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Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry

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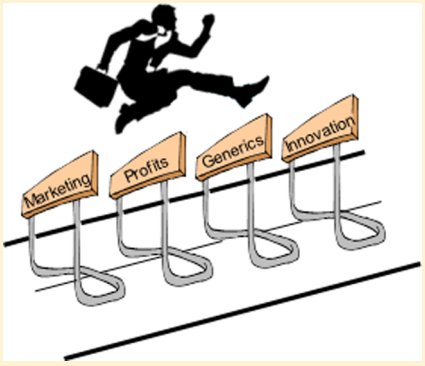
ABSTRACT: The pharmaceutical industry is facing enormous challenges, including reduced efficiency, declining innovation, key patent expirations, fierce price competition from generics, high regulatory hurdles, and a tarnished image. There is a clear need for change in the paradigms designed to address these challenges. Pharma has responded by embarking on a range of initiatives. However, along the way the industry has accrued critics whose accusations have tainted its reputation. The first part of this two-part series will discuss the criticisms that have been leveled at the pharmaceutical industry and summarize the supporting data for and against these criticisms. The second installment will focus on the current challenges facing the pharmaceutical industry and Pharma's responses to address these challenges. It will describe the industry's changing perspective and new business models for coping with the recent loss of talent and declining clinical pipelines as well as present some examples of recent drug discovery successes.



INTRODUCTION

Drug discovery is a noble profession but is poorly understood by the public. Over the past 50 years, the pharmaceutical industry ("Pharma") went from being one of the most admired professions to one of the most unpopular. Pharma's reputation is now perceived by many to be below that of the chemical and oil industries. Critical articles on the pharmaceutical industry began appearing in the scientific literature in the early 1980s, although legislators have been accusing the industry of questionable practices and garnishing unacceptable profits since the late 1950s. By the mid-2000s there was no shortage of critics and criticisms leveled at the sector. Whole books have appeared that essentially vilify big Pharma.[1−3] However, recent articles and books from former pharmaceutical "insiders" present alternate analyses that may be of interest to readers.[4−8] The following perspective discusses some of the commonly perceived criticisms of Pharma (Figure 1).

Figure 1. Commonly perceived criticisms of the pharmaceutical industry.

QUESTIONABLE MARKETING PRACTICES

Arguably, one of the most common complaints against Pharma is their marketing practices. There is no question that marketing budgets for pharmaceuticals have been and still are large. One 2004 estimate placed US pharmaceutical marketing expenditures at $57.5 B.[9] On the basis of surveys, these expenditures were roughly divided between free samples (56%), detailing to physicians (i.e., building one-to-one relationships with physicians, which sometimes involved gifts, office lunches, etc.) (25%), direct-to-consumer advertising (12.5%), hospital detailing (4%), and professional journal advertising (2%).[10] Each of these activities has come under fire from critics as being an inappropriate way to promote drug sales, often at the expense of the patient.

Data do not support the notion that free samples reduce prescription cost burden for the sample recipients. However, it is argued that free samples give patients immediate access to drugs and allow them to see if they work for that particular patient before incurring the cost of filling the prescription. Critics descry physician detailing, yet pharmaceuticals are among the most technically complex products in the world and a detailed briefing is often necessary to properly inform prescribers on the proper use of a given drug. Thus, physician detailing continues to be a major activity for pharmaceutical sales representatives, but the percentage of physicians who are amenable to sales representative visits is lower now compared to the early 2000s. One strategy

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that has emerged in response to this reduced face-to-face contact is "e-detailing", providing scientific and marketing information to the physician through e-mail, dedicated Web sites, smartphone/tablet applications, and other digital tools. The downside to e-detailing, unfortunately, is a concomitant loss of sales representative jobs as pharmaceutical companies look to cut costs.

The practice of gift giving has declined over the past 10 years, due in part to a 2009 update in the Voluntary Code of Interaction with Healthcare Professionals maintained by the Pharmaceutical Research and Manufacturers of America. Controversies over direct-to-consumer marketing have also arisen.[11] The United States and New Zealand are the only two developed countries that allow direct-to-consumer advertising (DTCA) of prescription drugs. Opposing camps argue over whether DTCA makes patients better informed or pressures physicians to "rubber stamp" self-diagnoses and self-prescribing. Originally limited to radio, television, and magazine advertisements, DTCA is increasingly appearing on the Internet (e.g., dedicated Web sites) and on social media sites such as Facebook and Twitter. A greater concern than the impact of DTCA is the accusation of misleading marketing and misinformation. Claims of over-exaggerated benefits, understated risks, promoting use of drugs for nonapproved uses, disease mongering (inventing diseases to boost drug sales and convincing potential patients that they need to take medicines in questionable situations), sponsoring scientific studies to promote drug sales, and employing key opinion leaders and colleagues to exert peer pressure on physicians abound. Pharma is also accused of withholding or not reporting negative data. However, the reality is that once a compound has entered clinical trials, pharmaceutical companies are required to report all additional data, whether positive or negative, to regulatory agencies. A list of all hypothesis-testing clinical studies is freely available on the Web site clinicaltrialresults.org, although the ability and willingness of the average patient to digest the >60 000 studies ongoing at any given time is questionable. "Company-sponsored" clinical trials have become synonymous with "tainted" or "biased" results. Yet these trials are conducted at leading medical centers, so the accusation would seem to be an indictment of academic medicine. Furthermore, companies are bound to the ethical principles laid down in the World Medical Association's "Declaration of Helsinki", so falsifying or withholding negative data is an unlikely event that would risk dire consequences if discovered.

It is no secret that pharmaceutical companies routinely perform phase 4 clinical trials in order to extend the indications for an approved drug and that part of the motivation behind this is to increase the drug's market share. A pharmaceutical company is just that, a company, and finding additional uses for a drug that provide a true therapeutic benefit is sound practice, both financially and ethically. However, promoting the use of a drug for nonapproved indications is a criminal act. Almost all pharmaceutical companies are the subject of lawsuits involving these types of claims every year. But congressional inquiries into the marketing of the antiepileptic drug gabapentin in 2004 led to a heightened public awareness of the possibility of inappropriate marketing practices.[12] From 1991 to 2011, a number of pharmaceutical companies were accused by the Department of Justice of violating the False Claims Act and the Federal Food, Drug & Cosmetic Act (primarily for off-label promotion) and had settlements imposed on them, the largest fines being in the $1−3 B range. Coupled with the ever-increasing number of lawsuits and a heightened sense of ethical responsibility by physicians and their professional organizations,[13] the current environment will hopefully discourage others from the past marketing practices that have tarnished the industry's image.

PHARMA WANTS TO SELL DRUGS, NOT CURE DISEASE

Another common criticism is the accusation that the pharmaceutical industry avoids and even suppresses the discovery of potential cures for diseases in favor of drugs that merely treat the symptoms so that they can be sold to patients for a longer period of time. Countless articles and Internet Web sites raise this issue, and at least one purported "whistleblower" (an ex-sales representative and author[14]) has waged a public campaign accusing pharmaceutical companies of being in the business of disease management and symptom treatment rather than curing disease. Some critics go as far as to accuse physicians and even the Food and Drug Adminstration (FDA) and the Federal Trade Commission (FTC) of being part of a large conspiracy to keep pharmaceutical companies in business at the expense of patients. It cannot be argued that many drugs provide symptomatic relief for patients rather than eradication of the disease for which they are prescribed. However, the claim that Pharma has identified cures for many diseases and is suppressing them is unfounded. The majority of biomedical researchers went into their respective fields because they sincerely want to have a positive impact on the human condition. It is unlikely that the discovery of a drug that can truly cure a disease would remain secret, especially in today's world where "whistleblowers" are not only protected from retaliation, they often profit from exposing unethical and criminal acts in industry. It should also be emphasized that the basic research that provides the fundamental understanding needed to discover drugs is not only performed in laboratories funded and controlled by Pharma. Government, academic, and not-for-profit research organizations also pursue this kind of research. There is a whole government-based funding system that supports health-related research in these environments. That funding comes with rules involving sharing of data and public disclosure of results. Also, many disease-specific private foundations fund basic and applied research with the sole intention of identifying better treatments and cures for their diseases of interest. Any given researcher's reputation and future would be guaranteed if they identified a disease cure. Therefore, one would expect that a fundamental, disease-curing discovery made in one of these settings would quickly become public knowledge and provide the driving force for drug discovery oriented around that finding.

