Discovery.* 1(8), 571–572.

Mansell, P. (2007) On the ascendancy. *PharmaTimes.* June.

Mattison, N. (2009) The impact of health technology assessment on drug development: How much does it matter? *OHE Briefing.* (28) London: Office of Health Economics.

Mestre-Ferrandiz, J. and Sussex, J. (2009) *Forward together: Complementarity of public and charitable research with respect to private research spending.* London: Office of Health Economics.

MMV (Medicines for Malaria Venture). (2008) *Ensuring success and targeting eradication: MMV business plan 2008-2012.* Geneva: Medicines for Malaria Venture. Available at: http://www.dfid.gov.uk/r4d/PDF/Outputs/MMV/MMV_2008to12_BP_exec_summary2.pdf [Accessed 21 September 2012].

Mudhar, P. (2006) Key challenges in pharma-biotech alliances and effective management. *Frost and Sullivan Market Access.* Available at: http://www.frost.com/prod/servlet/market-insight-top.pag?docid=68872997 [Accessed 21 September 2012].

Munos, B. (2009) Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery.* 8(12), 959-968.

Myers, S. and Howe, C. (1997) *A life-cycle financial model of pharmaceutical R&D.* POPI working paper 41-97. Cambridge, MA: MIT Sloan School of Management.

NLM (US National Library of Medicines, National Institutes of Health). (2012) *Map of all studies in ClinicalTrials.gov.* Available at: http://clinicaltrials.gov/ct2/search/map [Accessed 31 August 2012].

Osborne, B., Kaul, R. and Parker, J. (2011) Drug development risk in HIV-1 clinical trials: The effect of drug class. *Journal of Pharmaceutical Health Services Research.* 2(4), 211-216.

OTA (Office of Technology Assessment, US Congress). (1993) *Pharmaceutical R&D: Costs, risks and rewards.* Washington, D.C.: US Government Printing Office.

Pammolli, F. and Riccaboni, M. (2000) *Technological competencies in networks of innovators: The case for biopharmaceuticals.* Siena: University of Siena.

Pammolli, F. and Riccaboni, M. (2001) Innovation and markets for technology in the pharmaceutical industry. *In* Kettler, H.E. ed. *Consolidation and competition in the pharmaceutical industry.* London: Office of Health Economics. 48-61.

Pammolli, F., Magazzini, L. and Riccaboni, M. (2011) The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery.* 10(6), 428-438.

Parker, J. and Kohler, C. (2010) The success rate of new drug development in clinical trials: Crohn's Disease. *Journal of Pharmacy and Pharmaceutical Sciences.* 13(2), 191-197.

Parker, J., Zhang, Z. and Buckstein, R. (2011) Clinical trial risk in non-Hodgkin's lymphoma: Endpoint and target selection. *Journal of Pharmacy and Pharmaceutical Sciences.* 14(2), 227-235.

Paul, S.M. et al. (2010) How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery.* 9(3), 203-214.

Phlippen, S. and Vermeersch, A. (2008) *Complementarities and the R&D boundaries of the firm: A project level study on pharmaceutical R&D strategies.* Tinbergen Institute discussion paper. TI2008-022/3. Amsterdam: Tinbergen Institute.

Puig-Peiró, R. et al. (2012) *Reasons for project discontinuation in drug development.* Paper presented at the 9th European Conference on Health Economics. Zurich. July 18-21.

Scannell, J.W. et al. (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery.* 11(3), 191-200.

Shuchman, M. (2007) Commercialising clinical trials: Risks and benefits of the CRO boom. *New England Journal of Medicine.* 357(1), 1365-1368.

Van Brunt, J. (2005) Pharma's buying spree. *Signals.* Available at: http://pharmalicensing.com/articles/disp/1122891227_42edf5db34bfb [Accessed 21 September 2012].

Vernon, J., Golec, J. and DiMasi, J. (2009) Drug development costs when financial risk is measured using the Fama-French three-factor model. *Health Economics Letters.* doi: 10.1002/hec.1538 [Accessed 29 September 2012].

Walker, I. and Newell, H. (2009) Do molecularly targeted agents in oncology have reduced attrition rates? *Nature Reviews Drug Discovery.* 8(1), 15-16.

Wang, T. and McAuslane, N. (2012) *New drug approvals in ICH countries:* 2002–2011. London: Centre for Innovation in Regulatory Science. Available at: http://213.120.141.158/system/files/private/New%20drug%20approvals%20in%20ICH%20countries%2002-11%20for%20release.pdf [Accessed 29 September 2012].

Wiggins, S. (1987) *The cost of developing a new drug.* Washington, D.C.: Pharmaceutical Research and Manufacturers of America.

Wilsdon, T., Attridge, J. and Chambers, G. (2008). *The current state of innovation in the pharmaceutical industry.* London: CRA International.

Young, B. and Surrusco, M. (2001) *Rx R&D myths: The case against the drug industry's R&D "scare card".* Washington, D.C.: Public Citizen.

EXHIBIT I

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED,
Plaintiffs-Appellants

v.

SANDOZ INC.,
Defendant-Appellee

2015-1499

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-04741-RS, Judge Richard Seeborg.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges*.

PER CURIAM.

O R D E R

Appellants Amgen Inc. and Amgen Manufacturing Limited filed a petition for rehearing en banc. A response thereto was invited by the court and filed by Appellee

Sandoz Inc. A petition for rehearing en banc was filed by Sandoz Inc., and a response was invited by the court and filed by appellants Amgen Inc. and Amgen Manufacturing Limited. The petitions for rehearing were first referred to the panel that heard the appeal, and thereafter, to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petitions for panel rehearing are denied.

The petitions for rehearing en banc are denied.

The mandate of the court will issue on October 23, 2015.

FOR THE COURT

October 16, 2015
Date

/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk of Court

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, vs. APOTEX INC. and APOTEX CORP., Defendants.	Case No. 15-cv-61631-JIC/BSS

[PROPOSED] ORDER ON MOTION FOR PRELIMINARY INJUNCTION

THIS CAUSE has come before the Court upon the Motion of Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively "Amgen") for a Preliminary Injunction, DE [ ]. The Court having received and considered the briefs of the parties and their supporting exhibits and testimony, and the Court having received and considered the arguments of counsel at the December 4, 2015 hearing on this motion, and good cause having been shown, it is hereby

ORDERED AND ADJUDGED that the Motion for a Preliminary Injunction, DE [ ], be and the same is **GRANTED**. Defendants Apotex Inc. and Apotex Corp. (collectively "Apotex") "may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen, Inc.* v. *Sandoz, Inc.*,794 F.3d 1347 (Fed. Cir. 2015). Accordingly, if the FDA approves Apotex's Biologics License Application ("aBLA") for its pegfilgrastim product, Apotex may then provide Amgen with at least 180 days' notice before the date of the first commercial marketing of the biological product approved by the FDA. 42 U.S.C. § 262(*l*)(8)(A). Apotex and those acting in concert with it are enjoined from any commercial marketing of its biosimilar pegfilgrastim product, including selling that product or offering it for sale for use in the United States, until Apotex gives Amgen proper notice, at least 180 days

before first commercial marketing but not before its pegrilgrastim biosimilar product is licensed by the FDA, and the 180-day notice period is exhausted.

DONE AND ORDERED at Chambers, Fort Lauderdale, Florida, this __ day of October, 2015.

JAMES I. COHN
United States District Judge

Copies furnished to all counsel of record