No. 2013-1034

UNITED STATES COURT OF APPEALS

FOR THE FEDERAL CIRCUIT

GALDERMA LABORATORIES, L.P., GALDERMA S.A.,
and GALDERMA RESEARCH AND DEVELOPMENT, S.N.C.,

Plaintiffs-Appellees,

v.

TOLMAR, INC.

Defendant-Appellant.

On Appeal from the United States District Court for the District of Delaware
in Case No. 10-CV-0045, Judge Leonard P. Stark

BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF PLAINTIFFS-APPELLEES' PETITION FOR PANEL REHEARING AND REHEARING *EN BANC*

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The names of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

N/A

All parent corporations and any publicly held companies that own 10 percent or more of the stock of the parties represented by me are:

None

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INTERESTS OF *AMICUS CURIAE*

The interests of *amicus curiae* Washington Legal Foundation ("WLF") are set forth more fully in its motion for leave to file this brief. In brief, WLF is a non-profit public interest law firm that regularly appears before federal and state courts to promote economic liberty, free enterprise, and a limited and accountable government.[1] WLF has participated in numerous court proceedings raising important issues relating to the scope and validity of pharmaceutical and medical patents. *See, e.g.*, *Therasense, Inc. v. Becton Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (*en banc*) (opposing expansion of inequitable conduct doctrine).

WLF is concerned that the panel majority's decision in this case singles out improvement patents in the medicinal arts by presuming such patents obvious and shifting the burden to patentees at trial to prove otherwise, contrary to this Court's precedent precluding such burden shifting. WLF is concerned that this decision considerably reduces the incentive for innovators to develop improved medicines, and as a result, patients with disease will have fewer treatment options.

ARGUMENT

The appeal is ripe for rehearing so the full Court can consider the panel majority's newly adopted approach to the determination of obviousness in

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[1] Pursuant to Fed. R. App. P. 29(c)(5), WLF states that no counsel for a party authored this brief in whole or in part; and that no person or entity, other than WLF and its counsel, contributed monetarily to the preparation and submission of this brief.

pharmaceutical and biotechnology patent cases that shifts the burden at trial to the patentee to prove nonobviousness of improvement inventions. This ruling conflicts with statute and long-standing precedent requiring a patent challenger asserting obviousness to prove its case by clear and convincing evidence. The majority's decision establishes a presumption of ***obviousness*** that can only be rebutted by secondary considerations when a claimed invention is encompassed in a broad generic disclosure in the prior art. Under this Court's precedent, all evidence relevant to obviousness and nonobviousness should be reviewed by a court collectively, with the burden remaining on the patent challenger at all times to prove obviousness by clear and convincing evidence. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-80 & n.7 (Fed. Cir. 2012). And with good reason: 35 U.S.C. § 101 specifically allows for patents on "new and useful improvement[s]," and there is no rationale under our patent policy why the obviousness standard should be stricter for such inventions, especially in unpredictable technologies, such as the medicinal arts.

Rehearing is warranted for the additional reason that, by shifting the burden to the patent owner to prove nonobviousness, the panel decision decreases the incentive for innovators of improvement inventions to incur the cost and risk of research and disclose information that would otherwise be kept secret. These breakthroughs in drug dosing and formulation can alter how medications are given

to patients, improve patient compliance with medicinal treatments, and substantially increase efficacy and reduce intolerable side effects. Because these improvement inventions are so important to the advancement of medicine, rehearing is warranted to review the panel's erroneous determination that different patentability criteria should apply to inventions relating to improvements as opposed to those consisting of brand new products.

I. Rehearing Is Warranted Because The Panel Majority Improperly Shifted The Burden Of Proof To The Patentee Regarding Allegations Of Obviousness For Pharmaceutical Improvement Patents

Rehearing of the panel decision is warranted because the panel majority disregarded statute and Supreme Court precedent requiring patent challengers to prove invalidity of any patent – including improvement patents – by clear and convincing evidence. *See* 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). This conflicting precedent is likely to confuse the public, undermine the ability of businesses in the medical sector to fairly assess their intellectual property, and result in more costly and uncertain litigation.

According to the panel's opinion, the patents at issue in this case claim topical compositions for treating acne, formulated with the pharmaceutical compound adapalene in a specific 0.3% concentration. *See* Slip op. at 2-3. As explained by the panel majority, at the time of invention, it was thought that the optimal safe and effective dose for treating acne was ***0.1%*** adapalene – three times

lower than the claimed ***0.3%*** dosage. *See id.* at 5-6, 8, 10. In particular, the prior art suggested that such a several-fold increase of the dose would likely increase side effects such as severe burning and itching. *See id.* at 8, 10; *see also id.* at 10-11 (Newman, J., dissenting). Nonetheless, as explained in the panel's opinion, the clinical data obtained by the inventors unexpectedly demonstrated that the 0.3% adapalene formulation was tolerated as well by acne patients as the 0.1% formulation, while achieving even greater efficacy. *See id.* at 12. As the district court found, this improved 0.3% adapalene treatment has been well-received by patients and physicians, with strong sales even in the face of competition from generic 0.1% adapalene. *See id.* at 14 (Newman, J., dissenting).

In the district court below, Tolmar asserted that the claimed 0.3% adapalene formulations for treatment of acne were obvious in view of the "Shroot" prior art patents. But as the district court explained, the Shroot patents "disclose a general chemical formulation that could result in hundreds, if not thousands of different compounds to treat a broad range of diseases, in different dosage forms, administered in many different ways to the body, across a broad range of concentrations." (A73, ¶ 89; *see also* A82-83, ¶¶ 123-30.) Even the narrowest range in Shroot – 0.01 to 1% – covered a 100-fold range of dosages and included numerous compounds and diseases. (*See id.*) As the district court explained, nothing in Shroot specifically suggested selecting 0.3% adapalene for treatment of

acne out of the broad ranges of concentrations, compounds, and diseases disclosed. (*See* A82-83, ¶ 127.)

In view of this record, the district court found that the accused infringer failed to prove by clear and convincing evidence that the claimed invention of 0.3% adapalene was rendered obvious by Shroot. But in a 2-to-1 split decision on appeal to this Court, the panel majority reversed, taking an unprecedented and unwarranted approach to the law of obviousness. Specifically, the panel majority held that, because elements of the claimed 0.3% adapalene acne treatment could be identified through the broad generic disclosure of Shroot with the benefit of hindsight, the claims were presumptively invalid, and required the patentee to prove otherwise.

In shifting the burden of persuasion on obviousness to the patentee, the panel majority ignored this Court's precedent. *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1075-80 & n.7. While mentioning the accused infringer's burden of persuasion, and purporting to merely shift the "burden of ***production***" to the patentee (*see* Slip op. 6, 9), the majority singled out an entire class of improvement patents by shifting the burden of ***persuasion*** to the patentee. *See* Slip op. 18-19 (Newman, J., dissenting). Contrary to precedent, the majority required the accused infringer to only demonstrate that the claimed invention fell within a broad, generic prior art disclosure. *See id.* The majority then appeared to require the patentee to make a

"rebuttal" case limited to only certain "secondary considerations" of nonobviousness, contrary to this Court's precedent that "a fact finder consider ***all evidence*** relating to obviousness before finding a patent invalid on those grounds . . . ." *See In re Cyclobenzaprine*, 676 F.3d at 1075, 1077-78; *see also* Slip op. at 17, 19 (Newman, J., dissenting).

The panel majority compounded its error by employing an overly narrow interpretation of the secondary considerations of nonobviousness. Even though the prior art disclosed 0.1% adapalene as the optimal concentration and discouraged higher doses that could increase side effects, the panel majority found no "teaching away" because the art did not expressly discuss the claimed 0.3% adapalene formulation. *See* Slip op. at 10-12. But this Court's precedent recognizes that "[t]eaching away does ***not*** require that the prior art foresaw the specific invention that was later made, and warned against taking that path." *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011). The majority also reversed the district court's finding of "unexpected results," even though the 0.3% adapalene formulation unexpectedly deviated from the prior art trend where increased doses were understood to yield increased side effects. *See* Slip op. at 12-13. The majority's decision that this unexpected result is a mere "difference in degree" is unsupported and further illustrates the high burden of proof that the majority required ***the patentee*** to overcome. *See* Slip op. at 16 (Newman, J., dissenting).

The panel majority also improperly shifted the burden of proving validity by misapplying case law regarding prior art ranges. To the extent this Court has stated that a claimed range might be *prima facie* obvious when it falls within a narrow prior art range, that analysis does not pertain to prior art that, as with Shroot, "encompass[es] a very large number of possible distinct compositions." *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). In any event, it is doubtful that a burden-shifting inquiry based on *prima facie* findings of obviousness should ever be used in the litigation context, regarding prior art ranges or otherwise. *See In re Cyclobenzaprine*, 676 F.3d at 1079-80 & n.7; Slip op. at 18-19 (Newman, J., dissenting).

Contrary to the view of the panel majority, the value of patented improvements is assessed by the market and clinical demand. For example, in the present case, there is no dispute that Galderma's DIFFERIN® 0.3% adapalene gel sells well in view of the availability of generic 0.1% adapalene. Indeed, the district court found that the availability of the cheaper generic 0.1% adapalene after expiration of the patents covering that product did not appear to have affected consumer demand for the DIFFERIN® 0.3% product. *See* Slip op. at 14 (Newman, J., dissenting). From the viewpoint of the market of physicians and patients, the innovative 0.3% adapalene formulation patented by Galderma meets a clear

clinical need – one that might not have been met without the promise of a patent for Galderma's innovation.

Finally, the panel majority gave too much deference to the accused infringer's characterization of the facts, which contradicted the district court's findings of facts and evaluation of expert testimony. *See* Slip op. at 1-2, 14-18. In particular, the panel majority improperly overturned the district court's detailed findings without identifying any clear error. *See Celsis In Vitro v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012) (citation omitted) ("Credibility determinations by the trial judge can virtually never be clear error."). The majority's failure to credit the district court's sound factual findings appears to be a further extension of its decision to shift the burden of proving validity to the patentee.

II. Rehearing Is Warranted Because The Panel Majority's Decision Will Discourage Innovation In Developing Pharmaceutical Improvements That Are Critical To The Treatment Of Patients

Rehearing is warranted for the additional reason that, by shifting the burden to the patent owner to prove nonobviousness, the panel's decision decreases the incentive for innovators of improvement inventions to incur the cost and risk of research and disclose information that would otherwise be kept secret. The panel majority's approach effectively treats these improvement inventions in the area of the medicinal arts as being less worthy of patent protection. But these inventions

are important and, to the extent that they are novel and nonobvious, they warrant patent protection.

In some cases, research brings innovation in the form of a first-in-class medicine. But frequently, important advances in medicine occur as innovative improvements to existing medicines. *See* Ex. A (Graul *et al.*, *Drugs of Today* (2013) 49:33-68) at 34 (finding that 42% of worldwide drug launches in 2012 were new formulations, indications, or combinations of existing drugs). In many instances, the inventor of a new drug performs additional research following FDA approval, including new approaches to drug dosing and drug formulation, and new therapeutic indications for existing treatments. *See* Ex. B (Berndt *et al.*, *Pharmacoeconomics* (2006) 24:69-86 (suppl. 2)) at 71. While some of these improvements may appear simple, they can have meaningful therapeutic consequences. For example, these improvements can enhance the therapeutic efficacy and tolerability and safety of existing treatments. Innovations in dosage and formulation can also reduce many of the barriers to taking medication properly, such as complex dosage regimes or undesirable modes of administration, and can expand the number of treatment options available.

If improvement patents are presumed obvious consistent with the panel majority's decision, without regard to whether the claimed invention shows unexpected and counterintuitive results, the incentive will be lessened for

innovators to incur the cost and risk of research and to disclose information that otherwise may be kept secret. *See* Ex. C (Cohen, *Nature Rev. Drug Discovery* (2005) 4:78-84) at 80. As in the present case, without the promise of a *bona fide* patent, companies like Galderma would have less incentive to research and develop improved drug formulations in the face of conventional wisdom that they would not likely meet the desired therapeutic goals. Depriving the incentive for this research means depriving patients and physicians of safer, more effective, and more convenient treatments.

Further, if the panel majority's decision were allowed to stand, it could lead to a scenario where the same prior art disclosure that fails to give a reasonable expectation of success for a particular formulation improvement would also preclude inventors from obtaining a patent on that same improvement. Inventors would be discouraged from pursuing medicinal improvements regardless of the teachings of the prior art. And as Judge Newman recognized, "[t]he losers [would be] those afflicted with disease." Slip op. at 3 (Newman, J., dissenting).

CONCLUSION

WLF requests that the combined petition be granted.

Respectfully submitted,

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February 12, 2014

ADDENDUM OF CITED PUBLICATIONS

Ex. A: Graul *et al.*, *Drugs of Today* (2013) 49:33-68

Ex. B: Bernt *et al.*, *Pharmacoeconomics* (2006) 24:69-86 (suppl. 2)

Ex. C: Cohen, *Nature Rev. Drug Discovery* (2005) 4:78-84

CERTIFICATE OF SERVICE

I hereby certify that on February 12, 2014, I caused copies of the foregoing brief of *amicus curiae* Washington Legal Foundation to be electronically filed with the Clerk of Court using CM/ECF, which will send notification of such filing to all registered participants.

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Exhibit A

Drugs of Today 2013, 49(1): 33-68
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REVIEW

2012 IN REVIEW – PART I: THE YEAR'S NEW DRUGS & BIOLOGICS

A.I. Graul, B. Lupone, E. Cruces and M. Stringer

Thomson Reuters, Barcelona, Spain

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SUMMARY

Thirty-seven new launches are considered in the first part of this annual review article, including 36 drugs and biologics that reached their first markets worldwide in 2012 and one additional drug that was launched at the end of December 2011. In addition, 26 significant new line extensions (new indications, new formulations and new combinations of existing drugs) that were launched for the first time in 2012 are discussed in this review. Also included are new drugs and biologics and new line extensions that were approved for the first time between January and December 2012, although they were not launched before the end of the year.

Key words: New drug launches – New biologics – New approvals – Line extensions

INTRODUCTION

The year 2012 saw the first launch for 36 new drugs and biologics, including several new first-in-class agents, more than a dozen orphan drugs and a number of important new therapeutic advances in the treatment of a range of human diseases and conditions. Significant strides were made in the area of cancer therapy, with 10 completely new anticancer drugs launched for the first time worldwide in 2012 (see Table I). The United States was again the most active market for new drugs, accounting for exactly half of the new launches in 2012, although several important new introductions took place in other parts of the world such as Japan and the E.U., both of which closed the gap with respect to the U.S. as compared to previous years (see Fig. 1).

Although new chemical entities and biologic drugs are the primary focus of this article, attention is also given to major new line extensions (new indications, new formulations and new combinations of previously marketed drugs). These products made a strong showing again last year, with 26 line extensions launched for the first time and included in this review. Information is also included in this article on drugs that were approved but not yet launched during 2012. In this respect, notable advances were made in the field of infectious disease, with the U.S. Food and Drug Administration (FDA) approving two new countermeasures in the war against bioterrorism and granting last-minute approval to the first in a completely new class of antituberculosis drugs.

Table I. *Drugs & biologics introductions by therapeutic category, 2002-2012*

Therapeutics	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Central nervous system	5	3	6	6	1	3	4	7	4	5	2
Respiratory	2	3	0	1	0	2	2	2	1	1	2
Cardiovascular	3	1	0	2	2	2	2	1	1	1	1
Renal-urologic	0	3	2	3	3	1	2	2	0	2	1
Hematologic	1	1	1	1	0	2	6	3	1	3	2
Gastrointestinal	2	0	0	1	2	1	3	1	1	0	1
Endocrine drugs	0	1	2	3	3	2	0	3	2	1	4
Dermatologic	2	2	0	0	0	0	2	1	0	1	2
Anti-infective	5	5	1	6	2	5	3	1	2	6	0
Antiarthritic	2	1	0	0	1	0	1	3	0	1	2
Immunologic	0	2	2	6	9	4	3	17	5	4	5
Cancer	5	3	7	6	7	5	1	6	7	7	10
Ophthalmic	0	0	0	2	2	0	1	1	1	2	0
Metabolic drugs	5	4	2	1	7	2	2	3	4	2	2
Poisoning & drug abuse	1	0	0	1	1	0	0	0	0	0	1
Dental	0	0	0	1	0	0	0	0	0	0	0
Diagnostic agents	2	0	3	2	1	1	1	0	0	0	1
Total	35	29	26	42	41	30	33	51	29	36	36

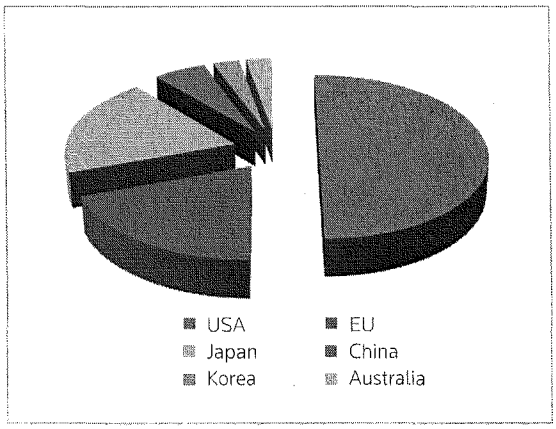

Figure 1. Distribution of new launches in 2012 by country.

The information in this review and the accompanying tables was compiled from company communications, *Thomson Reuters Drug News* and *Thomson Reuters Integrity*℠, the latter a unique drug discovery database incorporating biological, chemical and pharmacological data on more than 390,000 active compounds and more than 210,000 patent family records, as well as comprehensive information on targets and pathways, experimental pharmacology, pharmacokinetics and animal model assays and results; biomarkers; drug synthesis; and more.

AGENTS FOR ANALGESIA & ANESTHESIA

Gabapentin enacarbil (Horizant®), a prodrug of the antiepileptic agent gabapentin, was approved and launched last year in the U.S. for the treatment of postherpetic neuralgia in adults. This is a new indication for the product, which was first launched in 2011 for the treatment of restless legs syndrome. Gabapentin enacarbil was discovered by XenoPort and licensed to GlaxoSmithKline (GSK) for codevelopment. The prodrug uses the body's nutrient transport mechanisms that are believed to facilitate its absorption in the body. Once absorbed, it is converted into gabapentin, which binds to a specific type of voltage-gated calcium channel but does not exhibit affinity for other receptors. The exact mechanism of action of the compound in treating postherpetic neuralgia is unknown.

The opioid analgesic **tapentadol** (Nucynta® ER; Janssen) was approved and launched last year in the U.S. for a new indication: the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults requiring around-the-clock pain management. Tapentadol is the first and only opioid analgesic approved for this indication. Approximately 60% to 70% of patients with diabetes are believed to have some form of neuropathy, and DPN is the most common neuropathy in this patient population.

Exparel™ (**bupivacaine liposome injectable suspension**), a new analgesic formulation developed by Pacira, was launched for the first time in the U.S. in April 2012. Exparel is formulated as an injectable suspension that can be administered directly into the surgical site to produce postsurgical analgesia. In October the company announced topline results from the first completed IMPROVE study in its prospective phase IV clinical program. The study was designed to compare the difference in three primary endpoints—cost, opioid consumption and hospital length of stay (LOS)—between one group of patients receiving a standard opioid-based postsurgical pain management regimen and a second group of patients receiving Exparel as the foundation of an opioid-sparing multimodal regimen. The Exparel-based multimodal regimen achieved a statistically significant reduction in each primary endpoint, including a 60% reduction in LOS in patients undergoing open colectomy.

Mercury Pharma's Bufyl®, a fixed-dose combination anesthetic agent incorporating **bupivacaine hydrochloride and fentanyl citrate**, was launched for the first time in January 2012 in the U.K. It is indicated for maintenance of anesthesia postoperatively and for the maintenance of epidural anesthesia during labor.

PSYCHOPHARMACOLOGICAL DRUGS

In December 2012, the FDA approved Adasuve®, a new formulation of the atypical antipsychotic **loxapine succinate** incorporating Alexza's proprietary Staccato® delivery system. The Staccato® system is a hand-held inhaler that delivers a drug aerosol to the deep lung, resulting in rapid systemic delivery and absorption of the active agent. Adasuve is the first noninjectable treatment option for the acute management of agitation in patients with schizophrenia and bipolar I disorder. In clinical studies involving more than 1,600 patients, symptoms of agitation began to abate significantly within 10 minutes of administration of Adasuve. The product will be launched in 2013.

NEUROLOGIC DRUGS

α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors are pivotal mediators in seizure

propagation and may also be involved in seizure-related brain damage (Fig. 2). During 2012, the first selective, noncompetitive AMPA receptor antagonist was approved for the treatment of epilepsy: Eisai's **perampanel** (Fycompa®), indicated for the adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures, in patients with epilepsy aged 12 years and older. Perampanel was approved by the European Commission in July and by the FDA in October, and was launched in the U.K., its first market, in September 2012.

The dihydroorotate dehydrogenase inhibitor and immunomodulating agent **teriflunomide** (Aubagio®; Genzyme) was approved and launched last year in the U.S. for the treatment of patients with relapsing forms of multiple sclerosis (MS). Teriflunomide, an immunomodulator with anti-inflammatory properties, is the first and only oral MS therapy that has been shown in clinical trials to slow the progression of disability. Although the exact mechanism of action for teriflunomide in MS is not fully understood, it may involve a reduction in the number of activated lymphocytes in the central nervous

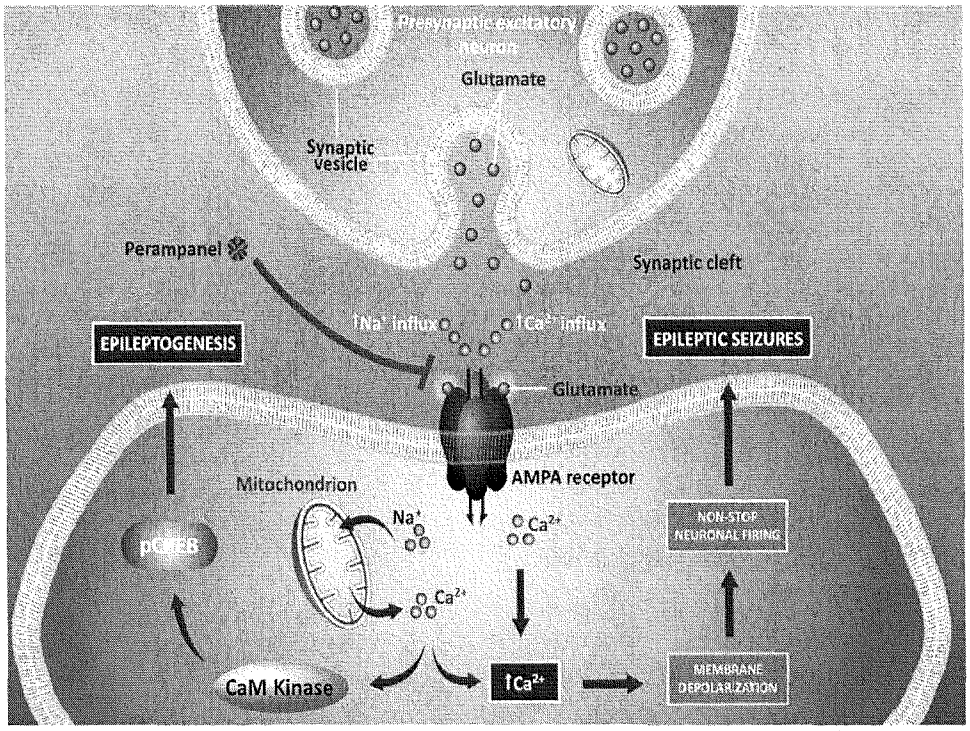

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Figure 2. AMPA receptor antagonism. Perampanel is a highly selective, noncompetitive antagonist of AMPA receptors, a class of ionotropic glutamate receptors that are involved in neurotransmission and synaptic transmission. When glutamate binds to these receptors, the channel opens up for the influx of cations such as calcium and sodium. Excessive activation of AMPA receptors by glutamate results in elevated levels of calcium entering into the brain via the excitatory postsynaptic potential (EPSP). This causes membrane depolarization and a non-stop action potential, ultimately leading to epileptic seizures. Perampanel suppresses AMPA receptor-mediated excitatory postsynaptic field potentials, i.e., the heightened activation of postsynaptic AMPA receptors sometimes referred to as the paroxysmal depolarization shift (PDS). By binding to a noncompetitive site, and therefore inhibiting AMPA receptor activation without blocking glutamate binding, perampanel redresses the excitatory-inhibitory nerve imbalance that results in neuron damage and causes seizures.

system. The efficacy of the drug was demonstrated in the TOWER study, a randomized, double-blind phase III trial that enrolled 1,169 patients with relapsing MS across 26 countries and compared 7 mg or 14 mg once-daily, oral teriflunomide with placebo. Among patients treated with the higher dose of the immunomodulator, the annual relapse rate decreased by 36%; a 22% decrease was reported for the lower drug dose. Fifty-two percent of patients on high-dose and 55% of those on low-dose teriflunomide were relapse-free during the study period, as compared to 38% of those given placebo.

In November 2011, the European Commission approved the transthyretin amyloid inhibitor **tafamidis meglumine** (Vyndaqel®) for the treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in adult patients with stage 1 polyneuropathy. Tafamidis is the first and only agent approved to treat this rare disorder, in which mutations in the transthyretin (*TTR*) gene lead to the production of unstable TTR proteins, which can accumulate as amyloid fibrils (Fig. 3). These fibrils deposit in the nerves, kidneys and heart, causing neurodegeneration and interfering with normal function. The disease is ultimately fatal. Acting as a TTR stabilizer, tafamidis was shown in clinical trials to delay peripheral neurologic impairment in both large and small fibers, and to improve nutritional status as compared to placebo. The drug has orphan drug status for this indication in

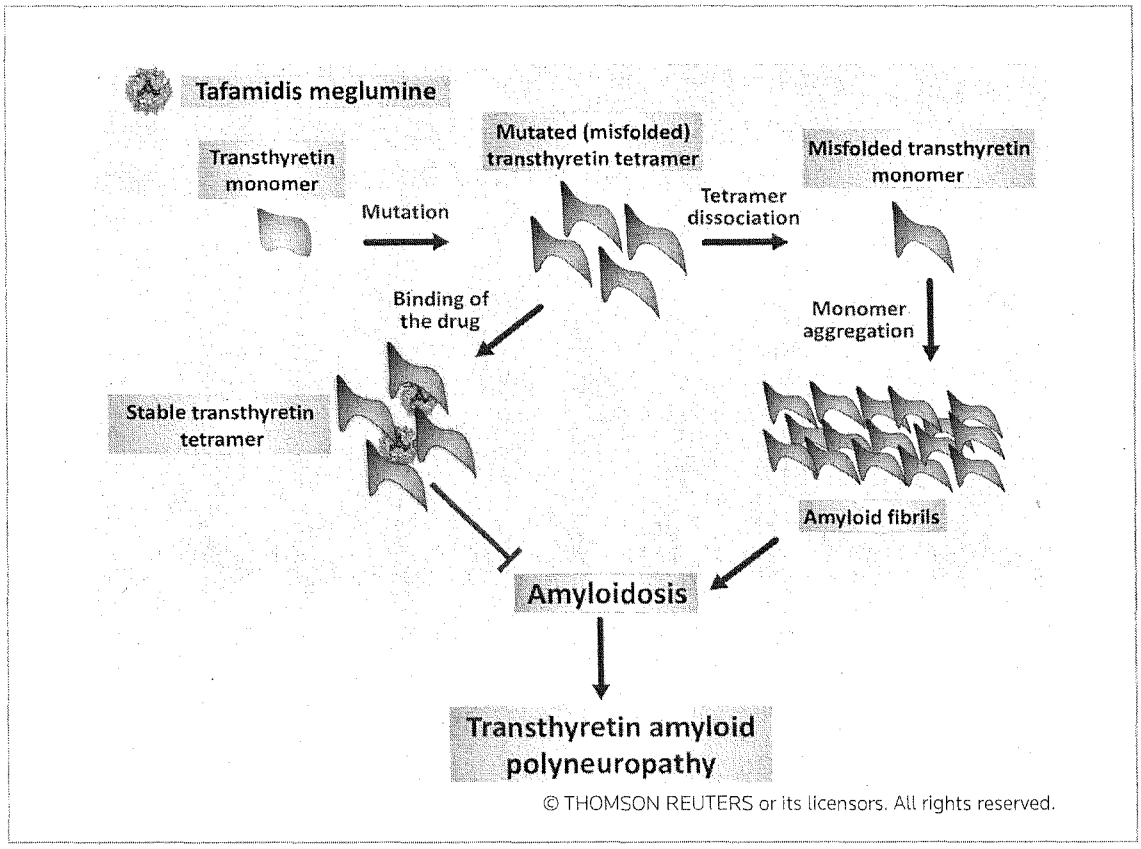

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Figure 3. Transthyretin amyloid inhibition. Tafamidis meglumine is a transthyretin amyloid inhibitor indicated for use in the therapeutic intervention of transthyretin amyloid polyneuropathy (ATTR-PN) and transthyretin familial amyloid polyneuropathy (TTR-FAP). Denaturation stress or single amino acid mutations in transthyretin can cause misfolding of the protein and dissociation of the transthyretin tetramer complex. The resulting protein monomers or dimers can form protein aggregates or amyloid fibrils in the brain, leading to neurodegeneration. Tafamidis blocks the formation of amyloid deposits by binding to and stabilizing the transthyretin tetramer, thereby preventing misfolding and dissociation.

the E.U. and U.S. Pfizer launched the product in Germany in December 2011, after the close of last year's edition of this article.