Despite the desire to cure disease, some diseases just do not seem to be amenable to cure, or else we still do not possess a good enough understanding of the disease. One classic example of a disease that falls into this category is cancer. Years of research have shown that cancers are very diverse and undergo changes and adaptations with time and in response to treatment (resistance). At some point, if left unchecked almost all metastatic cancers become untreatable. Some experts go as far as to assert that each individual cancer may be its own separate disease. This makes finding a universal cure for cancer, a "silver bullet" so to speak, difficult and unlikely with our current level of knowledge on cancer. Despite these limitations, significant strides have been made in some areas such as leukemia, breast cancer, and colon cancer, where the survival rates are high, especially when the disease is identified at an early stage. Another very public disease that continues to defy cure is Alzheimer's disease (AD). Symptomatic treatments exist but no curative drug has been identified. A major reason for this fact is that, despite

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heroic amounts of time and money invested by government, academic, foundation, and industrial groups, the underlying cause(s) of AD has not been identified. However, the pharmaceutical industry has spent considerable time, effort, and money attempting to identify "disease-modifying" AD drugs, drugs that will halt the progression of the neurodegenerative process.[15] A number of disease-modifying drugs based on the amyloid cascade hypothesis have entered clinical trials over the past ten years. Unfortunately, results to date have not been encouraging, but as our knowledge base and sophistication grow,[16] so does the hope that we will ultimately find a way of overcoming this devastating disease.

HIGH DRUG PRICES

The price of medicines is a popular criticism of the pharmaceutical industry, especially in the United States where drug prices are not government-controlled. Critics blame the patent system[17] and a healthy dose of greed on the part of pharmaceutical companies for increasing drug prices in the US. The industry counters with the high cost of bringing drugs to market and the relatively short amount of "exclusivity" time that is available to recoup the investment in those drugs before generic competition begins. Proponents on both sides cite studies and statistics and claim that the opponents' data are inaccurate and skewed. It is true that drugs cost more in the US than in other countries and that this fact has sensitized people to the cost of medicines. A recent report from Express Scripts, a pharmacy management company, suggests that prices of branded drugs in some therapeutic areas increased over 13% between September 2011 and September 2012.[18] However, the Pharmaceutical Research and Manufacturers of America (PhRMA) responded by pointing out that these data are based on the price of drugs in 10 specialty areas, many of which represent small markets or orphan diseases where the limited ability to recover high investment costs influences the final drug price. The Express Scripts report did suggest that the *overall* average of drug prices during this period trended downward, thanks mainly to generic alternatives that recently became available. While the yearly increase in the price of pharmaceuticals may be somewhat larger than the increase of other health care costs, it should be pointed out that the expenditure on pharmaceuticals (12−21%) is a relatively small percentage of total health care-related costs (Figure 2). Also, data suggest that the percentage of total health care expenditures on drugs and other medical supplies in the US is not significantly different from that seen in most other countries. Notwithstanding the continuing debate on prices, pharmaceuticals still remain a cost-effective way of managing disease and controlling health care costs. A 2011 joint study by the Batelle Technology Partnership Practice and Pharmaceutical Research and Manufacturers of America[19] concluded that medicines reduce health care costs for both providers and patients by reducing the need for costly hospitalization, institutionalization, or more costly medical procedures, and a recent Health Technology Assessment suggested that cholesterol-lowering statins are a cost-effective means of lowering the risk of primary and secondary cardiovascular events in adults with, or at a risk for, coronary heart disease.[20] Pharmaceuticals also have a beneficial impact on the economy in general by allowing patients to return to work more quickly following illness and to work in the midst of flair-ups of chronic maladies such as arthritis. Examples of the cost-benefit of pharmaceuticals include antipsychotic drugs which keep many patients from being institutionalized, stomach acid blocking drugs which have dramatically reduced the need for peptic ulcer surgery, anticoagulants (blood thinners), which are routinely used prophylactically to prevent stroke, myocardial infarction, and other thrombolytic events, and nonsteroidal anti-inflammatory agents that relieve pain and inflammation.

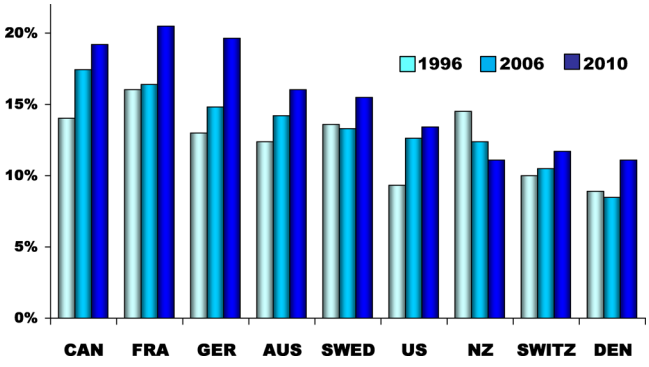

Figure 2. Percent of health care expenditures spent on pharmaceuticals for selected countries. Source of data: Organizations for Economic Cooperation and Development (www.oecd.org).

Some experts believe that it is the differential between US drug prices and those seen throughout the rest of the world rather than the actual drug price that antagonizes the US public. Despite accusations to the opposite, pharmaceutical companies do not willingly agree to lower prices outside of the US at the expense of US patients. Pharmaceutical companies ask for similar prices throughout the world but have no authority to set prices. In most countries the government regulates the price of a drug and the company has to accept that price to do business in those countries. In the US drug prices are set by development cost, manufacturing cost, and competition from alternatives via Average Manufacturing Price rules, which have recently come under scrutiny in the context of the 2010 Patient Protection and Affordable Care Act.[21] One study suggests that drug costs in the US do not reflect development time (which can be as much as 12−15 years), nor are they affected by government investment, although these factors do contribute to how soon new drugs become available to the patient population.[22] Critics of the industry are quick to assert that the $1−1.3 B price tag commonly cited for bringing a new drug to market does not justify the consumer cost of medicines. However, as pointed out recently in a Forbes Business article by Matthew Harper,[23] the cost of bringing a successful drug to market is not the only expense that a pharmaceutical company must bear. For every successful drug there are failed drugs and drug discovery programs that have also incurred substantial costs. These losses must also be figured into the company's bottom line. Data cited by Harper suggest that when all of the research costs are taken into account, the actual cost of bringing one drug to market could be between $4 B and $11 B. These data do not take into account the impact of the dramatic increase in litigation that the pharmaceutical industry has had to bear in recent years. Product liability and litigation have risen to an art form, and we all pay for it. Independent reports concur that the burden of increased private and government lawsuits has contributed significantly to the overall increase in pharmaceutical prices.[24,25]

Regardless of the debate over the appropriateness of drug prices, there is still a real issue of some patients not being able to afford some life-saving drugs, even after insurance contributions. At the beginning of the 2000s, this issue applied mainly to

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uninsured Americans and people on small, fixed incomes such as the elderly population. However, there has also been a steady increase in the percentage of working age adults who have elected not to have a prescription filled because of cost, even among those with prescription insurance.[26] The real impact of this issue is felt when patients are taking several medicines simultaneously (common in the elderly), in the area of specialty medicines such as cancer drugs, in chronic diseases such as AIDS where treatment could last a lifetime, and with biological agents which tend to cost more because their manufacture costs tend to be significantly higher than those of small molecules. In response to this increasing dilemma, many pharmaceutical companies are now offering prescription assistance programs for patients who cannot afford their medicines. A number of not-for-profit organizations maintain web-based databases that help qualifying patients find assistance with their prescription needs. Nevertheless, the issue of drug affordability has become a political issue, especially in the context of Medicare. The 2003 Medicare Prescription Drug Improvement and Modernization Act prohibits the US federal government from negotiating the price of prescription drugs. Part of the Health Care Plan put forward by President Barack Obama was a repeal of this prohibition, but little progress has been made on this front as of the writing of this article, although bills have been introduced into the US Congress to allow for such drug price negotiations. The current patent-based intellectual property system, established under the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch–Waxman Act), is blamed for the so-called "drug monopoly" that industry critics say allows pharmaceutical companies to charge high prices in the US. However, that act also sets forth the process whereby generic competition on a branded drug can begin and provides protection to the generic companies when they mount patent validity challenges. Supporters of the pharmaceutical industry take the position that the patent system is necessary to guarantee the investment recovery and profit that the companies need to reinvest in drug discovery research. They credit the intellectual property-based system as the reason why most new drugs today are invented in the US as a result of the reinvestment in research.[27]

As the US government continues to negotiate free trade agreements that would foster US-like intellectual property standards and drug financing policies in other countries, it appears that overt price regulation and repeal of the patent-based system are not likely to occur in the near future in the US. However, other less radical strategies for making drugs affordable and accessible have been proposed. One of the proposed strategies is to extend patent life for drugs even longer than the current limit of 20 years following first filing. The arguments for and against such a policy were recently debated in a 2012 article in the Wall Street Journal.[28] In this article, Dr. Josh Bloom, Director of Chemical and Pharmaceutical Sciences at the American Council on Science and Health, took the position that patent extensions would help overcome the issues the industry is suffering as a result of the recent loss of research jobs, the longer development times, the increased difficulty in treating the diseases targeted today versus 20 years ago, and the impending "patent cliff". In his opinion, enhancing the ability of pharmaceutical companies to recoup their drug discovery costs would allow them to continue to invest in research and promote innovation by encouraging them to invest in high risk targets with unmet medical need. He qualified his position by suggesting that patent life might be extended for high risk, first-in-class drugs and shortened for drugs that are merely extensions of available treatments. On the opposing side, Dr. Els Torreele, Director of the Access to Essential Medicines Initiative of the Open Society Foundation's Public Health System, argued that the current patent life extension policy has done little to lower prices or promote innovative research on high-risk targets and cited past examples of successful, beneficial drugs that were developed outside of the patent system, albeit many years ago (aspirin, the polio vaccine). As an alternative to the patent-based system, Dr. Torreele suggested drug approvals that were contingent on therapeutic advances and finding alternate private and public funding sources in place of pharmaceutical sales to support drug research.

A strategy for making drugs affordable and accessible that is currently being tested is the concept of value-based pricing, linking payment for medicine to value achieved rather than volume.[29] Under this scenario, consumers pay more for drugs that display a true benefit compared to available therapies and pay less for drugs that are extensions of available treatments. This concept mirrors Dr. Bloom's suggestions concerning extended patent lives for high-value drugs and shorter patent lives for extensions of available treatments.[28] The problem that has arisen in the implementation of this strategy is deciding how value is defined and measured and who makes those determinations. A good example of this dilemma is represented by recently approved, expensive cancer drugs that some insurers and national health societies have refused to cover over questions of the relative value that the drugs provide. There is concern that if pharmaceutical companies cannot count on adequate return for drug discovery investments then innovative research in high risk areas will decline or cease altogether. Alignment of stakeholder goals and values, clearly established, agreed-upon metrics for measuring therapeutic value, and a clear, early picture of the expected return on investment will have to occur if value-based pricing is to be successful. Another strategy that is currently in place is the concept of differential pricing (tiered pricing), adapting product prices to the geographic or economic status of different consumers. The World Health Organization recently published a document summarizing the concept, reviewing the existing literature, and analyzing successful and unsuccessful examples of differential pricing.[30] The practice is established in the developing world, although it has been limited to vaccines, contraceptives, and AIDS drugs. Providing low cost medicines to poor developing countries has brought criticism on the pharmaceutical companies in the US, where a similar or identical drug can cost significantly more. However, pharmaceutical companies have been quietly deploying some pricing differential campaigns in the US in the form of discount cards for low income seniors and prescription drug assistance programs for low income consumers. What is certain is that if the pricing differential strategy is to be successful in the US, it must be formulated in such a way as to provide suitable return to the industry to cover investment costs and support future research. One other tactic that is currently under investigation is subsidized payment for drugs, such as the pilot supranational subsidy program designed to increase access and affordability of artemisinin combination therapy (ACT) for malaria in Africa.[31] This program increased availability of ACT in remote regions of Tazania, but it is not clear how the concept would succeed in the US and where the funding for this subsidy would come from.

LOW RESEARCH AND DEVELOPMENT BUDGETS

The pharmaceutical industry is constantly accused of investing more of their yearly sales in marketing than in research and development. However, 2010 healthcare R&D spending accounted for 21% of R&D spending in the US, which was surpassed only by the computing and electronics industry (28%) and significantly higher than that spent by other US industries (Figure 3).[32] On average, the pharmaceutical industry reinvested

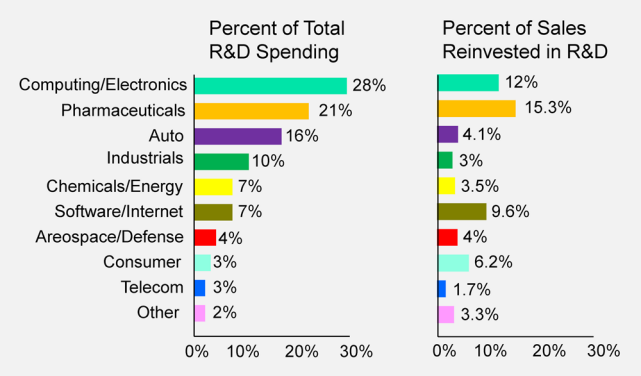

Figure 3. 2010 Figures. Left: Percent of total R&D spending by sector.[30] Right: Percent of yearly sales reinvested back in R&D.[33]

15.3% of its net sales back into R&D, which is higher than that reported for any other sector (Figure 3).[33] The combined annual R&D budgets for PhRMA members alone have consistently exceeded the total operating budget allocated to the National Institutes of Health, with estimated budgets for the entire pharmaceutical industry approaching twice that of the NIH.[34] The accuracy of marketing budget figures provided by marketing intelligence companies has been questioned,[35] but IMS Health estimated the 2008 marketing budget for the pharmaceutical industry at $11.3 B while the combined R&D budget in that year was over $63 B.[36] Even if the marketing numbers are somewhat inaccurate, it is obvious that the pharmaceutical industry has made a significant investment of its sales in research and development over the past years. In fact, the Congressional Budget Office claims that "the pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest as much as 5 times more in research and development, relative to their sales, than the average US manufacturing firm" and significantly more than generic pharmaceutical companies (2011 combined R&D budget for PhRMA members: $49.5 B;[34] 2011 estimated combined R&D budget for six top generic pharmaceutical companies: $2.8 B[37]). R&D budgets have been steadily increasing over the past decade. However, this increased spending has not led to an increase in approved drugs. The number of new chemical entities approved by the FDA since 2002 has remained at or around 20 per year (although the FDA's approval of 39 new chemical entities in 2012 is an encouraging deviation from this trend). This discrepancy has been labeled the "innovation gap"[38] and is a subject of discussion in the second part of this series.