RESPIRATORY DRUGS

Meda's Dymista™, a fixed-dose combination product incorporating the histamine H_1 receptor antagonist **azelastine hydrochloride and fluticasone propionate**, a corticosteroid, in a metered-dose spray formulation, was approved by the FDA last May. The product is indicated for the relief of symptoms of seasonal allergic rhinitis in patients aged 12 years and older who require treatment with both components for effective symptom relief. Dymista was launched in the U.S., its first market, in September 2012.

The anticholinergic agent **aclidinium bromide**, a long-acting muscarinic M_3 receptor antagonist developed by Almirall, was approved last July in the U.S. and the E.U., and was launched for the first time in Denmark in September. Aclidinium bromide is indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema. Almirall has signed marketing agreements with Menarini in Europe and with Forest Laboratories in the U.S. Menarini will have joint commercialization rights across the majority of E.U. member states (excluding the U.K., The Netherlands and Nordic countries, where Almirall retains sole marketing rights for the product) as well as Russia, Turkey and other CIS countries under the brand name Bretaris® Genuair®; Almirall will market the product in Europe under the brand name Eklira® Genuair®. The product is known as Tudorza™ Pressair™ in the U.S., where it was launched in December.

In September, the Japanese Ministry of Health, Labour and Welfare approved another anticholinergic agent, **glycopyrronium bromide** (Seebri® Breezhaler®), as a once-daily inhaled maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. This was the first approval worldwide for the new indication for glycopyrronium, which was developed by Novartis under license from Sosei and Vectura. Approval was based on data from three phase III trials enrolling nearly 2,000 patients with COPD from around the world. The trial GLOW1 demonstrated the clinically significant superiority of glycopyrronium bromide versus placebo on lung function improvements at 12 weeks measured by trough FEV_1. GLOW2 demonstrated a similar magnitude of effect and also showed that glycopyrronium was similar to open-label tiotropium over 52 weeks measured by improvements in trough FEV_1 compared to placebo. The GLOW3 study showed that following a morning dose of Seebri Breezhaler, patients experienced significant improvements in exercise tolerance from the first dose onward. Overall, patients treated with the product experienced a 21% improvement in exercise endurance versus placebo at the end of the study (day 21), with a 10% increase from day 1. Additional marketing approvals were obtained in October in the E.U. and Canada, and the product was launched in Japan in November. Glycopyrronium bromide has been available since the 1960s as an anesthetic and antiulcer agent.

The cystic fibrosis transmembrane conductance regulator (CFTR) protein is embedded in the membranes of several cell types in the body and plays a pivotal role in the pathogenesis of cystic fibrosis (CF). CFTR levels are highest in the epithelial cells lining the internal surfaces of the pancreas, sweat glands, salivary glands, intestines and reproductive organs, as well as in the submucosal glands of the airways — precisely the organs and tissues that are most affected in patients with CF. The most straightforward role of the CFTR involves its function as a chloride channel, regulating the flow of chloride ions in both directions. In addition to serving as a chloride channel itself, CFTR also acts as a channel regulator, influencing the function of other chloride channels and of sodium channels located nearby on the cell (Fig. 4). In patients with a defective *CFTR* gene, the deletion of a single amino acid (also known as a stop codon or premature termination codon) along a chain of 1,480 of them occurs at a critical juncture in the twisting, turning protein. As a result, instead of folding into an orderly, spiral shape, the molecule unwinds, unravels or otherwise comes undone, a process termed "misfolding". This misfolding leads to CF pathology, and constitutes an important target for corrective therapies. **Ivacaftor** (Kalydeco™; Vertex), the first drug designed specifically to target the defective CFTR protein, was approved by the FDA in early 2012 for the treatment of CF in patients ages 6 years and older who have the specific G551D mutation in the *CFTR* gene. The efficacy of the agent was demonstrated in two 48-week, placebo-controlled clinical trials involving 213 patients with this mutation. In both studies, treatment with ivacaftor resulted in significant and sustained improvements in lung function. Ivacaftor was launched in the U.S., where it has orphan drug status, in February 2012.

In March 2012, the U.S. FDA approved Discovery Laboratories' synthetic, peptide-containing surfactant

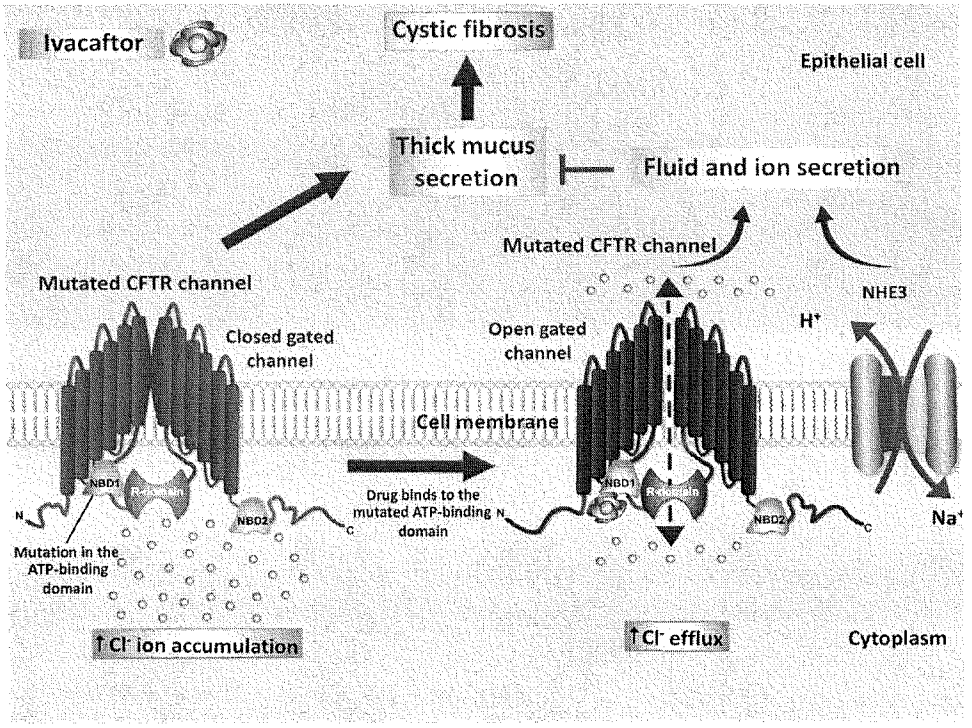

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Figure 4. Cystic fibrosis transmembrane conductance regulator (CFTR) channel activation. Ivacaftor is a small molecule CFTR chloride channel potentiator and a potent oral treatment option for cystic fibrosis resulting from a specific mutation (G551D) in the *CFTR* gene. The mutation prevents chloride ion transport from taking place via the channel following translocation of the CFTR to the epithelial cell surface. This leads to the build-up of mucus on the cell surface, which may result in cystic fibrosis and secondary respiratory tract infections. Binding of the drug directly to the CFTR channel opens the channel, thus facilitating chloride ion transport and regulating fluid secretion. Ivacaftor is believed to open the CFTR channel via an ATP-independent mechanism.

agent **lucinactant** (Surfaxin®), indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS. Lucinactant is the first FDA-approved synthetic surfactant; until now, all available surfactants have been animal-derived. The safety and efficacy of lucinactant have been demonstrated in a large phase III clinical trial program involving nearly 1,300 patients. Discovery Laboratories plans to launch the product during the second quarter of 2013.

CARDIOVASCULAR DRUGS

Angiotensin II blockers (ARBs) are well established in the treatment of arterial hypertension. The tremendous number of clinical studies conducted on ARBs to date and their wide use over the nearly two decades since the first drug in this class —losartan potassium— reached the market, has confirmed their tolerability and efficacy in terms of improving survival, prognosis and quality of life for patients with arterial hypertension as well as other cardiovascular diseases. Last year saw the approval and launch of a new antihypertensive ARB, Takeda's **azilsartan** (Azilva®), in Japan. This brings the total number of drugs in this class to nine, including the azilsartan prodrug Edarbi™ (azilsartan medoxomil potassium), which was approved and launched in the U.S. in 2011.

Edarbyclor™, a fixed-dose combination product incorporating **azilsartan medoxomil potassium and chlorthalidone**, a diuretic, was also launched in the U.S. last year by Takeda. The combination product is indicated for the treatment of hypertension in adults, and can be used as initial therapy if a patient is likely to need multiple drugs in order to achieve blood pressure targets.

Another antihypertensive drug combination was also approved last year in Japan: Dainippon Sumitomo Pharma's Aimix®, which delivers a fixed dose of the ARB **irbesartan and amlodipine besilate**, a calcium channel blocker. Aimix was approved in September by the Japanese Ministry of Health, Labour and Welfare for the second-line treatment of essential hypertension in patients whose high blood pressure is uncontrolled by usual doses of irbesartan or amlodipine besilate alone, and was launched in December.

In April 2012, AstraZeneca launched Dutoprol™ (**metoprolol succinate extended release/hydrochlorothiazide**) tablets in the U.S. It is the first once-daily combination antihypertensive product containing the active ingredient of Toprol-XL® (metoprolol succinate) plus a low-dose diuretic that provides proven blood pressure lowering for 24 hours. The company is using a direct-to-patient sales program for the product.

During the first quarter of 2012, the European Medicines Agency (EMA) granted marketing authorization of a new indication for Servier's **ivabradine hydrochloride** (Procoralan®), a selective and specific I_f inhibitor. Ivabradine was approved for the treatment of chronic heart failure (NYHA II to IV) with systolic dysfunction, in patients with sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including β-blocker therapy or when β-blocker therapy is contraindicated or not tolerated. Ivabradine is a pure heart rate-lowering agent that acts by selective inhibition of the cardiac pacemaker I_f current, which controls spontaneous diastolic depolarization in the sinus node and regulates heart rate. It has been approved in the E.U. since 2005 for the treatment of angina pectoris. It was launched for the new indication in the U.K. in April 2012.

RENAL-UROLOGIC DRUGS

The year 2012 also saw the approval and launch of **bixalomer**, a non-absorbed, metal-free polymer compound indicated for the treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis. In patients with reduced renal function, phosphorus is not sufficiently excreted in the urine and accumulates in the body, resulting in bone pain, increased risk of bone fracture, increased coronary artery calcification and subsequent cardiovascular events. Bixalomer binds phosphorus in the gastrointestinal tract, allowing for excretion of phosphorus and thereby ameliorating hyperphosphatemia. The phosphate-binding compound was discovered at Amgen and licensed to Astellas for development and marketing in Japan, where it is now available under the trade name Kiklin®. The product is being copromoted by Sanwa Kagaku.

HEMATOLOGIC AGENTS

Anemia is another major complication in patients with chronic kidney disease, as the damaged kidney is unable to produce enough erythropoietin. Peginesatide (formerly known as Hematide™) is a synthetic, peptide-based erythropoiesis-stimulating agent (ESA) linked to polyethylene glycol (PEG), which increases peptide solubility and stability, prolongs its half-life and decreases its immunogenicity. **Peginesatide** (Omontys®) was approved and launched last year in the U.S. as a once-monthly treatment for anemia due to chronic kidney disease in adult patients on dialysis. The product was discovered by Affymax, and was licensed to Takeda for codevelopment and comarketing. A regulatory application for peginesatide is also under review in the E.U.

Congenital factor XIII deficiency is a rare bleeding disorder with potentially life-threatening consequences, including bleeding in the central nervous system, if not treated. Factor XIII is the protein responsible for stabilizing the formation of a blood clot. In the absence of factor XIII, a clot will still develop but will remain unstable. The incidence of factor XIII deficiency is estimated at one in 1-3 million births, and affects men and women equally. It is estimated that about 300 patients in Europe and approximately 900 globally are diagnosed with the disease. In September 2012, the European Commission granted marketing approval for Novo Nordisk's **catridecacog** (NovoThirteen®), an orphan drug and the first treatment option for patients with congenital factor XIII-A subunit deficiency. Catridecacog is a genetically engineered pro-enzyme dimer that is identical in structure and function to the human FXIII-A subunit. Administered as prophylactic therapy to patients with the disorder, it restores normal clot solubility and increases clot strength and resistance. Catridecacog was launched in Denmark, its first market, in mid-December. Applications are also under review in the U.S., Canada and Switzerland.

ENDOCRINE DRUGS

The complex regulatory enzyme dipeptidyl peptidase 4 (DPP IV) plays a catalytic role in the processes of signal transduction during immune response leading to type 2 diabetes, and is currently one of the more actively pursued targets in diabetes therapy. A new addition to the DPP IV inhibitor class, **teneligliptin hydrobromide hydrate** (Tenelia®; Mitsubishi Tanabe Pharma), was approved and launched in Japan during the summer of 2012. Another DPP IV inhibitor was also approved and launched later in the year in Japan: **anagliptin** (Suiny®; Sanwa/Kowa), bringing the total of marketed DPP IV inhibitors to seven.

In January 2012, Boehringer Ingelheim and Eli Lilly received FDA approval for Jentadueto™ (**linagliptin/metformin hydrochloride**), a new treatment that combines the DPP IV inhibitor linagliptin, and metformin in a single tablet, taken twice daily, to lower blood sugar in adults with type 2 diabetes. Jentadueto is to be used along with diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate. Jentadueto was launched in the U.S., its first market, in March. The product was also approved in the E.U. in July 2012.

The year 2012 also witnessed the approval of the first in a completely new antidiabetic drug class: **dapagliflozin** (Forxiga™), a sodium/glucose cotransporter 2 (SGLT-2) inhibitor indicated for the treatment of type 2 diabetes. SGLT-2 inhibitors are unique in that they work independently of insulin to help remove excess glucose from the body, a unique mode of action not seen in any other currently available treatments for type 2 diabetes (Fig. 5). Dapagliflozin works in the kidney to selectively inhibit SGLT-2, resulting in the removal of excess glucose and its associated calories in the urine, thereby reducing blood sugar levels. In clinical studies, treatment with dapagliflozin was also associated with reductions in weight and blood pressure. The drug was discovered by Bristol-Myers Squibb and was developed in collaboration with AstraZeneca. It was approved by the European Commission in November, with the first national launches taking place before year end.

The basal insulin analogue **insulin degludec** (Tresiba®; Novo Nordisk) was approved in Japan, its first market, in September 2012. Insulin degludec has an ultra-long duration of action that extends beyond 42 hours, with a flat and stable profile. Once-daily insulin degludec has been studied in the large-scale clinical trial program BEGIN, which was designed to examine its impact on glucose control, hypoglycemia and the possibility to flexibly adjust dosing time to suit patient needs. Novo Nordisk expects to launch insulin degludec in Japan as soon as price negotiations have been successfully completed.

Japanese regulatory authorities were also the first to approve the related product Ryzodeg®, a fixed-dose combination incorporating **insulin degludec and insulin aspart**, which received the go-ahead from the Japanese Ministry of Health, Labour and Welfare on Christmas Day. Ryzodeg is a soluble co-formulation of the ultra-long-acting insulin analogue insulin degludec and the rapid-acting insulin analogue insulin aspart (marketed as NovoRapid®) that is indicated for once-daily administration.

In February 2012, the European Commission granted marketing authorization to Gedeon Richter's selective progesterone receptor modulator **ulipristal acetate** (Esmya®) as a preoperative treatment for moderate to severe symptoms of uterine fibroids. This is a new indication for the agent, which has been marketed since 2009 as an emergency contraceptive. The marketing application for the drug was supported by the PEARL I and PEARL II pivotal phase III studies. In PEARL I, a randomized, parallel-group, double-blind, placebo-controlled trial, uterine bleeding was controlled in 91% of women receiving ulipristal acetate 5 mg and in 92% of those receiving ulipristal acetate 10 mg, as compared to 19% of those receiving placebo. Additionally, the rates of amenorrhea were 73%, 82% and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving ulipristal acetate. Furthermore, as compared to placebo, both doses of the study drug led to reductions in pain. In PEARL II, a double-blind, double-dummy trial, ulipristal acetate was compared to the injectable gonadotrophin-releasing hormone receptor agonist leuprolide acetate. In this study, uterine bleeding was controlled in 90% of patients receiving ulipristal acetate 5 mg, in 98% of those given ulipristal acetate 10 mg and in 89% of those receiving leuprolide acetate. Excessive bleeding control was demonstrated with statistical significance to be more rapid in patients receiving either ulipristal acetate 5 or 10 mg, than in those receiving leuprolide acetate. Among the other results from this study was a finding showing that all treatments reduced the volume of the three largest fibroids, with median reductions at week 13 of 36% in the group receiving ulipristal acetate 5 mg, 42% in the group given ulipristal acetate 10 mg and 53% in the group receiving leuprolide acetate. Ulipristal acetate is an orally active drug that

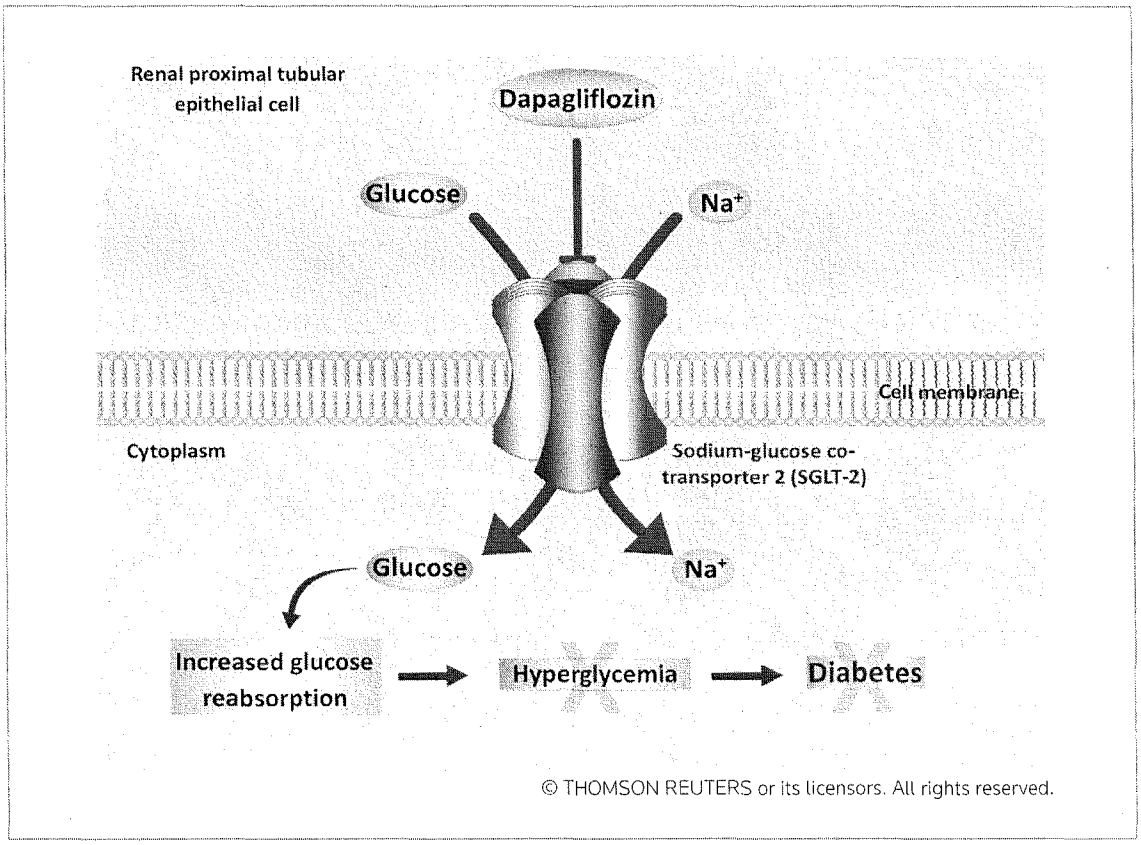

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Figure 5. Sodium/glucose cotransporter 2 (SGLT-2) inhibition. Dapagliflozin, a selective SGLT-2 inhibitor, is indicated for use in the treatment of type 2 diabetes. SGLT-2 is a high capacity, low-affinity carrier molecule that is predominantly located within the proximal convoluted tubule (PCT) of the nephron and accounts for approximately 90% of the glucose reabsorbed within the kidney. The active transport of glucose is facilitated via sodium ion movement into the cell. Blocking SGLT-2 is expected to eliminate blood glucose via the urine and offset the excessive reabsorption of glucose, which leads to hyperglycemia and may result in diabetes.

reversibly blocks the progesterone receptors in target tissues. The first E.U. commercialization for this new indication took place in Germany in March 2012, followed by the U.K. in April.

In February 2012, the U.S. FDA granted regulatory approval for Bio-T-Gel™, a **testosterone transdermal gel** for the treatment of male hypogonadism. The product was initially developed by BioSante Pharmaceuticals and was licensed to Teva Pharmaceuticals USA for late-stage clinical development. Teva is responsible for all regulatory and marketing activities.

Cushing's syndrome is a rare syndromic disorder caused by prolonged and pathological overexposure of tissues to the adrenal hormone cortisol, or to cortisol-like glucocorticoids. Until 2012, there were few approved drug therapies for patients with Cushing's syndrome, and treatment was largely empirical. The approval and launch of two new drugs in just one year, therefore, represents a major advance in the field of endocrinology.

Mifepristone (Korlym™; Corcept Therapeutics), a dual glucocorticoid and progesterone receptor antagonist that has been marketed for more than 20 years as an abortifacient, was approved by the FDA to control hyperglycemia in adults with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and are not candidates for surgery or who have not responded to prior surgery. With this approval, mifepristone became the first medical therapy to be approved in the U.S. for

the treatment of endogenous Cushing's syndrome, a form of Cushing's that is caused by overproduction of cortisol by the adrenal glands. The FDA granted orphan drug designation to the treatment in 2007. The safety and efficacy of mifepristone in patients with endogenous Cushing's syndrome was evaluated in a clinical trial that enrolled 50 subjects. In this study, patients experienced significant improvement in blood sugar control, with some patients experiencing marked reductions in their insulin requirements. Improvements in clinical signs and symptoms were also reported by some patients in the study. Mifepristone, which works by blocking the binding of cortisol to its receptor, does not decrease cortisol production but reduces the effects of excess cortisol, such as high blood sugar levels. Corcept launched the product in April 2012.

Also in April, the European Commission approved the somatostatin analogue **pasireotide** (Signifor®; Novartis) for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Cushing's disease is a form of pituitary tumor that results in the overproduction of adrenocorticotropic hormone (ACTH), an endogenous trigger for the production of cortisol. Due to its effects on cortisol production, Cushing's disease is a major cause of Cushing's syndrome. Pasireotide was launched over the following months in several European countries, including Austria, Germany, Denmark, the United Kingdom, Ireland and Norway.

DERMATOLOGIC DRUGS

Actinic keratosis (AK), also termed solar keratosis or keratinocytic intradermal neoplasia, is a precancerous pathology of the epidermis. It is characterized by scaly, crusted, keratotic papules and plaques with poorly defined borders that develop on chronically sun-exposed areas of the skin, such as the face and upper extremities. AK is an initial step in the process to invasive squamous cell carcinoma. Two new treatment options for this increasingly prevalent skin disorder reached the market in 2012, improving the outlook for patients and their physicians alike.

The protein kinase C activator and cell death-inducing agent **ingenol mebutate** (Picato®; Leo Pharma) was approved and launched for the first time last year in the United States as a topical treatment for AK. Ingenol mebutate is available as a gel in two concentrations — 0.015% and 0.05%— that can be applied to the face and scalp for as little as 2 or 3 days, and is the first and only treatment for AK that effectively clears actinic keratoses with such a short course of treatment.

Ameluz® (**BF-200 ALA**), a fixed-dose combination of the nanoemulsion BF-200 and 5-aminolevulinic acid (ALA), was introduced last February in Germany, where it is indicated for the treatment of AK of mild to moderate intensity on the face and scalp. The product, which was developed by Biofrontera, is administered topically, followed by a single session of photodynamic therapy for single or multiple lesions.

Cardium Therapeutics' Excellagen™, a wound care management device composed of formulated, fibrillar, high-molecular-weight **type I collagen** derived from bovine skin, was approved and launched last year in the U.S. for wound care management. It is indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds and draining wounds. Excellagen is intended for physician use following surgical debridement procedures, and is engineered to support a favorable wound-healing environment for non-healing ulcers such as lower-extremity ulcers in diabetes patients.

Gintuit™ (**allogeneic cultured keratinocytes and fibroblasts in bovine collagen**) is another novel wound-healing agent that received FDA approval during 2012. The product is a bilayered structure composed of an upper cornified layer formed by allogeneic human keratinocytes and a lower layer formed by bovine-derived collagen, human extracellular proteins and allogeneic human dermal fibroblasts. It is indicated specifically for topical application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. The product is manufactured by Organogenesis Inc. and will be launched in 2013.

GASTROINTESTINAL AGENTS

Linaclotide acetate (Linzess™), a new treatment for chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C), was approved last summer in the U.S. and launched there in December. Linaclotide is a first-in-class guanylate cyclase-C (GC-C) receptor agonist that acts locally in the intestine with minimal systemic exposure (Fig. 6). In nonclinical studies, linaclotide has been shown to reduce intestinal pain and accelerate gastrointestinal transit. Intestinal pain reduction is thought to result from an increase in cyclic guanosine monophosphate (cGMP),

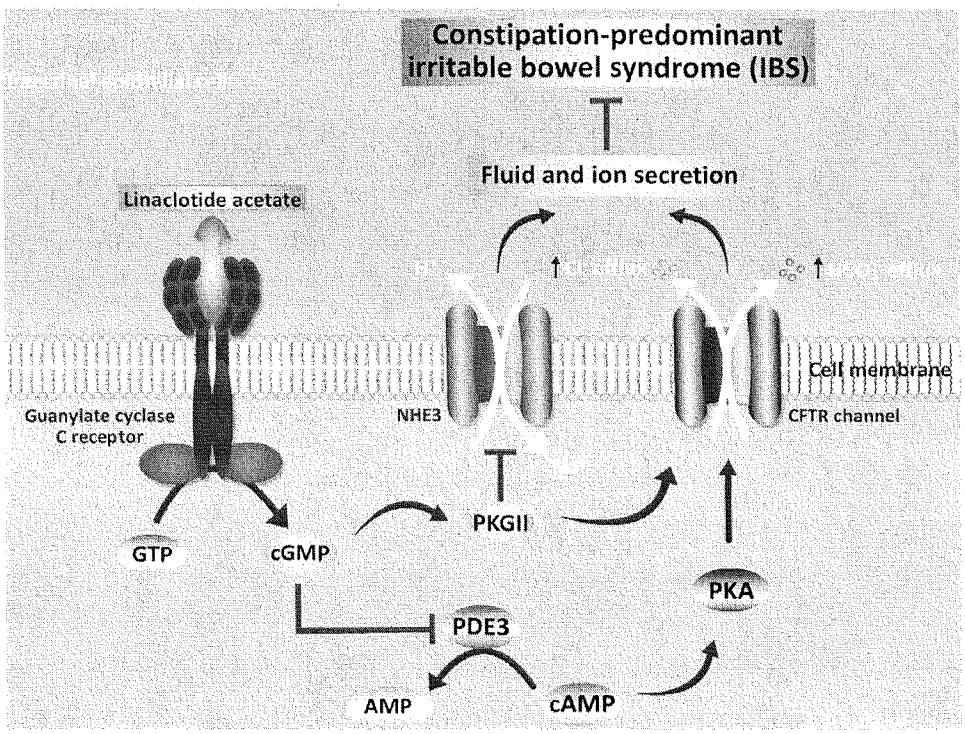

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Figure 6. Guanylate cyclase C (GC-C) receptor agonism. Linaclotide acetate is a peptide agonist of the GC-C receptor and is potentially useful as a treatment option for gastrointestinal disorders such as chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C). Activation of GC-C increases cGMP levels, thereby inducing chloride and bicarbonate ion secretion via the cystic fibrosis transmembrane conductance regulator (CFTR) into the intestinal lumen. This improves bowel movement and results in the alleviation of constipation.

which has been shown to decrease the activity of pain-sensing nerves. In placebo-controlled, crossover phase III clinical trials in more than 2,800 adults, linaclotide was shown to significantly reduce abdominal pain in IBS-C patients and significantly increase bowel movement frequency in both IBS-C patients and CIC patients. Improvements were reported in the first week of treatment and maintained throughout the treatment period. The drug was discovered by Ironwood and was licensed to Forest for codevelopment and comarketing in the U.S. In November, the drug was also approved for the IBS-C indication in the E.U., where it will be marketed by Almirall as Constella®.