PHARMA DELAYS ACCESS TO GENERICS

Since the mid-1980s, generic competition with branded pharmaceuticals has grown continuously. In 2011, the generic drug market reached a new high, with 80% of prescriptions being filled with a generic.[39] The loss in sales for pharmaceutical companies has been significant. Estimates place the decline in spending on branded drugs from 2007 through 2011 at $65.2 B. This decline is primarily due to the expiration of patents, especially patents on a number of "blockbuster" drugs (Table 1

Table 1. Blockbuster Drug Patent Expirations, 2011−2013. Source of Data: 2009 Medco Health Solutions, Inc.

year	brand name	2008 US sales ($ B)
2011	Actos	$2.569
2011	Zyprexa	$1.853
2011	Lipitor	$6.392
2012	Levaquin	$1.719
2012	Lexapro	$2.554
2012	Seroquel	$3.236
2012	Plavix	$3.971
2012	Lovenox	$1.107
2012	Singlulair	$3.204
2012	Diovan	$2,671
2013	Cymbalta	$2.294

and Figure 4). In 2011 alone, the pharmaceutical industry experienced a $14.9 B decline in sales due to first-time generic competition on drugs such as Lipitor, Zyprexa, Levaquin, and Actos. Patents on more blockbusters expired in 2012 (e.g., Seroquel, Plavix, and Singulair), and a number are expected to expire between 2014 and 2021. This "patent cliff" has become a serious issue for the industry.

Pharmaceutical companies protect and defend their intellectual property. All industries do. As discussed previously, long development times result in short periods of "exclusivity" during which drug companies can recoup their investment in the drug and other R&D efforts. Under the so-called "Paragraph IV" certification of the Hatch−Waxman Act, generic drug companies are allowed to attempt to invalidate patents and file Abbreviated New Drug Applications (ANDAs) as soon as 4 years following approval of that drug with limited risk of liability from infringement. The first to file and successfully defend an ANDA obtains a 180 day exclusivity period on the generic form of the drug in question. Paragraph IV challenges have become a core business strategy for many generic drug companies. Between 2001 and 2008, the number of branded drugs that came under attack from Paragraph IV challenges nearly tripled from 16 in 2001 to 43 in 2008.[40] Classic examples of drugs that lost exclusivity before the scheduled patent expirations include Fosamax and Prozac (Figure 4). Following a successful Paragraph IV challenge in 2008, Teva began selling alendronate, the generic form of Fosamax, four years before the Fosamax patents were scheduled to expire. In the first year following the loss of exclusivity, Fosamax sales dropped by 50%.[39] Following a successful patent challenge by Barr in 2001, market share of branded Prozac fell to generic fluoxetine by 65% in the first two months and by the end of 6 months, branded Prozac accounted for only 16% of the prescriptions written for the popular antidepressant drug (Figure 5).[41] While the blockbuster drug Lipitor (Figure 4) did not succumb to patent challenges, its primary patents did expire in 2012, resulting in similar decreases in sales and prescriptions dispensed.[42] These data demonstrate how generic entry impacts on a branded drug's market share and ability to generate revenue for the company that developed the drug.

The patent battle extends beyond the US. Three recent decisions in India have important implications on generic drugs and intellectual property. India is one of the largest providers of

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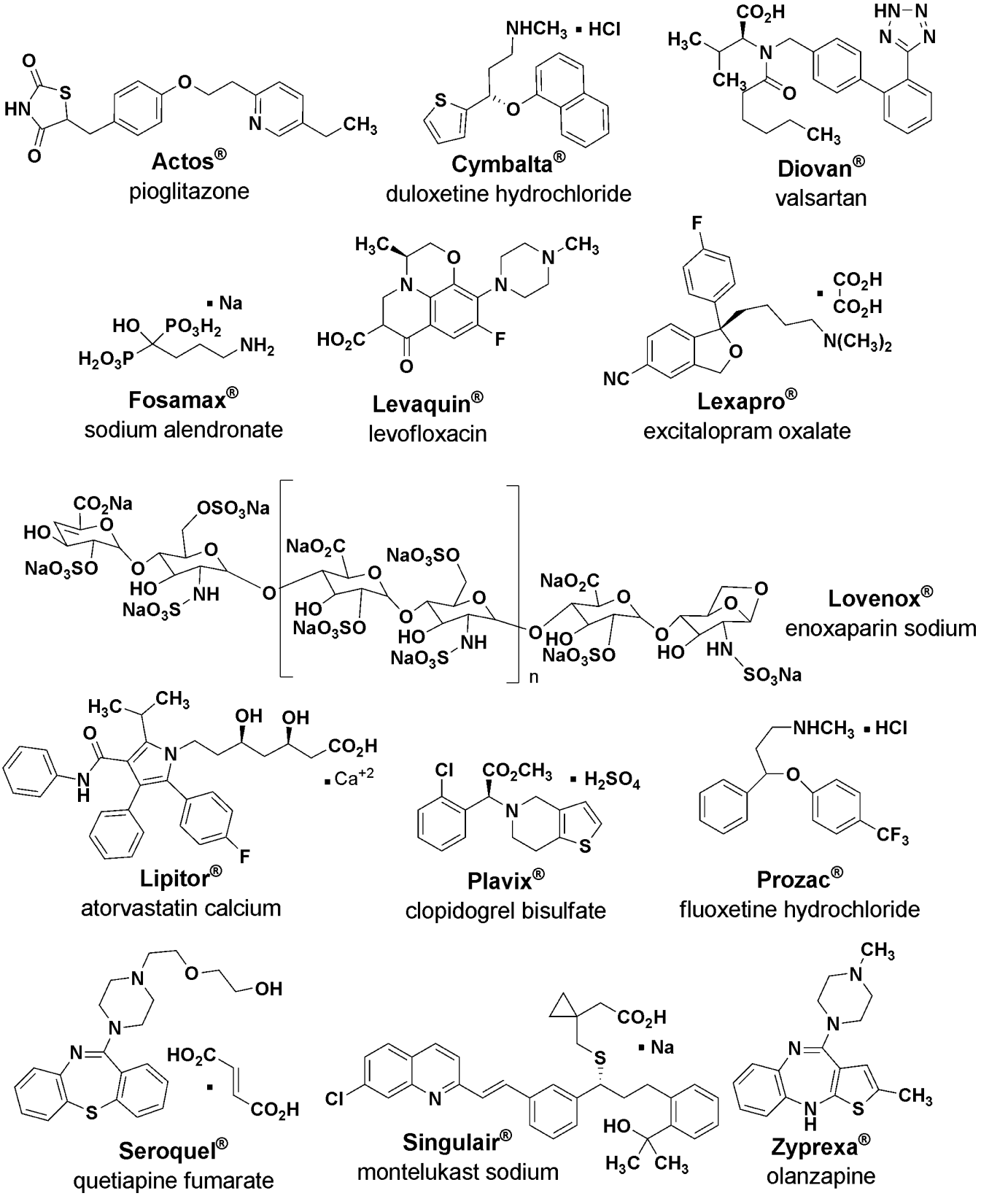

Figure 4. Drugs that recently lost patent protection.

generic drugs in the world and did not begin issuing patents on drugs until 2005. The 1995 Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) allows for compulsory licensing of patented drugs for public health reasons in some countries. In 2012, the Indian government issued a compulsory license authorizing Natco Pharma to make and sell a generic version of Nexavar, an anticancer drug that is under patent protection in several countries, including India. The controller

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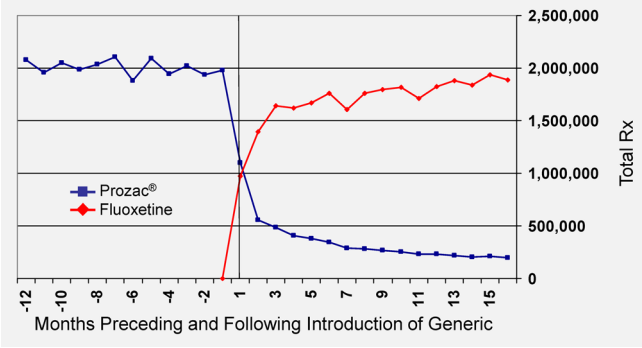