NPS Pharmaceuticals' glucagon-like peptide 2 (GLP-2) analogue **teduglutide** was approved for the first time last August in the European Union (as Revestive®), and later in the year in the U.S. (as Gattex®). The product, which has orphan drug status in both regions, is indicated for the treatment of adult patients with short bowel syndrome (SBS), a condition that results from the partial or complete surgical removal of the small and/or large intestine. Extensive loss of the small intestine can lead to poor absorption of fluids and nutrients from food needed to sustain life. As a result, patients with SBS often require parenteral nutrition. Administered once daily by s.c. injection, teduglutide helps improve the intestinal

absorption of fluids and nutrients, reducing the frequency and volume of parenteral nutrition. It is the third FDA-approved drug to treat adults with SBS receiving nutritional support: Zorbtive® (somatropin) and NutreStore® (glutamine) were approved in 2003 and 2004, respectively. Teduglutide has been licensed to Nycomed (Takeda) for development and marketing outside the U.S., Canada, Mexico and Israel. Takeda initially intends to provide patient access in Europe through a Named Patient Program, while NPS plans to launch the product in the U.S. during the first quarter of 2013.

On the last day of 2012, the U.S. FDA approved **crofelemer** (Fulyzaq; Napo Pharmaceuticals), a botanical drug derived from the red sap of the *Croton lechleri* plant and the first FDA-approved agent designed to relieve symptoms of watery diarrhea in HIV/AIDS patients taking combination antiretroviral drug therapy. Watery diarrhea in this patient population is caused by the secretion of electrolytes and water in the gastrointestinal tract. Crofelemer has a well documented, novel antisecretory mechanism of action which involves blockade of excess chloride ion secretion via the CFTR channel. At a functional level, diarrhea is often associated with increased intestinal secretion. The chloride channel CFTR regulates water balance in the intestines through control of chloride ion secretion and sodium absorption. The safety and efficacy of crofelemer were established in a clinical trial of 374 HIV-positive patients on stable antiretroviral therapy with a history of diarrhea lasting 1 month or longer. The median number of daily watery bowel movements was 2.5 per day. Patients who had diarrhea caused by an infection or a gastrointestinal disease were excluded from participating in the trial. Patients were randomly assigned to take crofelemer or placebo twice daily. The trial was designed to measure clinical response, defined as the number of patients who had two or fewer watery bowel movements weekly. Results showed that 17.6% of patients taking the active drug experienced clinical response, compared with 8% taking placebo. In some patients, antidiarrheal effect persisted for up to 20 weeks. Crofelemer is only the second botanical drug to be approved by the FDA; the first, sinecatechins (Veregen®), was approved in 2006 for the treatment of perianal and genital warts.

ANTI-INFECTIVE THERAPY

Gilead's combination anti-HIV product Truvada® (**emtricitabine/tenofovir disoproxil fumarate**) was approved and launched last year for an important new indication in the U.S., marking a major milestone in the war on AIDS; in June 2012 the U.S. FDA approved Truvada for use, in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. Truvada is the first agent to be approved for HIV prevention in uninfected adults, a strategy known as pre-exposure prophylaxis (PrEP). The approval was supported by the Pre-Exposure Prophylaxis Initiative (iPrEx), sponsored by the U.S. National Institutes of Health and the Bill and Melinda Gates Foundation, and by Partners PrEP, which was sponsored by the University of Washington and funded by the Bill and Melinda Gates Foundation. The iPrEx trial evaluated the drug in 2,499 HIV-negative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV infection, such as inconsistent or no condom use during sex with a partner of positive or unknown HIV status, a high number of sex partners, and exchange of sex for commodities. Results showed the product to be effective in reducing the risk of HIV infection by 42% compared with placebo in this population. Furthermore, efficacy was strongly correlated with drug adherence in this trial. The Partners PrEP trial was conducted in 4,758 heterosexual couples where one partner was HIV-infected and the other was not. Results showed a 75% reduced risk of becoming infected compared with placebo. Truvada, a fixed-dose combination of two nucleoside reverse transcriptase inhibitors, has been marketed since 2004 for the treatment of HIV, and is currently the most widely prescribed anti-HIV agent in the U.S.

The U.S. was also the first market for another new anti-HIV combination product from Gilead: Stribild™ (**elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate**). The once-daily combination product is indicated for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naive. Stribild is the first fixed-dose anti-HIV combination to incorporate the pharmacoenhancing agent cobicistat, a cytochrome P450 3A4 (CYP3A4) inhibitor. The incorporation of cobicistat enables the once-daily dosing of elvitegravir, an integrase inhibitor that is otherwise metabolized by CYP3A. Both elvitegravir and cobicistat as stand-alone agents are investigational products, and their safety and efficacy have not yet been established. Stribild was approved and launched in August.

Synriam™ (**arterolane maleate/piperaquine phosphate**), a novel fixed-dose combination product for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, was launched for the first time last year by Ranbaxy in India. The combination product has a

simplified dosing regimen that requires the patient to take just one tablet per day for 3 days; previous regimens, in contrast, required twice-daily administration of two to four tablets, for a total of 3 or more days. Other advantages of Synriam are freedom from dietary restrictions and production from a synthetic source, which ensures a steady supply at a low cost.

Pyramax® (**pyronaridine tetraphosphate/artesunate**), a fixed-dose artemisinin combination therapy codeveloped by Medicines for Malaria Venture and Shin Poong, was introduced last year in Korea, its first market. Pyramax is indicated for the treatment of acute, uncomplicated malaria infection caused by *P. falciparum* or by *P. vivax*. During 2012 the product also received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP). Under Article 58 of Regulation (EC) No 726/2004, the CHMP is empowered to give opinions, in cooperation with the World Health Organization (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union but that are needed to prevent or treat diseases of major public interest around the world. Like Synriam, Pyramax is taken just once daily for 3 days.

Tuberculosis (TB) is another major public health concern around the world, particularly due to the emergence in recent years of multidrug-resistant TB strains. Thus the development of several new classes of antituberculosis drugs has been regarded with great interest and has begun to bear fruit. On December 31, the U.S. FDA approved Janssen Therapeutics' **bedaquiline** (Sirturo™), the first new TB drug in 40 years. Bedaquiline is the first targeted inhibitor of proton-translocating ATP synthetase (F0F1 ATPase), the enzyme required by *Mycobacterium tuberculosis* to replicate and spread through the body. It was approved under the FDA's accelerated approval program; the drug also received orphan drug status, fast-track status and priority review status. Bedaquiline's safety and effectiveness were established in 440 patients in 2 phase II clinical trials. Patients in the first trial were randomly assigned to be treated with bedaquiline or placebo, both administered in combination with other TB drugs. All patients in the second trial, which is ongoing, are being administered the active drug plus other TB drugs. Both studies were designed to measure the length of time it took for a patient's sputum to be free of *M. tuberculosis* (sputum culture conversion, or SCC). Results from the first trial showed patients treated with bedaquiline combination therapy achieved SCC in a median time of 83 days, compared with 125 days in patients treated with placebo combination therapy. Results from the second trial showed the median time to SCC was 57 days, supporting the efficacy findings of the first trial. Sirturo carries a Boxed Warning alerting patients and health care professionals that the drug can affect the heart's electrical activity (QT prolongation), which could lead to an abnormal and potentially fatal heart rhythm.

Ivermectin is an oral antihelmintic agent that has been marketed for several decades in a tablet formulation for the treatment of strongyloidiasis, onchocerciasis (river blindness), scabies and filariasis. In February 2012, Sanofi Pasteur received FDA approval to commercialize a topical (lotion) formulation of ivermectin developed by Topaz for the treatment of head lice infestations in patients 6 months of age and older. Head lice cases have been increasing rapidly in the U.S., with an estimated 6 million to 12 million children aged 3-11 years affected each year. Commercialization of the new product, which has been given the trade name Sklice®, took place in August 2012.

The quinolone antibacterial agent **levofloxacin** (Levaquin®; Ortho-McNeil-Janssen) was approved by the FDA in April 2012 for the treatment and prevention of plague, a rare and potentially life-threatening infection caused by the bacterium *Yersinia pestis*. The three most common forms of plague are bubonic plague (infection of the lymph nodes), pneumonic plague (infection of the lungs) and septicemic plague (infection of the blood). Although plague is extremely rare, with only 1,000-2,000 natural infections reported worldwide each year, it is considered a potential agent for bioterrorism. Levofloxacin was developed for the plague indication under the FDA's Animal Efficacy Rule, which allows efficacy findings from adequate and well-controlled animal studies to be used in cases where it is not feasible or ethical to conduct trials in humans. The application for levofloxacin was granted a priority review by the FDA. It joins streptomycin, doxycycline, tetracycline and other antibacterial drugs in the tetracycline group as FDA-approved treatments for plague. Levofloxacin is also FDA-approved for the treatment of anthrax, another potential agent of bioterrorism, and has been stockpiled to this effect.

On December 14, 2012, the U.S. FDA approved the first anthrax antitoxin, **raxibacumab**, indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not

available or are not appropriate. Raxibacumab is a monoclonal antibody that neutralizes toxins produced by *B. anthracis* that can cause massive and irreversible tissue injury and death. Raxibacumab is the first monoclonal antibody approved under the FDA's Animal Efficacy Rule. In this case, because inhalational anthrax is a rare and lethal disease, it was not possible to conduct adequate efficacy trials in humans, and the agent's effectiveness was therefore demonstrated in one study in monkeys and three studies in rabbits. The safety of raxibacumab was evaluated in 326 healthy human volunteers. Raxibacumab was developed by Human Genome Sciences in conjunction with the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority. Human Genome Sciences was acquired by GSK in August 2012.

THERAPY OF MUSCULOSKELETAL & CONNECTIVE TISSUE DISEASES

Last year marked the first approval and launch of Pfizer's tyrosine-protein kinase JAK1/JAK2/JAK3 (Janus kinase) inhibitor **tofacitinib citrate** (Xeljanz®) for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to or are intolerant of methotrexate. Tofacitinib citrate is approved as a second-line therapy, which means that treatment with a biologic is not a prerequisite. The safety and effectiveness of tofacitinib were evaluated in seven clinical trials in adult patients with moderately to severely active rheumatoid arthritis. In all of the trials, patients treated with the drug experienced improvement in clinical response and physical functioning compared to patients treated with placebo. However, these studies also showed the use of tofacitinib to be associated with an increased risk of serious infections, including opportunistic infections and TB, and of cancer, including lymphoma. As a result, the product will carry a boxed warning regarding these safety risks. Treatment with the drug has also been shown to be associated with increases in cholesterol and liver enzyme tests and decreases in blood counts. Based on the risks associated with tofacitinib, the FDA has approved the drug with a risk evaluation and mitigation strategy. Furthermore, the agency is requiring a postmarketing study that will study the long-term effects of two doses of tofacitinib on heart disease, cancer and serious infections.

After taking a long, circuitous path to market, the nuclear factor NF-κB activation inhibitor **iguratimod** (Iremod) was finally launched last year for the first time in China for the treatment of active rheumatoid arthritis. The disease-modifying antirheumatic drug was originally discovered by Toyama; the latter, together with codevelopment partner Eisai, initially filed for marketing approval in Japan in 2003, although in 2009 the companies withdrew the Japanese marketing application in order to conduct further efficacy and safety testing. The Japanese application was resubmitted in 2011. Development in China was conducted by licensee Simcere Pharmaceutical, which obtained Chinese regulatory approval in August 2011 and launched Iremod in January 2012. Iguratimod was also approved and launched in Japan, where it is marketed by Toyama as Kolbet and by Eisai as Careram, later in 2012.

PG-201, a phytotherapeutic drug developed by the Korean company ViroMed, was approved last April by the Korean Food and Drug Administration as a treatment for osteoarthritis. PG-201 consists of an ethanol extract from 12 herbs: *Chaenomeles speciosa* Nakai, *Achyranthes bidentata* Blume, *Angelica sinensis*, *Cnidium officinale* Makino, *Gastrodia elata* Blume, *Acanthopanax senticosus* Maxim, *Carthamus tinctorium* L, *Cinnamomum aromaticum* Nees, *Gentiana macrophylla* Pall, *Ledebouriella seseloides* Wolff, *Clematis chinensis* Retz and *Phlomis umbrosa* Turczaninow. Preclinical studies show that PG-201 suppresses the production of inflammatory mediators such as interleukin-1β (IL-1β) and TNF-α, prevents cartilage degradation by matrix metalloproteinase (MMP) and increases the expression of tissue inhibitor of metalloproteinases 2 (TIMP-2). In phase II studies conducted in Korea, PG-201 produced potent pain-relieving activity in patients with arthritis, while inducing few to no side effects. It will be marketed under the brand name *Layla* by partner company PMG Pharmaceutical.

IMMUNOMODULATORS & AGENTS FOR IMMUNIZATION

Graft-versus-host disease (GVHD) may occur when immunologically competent cells are introduced into an immunoincompetent recipient. This form of rejection occurs most often in the context of hematopoietic stem cell transplantation, although it may also occur in recipients of solid organ transplants, blood transfusion or even maternal-fetal transfusion. GVHD is classified as acute or chronic. This distinction has traditionally been based on timing, with acute GVHD defined as that which develops within 100 days or less of transplantation, and chronic GVHD as that emerging at day 100 or later. Acute GVHD is characterized by dermatitis, enteritis and hepatitis. It consists of an augmented inflammatory and immune response by the donor lymphocytes directed

toward the host environment, which is perceived as foreign. Current first-line therapy consists of steroids, although the success rate is only 30-50% and there are few therapeutic options for patients who do not respond to steroid therapy. Last year Health Canada approved **remestemcel-L** (Prochymal®; Osiris Therapeutics), the first therapeutic option for the management of acute GVHD in children who fail to respond to steroids. The historic decision marks the world's first regulatory approval of a manufactured stem cell product as well as the first therapy specifically approved for GVHD.

Hepatitis E is a liver disease caused by the hepatitis E virus (HEV), a non-enveloped, positive-sense, single-stranded RNA virus that is transmitted mainly through contaminated drinking water. Globally, according to the WHO, there are approximately 20 million incident HEV infections every year. Last year the world's first **hepatitis E vaccine**, Hecolin®, was launched for the first time in China. Codeveloped by Xiamen University and Xiamen Innovax Biotech with funding from the Chinese government, the vaccine was approved by the Chinese Ministry of Science and Technology in January and was launched in October. Hecolin will be administered to high-risk members of the Chinese population. The Chinese government will work with international organizations to introduce it to other countries.

Two new tetravalent vaccines were approved and launched last year in Japan: Biken's **Tetrabik** (codeveloped with Mitsubishi Tanabe Pharma) and Astellas' **Quattrovac®** (manufactured and copromoted by Kaketsuken). Both are indicated for routine immunization against pertussis, diphtheria, tetanus and poliomyelitis, and were developed using inactivated, rather than attenuated, poliomyelitis vaccine derived from Sabin strains. The inactivated strain is associated with fewer adverse events and improved safety as compared to the traditional attenuated strain.

GSK's meningitis vaccine Nimenrix™ (**meningococcal group A, C, W-135 and Y conjugate vaccine**) was approved last April in the European Union. Nimenrix is indicated for active immunization of individuals from the age of 12 months and older against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W-135 and Y. GSK has begun rolling out the product in several European markets including the U.K., Germany and The Netherlands.

MenHibrix® (**meningococcal groups C and Y and Haemophilus b tetanus toxoid conjugate vaccine**), another new vaccine from GSK, received its first approval last year in the U.S. MenHibrix is indicated for active immunization against invasive disease caused by *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b in children 6 weeks of age through 18 months of age. In October 2012, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention voted for a limited recommendation for immunization of infants at an increased risk for meningococcal disease. GSK plans to launch the vaccine during the first half of 2013.

Sanofi Pasteur introduced the world's first single-dose **Japanese encephalitis (JE) vaccine**, Imojev®, in Australia in December 2012. The vaccine is approved for use in adults and children aged 12 months and older. About 3 billion people in the Asia Pacific Region are at risk of JE, for which there is no specific treatment. The clinical data supporting the use of Imojev in children and adults have been generated in multicenter studies conducted in the United States, Australia, Thailand and the Philippines with more than 2,400 adults and 2,200 children receiving the vaccine. The safety and immunogenicity of Imojev were compared to those of a licensed JE vaccine (JE-VAX®) and placebo in adults and to a control vaccine in children. A pivotal phase III study in adults showed that a single dose of Imojev is as immunogenic as three doses of JE-VAX. A single administration of Imojev elicited a protective level of neutralizing antibodies in approximately 93% and 99% of adults 14 days and 28 days after vaccine administration, respectively. Over 84% of adults were still seroprotected 5 years after vaccination. A phase III study in children showed that approximately 95% of JE virus-naive subjects were seroprotected 28 days after a single dose of Imojev. The vaccine was well tolerated and there was no indication during the clinical development program of any safety concerns.

In February 2012, the U.S. FDA approved MedImmune's FluMist® Quadrivalent, the world's first **quadrivalent seasonal influenza vaccine**. Like the company's trivalent flu vaccine, FluMist Quadrivalent is administered as a nasal spray. Unlike conventional flu vaccines, which contain three influenza strains (two strains of type A influenza [A/H1N1 and A/H3N2] and one B lineage strain), the quadrivalent vaccine will contain two influenza A and two influenza B lineages, providing greater protection against influenza B viruses. According to the Centers for Disease Control and Prevention, viruses from two different influenza B lineages (B/Yamagata and B/Victoria) have been circulating in the U.S. since the 2001-2002 flu season. However, in 5 of the 10 influenza seasons between 2001 and 2011, the wrong B strain was

selected for inclusion in the annual vaccine. FluMist Quadrivalent will be launched in time for the 2013-2014 flu season, according to MedImmune.

Vepacel® (Baxter Innovations), an **H5N1 prepandemic influenza vaccine** (whole virion, Vero cell-derived, inactivated) containing antigen of H5N1 strain A/Vietnam/1203/2004, was approved last February by the European Commission. Unlike traditional influenza vaccines, which are produced using egg-based methods, Vepacel is produced using a Vero cell culture method that would enable more rapid, larger-scale vaccine production in the case that an emerging, highly pathogenic influenza strain is identified. Approval of the vaccine, which is indicated for active immunization against H5N1 subtype of influenza A, extends to all E.U. member states as well as Iceland, Norway and Liechtenstein.

In December 2012, Biotest Pharmaceuticals' Bivigam™ (**immune globin intravenous [human]**) was approved by the U.S. FDA for the treatment of patients with primary humoral immunodeficiency. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich Syndrome and severe combined immunodeficiencies.

TREATMENT OF CANCER

Enzalutamide (Xtandi®; Medivation/Astellas) the first selective androgen receptor modulator (SARM), was approved and launched last year in the U.S., where it is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel. The compound has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. The efficacy and safety of enzalutamide were assessed in a randomized, placebo-controlled, multicenter phase III trial in which 1,199 patients with mCRPC who had previously received docetaxel were randomized 2:1 to receive either enzalutamide or placebo. In the trial, 48% of enzalutamide-treated patients and 46% of patients in the placebo arm were also treated with glucocorticoids. On the primary endpoint, patients treated with enzalutamide had a statistically significant improvement in median overall survival compared to the placebo group: 18.4 months in the enzalutamide group versus 13.6 months in the placebo group. Enzalutamide provided a 37% reduction in risk of death compared to placebo.

A new treatment option for patients with breast cancer —Genentech's **pertuzumab** (Perjeta™)— was also introduced in the U.S. in 2012. Pertuzumab is the first in a new class of targeted potential therapeutic agents known as HER dimerization inhibitors (HDI) designed to inhibit tumor growth and survival due to the antibody's binding to the dimerization domain of receptor tyrosine-protein kinase erbB-2 (HER2), thereby directly inhibiting the ability of HER2, the most common pairing partner, to dimerize with other HER receptor proteins (epidermal growth factor receptor [EGFR]/HER1, HER3 and HER4) and, in turn, preventing the activation of HER signaling pathways. Pertuzumab is indicated for use, in combination with trastuzumab and docetaxel chemotherapy, for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Pertuzumab and trastuzumab possess complementary mechanisms of action, as both bind to HER2 receptors, but to different regions. Genentech began marketing the product in June, just days after receiving approval from the U.S. FDA.

The angiogenesis inhibitor **axitinib** (Inlyta®), a vascular endothelial growth factor receptor (VEGFR-1, -2 and -3) inhibitor and platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor discovered and developed by Pfizer, was approved and launched in the U.S. early last year for the treatment of advanced renal cell carcinoma. It is indicated for use in patients who have not responded to treatment with one prior systemic agent. Axitinib is the seventh new drug to receive FDA approval for the indication of renal cell carcinoma since 2005, further improving the outlook for patients diagnosed with the disease.

Another antiangiogenic agent, Sanofi's VEGF inhibitor **ziv-aflibercept** (Zaltrap®), was approved and launched in the summer of 2012 for the treatment, in combination with the FOLFIRI (folinic acid, fluorouracil and irinotecan) regimen, of adult patients with metastatic colorectal cancer (mCRC). This is a new indication for the agent, which was introduced by Regeneron in 2011 for the treatment of macular degeneration.

The multikinase inhibitor **regorafenib** (Stivarga®) was approved and launched in the U.S. last September, indicated for the treatment of patients with mCRC who have been previously treated with currently available therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and, if *KRAS* wild-type, an anti-EGFR therapy.

Regorafenib was developed under the fast-track program and reviewed under the FDA's priority review program. It was approved 1 month before the Prescription Drug User Fee goal date. Regorafenib was discovered and developed by Bayer and is jointly promoted by Onyx Pharmaceuticals.

Another multikinase inhibitor, Exelixis' cabozantinib S-malate (Cometriq™), was approved by the U.S. FDA in November 2012, indicated for the treatment of progressive, metastatic medullary thyroid cancer (MTC). On the same day that the FDA approved the product, Exelixis announced that the EMA had accepted the company's marketing authorization application (MAA) for the MTC indication. Cabozantinib is an inhibitor of multiple receptor tyrosine kinases including VEGFR-1, -2 and -3, MET, RET, KIT, TRKB, FLT-3, AXL and TIE-2, which are involved in processes of oncogenesis, metastasis, tumor angiogenesis and maintenance of the tumor environment. Approval of the NDA was based on results of the EXAM study, a randomized, phase III clinical trial enrolling 330 patients with progressive, metastatic MTC which met its primary efficacy endpoint of improving progression-free survival. Cabozantinib has orphan drug status in the U.S. and E.U. for this rare form of cancer, which affects between 500 and 700 patients in the U.S. and a similar number in Europe. Cabozantinib will be marketed by a contract sales organization beginning in January 2013.

In January 2012, the U.S. FDA approved Genentech's vismodegib (Erivedge™) for the treatment of basal cell carcinoma (BCC) that has spread to other parts of the body, has recurred after surgery or cannot be treated with surgery or radiation. This first-in-class oral hedgehog pathway inhibitor is also the first FDA-approved medicine for advanced BCC (Fig. 7). Approval was based on results from ERIVANCE BCC (SHH4476g), a pivotal international, single-arm, multicenter, 2-cohort, open-label phase II study that enrolled 104 patients with advanced BCC, including locally advanced BCC (n = 71) and metastatic BCC (n = 33). Patients with locally advanced BCC had lesions that recurred after surgery, were not candidates for surgery (inoperable, or for whom surgery would result in substantial deformity), recurred after radiotherapy or were not candidates for radiotherapy (radiotherapy was contraindicated or inappropriate). Study participants received oral vismodegib once daily until disease progression or unacceptable toxicity. The primary endpoint of the study —lesion shrinkage as assessed by independent review— was achieved in 43% (27/63) of patients with locally advanced BCC and 30% of patients (10/33) with metastatic BCC. The median duration of response was 7.6 months. The drug candidate was originally developed at Curis, and was developed in collaboration with Genentech. Vismodegib was launched in the U.S. in February.

Chronic myelogenous leukemia (CML) is a rare —and until quite recently, nearly always fatal— malignant disease that typically affects older adults. The outlook for patients with CML improved noticeably last year with the approval of four new treatment options.

In January, Korean regulators approved Il-Yang's radotinib hydrochloride (Supect™), a Bcr-Abl tyrosine kinase inhibitor indicated for the second-line treatment of patients with Philadelphia chromosome-positive (Ph+) CML that is refractory to Gleevec™ (imatinib mesilate). Copromotion rights have been licensed to Daewoong.

In September 2012, the FDA approved Pfizer's bosutinib (Bosulif®) for the treatment of adult patients with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy. Bosutinib is a dual proto-oncogene tyrosine-protein kinase Src and tyrosine-protein kinase Abl1 blocker. Once-daily bosutinib is the only therapy approved with pivotal trial data that included patients with CML treated with imatinib mesilate followed by a second-generation tyrosine kinase inhibitor (TKI). Bosutinib was launched in the U.S. shortly after approval.

Just a month later, the FDA approved the antitumor alkaloid omacetaxine mepesuccinate (Synribo™; Teva), indicated for the treatment of adult patients with chronic phase or accelerated phase CML with resistance and/or intolerance to two or more TKIs. The drug was approved under the FDA's accelerated approval program and has orphan drug status. The mechanism of action of omacetaxine mepesuccinate in CML has not been fully elucidated, but includes inhibition of protein synthesis. Teva launched the product in November.

Finally in December, the multikinase inhibitor ponatinib (Inclusig™; Ariad Pharmaceuticals) was approved by the FDA. It is indicated for the treatment of adult patients with chronic, accelerated or blast phase CML that is resistant or intolerant to prior TKI therapy. Ponatinib was also approved for the treatment of Ph+ acute lymphoblastic leukemia (ALL) that is resistant or intolerant to prior TKI therapy.