Figure 5. Effect of introduction of generic fluoxetine on Prozac prescriptions. Source of data: Cap Gemini Ernst & Young.

general cited the high cost of Nexavar as the reason for the decision. On April 1, 2013 India's Supreme Court rejected Novartis's appeal of a landmark case involving the denial of an Indian patent on Novartis's anticancer drug Gleevec (Glivec in Europe and Asia). Norvartis had previously stated that a loss could influence whether or not the company introduced new generations of its medicines into the Indian market. The third case involves Roche's antiviral drug Pegasys, the first drug to secure an Indian patent in 2006. India's patent appeal board recently revoked the patent, clearing the way for Indian generic versions. While the financial implications of these cases to the three branded companies are not particularly imposing, the industry is concerned that the precedence set by these setbacks could threaten the intellectual property system in much broader terms and will threaten further investment in India by large drug companies. Critics tout the decisions as a victory in the battle to obtain early access to generic drugs.

Critics who accuse the industry of denying patients access to cheaper generic drugs often include patent extensions in their list of grievances. The Hatch–Waxman Act provides for patent extensions. Up to 50% of the time spent in initial clinical trials and 100% of the time spent in regulatory evaluation can be added onto the patent life of a drug, provided that the applicant does not cause undue delay in either of these two processes. However, perhaps a greater point of contention arises over matters such as patents for additional indications, patents for new formulations such as extended release and patenting active enantiomers ("eutomers") and active metabolites. Critics have come to refer to such activities as "evergreening".[43]

Patenting active enantiomers of approved racemic mixtures (sometimes referred to as "chiral switching"), a popular strategy in the 1990s, has led to a number of new drugs such Lexapro, the (*S*)-enantiomer of the racemic antidepressant Cylexa, and Nexium, the (*S*)-enantiomer of the racemic proton pump inhibitor Prilosec.[44] The active enantiomer is not considered a new chemical entity once the racemate has been disclosed and must display superiority over the racemate to be considered patentable. The interpretation of this distinction has led to patent challenges, such as Mylan's challenge of Ortho-McNeil's patent for Levoquin, the more soluble enantiomer of the racemic antibiotic Floxin. In that case, the courts upheld Ortho-McNeil's patent. In 1992, the FDA issued a policy statement for the development of stereoisomeric drugs, which was followed two years later by similar European guidelines. While the development of racemic mixtures is not strictly forbidden, the new guidelines encourage development of single enantiomers. The industry has accepted this guidance, especially with recent advances in chiral separation science and stereoselective synthetic techniques. In 2001, nearly 75% of approved new chemical entities were single enantiomers, compared to around 20% in 1983.[45] Thus, chiral switching is not likely to be as much of an issue going forward.

Properties such as crystallinity, polymorphic form(s), cocrystal form, and the salt form of a drug can influence that drug's solubility, bioavailability, stability, and dosage form preparation. Many of these properties are not predictable and, as such, are patentable. Patenting such properties to strengthen the intellectual property position of drug is a common practice. However, history has shown that relying on such a strategy to extend patent life of a drug can be risky. In 2007, a Federal Circuit court overturned a prior District Court decision and ruled that Pfizer's patent on Norvasc, the besylate salt of the calcium channel blocker amlodipine, was invalid on the grounds of obviousness, despite a number of advantages cited in the patent for Norvasc compared to the previously patented maleate salt. And while the Norvasc patenting strategy was intended to make up for lost time in development (amlodipine maleate turned out to be chemically instable and too sticky to formulate into a tablet), it was commonly perceived to be an evergreening ploy.

Patenting the use of approved drugs for new indications has been touted by industry critics as an evergreening tool. However, relying solely on additional "use" patents to extend the exclusivity period of a drug can also be risky. Off-label prescribing in the US is not regulated by the FDA. A physician may, at their discretion, prescribe a drug for a nonapproved indication although drug companies cannot advise physicians to do so. A physician can just as easily prescribe a generic version of a drug off-label as they can prescribe the branded version of a drug that is approved for the new indication. The use patent strategy has seen some success in the past. For example, the immunosuppressant drug Sirolumus (rapamycin) was originally patented and developed as an antifungal agent. Its use as an immunosuppressant was discovered and patented later, and that patent provided additional exclusivity for the drug's developer, Wyeth Pharmaceuticals. However, recent court decisions have paved the way for generic approval of drugs when use patents remain in effect after composition of matter patents have expired.[46] Generic companies have achieved successful ANDA approvals by "carving out" patented uses of a drug from their generic label. Branded drugs that recently fell to such generic challenges include Bayer's Yasmin and Novo Nordisk's Prandin, and it appears that the current environment will continue to support this approach for generic drug approval in the face of use patents. The only recourse that the branded company may have is to police the generic company's public marketing strategy for evidence that infringement of the valid use patent is being promoted.

Patenting new formulations of approved drugs, especially extended release formulations, is a common practice. Extended release formulations that reduce dosing frequency can offer significant advantages by improving patient compliance, but it is common for extended release versions of drugs to cost more than immediate release formulations. There have been cases where companies introduced higher priced extended release formulations and withdrew the lower priced immediate release formulations of drugs, and it is not hard to see how industry critics would interpret such an act as an attempt to boost profits. However, as long as branded or generic versions of the lower priced immediate release formulation are available, the patient has a choice which can be made with the consultation of his/her

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physician or pharmacist. Nanoformulation is another tool used by drug manufacturers to improve the stability, solubility, bioavailability, and, ultimately, effectiveness of some drugs. According to Pharma critics, it is also an evergreening tool. A patent on a new nanoformulation can extend the patent life of a drug in that particular dosing form. It is also likely that a new nanoformulated version of a drug would cost more than a simpler formulation. However, the same argument for extended release formulations applies in this case. As long as generic or older/cheaper branded versions of a drug exist, the patient can make a choice that fits his/her means.

Branded fixed dose combinations of drugs that are often taken simultaneously have also come under fire from industry critics. Fixed dose combinations offer the advantages of improved patient compliance and optimum synergy (by selecting proper doses of each of the components). One of the best known fixed dose combinations is Augmenten, a combination of the antibiotic amoxicillin and the β-lactamase inhibitor potassium clavulinate. However, another drug combination has recently appeared in the political spotlight. That drug is Atripla, a combination of three antiretroviral drugs for treating HIV and AIDS. In the US, the cost of a yearly regimen of Atripla exceeds $20 000. In countries where a generic version of the triple combination is available, the yearly cost is around $200/patient. Atripla is thought to be one of the more effective drugs for controlling HIV infection available today. If generic versions of the three components of Atripla were available, then taking those generic drugs together might offer a cheaper, albeit more cumbersome, alternative. However, two of the three components are still under patent coverage until the 2018−2021 time frame, so it is not currently possible to reproduce the combination of drugs in Atripla using generic components. There are patient assistance programs available to qualifying applicants, but Internet sites abound with stories and posts about patients having difficulties affording their Atripla prescriptions. Given the heightened political sensitivity of HIV in the US, it is likely that AIDS drugs like Atripla will continue to be at the forefront of the debate over drug costs and access to generics.