In August, the FDA approved Talon Therapeutics' Marqibo®, a nanoparticle-encapsulated cancer therapeutic for the treatment of ALL. Marqibo consists of **vin-**

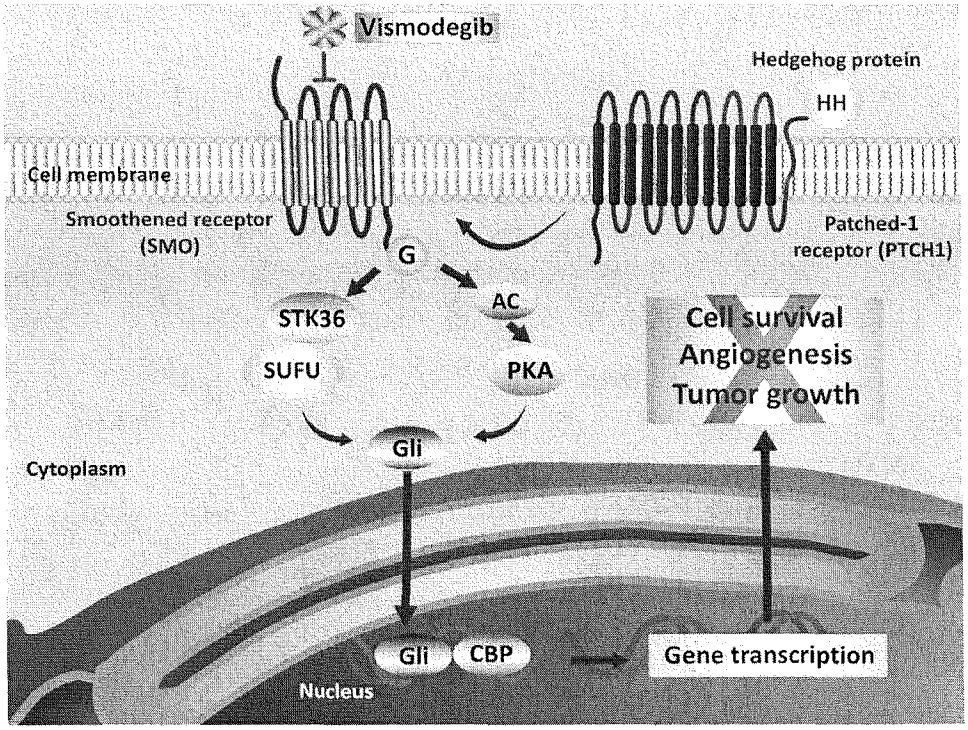

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Figure 7. Hedgehog signaling inhibition. Vismodegib is a small-molecule inhibitor of the hedgehog (Hh) signaling pathway that has potential for use in the treatment of various forms of cancer associated with the overexpression of the Hh protein, including basal cell carcinoma (BCC). The binding of Hh to the transmembrane receptor Patched-1 (PTCH1) prevents the PTCH1-mediated inhibition of signaling via smoothened (SMO receptor), which results in the activation of GLI transcription factors and the induction of Hh target genes such as *GLI1* and *PTCH1*. Vismodegib binds to and inhibits SMO, thereby suppressing hedgehog signaling and the expression of angiogenic factors, thus preventing tumor development and angiogenesis.

cristine sulfate, a potent vinca alkaloid antimitotic, encapsulated in the aqueous core of proprietary, sphingomyelin-based liposomes called Optisomes™. The product received accelerated approval for the treatment of adult patients with Philadelphia chromosome negative (Ph–) ALL in second or greater relapse or whose disease has progressed following two or more antileukemia therapies. This indication is based on overall response rate; clinical benefit such as improvement in overall survival has not been verified. Marqibo has received orphan drug designation for the treatment of ALL from the FDA and from the EMA. Talon intends to launch Marqibo in the U.S. during the first quarter of 2013, and will also submit an MAA to the EMA in 2013.

Further improving the prospects for patients with leukemia, the DNA methyltransferase inhibitor **decitabine** (Dacogen®; Astex/Janssen-Cilag) was approved by the European Commission in September 2012 for a new indication: the treatment of adult patients (age 65 years and older) with newly diagnosed de novo or secondary acute myeloid leukemia (AML) who are not candidates for standard induction chemotherapy. Decitabine has orphan drug status for this indication in the European Union. The marketing authorization was

based on the phase III DACO-016 trial, which compared decitabine to a patient's choice with physician advice of either supportive care or low-dose cytarabine in the treatment of older patients with AML. The analysis of the protocol-specified results demonstrated an increase of 54% in median overall survival in patients taking decitabine (7.7 months for decitabine patients compared with 5 months for patients in the comparator arm). An updated analysis of mature survival data confirmed this trend for improved overall survival and provided clinically significant evidence of decitabine efficacy. Decitabine, which has been marketed since 2006 by MGI Pharma for the treatment of advanced myelodysplastic syndrome, was introduced for the new indication in October.

Pixantrone maleate (Pixuvri®) is a novel DNA intercalating agent designed by scientists at Cell Therapeutics, who modified the structure of previously marketed DNA intercalators to remove portions of the molecules responsible for cardiotoxicity, while retaining those responsible for antitumor activity. In May 2012, the European Commission approved pixantrone maleate for use as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin's B-cell lymphomas who have failed two or more prior lines of therapy. First launches took place in Denmark, Sweden and Finland in September.

Adult T-cell leukemia/lymphoma (ATL) is an aggressive and frequently fatal lymphoproliferative malignant disease of viral origin. The causative agent, human T-cell leukemia virus (HTLV), was isolated in 1979 and was the first retrovirus discovered in humans. The geographic distribution of HTLV is not ubiquitous, but rather clusters in particular geographic areas and populations where the virus is endemic. The major hot spots of infection are in the Caribbean, South America, equatorial Africa and southwestern Japan; these are also the regions with the highest incidence of ATL. In 2012, Japanese regulatory authorities approved the first treatment specifically indicated for this malignancy: Kyowa Hakko Kirin's **mogamulizumab** (Poteligeo®). Mogamulizumab is a humanized monoclonal antibody targeting the chemokine CCR4 receptor, and is indicated for the CCR4-positive form of ATL. It was produced by applying the company's proprietary Potelligent® technology to manufacture antibodies with enhanced antibody-dependent cellular cytotoxicity and to reduce the amount of fucose in the carbohydrate structure. The product was launched in May 2012.

In July 2012, the FDA granted accelerated approval to Onyx Pharmaceuticals' proteasome inhibitor **carfilzomib** (Kyprolis™) for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval for this indication is based on response rate, as there are currently no data available showing an improvement in progression-free survival or overall survival based on treatment with carfilzomib. Specifically, the approval was supported by results of the 003-A1 phase IIb study, a single-arm, multicenter clinical trial that enrolled 266 patients with multiple myeloma who had received a median of five prior antimyeloma regimens. The overall response, which was the study's primary efficacy endpoint and determined by an independent review committee using the International Myeloma Working Group (IMWG) criteria, was 22.9%, while median response duration was 7.8 months. Carfilzomib was launched in the U.S., its first market, on August 1, 2012.

OPHTHALMIC DRUGS

Mobius Therapeutics introduced Mitosol®, a new formulation of **mitomycin-c**, last year in the U.S. The product is indicated for topical administration directly to the surgical site of glaucoma filtration surgery, delivering a precise dose of the active ingredient without requiring ophthalmic surgeons to modify their procedures or techniques in any way.

Nevanac®, an ocular suspension delivering the nonsteroidal anti-inflammatory drug **nepafenac**, was approved and launched in the U.K. in 2012. The product, which was developed by Alcon, is indicated to reduce the risk of postoperative macular edema associated with cataract surgery in diabetes patients.

During 2012, Alimera Sciences obtained the first marketing approvals for Iluvien®, a sustained-release intravitreal implant delivering the corticosteroid drug **fluocinolone acetonide**, in Austria, France, Germany, Portugal and the U.K. The product is indicated to treat vision impairment associated with chronic diabetic macular edema that is considered insufficiently responsive to other therapies. The company plans to begin launching Iluvien this year, with the first market introduction anticipated in Germany during the first quarter of 2013.

Mucosta® ophthalmic suspension, a new formulation of **rebamipide** developed by Otsuka, was approved in Japan in 2011 and was launched there in January 2012 for the treatment of dry eye syndrome. Rebamipide is a potent antioxidant and free radical scavenger that works

by enhancing tear secretion and increasing the levels of mucin covering the conjunctiva and cornea of the eye, thereby improving tear quality and corneal health. An oral form of the compound has been marketed since 1990 for the treatment of peptic ulcer and *Helicobacter pylori*-induced gastric inflammation.

Vitreomacular adhesion (VMA) is a potentially sight-threatening condition that develops when the vitreous begins to move away from the macula. This movement can lead to damage of the macula due to pulling or tugging, and until now could only be avoided via surgical vitrectomy to remove the vitreous. Last year, the U.S. FDA approved ThromboGenics' **ocriplasmin** (Jetrea®), the first nonsurgical treatment for symptomatic VMA. Ocriplasmin, a proteolytic enzyme, is a truncated form of human plasmin that cleaves fibronectin, laminin and collagen, three major components of the vitreoretinal interface that play an important role in VMA. The breakdown of these proteins allows better separation between the vitreous and macula and can reduce the chances that tugging will occur. The safety and effectiveness of ocriplasmin were established in two clinical studies involving 652 patients with symptomatic VMA. Patients were randomized to receive a single injection of ocriplasmin or an inactive placebo into the eye, then evaluated over the next 28 days for efficacy and for 6 months for side effects. The studies found that VMA resolved in 26% of patients treated with the proteolytic enzyme as compared to 10% receiving the inactive substance. ThromboGenics launched ocriplasmin in January 2013.

Cystinosis is a genetic disease that causes accumulation of the amino acid cystine, which forms crystals in major organs. Buildup of cystine crystals in the kidneys, eyes, liver, muscles, pancreas, brain and white blood cells slowly destroys the organs, eventually leading to kidney failure or end-stage renal disease. Ocular complications associated with deposition of corneal cystine crystals include photophobia, eye pain, squinting, corneal haziness and foreign body sensations. In some cases, the cystine crystal accumulation becomes so severe that the crystals can damage the cornea, resulting in serious vision difficulties. Cysteamine is a cystine-depleting agent that lowers cystine levels within the cells. Although an oral formulation of cysteamine has been available for some years to treat nephropathic cystinosis, it has no effect on the formation of crystals in the eyes. Last year, therefore, Sigma-Tau obtained FDA approval for a novel ocular formulation of **cysteamine hydrochloride** (Cystaran™), indicated specifically to treat corneal cystine crystal accumulation in patients with cystinosis. Due to the rarity of this disorder (approximately 300 patients in the U.S.) and lack of existing treatment, Cystaran has orphan drug status. The product was developed in collaboration with the National Institutes of Health.

METABOLIC DRUGS

Obesity and overweight are highly prevalent disorders worldwide and are notoriously difficult to treat. Until last year, the therapeutic options for treating obesity were limited to diet and exercise on least invasive end of the spectrum and bariatric surgery on the most invasive end, with only a handful of stimulants and the pancreatic lipase inhibitor orlistat as more widely applicable pharmacotherapeutic options. The FDA's approval in 2012 of two new antiobesity agents —although neither represents a miracle drug— was therefore generally considered to be a positive development.

The combination antiobesity drug Qsymia™ (**phentermine/topiramate**) was approved in July 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 or greater (obese), or 27 or greater (overweight) in the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes or dyslipidemia. Qsymia, developed by Vivus, is the first once-daily combination treatment for obesity and was the first drug in 13 years to be approved for this indication. The efficacy of Qsymia was demonstrated in the EQUIP study in severely obese patients and in the CONQUER study in overweight/obese patients with comorbidities. The average weight loss in EQUIP was 10.9% on Qsymia (15 mg/92 mg) and 1.6% on placebo. The average weight loss in CONQUER was 9.8% in patients receiving a dose of 15 mg/92 mg, 7.8% for a dose of 7.5 mg/46 mg and 1.2% for placebo. According to the National Institutes of Health, losing just 10% of body weight may help obese patients to reduce the risk of developing other medical conditions, while making a meaningful difference in health and well-being. Qsymia was launched in the U.S. in September. A marketing application for the combination has also been filed in the European Union.

The serotonin 5-HT_2 receptor agonist **lorcaserin hydrochloride** (Belviq®; Arena Pharmaceuticals) was approved by the FDA in June 2012 for the treatment of obesity. Lorcaserin is indicated as an adjunct to a reduced-calorie diet and increased physical activity for

chronic weight management in adult patients who are obese (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) and have at least one weight-related comorbid condition. Just days after the approval, Arena transferred all rights pertaining to the NDA to Eisai, such that the latter is now the U.S. marketing authorization holder and will be responsible for commercialization of the drug in U.S., including pharmacovigilance requirements. Subject to the U.S. Drug Enforcement Administration's final scheduling designation, launch of lorcaserin is expected to take place in the first quarter of 2013.

A novel, first-in-class lipid-lowering agent, Aegerion's microsomal triglyceride transfer protein (MTTP) inhibitor **lomitapide** (Juxtapid™), was approved by the FDA in December 2012. Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL cholesterol, total cholesterol, apolipoprotein B and non-HDL cholesterol in patients with familial hypercholesterolemia (FH). FH is a rare and potentially serious genetic disorder that impairs the function of the receptor responsible for removing LDL cholesterol from the body, which results in extreme elevation of blood cholesterol levels. According to the FH Foundation, the disorder affects approximately 666,000 Americans, although only 20% of those have been properly diagnosed. Because of the risk of liver toxicity, lomitapide will be available only through a restricted program called the Juxtapid Risk Evaluation and Mitigation Strategy (REMS) Program. Aegerion will certify all healthcare providers who prescribe the drug as well as all pharmacies that dispense it.

Amarin's Vascepa™ (**icosapent ethyl**), an ultra-pure omega-3 fatty acid product comprising not less than 96% EPA, was approved last year by the U.S. FDA as an adjunct to diet, to reduce triglyceride levels in adults with severe hypertriglyceridemia. In Amarin's MARINE clinical trial, Vascepa demonstrated a statistically significant, placebo-adjusted reduction in levels of triglycerides without increasing levels of LDL cholesterol. The company plans to launch the product during the first quarter of 2013.

Last year in Korea, Green Cross introduced a new enzyme replacement therapy product —**idursulfase beta** (Hunterase®)— for the treatment of mucopolysaccharidosis type II, also known as Hunter's syndrome. The product is only the second enzyme replacement therapy to become available worldwide for this rare metabolic disorder, which affects approximately one in 100,000-150,000 live births. Green Cross launched Hunterase in Korea, where it has orphan drug status, in July, and has announced plans to accelerate further introduction of the product in major markets in Europe, North America and China.

Taliglucerase alfa (Elelyso™), another orphan drug designed to treat an inborn error of metabolism, was approved and launched last year in the U.S. for the treatment of type 1 Gaucher's disease. Taliglucerase is a plant cell-based recombinant human glucocerebrosidase that is produced in genetically engineered carrot cells using Protalix BioTherapeutics's proprietary protein expression system, ProCellEx. Taliglucerase is the first plant-made drug to obtain FDA approval, and was developed as a more reliable alternative to human-derived enzyme products which have been subject to supply issues in recent years. It was codeveloped and is marketed by Pfizer.

Last year also witnessed the first approval by regulatory authorities in a Western country of a human gene therapy: in November, the European Commission approved uniQure's **alipogene tiparvovec** (Glybera®) for the treatment of lipoprotein lipase deficiency (LPLD), also known as familial hyperchylomicronemia. LPLD is an extremely rare genetic disorder caused by mutations in the *LPL* gene, resulting in highly decreased or absent LPL enzyme activity. This enzyme is needed in order to break down chylomicrons, large fat-carrying particles that circulate in the blood after a meal. In patients with LPLD, chylomicrons accumulate in the blood and obstruct small blood vessels, resulting in recurrent and severe acute pancreatitis. Until the approval of alipogene tiparvovec, the only method of managing LPLD was to severely limit patients' fat intake. uniQure plans to launch alipogene tiparvovec in the second half of 2013, and will file for approval in other countries such as the U.S. and Canada in the near future. The product has orphan drug designation in the U.S. and E.U.

TREATMENT OF POISONING & DRUG DEPENDENCY

BTG's **glucarpidase** (Voraxaze®), a recombinant form of the enzyme glutamate carboxypeptidase, was approved last January by the U.S. FDA for the treatment of life-threatening methotrexate overdose in the setting of cancer chemotherapy. Specifically, it is indicated for the treatment of toxic methotrexate concentrations (> 1 μm/L) in patients with delayed methotrexate clearance due to impaired renal function. Glucarpidase breaks down methotrexate into inactive metabolites that

can then be eliminated from the body by routes other than the kidney, primarily via hepatic clearance. It was launched in April, becoming the first and only drug available to reduce toxic methotrexate levels in plasma.

DIAGNOSTIC AGENTS

In April 2012, Lilly and its wholly owned subsidiary Avid Radiopharmaceuticals received approval from the U.S. FDA for the radioactive diagnostic agent Amyvid™ (**florbetapir F 18** injection), indicated for use in brain imaging of β-amyloid plaques in patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. It was approved as an adjunct to other diagnostic evaluations, meaning that a positive scan with Amyvid does not establish a diagnosis of Alzheimer's disease or any other cognitive disorder. Florbetapir F 18 binds to amyloid plaques, a hallmark of Alzheimer's disease, and is detected using PET scan images of the brain. A positive scan with the agent indicates moderate to frequent amyloid plaques are present. This amount of amyloid plaque is present in patients with Alzheimer's disease, but may also be present in patients with other neurologic conditions and in older people with normal cognition. A negative scan indicates sparse to no amyloid plaques are currently present, which is inconsistent with a neuropathological diagnosis of Alzheimer's disease and reduces the likelihood that a patient's cognitive impairment is due to Alzheimer's disease. The safety and effectiveness of florbetapir F 18 have not been established for predicting development of dementia or other neurologic conditions, or monitoring responses to therapies. Amyvid was launched in the U.S. in June 2012.

In September, the FDA approved an NDA filed by Mayo Clinical PET Radiochemistry Facility in Rochester, Minnesota for the production and use of **Choline C 11 Injection**, a PET imaging agent for the detection of recurrent prostate cancer. PET imaging with Choline C 11 injection is indicated in men whose blood prostate-specific antigen (PSA) levels are increasing after earlier treatment for prostate cancer. Although PET imaging with Choline C 11 injection has been performed at a small number of facilities over the past several years, none of these facilities were approved by the FDA to manufacture the agent. With this approval, the Mayo Clinic is now the first FDA-approved facility to produce Choline C 11 injection.

Table II presents an overview of all new drugs and biologics launched in 2012, including line extensions (new indications, new combinations and important new formulations of previously marketed products). Products in this table are listed in alphabetical order.

Based on sales information for competing products, at least a few of the 2012 new drugs and biologics have blockbuster potential. Table III summarizes the estimated market size for selected products introduced last year.

Part II of this review will be published in next month's issue and will cover first-time generic drug approvals, orphan drug launches and designations, discontinuations, and mergers and acquisitions.

DISCLOSURES

The authors state no conflicts of interest.

Table II. *New product intros – 2012.*

Trade name (country)[1]	Company	Active ingredient[2]	Indication
Eklira® Genuair® (DK)	Almirall	Aclidinium bromide, powder for inhalation, 400 µg equiv. to delivered dose of 322 µg aclidinium	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema
Tetrabik (JP)	Biken; codeveloped with Mitsubishi Tanabe Pharma	Adsorbed purified pertussis-diphtheria-tetanus-inactivated poliomyelitis (Sabin strain) combined vaccine, syringe, 0.5 mL for s.c. injection	Prophylaxis of pertussis, diphtheria, tetanus and poliomyelitis
Quattrovac® (JP)	Astellas; manufactured and copromoted by Kaketsuken	Adsorbed purified pertussis-diphtheria-tetanus-inactivated poliomyelitis (Sabin strain) combined vaccine, syringe, 0.5 mL for s.c. injection	Prophylaxis of pertussis, diphtheria, tetanus and poliomyelitis
Suiny® (JP)	Sanwa; codeveloped with Kowa	Anagliptin, tablets, 100 mg	Treatment of type 2 diabetes
Synriam™ (IN)	Ranbaxy	Arterolane maleate/piperaquine phosphate*, tablets, 150 mg/750 mg	Treatment of uncomplicated *Plasmodium falciparum* malaria in adults
Inlyta® (US)	Pfizer	Axitinib, tablets, 1 & 5 mg	Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy
Dymista™ (US)	Meda	Azelastine hydrochloride/fluticasone propionate*, metered-dose nasal spray: 137 µg azelastine hydrochloride/50 µg fluticasone propionate in each 0.137-mL spray	Relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief
Azilva® (JP)	Takeda	Azilsartan, tablets, 20 & 40 mg	Treatment of arterial hypertension
Edarbyclor™ (US)	Takeda	Azilsartan medoxomil potassium/chlorthalidone*, tablets, 40 mg/12.5 mg & 40 mg/25 mg	Treatment of hypertension in adults
Ameluz® (DE)	Biofrontera	BF-200 ALA*, gel, 78 mg/g in 2-g tube	Treatment of actinic keratosis of mild to moderate intensity on the face and scalp
Kiklin® (JP)	Astellas; licensed from Amgen; copromoted by Sanwa Kagaku	Bixalomer, capsules, 250 mg	Treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis
Bosulif® (US)	Pfizer	Bosutinib, tablets, 100 & 500 mg	Treatment of adult patients with chronic, accelerated or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy

Continued

Table II. *(Cont.) New product intros – 2012.*

Trade name (country)[1]	Company	Active ingredient[2]	Indication
Bufyl® (GB)	Mercury Pharma	Bupivacaine hydrochloride/fentanyl citrate*, solution for infusion, 1 mg/mL and 2 µg/mL & 1.25 mg/mL and 2 µg/mL	Maintenance of anesthesia postoperatively; maintenance of epidural anesthesia during labor
Exparel™ (US)	Pacira	Bupivacaine liposomal, injectable suspension, 1.3% ***	For administration into the surgical site to produce postsurgical analgesia
Kyprolis™ (US)	Onyx Pharmaceuticals	Carfilzomib, lyophilized powder in single-use vials, 60 mg	Treatment of patients with multiple myeloma who have received at least two prior therapies
NovoThirteen® (DK)	Novo Nordisk	Catridecacog, powder and solvent for injection, 2500 IU	Long-term prophylactic treatment of bleeding in patients aged 6 years and above with congenital factor XIII-A subunit deficiency
Forxiga™ (GB)	AstraZeneca/Bristol-Myers Squibb	Dapagliflozin, tablets, 10 mg	Treatment of type 2 diabetes
Dacogen® (EU)	Astex/Janssen-Cilag	Decitabine, powder solution for i.v. infusion, 50 mg	Treatment of adult patients (age 65 years and older) with newly diagnosed de novo or secondary acute myeloid leukemia (AML) who are not candidates for standard induction therapy**
Stribild™ (US)	Gilead	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate*, tablets, 150 mg/150 mg/200 mg/300 mg	As a complete treatment regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naive
Truvada® (US)	Gilead	Emtricitabine/tenofovir disoproxil fumarate, tablets, 200 mg/300 mg	In combination with safer sex practices, for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk**
Xtandi® (US)	Medivation; codeveloped and comarketed by Astellas	Enzalutamide, capsules, 40 mg	Treatment of patients with castration-resistant prostate cancer who have previously received docetaxel
Amyvid™ (US)	Lilly/Avid Radiopharmaceuticals	Florbetapir F 18, solution in multidose vials, 10, 30 & 50 mL at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis	Positron emission tomography (PET) imaging of the brain, to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline
Excellagen™ (US)	Cardium Therapeutics	Formulated bovine collagen, kit consisting of four single-use 1.0-cc syringes, each containing 0.5 cc of formulated collagen topical gel (2.6%) and four single-use sterile flexible applicators	Management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds and draining wounds

Continued

Table II. *(Cont.) New product intros – 2012.*

Trade name (country)[1]	Company	Active ingredient[2]	Indication
Horizant® (US)	XenoPort; codeveloped with GlaxoSmithKline	Gabapentin enacarbil, extended-release tablets, 300 & 600 mg	Treatment of postherpetic neuralgia in adults**
Voraxaze® (US)	BTG	Glucarpidase, lyophilized powder in single-use vials, 1000 Units, for reconstitution with 1 mL Saline for Injection (USP) and i.v. injection	Treatment of toxic plasma methotrexate concentrations (>1 μm/L) in patients with delayed methotrexate clearance due to impaired renal function
Seebri® Breezhaler® (JP)	Novartis; licensed from Sosei/Vectura	Glycopyrronium bromide, inhalation capsules, 50 μg	Once-daily, long-term inhaled maintenance bronchodilator treatment for the relief of symptoms due to airway obstruction in patients with chronic obstructive pulmonary disease**
Hecolin® (CN)	Xiamen University/Xiamen Innovax Biotech	Hepatitis E vaccine, prefilled syringes for i.m. injection	Active immunization against hepatitis E virus infection
Hunterase® (KR)	Green Cross	Idursulfase beta, vials for i.v. injection, 6.0 mg/3 mL	Treatment for mucopolysaccharidosis type II (Hunter's syndrome)
Iremod (CN)	Simcere; licensed from Toyama	Iguratimod, tablets, 25 mg	Treatment of active rheumatoid arthritis
Picato® (US)	Leo Pharma	Ingenol mebutate, gel, 0.015% & 0.05% for topical use	Topical treatment of actinic keratosis
Aimix® (JP)	Dainippon Sumitomo Pharma	Irbesartan/amlodipine besilate*, tablets, 100 mg irbesartan/6.93 mg amlodipine besilate (equiv. to 5 mg amlodipine) & 100 mg irbesartan/13.87 mg amlodipine mesilate (equiv. to 10 mg amlodipine)	Treatment (second-line) of hypertension
Procoralan® (GB)	Servier	Ivabradine hydrochloride, tablets, 5 & 7.5 mg	Treatment of chronic heart failure NYHA II to IV class with systolic dysfunction, in patients with sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including β-blocker therapy or when β-blocker therapy is contraindicated or not tolerated**
Kalydeco™ (US)	Vertex	Ivacaftor, tablets, 150 mg	Treatment of cystic fibrosis in patients ages 6 years and older who have a G551D mutation in the *CFTR* gene
Sklice® (US)	Sanofi Pasteur; developed by Topaz	Ivermectin, lotion, 0.5% for topical use***	Topical treatment of head lice infestations in patients 6 months of age and older**
Imojev® (AU)	Sanofi Pasteur	Japanese encephalitis vaccine (live, attenuated), freeze-dried powder in vials, for reconstitution in sodium chloride and s.c. injection at a dose of 0.5 mL	Prophylaxis of Japanese encephalitis in individuals from 12 months of age and over

Continued

Table II. *(Cont.) New product intros – 2012.*

Trade name (country)[1]	Company	Active ingredient[2]	Indication
Levaquin® (US)	Janssen	Levofloxacin, tablets, 250, 500 & 750 mg; solution for injection, 500 mg/20 mL & 750 mg/30 mL	Treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis*, and prophylaxis for plague in adults and pediatric patients 6 months of age and older**
Linzess™ (US)	Ironwood codeveloped and comarketed by Forest	Linaclotide acetate, capsules, 145 & 290 µg	Treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation
Jentadueto™ (US)	Lilly/Boehringer Ingelheim	Linagliptin/metformin hydrochloride*, tablets, 2.5 mg/500 mg, 2.5 mg/850 mg & 2.5 mg/1000 mg	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate
Nimenrix™ (GB)	GlaxoSmithKline	Meningococcal group A, C, W-135 and Y conjugate vaccine, powder and solvent for solution for injection, 0.5 mL containing 5 µg each of *Neisseria meningitidis* serogroup A, C, W-135 and Y polysaccharides, each conjugated to tetanus toxoid carrier protein (44 µg total protein), supplied as vials + prefilled syringes and as vials + ampules	Active immunization of individuals from 12 months of age against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y
Dutoprol™ (US)	AstraZeneca	Metoprolol succinate extended-release/hydrochlorothiazide*, tablets, 25 mg/12.5 mg, 50 mg/12.5 mg & 100 mg/12.5 mg	Treatment of hypertension
Korlym™ (US)	Corcept Therapeutics	Mifepristone, tablets, 300 mg	Treatment of endogenous Cushing's syndrome**
Mitosol® (US)	Mobius Therapeutics	Mitomycin-c for solution, 0.2 mg/vial, kit for ophthalmic use***	For topical administration to the surgical site of glaucoma filtration surgery**
Poteligeo® (JP)	Kyowa Hakko Kirin	Mogamulizumab, vials for i.v. injection, 5 mL	Therapeutic antibody for patients with relapsed or refractory chemokine CCR4 receptor-positive adult T-cell leukemia-lymphoma (ATL)
Nevanac® (GB)	Alcon	Nepafenac, ocular suspension, 1 mg/mL	To reduce the risk of postoperative macular edema associated with cataract surgery in diabetes patients**
Synribo™ (US)	Teva	Omacetaxine mepesuccinate, lyophilized powder in vials, 3.5 mg for reconstitution with 1.0 mL of 0.9% Sodium Chloride Injection, USP, for s.c. injection	Treatment of adult patients with chronic phase or accelerated phase chronic myeloid leukemia with resistance and/or intolerance to two or more tyrosine kinase inhibitors
Signifor® (DE)	Novartis	Pasireotide, solution for injection, 0.3, 0.6 & 0.9 mg	Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed

Continued

Table II. *(Cont.) New product intros – 2012.*

Trade name (country)[1]	Company	Active ingredient[2]	Indication
Omontys® (US)	Affymax codeveloped and comarketed by Takeda	Peginesatide, single-use vials, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL & 6 mg/0.5 mL; single-use prefilled syringes, 1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL & 6 mg/0.5 mL; multiple-use vials, 10 mg/mL & 20 mg/2 mL; for i.v. or s.c. injection	Treatment of anemia due to chronic kidney disease in adult patients on dialysis
Fycompa® (GB)	Eisai	Perampanel, tablets, 2, 4, 6, 8, 10 & 12 mg	Adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures, in patients with epilepsy aged 12 years and older
Perjeta™ (US)	Genentech (Roche)	Pertuzumab, solution in single-use vials, 420 mg/14 mL (30 mg/mL)	In combination with trastuzumab and docetaxel chemotherapy, for the treatment of patients with HER2-positive metastatic breast cancer
Qsymia™ (US)	Vivus	Phentermine/topiramate*, extended-release capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg & 15 mg/92 mg	As an adjunct to a reduced-calorie diet and increased physical activity, for chronic weight management in adults
Pixuvri® (DK, FI)	Cell Therapeutics	Pixantrone maleate, powder for concentrate for solution for infusion, 29 mg pixantrone (as maleate). After reconstitution, each mL of concentrate contains 5.8 mg pixantrone	Monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas
Pyramax® (KR)	Medicines for Malaria Venture/Shin Poong	Pyronaridine tetraphosphate/artesunate*, film-coated tablets, 180 mg/60 mg	Treatment for uncomplicated *Plasmodium falciparum* malaria and *Plasmodium vivax* malaria
Mucosta® (JP)	Otsuka	Rebamipide, ophthalmic suspension, 2%***	Treatment of dry eye**
Stivarga® (US)	Bayer/Onyx	Regorafenib, film-coated tablets, 40 mg	Treatment of patients with metastatic colorectal cancer who have been previously treated with currently available therapies (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy)
Vyndaqel® (DE)****	Pfizer	Tafamidis meglumine, soft capsules, 20 mg	Treatment of transthyretin familial polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy
Elelyso™ (US)	Protalix BioTherapeutics; codeveloped and marketed by Pfizer	Taliglucerase alfa, lyophilized powder for injection in single-use vials, 200 Units, for reconstitution in diluent and i.v. infusion	Long-term replacement therapy for adults with a confirmed diagnosis of type 1 Gaucher's disease

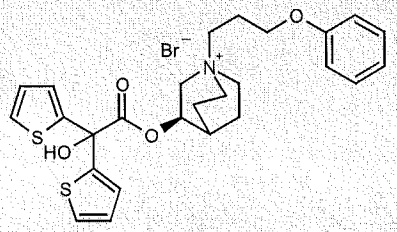
Continued

Table II. *(Cont.) New product intros – 2012.*

Trade name (Country)[1]	Company	Active ingredient[2]	Indication
Nucynta® ER (US)	Janssen	Tapentadol, tablets, extended-release, 50, 100, 150, 200 & 250 mg	Management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time**
Tenelia® (JP)	Mitsubishi Tanabe Pharma	Teneligliptin hydrobromide hydrate, tablets, 20 mg	Treatment of type 2 diabetes
Aubagio® (US)	Genzyme (Sanofi)	Teriflunomide, film-coated tablets, 7 & 14 mg	Treatment of patients with relapsing forms of multiple sclerosis
Xeljanz® (US)	Pfizer	Tofacitinib citrate, tablets, 5 mg	Second-line treatment of adults with moderately to severely active rheumatoid arthritis
Esmya® (GB)	PregLem (Gedeon Richter)	Ulipristal acetate, tablets, 5 mg	Preoperative treatment for moderate to severe symptoms of uterine fibroids**
Erivedge™ (US)	Genentech (Roche)	Vismodegib, capsules, 150 mg	Treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation
Zaltrap® (US)	Sanofi Aventis	Ziv-aflibercept, single-use vials, 100 mg/4 mL & 200 mg/8 mL (25 mg/mL) for intravenous infusion	For use in combination with a FOLFIRI (folinic acid, fluorouracil and irinotecan) regimen to treat adults with colorectal cancer**

[1]Country codes are the abbreviations used by the World Intellectual Property Organization.
[2]Products are ordered alphabetically by active ingredient.
*New combination.
**New indication.
***New formulation.
****Launched in 2011.

Chemical structures of NCEs launched in 2012



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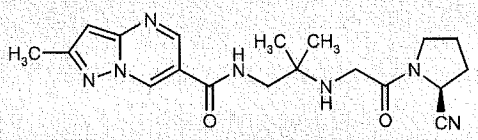

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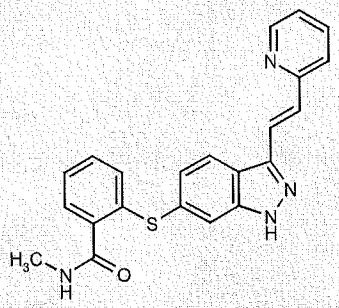

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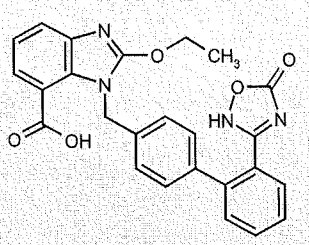

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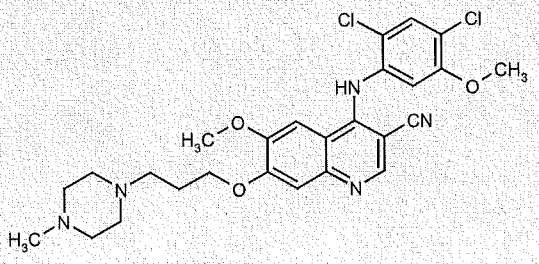
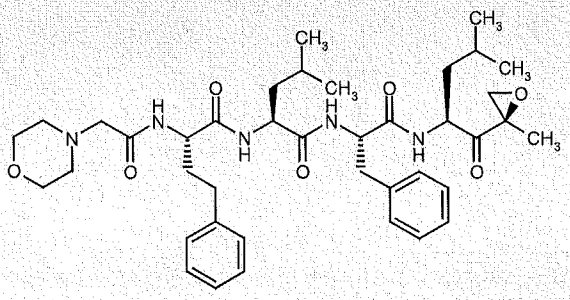
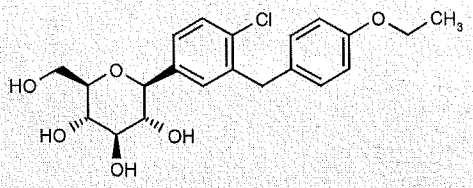


Bosutinib

Chemical structures of NCEs launched in 2012



Carfilzomib



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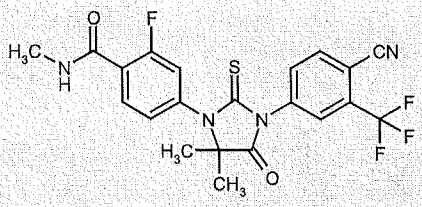
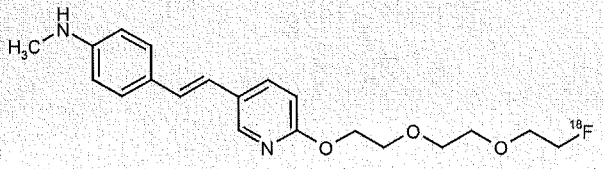


Enzalutamide



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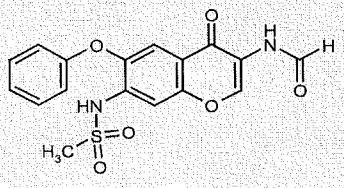
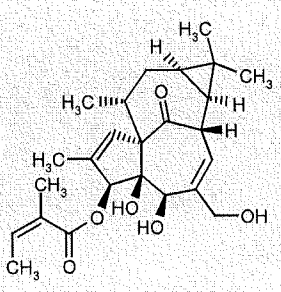
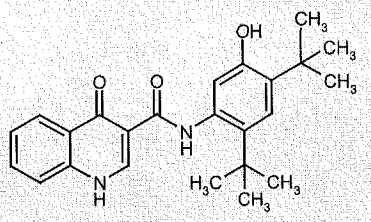


Iguratimod

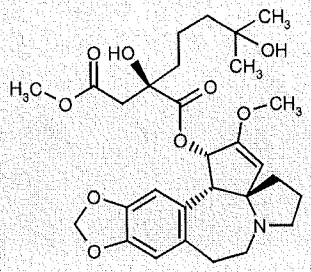


Ingenol mebutate

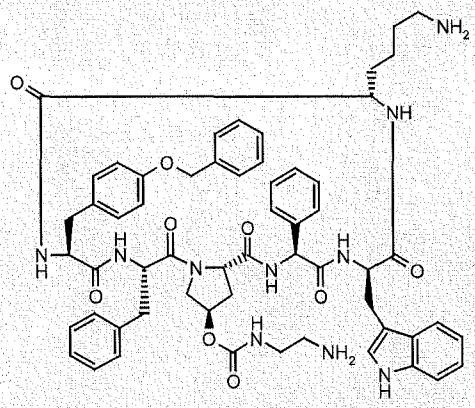
Chemical structures of NCEs launched in 2012



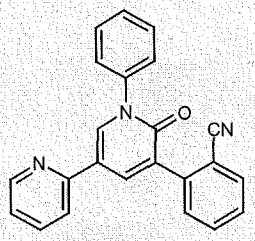
Ivacaftor



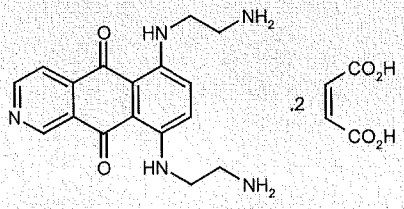
Omacetaxine mepesuccinate



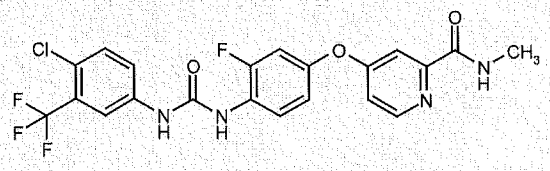
Pasireotide



Perampanel

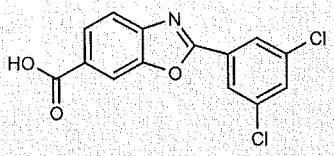


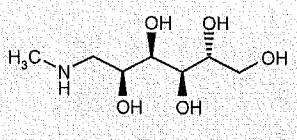
Pixantrone maleate



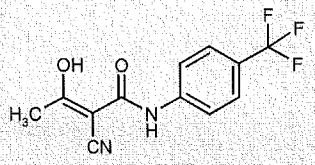
Regorafenib

Chemical structures of NCEs launched in 2012

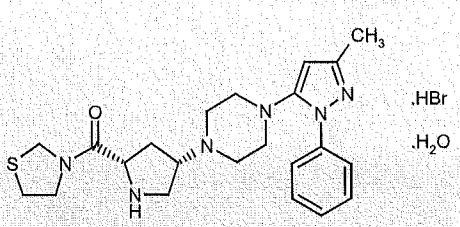




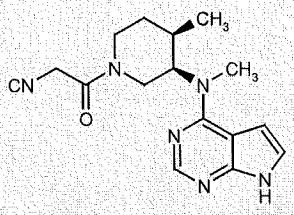
Tafamidis meglumine

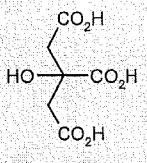


Teriflunomide

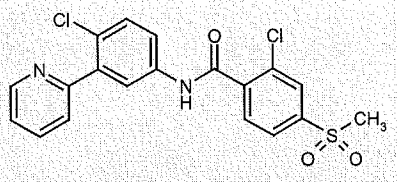


Teneligliptin hydrobromide hydrate





Tofacitinib citrate



Vismodegib

Table III. *Estimated market size for selected new drugs and biologics and new line extensions launched in 2012.*

Product (trade name)	Company	Indication	Competitors' trade names	2012 total sales (forecast) (million, USD)
Azilsartan (Azilva)	Takeda	Treatment of arterial hypertension	Coversyl; Bystolic; Avapro; Irbetan; Parapres; Atacand; Blopress; Tanatril; Nisis/Nisisco; Diovan/Codiovan; Tracleer; Micardis/Micardis HCT; Olmetec/ Olmetec Plus/Benicar/Benicar HCT; Tekturna/Rasilez; Seloken/ Tropol XL; Hyzaar/Cozaar; Caduet; Exforge; Calblock; Atelec; Zanidip; Calvan; Maintate; Artist	21,382.95
Azilsartan medoxomil potassium/ chlorthalidone (Edarbyclor)	Takeda			
Irbesartan/amlodipine besilate (Aimix)	Dainippon Sumitomo Pharma			
Metoprolol succinate extended-release/ hydrochlorothiazide (Dutoprol)	AstraZeneca			
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	Gilead	HIV-1 infection in adults	Epivir; Emtriva; Sustiva; Viread; Reyataz; Combivir; Trizivir; Lexiva; Intelence; Kaletra; Prezista; Selzentry; Kivexa/Epzicom; Truvada; Atripla; Isentress; Complera/Eviplera	17,133.97
Anagliptin (Suiny)	Sanwa/Kowa	Treatment of type 2 diabetes	Glucobay; Amaryl; Basen; Fastic; Actos; Surepost; NovoNorm/ Prandin/Prandimet; Glufast; Metgluco; Byetta; Bydureon; Victoza; Galvus; Kombiglyze XR/Onglyza; Januvia; Glactiv; Nesina; Efficib/Tesavel; Janumet; Liovel; Glubes	13,800.87
Dapagliflozin (Forxiga)	Bristol-Myers Squibb/AstraZeneca			
Linagliptin/metformin hydrochloride (Jentadueto)	Lilly/Boehringer Ingelheim			
Teneligliptin hydrobromide hydrate (Tenelia)	Mitsubishi Tanabe Pharma			
Teriflunomide (Aubagio)	Genzyme (Sanofi)	Treatment of multiple sclerosis	Betaferon/Betaseron; Copaxone; Avonex; Tysabri; Rebif	11,483.28
Aclidinium bromide (Eklira Genuair)	Almirall	Treatment of chronic obstructive pulmonary disease	Foradil; Ventolin; Serevent; Spiriva; Xopenex; Daliresp; Daxas; Brovana; Symbicort; Turbuhaler; Arcapta, Neohaler/ Onbrez Breezhaler; Combivent	11,287.98
Glycopyrronium bromide (Seebri Breezhaler)	Novartis			
Pertuzumab (Perjeta)	Genentech (Roche)	Treatment of patients with HER2-positive metastatic breast cancer	Fareston; Faslodex; Herceptin; Halaven; Abraxane; Tykerb/Tyverb	8,153.17
Azelastine hydrochloride/fluticasone propionate (Dymista)	Meda	Relief of symptoms of seasonal allergic rhinitis	Rhinocort; Nasacort; Onon; Nasonex; Baynas; Omnaris; Zetonna; Flixonase/Flonase; Singulair; Kipres; Avamys/ Veramyst; Erizas	7,511.55
Peginesatide (Omontys)	Affymax/Takeda	Treatment of anemia	Espogen; Epogen; Aranesp; Procrit/Eprex; Mircera	6,589,05

Continued

Table III. *(Cont.) Estimated market size for selected new drugs and biologics and new line extensions launched in 2012.*

Product (trade name)	Company	Indication	Competitors' trade names	2012 total sales (forecast) (million, USD)
Carfilzomib (Kyprolis)	Onyx Pharmaceuticals	Treatment of multiple myeloma	Thalomid; Doxil/Caelyx; Velcade; Revlimid	4,945.42
Tapentadol (Nucynta ER)	Janssen	Management of neuropathic pain	Cymbalta; Qutenza	4,909.63
Nepafenac (Nevanac)	Alcon	Prevention of postoperative macular edema associated with cataract surgery	Lucentis	3,931.34
Ivabradine hydrochloride (Procoralan)	Servier	Treatment of chronic heart failure	Atacand; Blopress; Artist; Inspra	3,679.31
Regorafenib (Stivarga)	Bayer/Onyx	Treatment of metastatic colorectal cancer	Eloxatin; Erbitux; Vectibix	2,892.93
Ziv-aflibercept (Zaltrap)	Sanofi Aventis			
Axitinib (Inlyta)	Pfizer	Treatment of advanced renal cell carcinoma	Nexavar; Votrient; Sutent	2,463.87
Iguratimod (Iremod)	Simcere/Toyama	Treatment of rheumatoid arthritis	Azulfidine EN; Hypen; Rimatil; Metolate; Rheumatrex; Kineret; Enbrel; Orencia; Arthrotec; Simponi	2,286.86
Tofacitinib citrate (Xeljanz)	Pfizer			
Bosutinib (Bosulif)	Pfizer	Treatment of chronic myelogenous leukemia	Sprycel; Tasigna	1,926.67
Omacetaxine mepesuccinate (Synribo)	Teva			
Enzalutamide (Xtandi)	Medivation/Astellas	Treatment of castrate-resistant prostate cancer	Odyne; Estracyt; Lupron; Enanton; Casodex; Vantas; Eligard	1,510.40
Perampanel (Fycompa)	Eisai	Treatment of epilepsy	Sabril; Excegran; Zonegran; E Keppra; Keppra/Keppra XR	1,456.77
Bixalomer (Kiklin)	Astellas/Amgen/ Sanwa Kagaku	Treatment of hyperphosphatemia	RenaGel/Renvela; Fosrenol	1,260.89
Taliglucerase alfa (Elelyso)	Protalix BioTherapeutics/Pfizer	Treatment of type 1 Gaucher's disease	Zavesca; Cerezyme; VPRIV	1,184.35
Rebamipide (Mucosta)	Otsuka	Treatment of dry eye	Hyalein; Restasis; Diquas	1,097.86
Pertussis-diphtheria-tetanus-inactivated poliomyelitis vaccine (Tetrabik)	Biken/Mitsubishi Tanabe Pharma	Prophylaxis of pertussis, diphtheria, tetanus and poliomyelitis	Pentacel; Pentaxim	792.00
Pertussis-diphtheria-tetanus-inactivated poliomyelitis vaccine (Quattrovac)	Astellas/Kaketsuken			

Continued

Table III. *(Cont.) Estimated market size for selected new drugs and biologics and new line extensions launched in 2012.*

Product (trade name)	Company	Indication	Competitors' trade names	2012 total sales (forecast) (million, USD)
Meningococcal vaccine (Nimenrix)	GlaxoSmithKline	Prevention of invasive meningococcal diseases	Menactra	641.29
Pixantrone maleate (Pixuvri)	Cell Therapeutics	Treatment of non-Hodgkin B-cell lymphomas	Treanda; Zevalin	626.00
Ivacaftor (Kalydeco)	Vertex	Treatment of cystic fibrosis	Pulmozyme; Cayston	609.92
Linaclotide acetate (Linzess)	Ironwood/Forest	Treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation	Zelmac; Resolor; Dulcolax; Amitiza; Laxoberon; Forlax	601.91
Idursulfase beta (Hunterase)	Green Cross	Treatment of mucopolysaccharidosis type II (Hunter's syndrome)	Elaprase	477.73
Gabapentin enacarbil (Horizant)	XenoPort/ GlaxoSmithKline	Treatment of postherpetic neuralgia	ReQuip; Neupro	407.47
Formulated bovine collagen (Excellagen)	Cardium Therapeutics	Wound management	Dermagraft	179.87
Phentermine/topiramate (Qsymia)	Vivus	Chronic weight management in adults	Xenical	131.97
Japanese encephalitis vaccine (Imojev)	Sanofi Pasteur	Prophylaxis of Japanese encephalitis	Jebik V	75.64
BF-200 ALA (Ameluz) Ingenol mebutate (Picato)	Biofrontera Leo Pharma	Treatment of actinic keratosis	Solaraze/Actikerall	40.36
Ulipristal acetate (Esmya)	PregLem (Gedeon Richter)	Preoperative treatment for uterine fibroids	Suprecur	13.87

Exhibit B

ORIGINAL RESEARCH

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The Impact of Incremental Innovation in Biopharmaceuticals

Drug Utilisation in Original and Supplemental Indications

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3 Harvard University, Cambridge, Massachusetts, USA

Abstract

Background. The apparent decrease in the rate of approval of new molecular entities has provoked extensive discussion and fears that the productivity of biopharmaceutical research and development has severely declined in recent years.
Objective. To investigate the extent to which traditional measures of innovative output neglect important innovations that occur after a drug receives initial market approval.
Methods and Results. Data on drug utilisation by diagnosis for the period 1999–2004 were combined with data on the approval histories of three important classes of drugs: ACE inhibitors, histamine H_2-antagonists/proton-pump inhibitors, and selective serotonin/norepinephrine reuptake inhibitors. Counts of new drug approvals by the FDA were classified as new indications, new dosages, new combinations, new formulations, and labeling for expanded populations. Large numbers of such "supplemental" approvals were obtained. The share of drug utilisation in indications other than that specified in the initially approved labeling was computed, and found to be very substantial in two out of the three drug classes considered.
Conclusions. Significant incremental innovation to existing pharmaceutical products has been occurring in the form of supplementary approvals for new dosages, formulations, and indications. These innovations account for a substantial share of drug utilisation and associated economic and medical benefits. Productivity trends for research and development based on counts of new molecular entities alone have therefore overlooked an important source of innovation in biopharmaceuticals.

Incremental Innovation in Pharmaceuticals

The rising costs of bringing new drugs to market have focused attention on the productivity of biopharmaceutical research. The apparent sharp decline in the rate of new drug approvals in recent years from a high of 62 new molecular entities (NMEs) in 1996 to less than 30 per year in 2003-4[1] has provoked extensive discussion of an innovation 'crisis' in the industry (see, for example, El Feki[1]). Set against continued substantial growth in industry research and development (R&D) spending, this trend suggests sharply falling research productivity. But has the rate of innovation really declined? Counting approvals of new molecules captures only a portion of the economic and health benefits generated by biopharmaceutical research. Although the approval of a new drug normally represents a significant advance in therapy, and therefore merits close attention, a focus on counting new drug approvals may present a significantly distorted picture of the outputs and impacts of biopharmaceutical research.

Simple counts of NMEs conceal the fact that not all new drugs are of the same quality; 'blockbusters' with more than $US1 billion in annual US sales, for example, are treated equally with newly approved drugs that achieve only $US50 million in annual US sales. Weighting such counts by measures of the scientific, economic or health impact of each drug can give a more accurate measure of the industry's innovative output.[2] However, such a quality-weighted output measure would still be driven by the initial regulatory approval of a drug, completely overlooking follow-on or incremental innovations that result in improved formulations or new uses of the drug in treating additional diseases and disorders.

As part of the New Drug Application (NDA) or Biologics License Application (BLA), the sponsor of a new drug typically provides clinical evidence in support of US FDA approval for a particular medical condition, commonly designated as the original or primary indication[3]. However, in many cases, this is not the end of research on the drug. Simultaneous with or prior to undertaking phase III trials in support of the primary indication approval, the sponsor may engage in additional phase II or phase III trials that examine the efficacy and safety of the drug in treating other medical conditions. Moreover, after receiving initial FDA approval, the sponsor may carry out further research in so-called phase IV trials, developing evidence to support supplemental FDA approvals for additional indications.[4]

Many analysts implicitly or explicitly exclude such supplemental or secondary approvals when measuring research output, presumably on the grounds that they are perceived as constituting trivial forms of innovation. Even though the scien-

1 This count aggregates US FDA approvals of 'small molecule' New Drug Applications and 'large molecule' Biologics License Applications.

2 Comanor,[2] for example, calculated the output of the pharmaceutical industry as the sum of the first two years' sales of all new chemical entities. Vernon and Gusen[3] went a step further and decomposed the Comanor output measure into two parts: the number of newly approved chemical entities (a function of R&D), and the discounted sales per newly approved chemical entity (over 2 years, hypothesised to reflect in part the effectiveness of marketing promotional efforts). More recently, Mason[4] has combined these various themes, suggesting that R&D productivity distinguishes efficiency (total milestones/total R&D resources) from effectiveness (discounted new product sales/number of major first approvals). Dranove and Meltzer[5] have attempted to differentiate the quality of new drugs, developing measures of importance from scientific novelty as measured by whether the US FDA designated the NDA 'priority' rather than 'standard' review status; number of citations in medical textbooks and journals and in subsequent patent applications; number of worldwide introductions; and economic indicators such US sales in the first 5 years on the market. Wardell and DiRaddo[6] discuss using various possible compromises of both commercial and technological success measures to quantify innovation, with technological success determined by a consensus expert panel.

3 In some cases, several distinct indications are simultaneously approved with the initial NDA/BLA.

4 Not all such studies have positive outcomes. For example, the clinical trial that led Merck to voluntarily withdraw its acute pain and osteoarthritis agent, Vioxx®, in September 2004 was a phase IV study designed to obtain evidence in support of the use of this drug for preventing colorectal cancer.

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tific breakthroughs associated with the early development of the drug may not be present, the economic and health impacts of this additional research can be substantial. Researchers have long argued that follow-on research in medicine can generate very significant advances in treatment, often for an indication quite unrelated to the initial major breakthrough. For example, Spivey et al.[7] (page 368) have stated: "Examples of this phenomenon include the protective effects of ß-blockers against myocardial infarction and coronary death, the use of ß-blockers to prevent migraine and reduce blood pressure, the antiarrhythmic actions of lidocaine, the use of amantidine to treat parkinsonism, the anti-epileptic efficacy of carbamazepine, the use of diazepam for status epilepticus, and the uricosuric effect of probenecid." (For related discussions, see Beales[8] and the references cited therein.)

Research that supports the use of existing drugs in new indications can therefore generate substantial health benefits. One measure of these benefits is the utilisation and sales volumes for new indications. Anecdotal evidence suggests that sales volumes for supplemental indications can in some cases be considerably larger than sales from the original primary approved indications. For example, while Zantac®[5] (ranitidine) was originally approved for treatment of a hypersecretory condition known as Zollinger-Ellison syndrome (a relatively rare condition) and for short-term treatment of active duodenal ulcer (a considerably more common condition but limited to acute episodes), supplementary indication approvals have been obtained for much larger populations, and presumably much greater sales volumes, such as for the treatment of gastroesophageal reflux disease (GERD; a severe but relatively common form of heartburn) and the maintenance of healing of erosive esophagitis (a common condition requiring long-term treatment).

In addition to the use of a drug in new indications, innovation that takes the form of improved formulations, delivery methods and dosing protocols may also generate substantial benefits associated with improved patient compliance, greater efficacy as a result of improved pharmacokinetics, reduced adverse effects or the ability to effectively treat new patient populations. Again, anecdotal evidence suggests that these innovations can generate significant increases in utilisation and sales. For example, the development of Valtrex® (vancyclovir), a prodrug version of aciclovir (acyclovir), enabled use of the drug in suppression and prevention of genital herpes with once-daily dosing, significantly expanding its use beyond its initial labelling.[9]

One economic indicator of the magnitude of these benefits is the extent to which supplemental indication approvals provide incentives for industrial R&D. The available evidence suggests that the prospect of additional sales beyond the initial indication provides commercial justification for extensive R&D expenditure. For example, in their study of the costs of developing new drugs, DiMasi et al.[10] estimate that post-approval R&D is about 25.8% of total out-of-pocket R&D costs ($US140 of $US543 million), whereas in capitalised costs it is about 10.6% of total costs ($US95 of $US897 million) (currency values for year 2000). CMR International estimates that 30% of industry R&D spending is devoted to "line extensions" (quoted in Frank[11]), which are new or modified uses for an existing product.