However, other activities that do not directly involve extending the patent life of the drug in question have caught the attention of media and industry critics. One of these practices is the marketing of authorized generics. Under the Hatch−Waxman Act, when a generic drug company successfully prosecutes a Paragraph IV challenge, the "first to file" enjoys a 180 day exclusivity period during which other generic companies cannot market their own versions of the drug. The price of the generic drug during this time is usually higher than when additional generic competition begins 6 months later. However, that proviso does apply to the owner of the branded drug, who can market their own generic version of the drug during the exclusivity period. The branded company usually authorizes a generic company to do it under their name, although there has been a steady increase in the number of subsidiary generic companies established by big pharmaceutical companies since 2005. The practice of marketing authorized generics has been around since the 1990s but escalated significantly in the 2000s when the frequency of Paragraph IV challenges increased. Critics claim that this practice is an attempt to deter generic companies from pursuing Paragraph IV challenges by removing the "exclusivity incentive", thus slowing down access to generic drugs. The pharmaceutical industry counters that the practice is business-oriented and provides consumers access to lower priced generic drugs within the same time frame as a successful Paragraph IV challenge. A 2011 report by the FTC[47] concluded that the practice of marketing authorized generics actually resulted in lower generic drug prices during the 180 day exclusivity period. Analysis showed that the practice of releasing authorized generics did not significantly reduce the number of patent challenges by generic firms and suggested that any impact would likely be experienced in small markets or in cases where the generic company felt they had a weak case to begin with. Another option for a company whose drug is coming off of patent is to switch the drug from prescription to over-the-counter (OTC) status.[48] Of course, the drug under consideration must possess a high level of safety to secure FDA approval for the OTC switch since patients will be treating themselves. The switch of a drug to OTC status may have negative impact on generic companies' revenues but could positively impact consumers and health costs by eliminating the need for insurer payments and physician's visits to obtain the drug. In addition, by entering an OTC market early, the brand company can establish a strong market position and user loyalty, which insures continued revenue flow that can be invested back into innovative drug discovery.

A practice that has come under FTC scrutiny is what is referred to as "pay for delay". In this case, critics blame both the big pharmaceutical companies and the generic drug firms. According to a report from the FTC, in the fiscal year 2012 they received notice of 140 final settlements between branded companies and generic challengers, 40 of which may have involved payments or promises not to market an authorized generic in exchange for delayed generic entry into the market.[49] The FTC contends that such practices are anticompetitive and unlawful. To date, the FTC has realized limited success in litigating against pay-for-delay settlements. However, the US Supreme Court recently agreed to hear an appealed case involving Solvay Pharmaceuticals, the generic company Watson Pharmaceuticals, and Androgel, a topical testosterone replacement drug. The outcome of this landmark case will likely determine the future of pay-for-delay settlements.

Another issue centers around the FDA Amendment Act of 2007. The act was intended to better inform the public concerning drug safety and provide the FDA with tools to reduce unsafe drug use. One proviso in the Act requires drug manufacturers to establish Risk Evaluation Mitigation Strategies (REMS) on branded drugs that the FDA determines could pose a safety risk if used improperly. The wording incorporated into the Act prohibiting the use of REMS to block or delay approval of an ANDA was vague and nonspecific, and generic drug firms have accused pharmaceutical companies of stifling generic competition by improperly using REMS to deny access of a branded drug to the generic firm to support the bioequivalence studies needed for their ANDA. Two of the most publicized cases involve Celgene. In 2009 the generic company Dr. Reddy's Laboratories filed a Citizen's Petition with the FDA accusing Celgene of refusing to sell samples of the anticancer drug Revlimid for bioequivalence studies. Celgene cited REMS concerns among the reasons for not agreeing to provide the drug. Starting in 2006, Lannett Company began a 5-year quest to obtain samples of Celgene's anticancer drug Thalomid, a request that Celgene denied for REMS reasons. The process culminated in Lannett filing an antitrust suit in 2008 which was settled prior to going to trial in 2011. The settlement postponed further judicial review of antitrust claims premised on abuse of REMS restrictions, but the involvement of the FTC and at least one state Attorney General in REMS-associated antitrust investigations confirm that using

REMS to deny drug access for generic application support is under scrutiny. Yet, the question still remains: should the owner of a patented drug be obligated to sell that drug to someone who clearly intends to use it in a way that will take business away from the owner?

Another issue that plays into the intellectual property argument is the role of patients in driving innovation. A continuous goal of drug discovery is to make medicines safer and more effective for patients. Since the essential completion of the Human Genome Project in the mid-2000s, the pursuit of "personalized medicine" has grown. The role that a patient's genetic makeup plays in the efficacy (pharmacogenomics) and safety (pharmacogenetics) experienced by that particular patient has become a focus of pharmaceutical companies and regulatory agencies alike. In 2011, the FDA announced its innovation initiative.[50] A large part of that initiative involved promoting personalized medicine approaches to drive innovation, curtain development costs (especially clinical trial costs), and provide better drugs to patients by targeting those drugs to appropriate populations. In fact, the practice of personalized medicine is evident today, especially in the area of cancer treatment where tumors are often "typed" for particular kinase signaling pathways prior to administering certain kinase inhibitors. However, the price of personalized medicine is also evident in the case of targeted cancer therapy. While targeting clinical trials to more susceptible patients may reduce development costs somewhat, smaller numbers of patients translate to high drug prices in order for the company that makes the significant investment in the drug's development to recover that development. Without the exclusivity provided by patent coverage, it is probably that many of the NCEs approved in the past two years would not have been brought to market because they target smaller numbers of patients and are not likely to achieve blockbuster status. If personalized medicine is to continue and advance, then an answer to the conundrum between high drug costs and recovery of development investment must be found, and that answer, at least for the foreseeable future, is likely to include patent coverage.

PHARMA BLOCKS REIMPORTATION OF CHEAPER DRUGS

Some US patients buy their medicines from Mexican or Canadian pharmacies at the reduced prices afforded by the government control that exists in those countries. Individuals are allowed to "reimport" a 90-day supply of a drug for personal use. Originally, this practice involved traveling to the country and bringing back the medicine. However, patients are now able to order their reimported medicine via dedicated Web sites. In fact, Internet pharmacies have become a very lucrative business. Until 2000, reimportation of drugs for sale was limited to the actual manufacturer and only in cases of emergency need. Passage of the Medicine Equity and Safety Act in early 2000 made it legal for pharmacists and wholesalers to reimport approved drugs for sale but required certification by the Department of Health and Human Services, which never came. The act was terminated later that year.

Several attempts have been made to more broadly legalize drug reimportation but have met with no success.[51] As recently as May 2012, a bill introduced into the US Senate to legalize drug reimportation was defeated. In the face of this defeat, proponents of the bill echoed a criticism of the pharmaceutical industry voiced by many Americans, that the pharmaceutical industry uses its influence over the US law making bodies to block the reimportation of drugs.

The cases both for and against drug reimportation are summarized in a recent commentary.[52] For supporters of drug reimportation, the driving forces are cost and access. There is no question that a greater number of Americans are finding it difficult to afford their branded medicines today, especially those with lower incomes or no prescription insurance coverage. Branded drugs in Canada can cost up to 50% less compared to the US. Big Pharma is accused of blocking reimportation because it will cut into their profits, thereby putting money ahead of patient needs. Opponents of drug reimportation cite safety and effectiveness as the main reason for not legalizing the practice, a position supported by the National Association of Boards of Pharmacy. The common perception is that the all Canadian and Mexican drugs were originally manufactured in the US so they must be as safe and effective as the ones sold in the US. Drugs manufactured and intended for Canadian use are regulated by the Canadian Health Products and Food Branch (HPFB), the Canadian equivalent of the FDA. However, the HPFB does not monitor drugs intended for export. Exported drugs may have been originally manufactured in the US, but neither the HPFB nor the FDA has control over the packaging, storage, and shipment of those drugs once they are exported and therefore cannot guarantee that they meet the standards required of drugs sold in the US. The FDA has repeatedly stated that it does not have the capacity to monitor and certify reimported drugs and has actively opposed the attempts of several US states to reimport drugs. There has also been concern that the growing demand for reimported drugs in the US strain's Canadian and Mexican drug supplies and that, to fulfill their needs, foreign pharmacies may turn to less regulated sources where drug counterfeiting is more prevalent. Past evidence has corroborated the FDA's concern, with a number of investigations on reimported drugs identifying issues with labeling, storage, shipment, quality, or the presence of counterfeit drugs.[52] For example, 1982 FDA "sting" operations revealed that nearly 90% of seized reimported drugs did not meet the standards for dispensing in the US. The current situation is unclear, although as recently as last year 40 lots of a foreign-produced generic version of the popular cholesterol-lowering drug Lipitor were recalled because of the unexplainable presence of glass shards in the medicine. Thus, while consumer advocacy groups continue to support drug reimportation as a solution for lowering the price of drugs in the US, it does not appear that legalization of this practice will occur in the near future.