Mason[4] therefore recommends adjusting the standard NME-based measures of the innovative output of biopharmaceutical R&D by counting each new indication approval as equal to 0.5 of an NME, and each major line extension as equal to 0.25 of an NME, and then adding these to the traditional measure. While this *ad hoc* procedure is a step in the right direction, it has surprisingly little quantitative foundation; indeed, there is relatively little systematic evidence on the extent to which drug utilisation is driven by these forms of incremental innovation, and therefore little basis for assigning them these particular weights.

To address this lack of evidence, we seek to characterise and quantify incremental innovation for a number of commonly used drug classes.

5 The use of trade names is for product identification purposes only and does not imply endorsement.

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Incremental innovation is defined here as the number and kinds of supplementary indication approvals received by therapeutic class, as well as the actual utilisation of these medicines beyond their primary indication. We have chosen to focus on three therapeutic classes: ACE inhibitors; histamine H_2-antagonists and proton pump inhibitors (PPIs); and selective serotonin/noradrenaline reuptake inhibitors. These classes were selected based on the fact that they represent three very commonly used classes of drugs and the fact that the first drug in each class was approved at least 20-30 years ago, thereby allowing sufficient time for us to investigate the lifecycle of these drugs. Moreover, these therapeutic classes have been the focus of previous research by the current authors.

Supplementary Indication Approvals

The US FDA classifies NDAs into seven categories that correspond to markedly different types of innovation. These categories are: (1) New Molecular Entity (NME); (2) New Salt of Previously Approved Drug; (3) New Formulation of Previously Approved Drug (not a new salt or new molecular entity); (4) New Combination of Two or More Drugs; (5) Already Marketed Drug Product – Duplication (i.e. new manufacturer); (6) New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription-only to over-the-counter); and (7) Already Marketed Drug Product – No Previously Approved NDA. The FDA defines an NME as "a new drug product containing, as its active ingredient, a chemical substance marketed for the first time in the United States." Between 1990 and 2003, the Center for Drug Evaluation and Research (CDER) approved 1171 NDAs.[6] Of these, 399 (34%) were NMEs and 769 (66%) were non-NMEs.[7]

With respect to category 3, new formulations treating the primary approval indication can take the form of new dosage forms (e.g. continuous or sustained release) or new delivery systems (inhaled vs injection), that are frequently claimed to facilitate better patient tolerance and adherence to recommended therapy, and/or to have better pharmacokinetic properties, thereby possibly increasing the size of the potential treatment population. Such product improvements are probably almost all driven by the innovating sponsor's in-house R&D. While these incremental product improvements are usually envisaged as examples of product lifecycle management, and are often portrayed as attempts to extend artificially the patent life of the product, they may also be impor-

6 See Graham[12] (chapter 2) for further discussion and references. The BLA classification system differs somewhat from that for the NDA. Until 1 October 2003, the BLA oversight was performed by the Center for Biologics Evaluation and Research (CBER). On 1 October 2003, product oversight responsibilities for new biologics were transferred from CBER to CDER.

7 Tufts Center for the Study of Drug Development has defined an alternative to the NME, the New Chemical Entity (NCE). Tufts CSDD defines an NCE as "any new molecular compound (excluding diagnostic agents, vaccines and other biologic compounds) not previously approved for human use by CDER," excluding new salts, esters and dosage forms of previously approved compounds. When measuring the output of biopharmaceutical R&D, the Tufts investigators typically sum the number of NCEs and new BLA approvals.[13]

8 For example, NitroMed Inc. recently obtained US FDA approval for their combination product BiDil® (a fixed-dose combination of two off-patent drugs, isosorbide dinitrate and hydralazine hydrochloride), which has been newly indicated "... to improve survival, prolong time to hospitalization for heart failure and improve patient-reported functional status, as an adjunct to current heart failure therapy in self-identified black patients." Evidence supporting this unusual FDA approval was based on the African American Heart Failure Trial, in which self-identified black patients taking BiDil® in addition to current standard heart failure therapies experienced a significant 43% decrease in the risk of mortality ($p = 0.012$). An earlier trial with this combination therapy was unable to achieve statistical significance over a mixed-race treatment population, but detailed retrospective analysis of the data by Dr Anne Taylor at the University of Minnesota Medical School documented an apparently statistically significant placebo-treatment separation for the black subpopulation. This retrospective analysis led NitroMed to sponsor the additional confirmatory clinical study leading to its obtaining final FDA approval. Hence, in some cases new combination treatments embody clinically significant new treatment therapies, which in this case were observed only in a subpopulation.[14]

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tant drivers of increased utilisation earlier in the product lifecycle.

Category 4 – new combinations of previously approved drugs – frequently includes several off-patent drugs in a fixed dosage combination produced by generic drug manufacturers. In these situations, little R&D is required to obtain US FDA approval to market the drug, but patients can benefit from less complicated dosing. However, in some cases the combination drug offers surprising additional efficacy, not just convenience, and is the result of considerable additional clinical investigation.[8]

Category 6 – new indication claims for already marketed products – reflects the results of innovative activity that establishes safety/efficacy in the treatment of additional diseases or conditions beyond that approved in the primary indication approval. These product improvements may be the result of purposeful R&D expenditures by the innovator, but in some cases may emerge from unexpected discoveries made by physician/clinician 'users'. An example in the context of medical devices is the discovery that the vagus nerve stimulator initially approved for the use of treatment-resistant epilepsy was also apparently effective in dealing with treatment-resistant major depressive disorder.[9] There is, incidentally, a large body of literature, much of it dealing in the electronics and related product industries, that documents and champions the role of users in communicating back to manufacturers the results of users' adaptations or unapproved 'experiments' with the manufacturer's product, thereby leading to 'customer-induced innovation'; see, for example, von Hippel[16,17] and the references cited therein.

To better understand the sources of innovation and the relative importance of follow-on innovation, it is useful to decompose total drug utilisation in a way that corresponds to those innovations identified by the FDA as being in NDA categories 1, 3, 4 or 6 – NMEs, new formulations, new combinations and new indication claims.[10] Each of these categories of innovation may be an important source of increased utilisation, having associated health and economic benefits.

A further category of drug utilisation that falls outside the FDA's approval categories is so-called off-label use, which could be defined in a number of ways, but generally refers to use beyond that stated in the product labelling associated with the FDA primary and supplemental approvals. Off-label use is controversial and raises some difficult issues that we do not address here; these are discussed by other authors.[8,19-26] Off-label use may be particularly difficult to identify. In some cases the off-label indication is unambiguously clinically differentiated from the on-label indication and there is little difficulty distinguishing between the two in data on drug usage. However, in other cases, the clinical features of the condition may require detailed diagnostic testing or involvement of specialists to distinguish among conditions with overlapping symptoms. Moreover, specialists and primary care doctors may employ differing diagnostic criteria. For example, a primary care/internal medicine physician may give a broad 'catch-all' descriptive diagnosis such as abdominal pain, which could encompass a number of different and more specific diagnoses identifiable by a specialist gastroenterologist. Even more difficult to identify from aggregate data is off-label use taking the form of using the drug for an indicated diagnosis but for a patient in an unapproved population (e.g. paediatric or geriatric use).

Data and Methods

We examine product labelling and utilisation issues for three widely prescribed therapeutic classes: ACE inhibitors (initially indicated for essential hypertension), PPIs and H_2-antagonists (PPI/H_2, typically initially indicated for acute phase treatment of duodenal ulcers and for the

9 For a case study of Cyberonics' development history of its vagus nerve stimulator system, see Berndt and Russell.[15]
10 Yet another category might be the utilisation of spin-off drug/biologic therapies, new molecules derived from the original innovation that have improved therapeutic properties. For a discussion of such follow-on drug development, see DiMasi and Paquette.[18]

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Zollinger-Ellison hypersecretory condition) and the selective serotonin/noradrenaline reuptake inhibitors (SSRI/SNRIs, initially indicated for treatment of acute phase major depressive disorder). In each of these three classes, supplemental NDA approvals by the US FDA widened the range of approved uses, particularly so in the case of the SSRI/SNRIs.[27]

Two broad categories of data were required for our empirical analysis: FDA approval dates for original and supplemental indications, including the wording of approved labelling, and quantitative data on the composition of the utilisation of various drugs by diagnosis. FDA-approved labelling was then linked to the diagnostic composition of drug utilisation.

Timelines of all major NDA, supplementary new drug application (sNDA) and Abbreviated New Drug Application (ANDA) approvals were constructed for each molecule using as a primary source the NDA Pipeline database published by FDC Reports (see http://www.inteleos.com); ANDAs are typically filed by generic manufacturers either in anticipation of or following expiration of the innovator's patent). This database contains a summary of all major FDA applications and approvals since 1991. In addition, the approvals were compared with the FDA's Drugs@FDA online database,[28] which provided information prior to 1991 and validation of post-1991 data. When information was not complete and/or when there were inconsistencies, the data were compared with the labelling language published in historical volumes of the *Physicians' Desk Reference* (1977-92). In a very small number of cases, precise approval dates were not available; however, this occurred only for several drugs approved in the early 1980s. In addition, complete information on dates of ANDA and formulation NDA approvals were not readily available prior to 1991.

Data from the National Drug and Therapeutic Index (NDTI), a nationally representative continuing survey of a random sample of approximately 3500 office-based US physicians administered by IMS Health (Plymouth Meeting, PA, USA), was used to estimate the volume of utilisation of each drug, and the corresponding proportion of usage attributable to different diagnoses. The NDTI survey is based on a two-stage stratified cluster design, where in the first stage physicians are sampled from 29 specialty groups and four geographic regions. In the second stage, sampled physicians are asked to complete survey questionnaires at each patient-physician encounter from two randomly selected consecutive workdays per quarter (including weekends and holidays).

Physician contact with patients in the NDTI survey consists largely of office visits, although encounters with patients during telephone calls, as well as hospital and nursing home visits, are also included. Physicians report information on all new or continuing drugs for each patient. NDTI does not capture patient adherence to medications, but reflects the physician's best knowledge of the medications taken by each patient. Certain non-prescribing specialties, including anaesthesiology, radiology and pathology, are not included in the NDTI survey. National estimates are projected based on the sample data. Further information on the NDTI database is available elsewhere.[24,29,30]

At each patient encounter, physicians are required to record at least one diagnosis code (using the International Classification of Diseases, 9th edition [ICD-9] coding system) and also to record any medication recommended (using the USC [Universal System of Classification]) to the patient either on a prescription or over-the-counter basis. Physicians are instructed to make the 'reason for visit' the primary diagnosis code and are able to add additional diagnoses if necessary. Physicians may also choose not to recommend any medications; when this occurs, this is also recorded.

Thus, the NDTI survey data can provide estimates of drug mentions for a given ICD-9 diagnosis. The NDTI reports drug mentions separately for both generic and branded versions of the drug; however, since the consistency and accuracy with which branded and generic versions were distinguished in the survey is unclear, for the purposes of this analysis, these quantities were combined. The information collected at each patient

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Table I. Comparison of approvals by therapeutic class

	ACE inhibitors	PPI/H_2-antagonists	SSRI/SNRIs
Number of molecules	10	9	10
Number of indications	6	8	10
Date (given in mm/dd/yy) of earliest approval	6/4/1981	16/8/1977	30/12/1985
Number of sNDA new indication approvals	35	41	59
Number of new dosage approvals	10	30	8
Number of new combination approvals	13	4	1
Number of new formulation approvals	1	34	16
Number of expanded population approvals	2	3	7

PPI = proton pump inhibitors;
sNDA = supplementary new drug application;
SSRI/SNRIs = selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors.

encounter by NDTI is used for research purposes only and not for reimbursement reasons, implying that it is not likely to be subject to many of the biases that affect other data sources, such as upcoding for reimbursement reasons, and altered diagnosis to avoid stigma (see, for example, Pomerantz[31] and the references cited therein).

Quarterly NDTI data were obtained from IMS Health for the period 1999Q2 to 2004Q4 for ACE inhibitors, and for 1999Q2 to 2005Q1 for the SSRI/SNRI and PPI/H_2 classes. Important challenges in working with NDTI data include the inability to control for comorbidities and occasional poor correspondence between ICD-9 codes

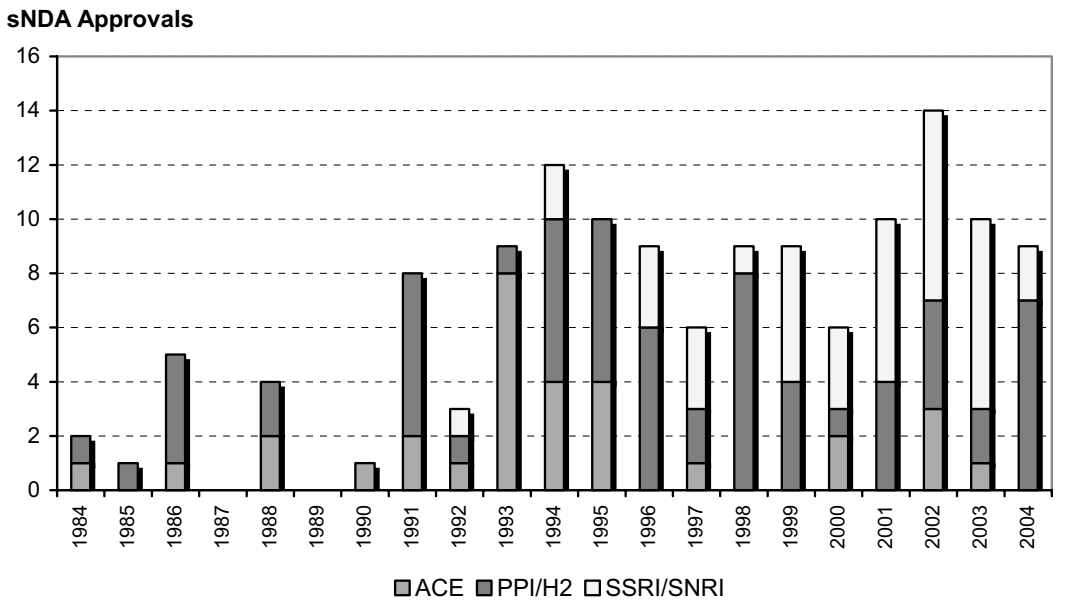

Fig. 1. Supplementary new drug application (sNDA) approvals for new indications per year, by therapeutic class. **ACE** = ACE inhibitors; **PPI/H_2** = proton pump inhibitors/H_2-antagonists; **SSRI/SNRI** = selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors.

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Table II. Date of approval of primary and supplementary indications, ACE inhibitors (see Appendix for more details); dates (given in dd/mm/yy) in bold type indicate primary indication approval

	Hypertension	Heart failure	Ventricular dysfunction	Acute MI	Diabetic nephropathy	Risk reduction[a]
Accupril®	**19/11/91**	23/10/93	-	-	-	-
Prinivil®/Zestril®	**29/12/87**	6/6/93	-	24/11/95	-	-
Capoten®	**6/4/81**	1984[b]	23/9/93		25/1/94	-
Vasotec®	**24/12/85**	24/6/88	4/11/93	-	-	-
Altace®	**28/1/91**	22/8/95	-	-	-	4/10/00
Monopril®	**16/5/91**	2/5/95	-	-	-	-
Mavik®	**26/4/96**	2/7/97	2/7/97	-	-	-
Lotensin®	**5/6/91**	-	-	-	-	-
Aceon®	**30/12/93**	-	-	-	-	-
Univasc®	**19/4/95**	-	-	-	-	-

a Risk reduction of myocardial infarction, stroke and death from cardiovascular causes.

b More detailed date of approval information not available.

and FDA-approved indications. ICD-9 codes recorded in the NDTI data are typically quite narrow and highly specific (e.g. ICD-9 250.3 Diabetes with Renal Manifestations), whereas FDA-approved indications may be much broader, or very difficult to match to specific ICD-9 diagnoses. For example, while the FDA labelling states that certain SSRIs are indicated for the treatment of generalised anxiety disorders, there are specific ICD-9 codes corresponding to anxiety states and hysteria. In other cases, ICD-9 codes are very broad, e.g. 311.0 Depressive Disorder Not Elsewhere Classified, and 789.0 Abdominal Pain. Some ICD-9 diagnosis codes are known to be common symptoms associated with treatment of FDA-indicated conditions, such as oedema, atrial fibrillation and flutter for heart failure, and proteinuria for diabetic nephropathy. Comorbidities or multiple drug therapy for a single condition may also result in significant problems in inter-

Table III. Date of approval of primary and supplementary indications of proton pump inhibitors/H_2-antagonists (see Appendix for more details); dates (given in dd/mm/yy) in bold type indicate primary indication approval

Drug	GERD/oesophagitis	Duodenal ulcer	Gastric ulcer	Hypersecretory condition	Helicobacter pylori eradication	NSAID ulcer	Gastrointestinal bleeding	Over-the-counter heartburn
Nexium®	**20/2/01**	-	-	-	**20/2/01**	24/11/04	-	-
Prilosec®	**14/9/89**	21/6/91	22/3/96	21/6/91	15/4/96	-	-	20/6/03
Prevacid®	8/4/96	17/4/97	**10/5/95**	**10/5/95**	17/6/97	30/11/00	-	-
Zantac®	30/5/86	**9/6/83**	30/5/86	**9/6/83**	-	-	-	19/12/95
Tagamet®	7/3/91	**6/8/77**	1984[a]	**6/8/77**	-	-	13/11/91	15/11/95
Pepcid®	10/12/91	**15/10/86**	17/10/88	**15/10/86**	-	-	-	28/4/95
Protonix®	**2/2/00**	-	-	19/10/01	-	-	-	-
Aciphex®	**19/8/99**	**19/8/99**	-	**19/8/99**	8/11/02	-	-	-
Axid®	26/7/91	**12/4/88**	21/9/93	-	-	-	-	9/5/96

a More detailed date of approval information not available.

GERD = gastroesophageal reflux disease.

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preting counts of drug mentions. For example, if a patient were to present with osteoarthritis, the primary diagnosis may be recorded as osteoarthritis, and if the physician were to recommend a nonsteroidal anti-inflammatory drug (NSAID) as well as a PPI to prevent NSAID-associated ulcers, in the NDTI database this visit would result in a mention for a PPI for the diagnosis code of osteoarthritis. While treating arthritis with a PPI is a non-indicated use of this medicine, using it to prevent an ulcer is an indicated usage.

To understand these complexities, we also interviewed an independent panel of three physicians (two internal medicine physicians and a psychiatrist) to establish a basis for classifying major indications. This was done for each diagnostic code for which there was at least a minimum 100 000 mentions over the study period. As part of our data gathering and analysis, we also interviewed a local expert in medical coding to better understand the diagnosis coding process. Based on this information and research, we classified each of these ICD-9 codes into one of the following five categories: exactly or almost exactly matched to the FDA-approved indication (EXACT); no clear match to the FDA-approved indication but drug likely being used for an FDA-approved indication (LIKELY); no match to the FDA-approved indication but the diagnosis was one that the drug could plausibly be used in treating the condition (PLAUSIBLE); no match to the FDA-approved indication and no immediately apparent rationale for recommendation (IMPLAUSIBLE); and others (OTHER). The OTHER category mainly includes very unspecific diagnosis codes and/or test codes. Interviews with the three physicians provided somewhat different classifications, highlighting the inherently subjective nature of this process and the variability in physician prescribing behaviour such as that between specialists and primary care physicians. Further details on mapping the FDA labelling to ICD-9 diagnostic codes are given in the Appendix.

Over the time period of this study EXACT or LIKELY diagnoses accounted for an average of 91.8% of total drug mentions for ACE inhibitors, 75.6% of total drug mentions for PPI-H_2, and 40.9% of total drug mentions for SSRI/SNRIs.

Results

Approval Patterns

As discussed above, we assembled data on the complete set of approvals for all molecules in each of the three therapeutic classes under consideration. These approvals can be divided into at least two groups:

• indication approvals – including the primary or

Table IV. Date of approval of primary and supplementary indications of selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors (see Appendix for more details); dates (given in dd/mm/yy) in bold type indicate primary indication approval

Drug	Major depressive disorder	Social affective disorder	Generalised anxiety disorder	Obsessive-compulsive disorder	Bulimia	Panic disorder	Premenstrual dysphoric disorder	Post-traumatic stress disorder	Smoking cessation	Bipolar disorder
Prozac®	**19/12/87**	-	-	23/12/92	21/11/96	29/7/02	6/7/00	-	-	24/12/03
Paxil®	**29/12/92**	11/5/99	13/4/01	7/5/96	-	7/5/96	28/8/03	13/12/01	-	-
Lexapro®	**14/8/02**	-	18/12/03	-	-	-	-	-	-	-
Zoloft®	**30/12/91**	7/2/03	-	25/1/96	-	8/7/97	16/5/02	7/12/99	-	-
Effexor®	**28/12/93**	11/2/03	11/3/99	-	-	-	-	-	-	-
Celexa®	**17/7/98**	-	-	-	-	-	-	-	-	-
Wellbutrin®	**30/12/85**	-	-	-	-	-	-	-	14/5/97	-
Luvox®	-	-	-	**5/12/94**	-	-	-	-	-	-
Remeron®	**14/6/96**	-	-	-	-	-	-	-	-	-
Serzone®	**22/12/94**	-	-	-	-	-	-	-	-	-

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original indication as well as supplementary indications approved subsequent to the initial application
- non-indication approvals – these include approvals for new dosages, formulations, combinations with other drugs, or use in expanded patient populations.

In what follows we designate approvals for additional indications beyond the primary indication as sNDAs and non-indication approvals following the initial approval as other NDA approvals.

The number of sNDA approvals obtained per year in these three classes has generally increased since the early 1990s (figure 1). However, a comparison of the type and number of approvals in each therapeutic class demonstrates very different patterns of approval among the classes. As seen in table I, while each class contains approximately the same number of molecules (nine or ten), they differ markedly in terms of the number of sNDAs, new dosage approvals and new combination approvals. The large number of combination approvals among the ACE inhibitors (13 vs only 1 for the SSRI/SNRIs and 4 for the PPI/H_2-antagonists) can be attributed to the fact that most of the ACE inhibitors have been approved in combination with a diuretic.

The SSRI/SNRI class has experienced the largest number of supplementary approvals per molecule (an average of 5.9 sNDAs per molecule vs 4.6 sNDAs per molecule for the PPI/H_2-antagonists and 3.5 for the ACE inhibitors). Some of these differences may reflect variations in medical practice and in norms of diagnostic precision across therapeutic classes, as well as differing market and competitive incentives for firms to seek approvals for additional indications. Both the PPI/H_2-antagonist and SSRI/SNRI classes have received a large number of new formulation approvals, resulting largely from the approval of various extended-release/controlled-release presentational forms of these molecules, as well as over-the-counter versions.

Approval Timelines for Indications

A more detailed analysis of the indications in each therapeutic class provides additional insight into the approval patterns of these molecules. The

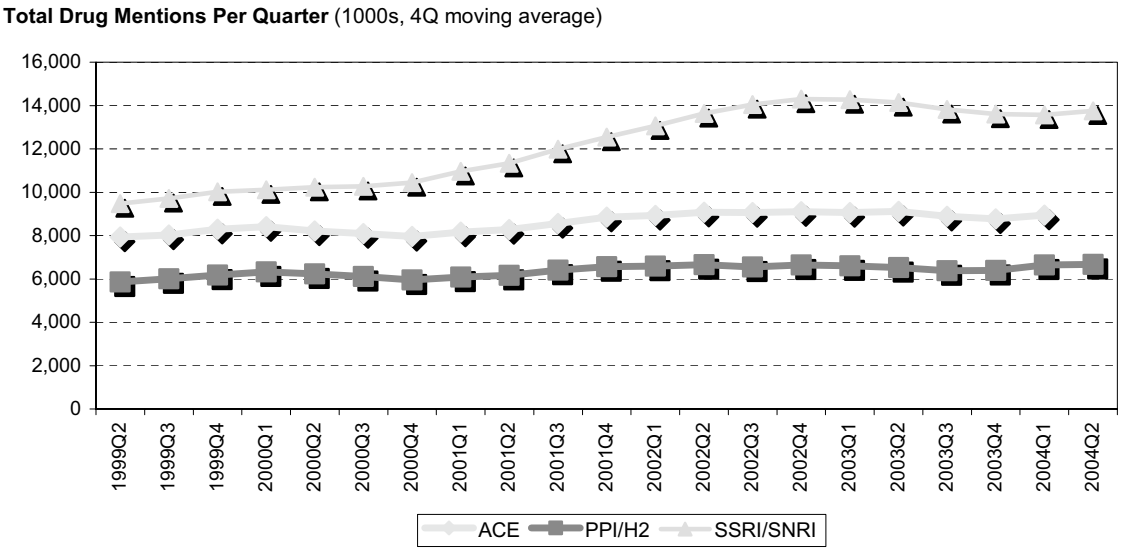

Fig. 2. Overall utilisation of drugs by therapeutic class. **ACE** = ACE inhibitors; **PPI/H_2** = proton pump inhibitors/H_2-antagonists; **SSRI/SNRI** = selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors.

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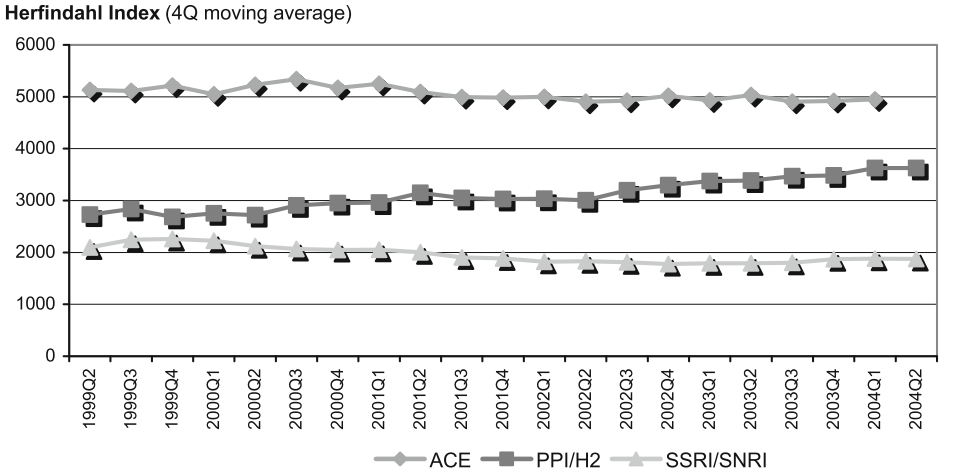

Fig. 3. Mean Herfindahl Index across diagnoses by therapeutic class. **ACE** = ACE inhibitors; **PPI/H_2** = proton pump inhibitors/H_2 antagonists; **SSRI/SNRI** = selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors.

ACE inhibitors, which represent the oldest class of drug investigated, have had six distinct indication approvals across all molecules in the class (table II). Among these, almost all molecules have received approval for both hypertension and heart failure. While no molecule has received approvals for more than four distinct indications, three have been approved for indications that are unique to that molecule, thereby potentially generating a source of product differentiation in the marketplace.

The PPI/H_2-antagonists have experienced an even larger number of supplementary indication approvals relative to the ACE inhibitors (table III).

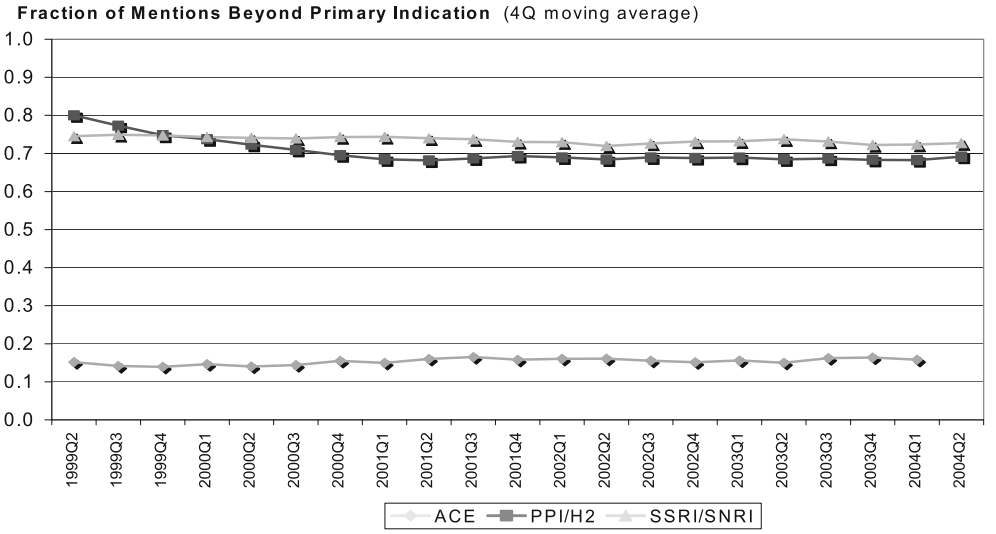

Fig. 4. Proportion of drug mentions beyond primary indication. **ACE** = ACE inhibitors; **PPI/H_2** = proton pump inhibitors/H_2-antagonists; **SSRI/SNRI** = selective serotonin reuptake inhibitors/selective noradrenaline reuptake inhibitors.

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The earliest molecules were H_2-antagonists initially approved for treatment of duodenal ulcers and then later on for GERD/oesophagitis, while the subsequent PPI molecules obtained approval for GERD/oesophagitis as their primary indication.[11] With considerable numbers of additional indications approved for all drugs in the class, there is now significant overlap in terms of the approved indications among the molecules in this class, raising the potential for less product differentiation and greater substitutability among them. However, itt should be noted that many of the approved indications within this class are closely related to one another, and a number of the molecules received approval for more than one indication at a time. In contrast to the ACE inhibitors, there is no one dominant primary indication for the PPI/H_2-antagonists.

The SSRI/SNRIs have experienced the largest number of supplementary indication approvals, but these approvals appear to be concentrated in a few versatile molecules (table IV). Prozac®, Paxil® and Zoloft® have each been approved for at least six distinct indications, while Celexa®, Luvox®, Remeron® and Serzone® have all been approved for only a single indication.

Figure 1 provides a timeline for the various sNDA approvals in each therapeutic class. The number of new sNDAs obtained per year has increased significantly since the early 1990s, a trend that is markedly different from that for NDA/BLAs. Specifically, in the 5-year period between 1990 and 1994, the number of sNDA approvals was 33; this increased to 43 between 1995 and 1999, and since 2000 the number has increased further to 49. Moreover, despite the age of the ACE inhibitors and the PPI/H_2-antagonists, new sNDA approvals for new indications continue to be obtained more than 20 years after the first approval within the class.

Utilisation Trends

Over the period 1999-2004 there has been a substantial increase in utilisation as measured by the number of drug mentions in the NDTI across all three of the drug classes considered in this study. However, this growth has been the most pronounced in the SSRI/SNRI class, which has experienced an approximately 50% increase in drug mentions over the 5-year period (figure 2).

Concentration of Utilisation across Diagnoses

To measure how concentrated or versatile the actual utilisation of these molecules is among the various diagnoses, we used NDTI data to calculate a Herfindahl Index, a common measure of concentration, across ICD-9 diagnoses per molecule and per quarter. The Herfindahl Index for a drug is computed first by calculating the share of drug mentions by diagnosis within a drug (between 0% and 100%), squaring this share, and then summing over all diagnoses; for a drug solely used for one diagnosis, the Herfindahl Index would be 10 000 (100 squared), but if it were instead used equally among ten diagnoses, the Index would equal 1000 (100 summed 10 times). Hence, a larger Herfindahl Index represents increased concentration and less versatility for a molecule. Figure 3 plots the mean value of the Herfindahl Index over time for all of the molecules in each therapeutic class. ACE inhibitors are most concentrated in their usage, having a roughly constant Herfindahl Index of about 5000; hypertension indications represent the most prevalent usage of these molecules. The PPI/H_2-antagonists have become more concentrated over time, with their mean Herfindahl Index rising from about 2800 in 1999 to about 3700 in 2004. This rising concentration is due largely to the increase in utilisation of these medicines for treatment/prevention of GERD and oesophagitis, which were secondary indications

11 However, perhaps fortuitously for AstraZeneca, less than 2 months after Vioxx® was voluntarily withdrawn from the market by Merck, on 24 November 2004 an sNDA submitted by AstraZeneca resulted in Nexium gaining approval for treatment and prevention of NSAID-induced ulcers, ulcers that were more likely to occur as some patients were switched from Vioxx and other COX-2 inhibitors to various NSAIDs for treatment of arthritic pain.

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for the H_2-antagonists but were the primary indications for the later-generation PPIs. The SSRI/SNRIs are the least concentrated therapeutic class with total drug mentions distributed across a wide variety of indications, and a Herfindahl Index that declines from just above 2000 to slightly below 2000 between 1999 and 2004.

Utilisation beyond the Primary Indication

As discussed in the Data and Methods section, mapping ICD-9 diagnoses to US FDA-approved labelled indications is not always straightforward; details of our mapping are provided in the Appendix. After matching diagnoses to FDA-approved indications, we obtained the number of drug mentions for the primary indication of each drug as the sum of mentions for diagnoses that fall into the EXACT and LIKELY matching categories. From this, we computed the proportion of total mentions for indications beyond the primary indication. Figure 4 plots the evolution over time of the share of this non-primary category in total mentions for each of the three drug classes. Note that this utilisation in non-primary indications includes both usage of drugs that was identified as being for approved supplementary indications and off-label use.

The non-primary category represents a significant share of total utilisation for all of the drug classes, but is especially high for the SSRI/SNRI and the PPI/H_2 classes. In the case of the SSRI/SNRIs, over 75% of total utilisation has been prescribed for conditions other than the primary indication, which in this class was generally acute-phase major depressive disorder. For the PPI/H_2-antagonists, the non-primary share was also very high, accounting for between 70% and 80% of drug mentions over the sample period, albeit declining slightly in later years. However, this was not driven by a single non-primary indication. While much of the non-primary utilisation for older drugs in this class was for indications such as GERD/oesophagitis that received sNDA approvals, the reverse holds for newer drugs that had GERD/oesophagitis as their primary indication and subsequently obtained sNDAs for indications such as ulcers. Indeed, the downward trend in non-primary utilisation in this class over time from about 80% in 1999 to <70% in 2004 is due largely to the introduction of Protonix® in 2000 and Nexium® in 2001, each with a primary indication approval for treatment of GERD/oesophagitis.

In contrast, the primary indication accounts for the great majority of utilisation of ACE inhibitors. The share of non-primary utilisation in this class is much lower, although still significant, at about 15%. To a great extent this reflects the expansive and straightforward nature of the hypertension diagnosis, which was the primary indication for all of the drugs in this class.

Conclusions

This investigation has demonstrated that innovation in biopharmaceuticals can manifest itself in ways beyond the introductions of new drugs, measured by simply counting approvals of new chemical entities and biologics. Our findings suggest that neglecting to account for the contribution of incremental or follow-on innovation in the form of approvals obtained for new indications and formulations of drugs that are already in use probably results in a substantial underestimate of innovative output in biopharmaceuticals. In two of the three drug classes considered here, utilisation in patients with diagnoses outside each drug's initially approved indication accounts for 70-80% of total use. All three drug classes have experienced the approval of numerous new indications, some targeting markedly distinct populations from that of the original indication, significantly expanding the economic and medical benefits of these drugs.

While these classes may not be fully representative of the entire range of drugs, these results suggest that conventional measures of innovative output based on counting NMEs or NCEs plus BLAs may seriously understate the productivity of research in this industry. These findings also suggest that investments in incremental innovation may have significant benefits both for drug developers and for patients, since the incremental gains from supplementary indications may be large rela-

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tive to the investments made for supplementary approvals. However, a better understanding of the incentives for and process of incremental innovation investments is necessary to fully understand the potential implications of this research.[12] As long as the supplementary indications that result from these investments provide new treatments or new treatment modalities, they represent an important, but largely overlooked, component of the total research productivity of the biopharmaceutical industry.

The findings reported here suggest a number of interesting topics for further research. Substantial heterogeneity was observed in utilisation in diagnoses beyond the primary approved indication, ranging from 15% to 80% of total utilisation, and it would surely be useful to expand this analysis to a wider set of drug classes. Furthermore, causal factors underlying expansion of drug utilisation beyond the initially approved indication are unclear. There are many sources of changes over time in the utilisation of prescription pharmaceuticals, including evolving characteristics of drugs (such as their efficacy, tolerability and side effect and adverse interaction profiles), pricing and the role of information transmitted through mechanisms such as word-of-mouth exchanges among medical practitioners and patients, publications in medical journals and the press, communications from the FDA, advertising in medical professionals, and direct-to-consumer marketing.[13] Identifying the contributions of these various factors would help develop a richer understanding of the important role of incremental R&D in this industry.

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Appendix

The following is a summary of the mapping from the actual US FDA-approved language and International Classification of Diseases, 9th Edition (ICD-9) codes to the indication categories used throughout the analysis. The names of the drugs approved for the given indication are given after each FDA-approved language entry.

12 Sankar and Kahn[32] have raised the issue of whether some forms of incremental research may be primarily motivated by commercial rather than social goals in the context of BiDil®, the first drug to receive a race-specific indication from the FDA.
13 For a further discussion and quantification in the context of antidepressants, see Berndt et al.[33] and for the H_2-antagonists, see Berndt et al.[34]

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Table AI. Summary of mapping of approved indications to ICD-9 diagnosis codes

Indication	FDA-approved language	ICD-9 codes
ACE inhibitors		
Hypertension	Hypertension (Accupril®, Altace®, Capoten®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec®) Essential Hypertension (Aceon®)	277.7 - Metabolic Syndrome 401.0 - Essential Hypertension, malignant 401.1 - Essential Hypertension, benign 401.8 - Essential Hypertension, benign, complicated 401.9 - Essential Hypertension, unspecified 402.9 - Hypertensive Heart Disease, unspecified 403.9 - Hypertensive Renal Disease, unspecified 404.9 - Hypertensive Heart and Kidney Disease, unspecified 412.0 - Old Myocardial Infarction with Hypertension 413.0 - Angina Pectoris with Hypertension 414.2 - Coronary Atherosclerosis with Hypertension 414.5 - Chronic Ischemic Disease with Hypertension, unspecified 414.9 - Chronic Ischemic Disease, unspecified 416.0 - Primary Pulmonary Hypertension 433.1 - Occlusion and stenosis of precerebral arteries, carotid artery 435.0 - Transient cerebral ischemia, Basilar artery syndrome 436.0 - Acute, but ill-defined, cerebrovascular disease 592.0 - Calculus of the Kidney
Heart failure	Heart Failure (Accupril®, Monopril®, Prinivil®) Heart Failure post Myocardial Infarction (Altace®, Mavik®) Congestive Heart Failure (Capoten®) Symptomatic Congestive Heart Failure (Vasotec®)	427.3 - Atrial Fibrillation and Flutter 428.0 - Congestive Heart Failure 428.9 - Heart Failure, unspecified 782.3 - Edema
Ventricular dysfunction	Left-Ventricular Dysfunction post Myocardial Infarction (Mavik®, Capoten®) Asymptomatic Left Ventricular Dysfunction (Vasotec®)	Could not be adequately identified from ICD-9 codes
Acute myocardial infarction	• Acute Myocardial Infarction (Prinivil®)	410.0 - Acute Myocardial Infarction with Hypertension 410.9 - Acute Myocardial Infarction without Hypertension
Diabetic nephropathy	Diabetic Nephropathy (Capoten®)	250.3 - Diabetes mellitus, with other coma 581.9 - Unspecified Nephrotic Syndrome 583.9 - Nephritis and nephropathy, with unspecified pathological lesion in kidney 585.0 - Chronic Renal Failure 791.0 - Proteinuria
Risk reduction	Risk Reduction of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes (Altace®)	Could not be adequately identified from ICD-9 codes

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PPI/H_2-antagonists		
GERD/oesophagitis	Treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis and associated heartburn due to GERD (Axid®, Zantac®) Short-Term Treatment of Erosive Esophagitis Associated With GERD (Protonix®, Prevacid®) Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy (Prilosec®) Healing of Erosive Esophagitis (Nexium®) Maintenance of Healing of Erosive Esophagitis (Protonix®, Nexium®, Prevacid®, Prilosec®, Zantac®) Healing of Erosive or Ulcerative GERD (Aciphex®, Tagamet®) Maintenance of Healing of Erosive or Ulcerative GERD (Aciphex®) Treatment of GERD (Zantac®) Treatment of Symptomatic GERD (Aciphex®, Nexium®, Prilosec®) Short term treatment of GERD (Pepcid®) Short-Term Treatment of Symptomatic GERD (Prevacid®)	530.1 - Esophagitis 530.2 - Ulcer of Esophagus 150.9 - Malignant neoplasm of esophagus, unspecified 456.0 - Varicose veins of other sites, Esophageal varices with bleeding 530.0 - Achalasia and cardiospasm 530.3 - Stricture and stenosis of esophagus 530.5 - Dyskinesia of Esophagus
Duodenal ulcer	Healing of Duodenal Ulcers (Aciphex®) Short term treatment of active duodenal ulcer (Axid®, Pepcid®, Prevacid®, Prilosec®, Tagamet®, Zantac®) Maintenance therapy for duodenal ulcer patients (Axid®) Maintenance therapy for duodenal ulcer patients after healing of an active ulcer (Pepcid®, Tagamet®, Zantac®, Prevacid®)	532.0 - Duodenal Ulcer
Gastric ulcer	Short term treatment of active benign gastric ulcer (Axid®, Pepcid®, Prevacid®, Prilosec®, Tagamet®, Zantac®) Maintenance therapy for gastric ulcer patients after healing of acute ulcer (Zantac®)	531.0 - Gastric Ulcer 534.0 - Gastrojejunal Ulcer
Hypersecretory	Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome (Aciphex®, Protonix®, Pepcid®, Prevacid®, Prilosec®, Tagamet®, Zantac®)	Could not be adequately identified from ICD-9 codes
Helicobacter pylori eradication	*Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (Aciphex®, Nexium®, Prevacid®, Prilosec®) Treatment of patients with *H. pylori* infection and duodenal ulcer disease (Prilosec®) Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* (Prilosec®)	Could not be adequately identified from ICD-9 codes
NSAID ulcers	Risk Reduction of NSAID-Associated Gastric Ulcer (Nexium®, Prevacid®) Healing of NSAID-Associated Gastric Ulcer (Prevacid®)	715.9 - Osteoarthrosis, unspecified whether generalized or localized
Upper GI bleeding	* Prevention of upper gastrointestinal bleeding in critically ill patients (Tagamet®)	578.0 - Hematemesis 578.1 - Malena 578.9 - Gastrointestinal hemorrhage, unspecified
OTC heartburn	Relief of heartburn, acid indigestion, and sour stomach (Axid®, Tagamet®, Zantac®, Pepcid®) Prevention of these symptoms brought on by consuming food or beverage (Axid®, Tagamet®, Zantac®, Pepcid®) Treatment of frequent heartburn (Prilosec®)	646.8 - Other specified complications of pregnancy 787.1 - Heartburn 536.8 - Dyspepsia and other specified disorders of function of stomach 787.2 - Dysphagia 789.0 - Abdominal Pain 787.0 - Nausea and Vomiting

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SSRI/SNRIs		
Major depressive disorder (MDD)	Major Depressive Disorder (Paxil®, Effexor, Prozac®, Remeron®, Wellbutrin XL, Zoloft®) Depression (Celexa®, Serzone®, Wellbutrin)	MAJOR DEPRESSION: 296.2 - Major Depressive Disease, single episode 296.3 - Major Depressive Disease, recurrent episode 296.9 - Other and unspecified episodic mood disorder 298.9 - Psychoses, unspecified
Social anxiety disorder (SAD)	Social Anxiety Disorder, also known as social phobia (Paxil®, Effexor, Zoloft®)	300.2 - Phobic States
Generalised anxiety disorder (GAD)	Generalized Anxiety Disorder (Paxil®, Effexor)	300.0 - Anxiety States 300.1 - Hysteria 300.5 - Neurasthenia
Bulimia	Treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa (Prozac®)	307.5 - Disorders of Eating, other and unspecified
Panic	Panic disorder, with or without agoraphobia (Paxil®, Prozac®, Zoloft®)	Could not be adequately identified from ICD-9 codes
Premenstrual dysphoric disorder (PMDD)	Premenstrual dysphoric disorder (Prozac®/Serafem, Paxil®, Zoloft®)	625.4 - Premenstrual Tension Syndrome
Post-traumatic stress disorder (PTSD)	Post traumatic Stress Disorder (Paxil®, Zoloft®)	Could not be adequately identified from ICD-9 codes
Smoking	Smoking cessation treatment (Zyban)	305.1 - Nondependent abuse of drugs, tobacco
Bipolar	Bipolar depression (Prozac®/Symbiax)	296.5 - Bipolar Affect Disorder, depressed 296.6 - Bipolar Affect Disorder, mixed 296.7 - Bipolar Affect Disorder, unspecified

GERD = gastroesophageal reflux disease; **GI** = gastrointestinal; **NSAID** = nonsteroidal anti-inflammatory drug; **OTC** = over-the-counter; **SNRI** = selective noradrenaline reuptake inhibitors; **SSRI**= selective serotonin reuptake inhibitor.

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Exhibit C

OPINION

Macro trends in pharmaceutical innovation

Fredric J. Cohen

Abstract | Critics decry the lack of 'truly innovative' new medicines and question the role of the pharmaceutical industry in creating the few that are developed. Is this an accurate portrayal of the state of pharmaceutical innovation? Does major pharma still innovate? If so, how? Must the industry innovate to survive? These and related issues are discussed.

Employees in the pharmaceutical industry have become accustomed to reading criticisms of their work in the lay press. Some of that criticism is, no doubt, deserved. But what about the charge that the pharmaceutical industry, particularly major pharma, is no longer innovative? This is not a new claim, but it is being recycled and has recently featured prominently in the media. The indictment usually takes this form: the pharmaceutical industry does not innovate much, as it has little incentive to innovate. Very few new drugs are truly innovative; most are 'me-toos'. The few truly innovative drugs were mostly discovered using government funds (BOX 1).

The truth is that there are no generally accepted measures of innovation that would conclusively prove the point one way or another (BOX 2). However, the current analysis identifies trends in several measures that support both sides of the innovation debate. Overall, though, the bulk of evidence suggests, to this admittedly biased observer, that the pharmaceutical industry continues to regard pioneering innovations as important, as evidenced by the motivation, effort and ability of the industry to create such innovations. However, like other mature manufacturing industries, the pharmaceutical industry relies heavily on incremental innovations (what critics call 'me-too' drugs) to sustain its profits[1]. To a large extent, these incremental innovations are themselves medically beneficial and should be encouraged, rather than dismissed as merely imitative.

Here I describe some of the findings that support these conclusions, focusing only on macro trends in major pharmaceutical industry innovation and avoiding anecdotes concerning specific innovations. The discussion is organized into two parts. In the first part, trends in industry's capacity for (also called commitment to) innovation are described, and in the second, trends in the industry's innovative output.

Defining innovation

According to the US Office of Technology Assessment (OTA), "Innovation encompasses both the development and application of a new product, process, or service. It assumes novelty in the device, the application, or both. Thus, innovation can include the use of an existing type of product in a new application or the development of a new device for an existing application. Innovation encompasses many activities, including scientific, technical, and market research; product, process, or service development; and manufacturing and marketing to the extent they support dissemination and application of the invention."[2]

As referred to here, innovation usually means the outcome itself — the actual creation or invention, and not just the process. Processes and resources that contribute to innovation are described as such. The phrase 'incremental innovation' denotes innovations that are improvements, from modest to major, on existing innovations. Incremental innovations are sometimes referred to as sequential, subsequent or follow-on innovations. In the pharmaceutical industry specifically, the modification of existing medicines — for example, by re-formulation — is often referred to as sequential innovation, whereas a second- or third-generation product in a chemical class is often referred to as a follow-on innovation. Critics dispense with these formalities and refer to any drug that is not pioneering as a 'me-too', a tactic obviously intended to denigrate the practice of incremental innovation. Pioneering innovations, which are also referred to as major, stand-alone, discontinuous or radical, usually describe the subset of innovations that represent something completely new and different. In pharmaceuticals, pioneering innovations are first-in-class drugs, although some critics also label first-in-class drugs that are similar to those in existing classes as 'me-too'.

Importance of incremental innovation

In its comprehensive report on commercialization of emerging technologies, the OTA concluded that "In most industries, innovation proceeds in an evolutionary fashion

Box 1 | **Whose drug is it anyway?**

Some critics charge that the pharmaceutical industry is not primarily responsible for medical innovations, because they are the fruits of indirect — and frequently direct — involvement of researchers in academia and government-supported laboratories. But that is not what US government studies indicate, as the following excerpts demonstrate:

"Pharmaceutical innovation has resulted primarily from the activities of private industry. Of the new drugs introduced in the United States between 1960 and 1969, 91 percent were discovered and developed by the industry. Government, nonprofit research organizations, and universities were responsible for the remainder of the new drugs."[15]

"It is important to note that while NIH's federally funded research has contributed in a substantial, dramatic, yet general, way to advances in medicine and biology, the direct contributions to a final therapeutic product as a consequence of the Bayh-Dole process is limited and difficult to determine ... For each drug listed, NIH sought to determine whether the agency, directly, or through a grantee or contractor, held any patent rights to the drugs. From the comprehensive cross-analysis of all 47 [top-selling] drugs, it was determined that NIH has Government use or ownership rights to patented technologies used in the development of four of those drugs. Those four are Taxol, Epogen, Procrit, and Neupogen."[27]

"Even in those few cases in which an NIH-invented technology is an identifiable part of a final product, the invention would typically be one of numerous components... The research supported and conducted by the NIH is sometimes mischaracterized as necessarily resulting in the commercialization of drug products. In truth, much of NIH funding supports the exploration of fundamental biological mechanisms that would otherwise not be pursued due to the lack of market incentives ... [O]f the top 100 pharmaceuticals procured by the Department of Veterans Affairs in fiscal year 2001, only five implicated Government rights. Additionally, of the top 100 pharmaceuticals dispensed by the Department of Defense between July 1, 2001 and June 30, 2002, only three had active Government right."[28]

through long periods of cumulative incremental innovation punctuated by moments of radical innovation. Although incremental innovation and adaptations of existing technology to new markets might seem mundane, they account for most innovative activity and, in aggregate, generate returns equal to those created by less frequent radical innovations."[2]

Speaking specifically about pharmaceutical innovation, the US National Research Council noted that "breakthrough products, which are usually the first of a class, inevitably display deficiencies after they are widely distributed. Pharmaceutical companies use these revealed deficiencies as opportunities to develop related compounds that are more effective, more selective, and less toxic"[3]. A more recent McKinsey study concurs with these observations: "Of the 32 such drugs introduced over the past decade, only a quarter targeted novel mechanisms of action .... Some of these were 'me-too' compounds, but a majority had at least one source of significant clinical differentiation..."[4].

As Wertheimer and colleagues have observed, "The therapeutic power, stability, and utility of a [drug] class are defined through the contributions of its multiple agents ... [therefore,] the collective therapeutic advantage of the class as a whole may be of greater clinical significance than the original advantage of the pioneer compound."[5]

Ironically, the radical innovation collectively described as 'personalized medicine' is dependent on incremental innovations — in the form of expansions in the members of each drug class. Offering choices requires choices to offer.

Finally, whether one accepts evidence pointing to the medical and social importance of incremental innovations or not, such innovations are an important source of industry revenues and profits because of their inherently lower risk and cost basis, and are therefore an important source of R&D funds. If policy changes dry up the flow of incremental innovations — and in the absence of an alternative mechanism for replenishment — the R&D well will inevitably run dry and, along with it, the resolve of this industry to pursue pioneering innovations.

Motivations to innovate

Pharmaceutical proponents generally suggest that the industry is primarily motivated to create two things: drugs that serve society and drugs that serve investors. Critics begrudge these proponents their first point; so, for the sake of argument, let us just assume that the industry is motivated by profits alone, without concern for the welfare of society. Do profits alone serve as an incentive for innovation in general? The answer, as provided by studies unique to the pharmaceutical industry[6] and to manufacturing industries generally[2], is an unequivocal 'yes'. Profits are directly related to R&D investment[1,7], appropriation of inventions (for example, patents) and to innovative products themselves[2]. The reasons for this are primarily two-fold: innovations improve sales, both in terms of volume[8], by expanding the population being treated, and price[9]. Process innovations further improve profits by reducing costs relative to output[10].

The competitive environment for new drugs has shifted in the past 20 years, causing increased pressure on innovator firms to 'innovate or die'. Because of changes in federal and local laws in the 1980s that increased the availability and encouraged the use of generic medicines, generic competition is now much stiffer than prior to this time. Generic competition erodes innovator drug profits by reducing revenues owing to reductions in

Box 2 | **Innovation metrics: quality versus quantity**

Assessing the quantity of innovation is relatively easy compared with measuring quality. Industry critics have proposed schemes for lumping together innovations into buckets and labelling them (for example, 'highly innovative', 'moderately innovative' and so on), sometimes using the FDA's assessment of a drug's therapeutic potential at the time of New Drug Application filing. But this approach is far from reliable and is just as subjective as selective as anecdotal descriptions of innovations. A few examples illustrate this point — in the following, which drug in each pair is more innovative?

A reformulation of an existing cytotoxic chemotherapy that allows it to be delivered at a higher concentration over a longer duration, resulting in longer disease-free survival and reduced toxicity compared with the original formulation; or, a novel, fast-tracked, priority-reviewed New Molecular Entity (NME) that was designed to supplant the original cytotoxic and demonstrates survival improvements and toxicities comparable to that of the reformulated cytotoxic?

A first-in-class, priority-rated NME with identical indications for usage, and indistinguishable safety and efficacy markers, as the first four members of an older drug class; or, a fifth-in-class NME that has been demonstrated to improve survival, when its four predecessors were not studied adequately to ascertain their effects on survival?

A combination of two older drugs that has been shown to have a heretofore unexpected benefit to treat a serious disease for which neither was previously studied; or, a novel, fast-tracked, priority-reviewed NME that has comparable efficacy and safety to the combination of the two older drugs?

both volume and price[11]. For example, a 1993 study by the OTA found that a 43% erosion of innovator-drug sales (measured by volume, not price) occurred over 3 years for generic drug introductions in the period 1984–1987[12]. Just 6 years later, a US Congressional Budget Office study found that market erosion by generic competitors was 44% after the *first year* of generic competition for generics introduced between 1991 and 1993[9]. The innovator market had therefore eroded at least three times faster during this interval[9]. As a result, the volume share of generic prescription drugs has increased from 19% to 45% between 1984 and 2001[13].

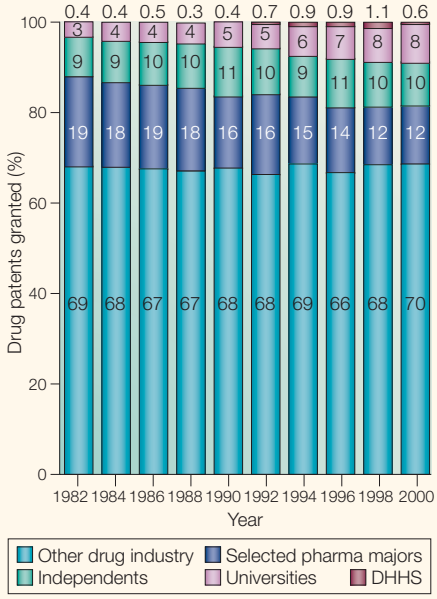

Figure 1 | **Distribution of drug patents by assignee 1982–2000.** Data are from searches of the US Patent and Trademark Office (USPTO) database in September 2004 and from USPTO's Patent Technology Monitoring Division[25] . The USPTO assigns each utility patent (a category that includes, for example, composition of matter, crystal form, formulation, and methods of manufacture and administration) a classification code according to how it will be used. For example, there are two classification codes for "drugs and bio-affecting and body treating" inventions. Patents from these classes are highly correlated with those that are discovered via searches for the term 'pharmaceutical' in the claims of patents ($R^2 = 0.98$). Light blue columns represent issued US patents classified as 'drugs' as a percentage of utility drug patents issued during the labelled year that were assigned to drug companies, excluding those in the major pharma cohort (included: Abbott Laboratories, AstraZeneca, Aventis, Ciba-Geigy, Eli Lilly, Hoechst Aktiengesellschaft, Hoechst Marion, Hoffmann-La Roche, Imperial Chemical Industries, Marion Laboratories, Marion Merrell, Merck & Co., Bristol-Myers Squibb, Merck Patent, Novartis, Pfizer, Rhone-Poulenc, Roussel-Uclaf, Sandoz Ltd., Sandoz Pharm., Schering Aktiengesellschaft, Schering Corp., Schering-Plough, Takeda Chemical, Warner-Lambert, Zeneca Limited). Note that light blue columns were obtained by deducting the contributions of all other assignee categories from the total. Other columns were for utility drug patents assigned to the following categories: blue, major pharma; green, independent (unaffiliated); pink, university or college; red, US Department of Health and Human Services (DHHS; includes National Institutes of Health, Food and Drug Administration and Centers for Disease Control).