PHARMA DOES NOT CARE ABOUT PROVIDING DRUGS TO THE DEVELOPING WORLD

Access to life-saving drugs, something that many Americans take for granted, are a major issue in many countries of the developing world. One of the most politically charged examples of this problem has been HIV/AIDS and the ability of patients in resource-challenged countries to afford antiretroviral therapy. The drug cost/income ratio is so disproportionate in many developing countries that patients simply cannot afford AIDS treatment, even when it was available. In fact, reports surfaced in the late 1990s describing a lottery that was held in Guatamala. The contestants were AIDS victims, and the prizes were regimens of life-saving antiretroviral therapy, which none of the contestants would have had access to under normal circumstances. AIDS is not the only example of need going unaddressed. Chronic infectious diseases account for nearly 25%

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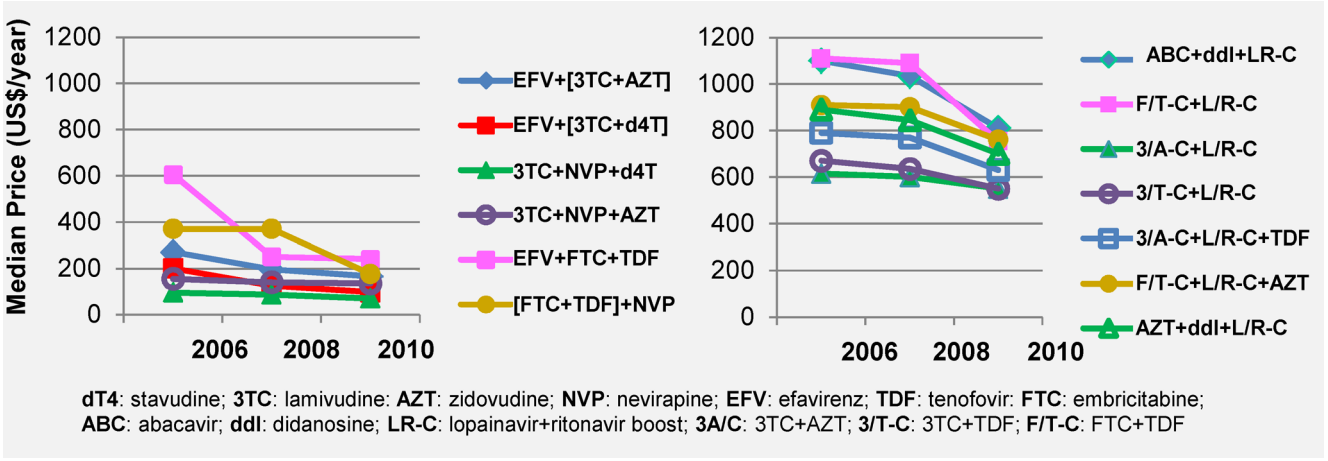

Figure 6. Median annual cost of first-line ART regimens for adults in low-income countries.

of the mortality on the African continent, yet there has been relatively little drug discovery research devoted to unmet medical needs such as trypanosomiasis, leishmaniasis, Dengue fever, and lymphatic filariasis. The WHO estimates that nearly one billion people (one-sixth of the world population) suffer from one or more "neglected diseases". Recently, some pharmaceutical companies have initiated programs targeting "rare and neglected" diseases, and one program of the of the NIH's new NCATS division aims to foster research and drug discovery on such targets. However, since the early 1980s, when the medical community became concerned with the almost epidemic spread of AIDS throughout the developing world and the first antiretroviral drugs were introduced, critics have accused big Pharma of not doing enough to provide medicines to patients in poor, underdeveloped countries.

When antiretroviral drugs first became available, the cost of these drugs was too high for patients in developing countries to afford. During the period 1997−2002, prices of antiretroviral drugs, at least in a representative sampling of developing countries, decreased significantly. The most significant drop was seen in 2001.[53] This price drop coincided with a number of initiatives to address the world AIDS problem. The United Nations General Assembly Special Session, the first UN session totally devoted to fighting a specific disease, unanimously adopted a Declaration of Commitment to encourage the adoption of national strategies to combat the AIDS pandemic, including the use of antiretroviral drugs. The Global Fund to fight AIDS, Tuburculosis and Malaria, a dedicated fund-raising institution, became operational and committed over $1.5 B to helping poor countries establish these national strategies. A number of other initiatives followed closely, including the World Health Organization's 3 × 5 strategy which contributed to significant progress in expanding access to ART in resource-limited countries.[54] During this time, it was hard to accurately measure how much the price drops were the result of philanthropy on the part of the pharmaceutical industry and how much they were the result of increases in supply and demand (thanks to the scale-up of national treatment programs), and initiatives to bargain drug price and build approved generic supply chains by groups such as WHO and the William J. Clinton Foundation. The price drop during this time applied only to older drugs and first-line therapies, not to newer drug combinations that were developed as part of the Highly Active Antiretroviral Therapy (HAART) campaign. More recent figures show that the price of first line drug combinations have dropped during the period 2008−2010, although prices for second line therapy continue to be difficult for patients in developing countries to afford (Figure 6).[55]

But what contribution has the pharmaceutical industry made to treating neglected diseases, which do not have as much market potential as AIDS-related antiretroviral agents? Drug companies have made and continue to make significant donations of available drugs to treat neglected diseases, as detailed in WHO's 2010 report on neglected diseases.[56] However, until recently, pharmaceutical companies have not tackled new drug development on neglected diseases by themselves. Partnerships between companies and public organizations were, for many years, the primary mechanism for drug research on neglected diseases. Examples of such partnerships included Lilly's MDR-TB partnership to address treatment resistant tuberculosis, Wyeth's collaboration with WHO to develop moxidectin for the treatment of onchocerciasis (river blindness), and the Medicines for Malaria Venture and Global Alliance for Tuburculosis. Opposing sides argue over the relative impact that such partnerships have had on advancing innovative drug discovery for neglected diseases. However, in the late 2000s private sector partnerships began to appear, such as the GSK/Merck partnership to address lymphatic filariasis.[57] In January 2012, WHO published its roadmap for eradicating neglected tropical diseases by the year 2020 and a community of global partners, including several pharmaceutical companies, endorsed the London Declaration committing them to enhance and expand research on new treatments of neglected diseases. Later that year 13 pharmaceutical companies announced the formation of a coalition with public and private members to increase world access to drugs for neglected diseases and expand research on new therapies. The results of this broad initiative remain to be seen, but it appears that big Pharma is beginning to take a greater role in the quest to eradicate this horrible burden that the developing world bears.