It has been argued that generic competition alone does not serve as an incentive to innovate, because companies can respond by creating more drugs with minor modifications (more me-toos). There is a problem with this argument, however, because it does not account for how the industry actually generates returns on its R&D investments, which in the pharmaceutical industry are highly skewed: the top 10% of new drugs (by net present value (NPV)) account for 52% of the total NPV for all new drugs sold worldwide[14]. Because utility is the primary driver of new drug adoption, profits could actually fall unless the quality of some new drugs is sufficient to compete effectively with older drugs. In other words, a pharmaceutical company must have a blockbuster every so often to keep returns growing. Therefore, increasing production of new drugs *per se* will not guarantee that profits grow at a pace sufficient to cover the uncertainty and costs of maintaining a drug pipeline. It follows from this line of reasoning that targeting the best-selling drugs — for example, with restrictive reimbursement, or regulatory or patent policies — can adversely affect innovation[11].

The industry's capacity for innovation

Patents. The pharmaceutical industry relies heavily on patents to appropriate its innovations, perhaps more heavily than any other industry[6,10,11]. As the OTA has described, "Patents were designed to promote innovation by providing the right to exclude others from making, using, or selling an invention. They enable innovators to obtain greater profits than could have been obtained if direct competition existed. These profits act as incentives for innovative activities"[15]. A US Federal Trade Commission survey recently concluded that "pharmaceutical companies ... rely on patents to prevent free riding, recoup their R&D investments, and learn about new technological breakthroughs"[10]. Also, "by requiring public disclosure of new inventions, the patent process ... encourages dissemination of new technical information"[2]. Given the importance of patents to the pharmaceutical enterprise, it is unlikely that companies would develop innovations without them, and so they should be good surrogates of innovation capacity. On the other hand, there are incentives for companies to delay patent filings as long as possible (to lengthen the effective patent life during marketing) and to file multiple patents around the same fundamental technology to provide maximal protection against competitors. These incentives make patents an imperfect metric of innovation capacity.

Changes in US patent law in the mid-1980s (specifically the Hatch–Waxman Act) seem to have had, overall, a neutral effect on the industry's incentives to innovate. On the one hand, Hatch–Waxman increased average effective patent life from about 10 years to about 12 years[11]. On the other hand, anecdotal evidence suggests that improvements in technology have allowed 'fast followers' to follow faster than before[16]. These two trends have tended to counteract each other in terms of aggregate return.

US pharmaceutical patent activity, relative to overall US patent activity, increased beginning in the mid-1990s. Before then, it had been stable, at least as far back as 1976 (data not shown). The increase in activity seems to have been largely due to an increase in biotech-related patenting rather than an increase in patents on small-molecule drugs[17] (data not shown). Consistent with this notion, increased drug patent activity seems to be largely due to an increase in patenting by universities and colleges; patent activity by a cohort of major pharmaceutical companies decreased relative to other assignees during this period (FIG. 1). The finding of relatively reduced drug patenting by the majors is consistent with the observations by McGahan and Silverman that, as industries mature, their leaders tend to diversify their patent output beyond the industry's original activities[18]. The current study did not track patenting in areas in which these industry leaders might have diversified their efforts, such as research technologies, medical devices and clinical diagnostics.

R&D. The pharmaceutical industry spends more on R&D as a percentage of gross output than any industry except aerospace[19]. Pharmaceutical industry R&D expenditures (unadjusted for gross domestic product (GDP)), as reported yearly in the Pharmaceutical Research Manufacturers of America (PhRMA) Annual Survey, increased exponentially from 1970 to 2001, with some evidence of a moderation of spending growth more recently (FIG. 2a). It should be noted that these figures represent both pre- and post-approval R&D expenditures. When spending

is reflected as a percentage of net sales, a different picture emerges. R&D as a percentage of sales was stable until the latter half of the 1970s and then increased linearly until the mid-1990s, when it initially stabilized and then began diminishing slightly (FIG. 2a). So, although the industry was enthusiastically returning an increasing proportion of its revenues to R&D throughout much of the past 30 years, it now seems to be less inclined to do so.

R&D spending by the pharmaceutical industry was compared with other industries using the National Science Foundation Survey of Industrial Research and Development[20] as the data source (FIG. 2b). Although the actual R&D spending and sales amounts are different between the PhRMA and NSF surveys, the patterns of spending and sales over time are similar. Pharmaceutical industry R&D as a percent of sales peaked in the 1990s after a run-up in the 1980s, and has since plateaued at around 10%. Pharmaceutical industry R&D as a percentage of sales has exceeded aggregate industry R&D spending by a two-to-one margin since at least the late 1950s, when this survey began. Pharmaceutical industry R&D increased further relative to other industries beginning in the early 1960s (perhaps in response to US regulatory changes that called for clear demonstrations of efficacy and safety prior to marketing approval). Throughout the 1970s and early 1980s, pharmaceutical R&D spending generally exceeded aggregate industry spending by a ratio in excess of three to one. Following this period there was a brief lull in relative R&D spending by the pharmaceutical industry, followed by a surge in 1993 and then a return to the relative strength of the 1970s period.

The way in which R&D expenditures have been apportioned were examined by returning to the NSF Survey of Industry, which periodically collected information on pharmaceutical industry spending from 1965 to 1999 in three categories: basic, applied and development. Throughout this 34-year period, the allocation of pharmaceutical industry R&D expenditures gradually shifted away from applied research and towards development, with basic research remaining relatively stable (data not shown). Development accounted for more than 60% of R&D expenditures in 1999.

The annual PhRMA survey also collected data on the allocation of R&D funds, the findings of which are summarized in FIG. 3. Since 1976, the pharmaceutical industry has allocated relatively more funds to clinical research (Phases I–IV) and regulatory functions, at the expense of preclinical research. Together, these three categories accounted for 55% of all R&D expenditures in 2002. PhRMA member companies also indicated that approximately 20% of domestic R&D spending — which was stable throughout the time interval examined — was allocated to projects that represented sequential innovations to drugs already developed (not shown).

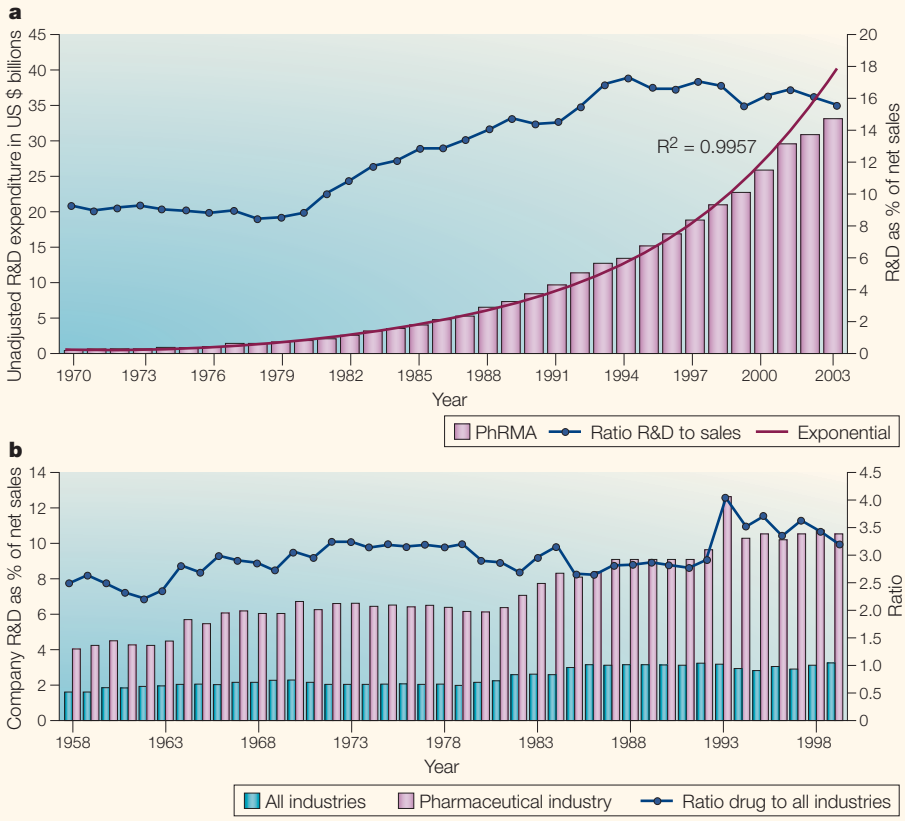

Figure 2 | **Pharma R&D spending. a** | Pharmaceutical industry R&D spending 1970–2003. Pink columns represent unadjusted annual R&D expenditures of Pharmaceutical Research Manufacturers of America (PhRMA) member companies as reported in their annual surveys. Spending is as reported, unadjusted for gross domestic product. An exponential curve (red) has been fitted to these data along with the square of the correlation coefficient. The blue curve represents annual R&D expenditure as a percentage of net sales. Source: REF. 26. **b** | Pharmaceutical industry R&D spending compared with aggregate industrial R&D spending 1958–1999. Light blue columns represent annual R&D expenditures expressed as a percentage of net sales for the aggregate of all industries represented in the National Science Foundation Annual Survey of Industrial Research and Development[20]. Pink columns are data from the same surveys from just the pharmaceutical manufacturers (US Standard Industrial Classification 283). The blue curve represents the ratio of annual pharmaceutical R&D spending to aggregate industrial R&D spending.

Combining the PhRMA surveys' findings with those from the NSF surveys suggests that applied non-/preclinical research might have been sacrificed at the expense of the increasing cost of funding clinical studies (it should be noted that in absolute terms there was a large increase in applied expenditures as well throughout this period). It is not known from these surveys how much of the relative scaling back in preclinical research affected discovery research compared with efforts in other areas.

Personnel are another surrogate of R&D investment. One advantage of the NSF survey is that it separates scientists and engineers from other types of R&D personnel, which allows an examination of R&D investment in those personnel who are primarily responsible for performing the experiments and developing the processes that lead to drug innovations. This addresses the concerns expressed by some industry critics that R&D expenses reflect costs such as administration and market research that, they assert, are not relevant to pharmaceutical innovation. As shown in FIG. 4, the pattern of employment of scientists and engineers in the pharmaceutical industry largely parallels R&D expenditures as a percentage of net sales (compare with FIG. 2b). Furthermore, the ratio of pharmaceutical industry employment of scientists and engineers exceeds aggregate industry employment of such personnel by about the same ratio as pharmaceutical industry R&D spending exceeds aggregate industry R&D spending (that is, by two or three to one). More recent pharmaceutical industry

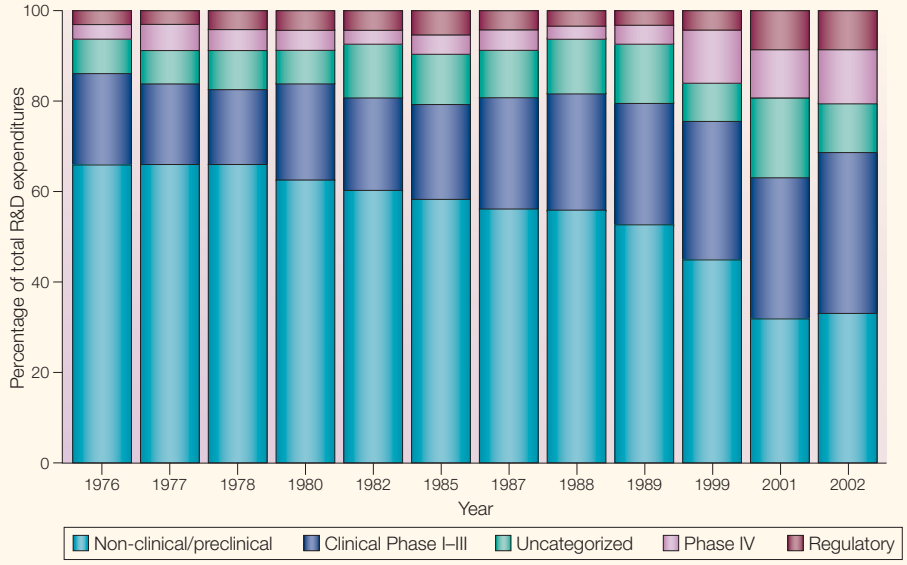

Figure 3 | **Pharmaceutical industry allocation of R&D expenditures selected years 1976–2002.** PhRMA used different categories than the NSF survey, and the PhRMA categories were changed after 1999. For this analysis, the earlier-years survey categories were collapsed to five to correspond with the more recent categorization. Allocation of funds summed to 100% for all years for which there were data. Stacked columns represent annual R&D expenditures as a percentage of total R&D allocated to: light blue, non-/preclinical research; blue, clinical Phases I–III; green, uncategorized R&D; pink, Phase IV clinical; and red, regulatory functions. Source: REFS. 13,26.

employment statistics indicate a trend of a steadily increasing proportion of scientists, relative to all pharmaceutical industry employees, for the past 5 years[21] (data not shown).

Innovation output

Past and present drug approval trends. Between 1990 and 2003, the Center for Drug Evaluation and Research (CDER) of the US FDA approved 1,171 New Drug Applications (NDAs). Of these, 400 (34%) were New Molecular Entities (NMEs, defined as an active ingredient that has never previously been marketed in the United States) and 771 (66%) were non-NMEs. Most commonly, 'non-NME' refers to new formulations of previously approved active ingredients. Of the NMEs approved, 166 (41% of NMEs) were granted priority-review status, compared with 98 (12.7%) priority-status non-NMEs. (A drug is assigned priority status when the drug product, if approved, would be a significant improvement compared with marketed products in the treatment, diagnosis or prevention of a disease. The CBER definition of a priority review is stricter than the definition that CDER uses. The biological drug, if approved, must be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease). The trend of NDA approvals over time by therapeutic potential rating is shown in FIG. 5. With the exceptions of 1996 and 1997, which were particularly productive years for standard-rated NDA approvals, NDA approvals were generally stable throughout this interval. This is another way of saying that NDA approvals were not growing commensurately with the increase in R&D spending that occurred throughout this period (FIG. 2a).

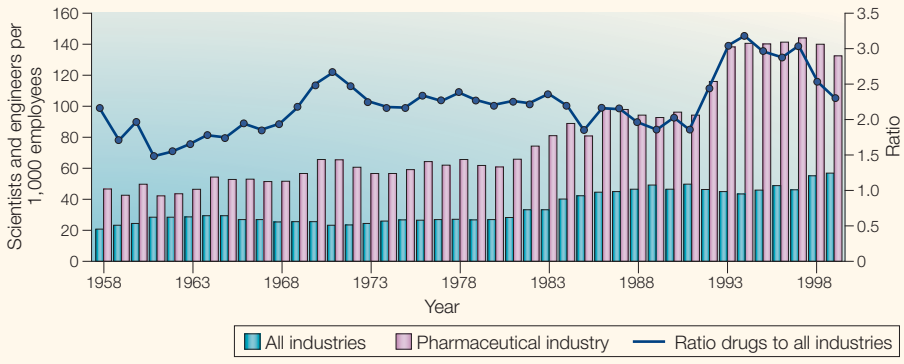

Figure 4 | **Pharmaceutical industry scientific and engineering personnel compared with aggregate industrial scientific and engineering personnel 1958–1999.** Light blue columns represent annual science and engineering employment expressed as number of active full-time equivalents (FTEs) per 1,000 FTEs employed for the aggregate of all industries represented in the National Science Foundation Annual Survey of Industrial Research and Development[20]. Blue columns are data from the same surveys from just the pharmaceutical manufacturers (US Standard Industrial Classification 283). The blue curve represents the ratio of annual pharmaceutical science and engineering employment to aggregate industrial science and engineering employment.

In contrast to NDA approvals by CDER, the majority of which were for small-molecule drugs and diagnostics, Biologic License Application (BLA) approvals for recombinant protein drugs by the Center for Biologics Evaluation and Research (CBER) increased during this interval (from 11 between 1989 and 1996 to 17 between 1997 and 2002). The majority of BLA approvals for therapeutic proteins were granted to 'biotech' firms (17 out of 28) as opposed to traditional pharmaceutical firms (11 out of 28), but there was no trend suggesting a change in the innovators of such drugs with time[22].

The priority-review classification provides a sense of the FDA's judgment of the value of a new drug or use as it relates to previously approved drugs at the time of NDA filing. It is an unaudited, subjective determination that is subject to changes in personnel and policy, is limited to information available at the time of filing, and lacks strict guidelines for its application to individual drugs (but is otherwise a useful research tool). With that caveat in mind, FIG. 6a presents trends in NME filings (not approvals) with CDER for the interval 1995–2003. Two trends are worth noting. The first is that there has been a pronounced decline in recent NME filings with CDER, from 50 in 1995 to 24 in 2003. The second trend is that the ratio of priority- to standard-rated filings has increased year over year for 6 of the 8 years in this series. In 2003 there were as many priority-rated filings as standard-rated. This might be a coincidence, or it might reflect policy changes at CDER, but perhaps it helps explain why there are fewer NME filings in general. It seems reasonable to assume that priority-rated filings are preceded by higher-risk development programs than standard-rated filings. This is another way of implicating the theory of 'low-hanging fruit' in the decline of pharmaceutical productivity, which suggests that the easily picked fruit has already been harvested.

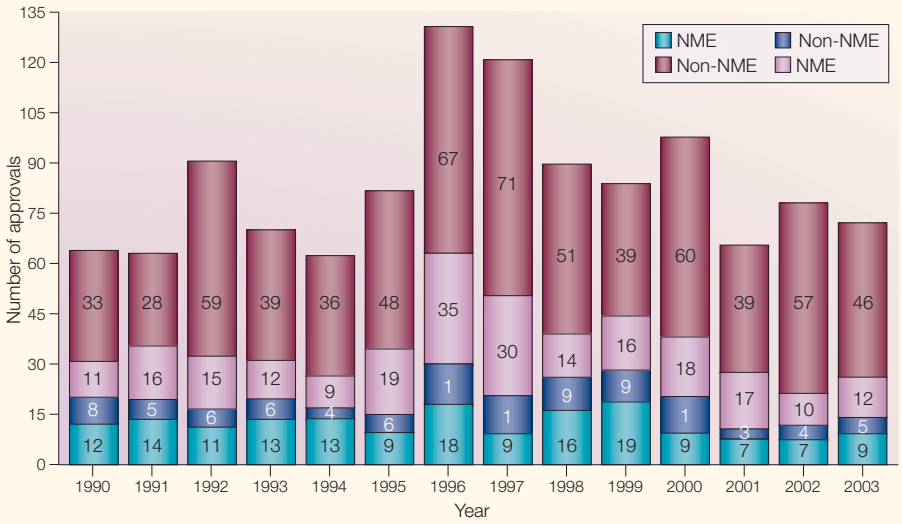

Figure 5 | **Center for Drug Evaluation and Research NDA approvals 1990–2003.** The light blue and blue stacked columns represent the number of priority-rated non-New Molecular Entity (NME) and NME New Drug Applications (NDAs), respectively, approved during the calendar year. The pink and red stacked columns represent approved standard-rated non-NME and NME NDAs, respectively. Source: Center for Drug Evaluation and Research.

As a means to assess its review performance according to the newly implemented user-fee goals of 1992, the FDA, beginning in fiscal year (FY) 1993, started tracking filings and actions taken on supplements to original NDAs (that is, efficacy supplements) separately from other NDAs. Efficacy supplements are filed when a new or modified indication or label change with new efficacy data is sought by the original manufacturer for previously approved drugs. Comparative efficacy claims, new dosage or route of administration, altered patient population, change in status from prescription to over-the-counter, and traditional approval following accelerated approval also require efficacy supplements. Efficacy supplement filings to CDER by fiscal year are shown in FIG. 6b. In contrast to NME filings, which declined in the past decade, efficacy supplement filings increased markedly, reaching a peak of 175 during FY 2000, a 90% increase over FY 1993 filings. More recently, efficacy filings have moderated slightly, but still remain 42% higher than in 1993. As discussed earlier, PhRMA members have indicated that R&D spending as a percentage of sales on sequential innovations — those that culminate in efficacy supplements — has remained stable over time. Therefore, either the pharmaceutical industry has developed processes that provide for relatively better productivity for sequential innovations as compared with non-sequential innovations, or opposing factors that influence one type of innovation preferentially, such as regulatory constraints, have eased with time.

At the same time as NME filings were increasing, the proportion of efficacy supplement filings granted priority-review designation was also increasing. Whereas just 7% of efficacy supplement filings were designated as priority in 1997, 19% were designated as such in 2002 and 2003. Because data for only 7 years are available, it is premature to reach definitive conclusions regarding a trend in filing status. Nevertheless, the available data do not indicate a trend towards reduced quality of supplement filings. Therefore there is no evidence to support the criticism that the industry in general has focused its recent development efforts on minor modifications to existing drugs that have little social utility; indeed, the available data suggest the opposite.

The future? Having a glimpse of what is 'on the horizon' is perhaps the only advantage to a protracted product-development cycle. FIGURE 7 provides a look at trends in the aggregate active drug development pipeline, as determined by a sampling of a proprietary investigational drugs database at approximately the same time each year since 1995[23]. There has been a marked trend towards increases in preclinical, Phase I and Phase II projects without a concomitant increase in Phase III projects. This is the Phase II roadblock that industry veterans speak of, the reasons for which remain unknown.

But all is not grim on the output front. As of May 2004, 56 drugs (all categories) had been approved, and another 165 were awaiting approval at the FDA. Nearly 400 Phase III programmes were ongoing — approximately equal numbers of which were for NMEs as for non-NMEs[24]. Assuming an 80% probability that a given drug awaiting FDA approval will be launched, and a 60% probability of launch for the Phase III drugs in development, a total

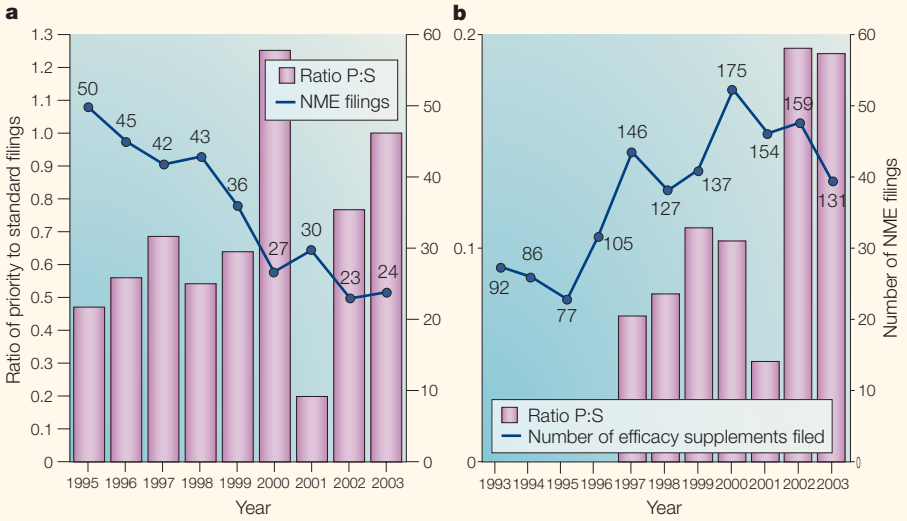

Figure 6 | **Recent trends in marketing authorization filings with the FDA. a** | New Molecular Entity (NME) filings with the Center for Drug Evaluation and Research (CDER) 1995–2003. The columns represent the ratio of priority- to standard-rated NME filings (P:S) received during each calendar year. The blue line and corresponding data label represent the total number of NME filings received by CDER during each calendar year. Source: REF. 29. **b** | Efficacy supplement filings with CDER 1993–2003. The columns represent the ratio of priority- to standard-rated efficacy supplement filings received during each fiscal year beginning with 1997 (the first year such data were summarized by the FDA). The blue line and corresponding data label represent the total number of efficacy supplement filings received by CDER during each fiscal year. Source: CDER.

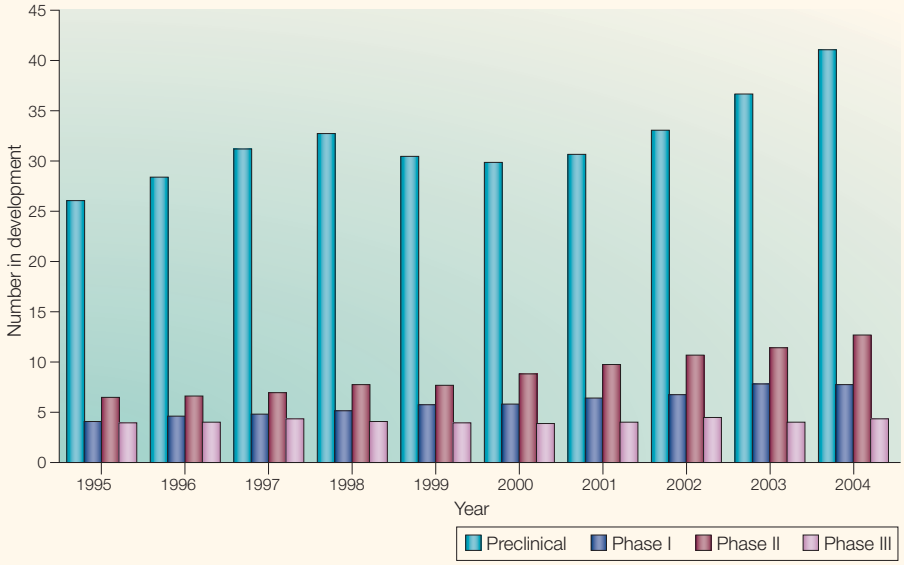

Figure 7 | **Drugs in development by Phase, 1995–2004.** Light blue, blue, red and pink columns represent preclinical, Phase I, Phase II and Phase III drugs, respectively, reported to be in active development during the first quarter of each year shown. Source: REF. 23.

of approximately 370 new drugs could be approved by the FDA within the next 3 or 4 years. This could represent as much as a 70% increase in innovative output compared with the 2001–2003 period.

Conclusions

The pharmaceutical industry is motivated to innovate, not just incrementally or sequentially but also to produce pioneering innovations that drive profits and provide competitive advantages. In this respect, it resembles most other mature manufacturing industries. Incremental innovations, for the most part, have an important role in sustaining the industry's incentives to innovate and should not be discouraged by policy. The evidence from R&D expenditures, allocation of R&D resources and drugs being produced, when taken together, support the industry's ongoing commitment to innovate. R&D investments as a percentage of sales are historically high relative to all other industries and are second only to the aerospace industry. As a proportion of funds invested in R&D, basic and applied research by industry is waning, and R&D investment is being apportioned increasingly to clinical development and regulatory requirements. It is not clear whether this nonclinical research gap is being filled by non-profit institutional research, but the increased issuance of drug patents to universities and colleges suggests that this is indeed occurring. Fewer NMEs are being approved, including fewer priority-rated NMEs. But on the basis of NME filings, the decline in priority-rated NME approvals does not seem to be related to an industry aversion to developing drugs destined for a priority review, because the proportion of NME and efficacy supplement filings that receive this rating has been increasing, not decreasing, recently. Finally, the future looks brighter in terms of innovative output, with the possibility for large relative increases in new drug approvals over the coming few years.

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Competing interests statement

The author declares no competing financial interests.

Online links

FURTHER INFORMATION
Center for Biologics Evaluation and Research: http://www.fda.gov/cber/
Center for Drug Evaluation and Research: http://www.fda.gov/cder/
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