Until recently, a lack of communication and publicity made it difficult to quantify the voluntary contributions of the pharmaceutical industry to global drug accessibility. More detailed information began to emerge in 2008 with the publication of the first Access to Medicine Index, founded by Dutch entrepreneur Wim Leereveld.[58] His philosophy was to encourage pharmaceutical companies to take part in the global effort to make medicine accessible to resource-challenged

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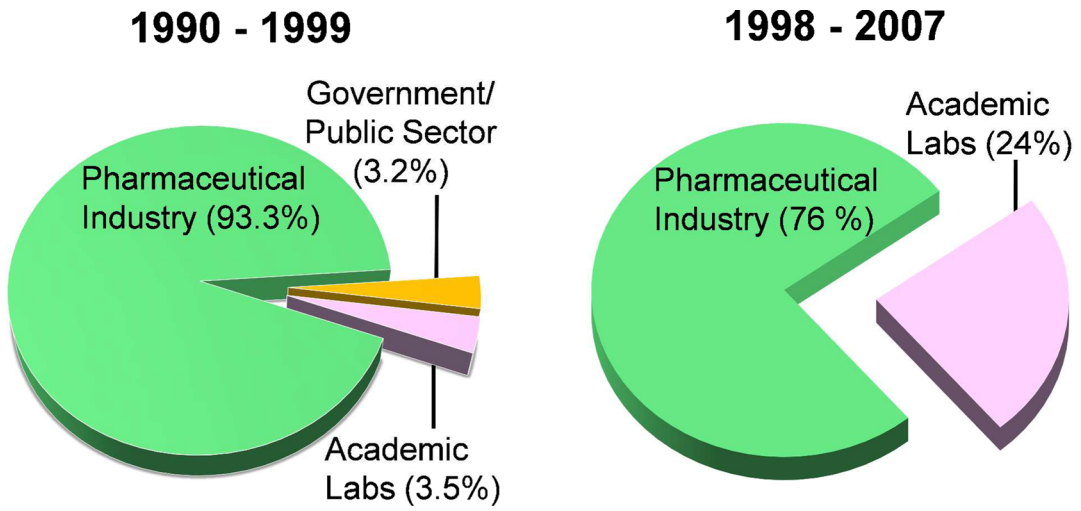

Figure 7. Estimates on the origin of new drugs. Left: data taken from DiMasi et al., 2003.[59] Right: Data taken from Kneller, 2010.[60]

countries by praising their good practices rather than blaming them for perceived inadequacies. The semiannual report grades companies based on a number of criteria, including presence/strength of a drug access management system, role in establishing/influencing public policy on drug access, presence of research programs targeting neglected diseases, proaccess patenting and licensing practices, capability advancement, pricing practices, and drug donations/philanthropic activity. In general, the 2012 report concluded that 17 out of 20 companies surveyed are doing more to support drug access to the developing world than they were at the report's initiation in 2008 and that previous bottom performers are catching up to the leaders in their efforts to make medicines more accessible. Suggestions for improvement include being more transparent about lobbying practices and clinical trial outcomes, expanding tiered pricing schemes to better accommodate varying income levels, making drug donations more need-based, adapting packaging to meet local needs, and allowing regulators in developing countries to use their clinical data to accelerate the approval of generic medicines.

PHARMA DOES NOT DISCOVER NEW DRUGS; IT JUST SELLS THEM

There is a popular misconception that pharmaceutical companies do not discover innovative new drugs; they just buy them from other sources and develop them. A few studies on this subject have been published over the past 10 years. In 2003, DiMasi et al.[59] concluded from an examination of the Tufts Center for the Study of Drug Development database and other commercial databases (Figure 7) that 93% of drugs approved during the period 1990−1999 originated from industrial sources (big Pharma, biotechs). Government/public sector sources accounted for 3.2% of those approved drugs, and 3.5% originated from academia and other nonprofit institutions. A 2010 study by Kneller surveyed the period 1998−2007 using information from the FDA Web site.[60] Of the 252 new drugs approved by the FDA during that time, 76% came from industrial sources and 24% were attributed to university discoveries that were subsequently transferred to a company for further development (Figure 7). Government funding was credited with supporting the basic research that contributed to drug discovery, but this study concluded that no approved drugs were associated with government/public sector laboratories during this time period. Another report by Stevens et al. reached somewhat different conclusions than those arrived at by Kneller concerning the discovery of new drugs by public sector laboratories.[61] Based on data obtained from the FDA Orange Book, Stevens' study provided data suggesting that 9−10% of the drugs approved by the FDA during the period 1970−2009 were discovered in government/public sector laboratories, primarily anti-infectives and anticancer drugs. This study did not address the relative contributions from industry and academic laboratories. The three studies differ in their portrayal of how many new drugs were discovered in academic and public sector institutions, but they all agree that the majority of new drugs during the past 20−40 years came from industrial sources.

CONCLUSION

The debate continues. On one side, the pharmaceutical industry is touted as an evil entity that not only puts profits above the welfare of patients but also propagates sickness to the exclusion of curing disease as a means of maintaining those profits. Those who cannot afford their medicines are out of luck, especially those in the developing world where there is no profit to be made developing drugs for region-specific illnesses. On the other side, supporters of the pharmaceutical industry believe the criticisms to be unreasonable and exaggerated. The drugs designed and produced by the industry are a major contributor to the improvement in overall health experienced by people in the last century. Medicines have been and continue to be a cost-effective way of managing sickness despite increasing costs of those medicines. Pharmaceutical companies are, after all, businesses that must provide return for their investors even though their products contribute to the good of human kind. Without profit there is no reinvestment in the drug discovery of tomorrow.

As with many things, perhaps the truth lies somewhere between the two extremes. Pharmaceutical companies must balance the fact that they are businesses with the social responsibility that comes from providing products that alleviate suffering and treat illness. Until recently there has been little incentive for drug companies to discover drugs for treating "neglected diseases" such as chronic tropical infectious illnesses. In fact, many critics see the recent attempts by Pharma to have patents enforced in strongholds of generic drug development research such as India as a blow against access to affordable medicines in the developing world. Many also feel that the

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industry is behind the US government's campaign to enforce and expand TRIPS. However, the industry has been more philanthropic than many give them credit for, donating available drugs to help resource-limited populations. The participation of several companies in the recent public/private coalition targeting neglected diseases suggests that the industry is becoming interested in drug discovery in this arena despite the less-than-encouraging financial consequences.

The industry is accused of blocking reimportation of drugs and denying this cheaper alternative to patients. In fact, it is the law that blocks drug reimportation, primarily because of previous experience showing that reimported drugs, for the most part, do not meet US quality standards. The FDA has made it clear that they do not possess the resources needed to ensure the quality of reimported drugs. The industry has also been accused of delaying access to cheaper generic drugs, which is true to the extent that companies fight to maintain the full patent lives on their inventions. However, the Waxman−Hatch Act not only paved the way for generic competition, it actually provides protection for generic companies that attempt to shorten patent lives through Paragraph IV challenges. Pharmaceutical companies routinely seek to expand their market potential with new, more convenient formulations and additional indications. However, physicians often (but not always) have the option of prescribing generic versions of drugs in place of new formulations or drug combinations and the recent precedent set by the judicial system of "carving out" patented indications from generic labels may ultimately limit the impact that patenting new indications will have.

The industry's marketing practices have come under fire and continue to be a point of contention. Critics see marketing as being excessive and targeted at promoting sales of branded drugs over cheaper generic alternatives. Yet the figures suggest that the industry is among the leaders in percent of sales reinvested into research. Other aspects of industry marketing practices have not held up to scrutiny as well, such as the accusations of off-label promotion. In many cases, these accusations have evolved into litigation, with resulting settlements lending validity to at least some of the claims. It is hoped that a growing corporate and individual moral responsibility will lead to an end in this darker chapter of the industry's history. The ultimate criticism and overarching issue is the price of drugs and the ability of everyone who needs them to afford them. Critics blame the patent system, yet without the promise of reasonable return on investment which that system provides, it is not clear how pharmaceutical companies will be able to reinvest in the innovative research that will provide the drugs of tomorrow. A number of alternative strategies for funding research have been suggested and some have been tried on a small scale. None of the alternatives seems to be the ultimate solution that is needed so badly. To make matters worse, recent changes and challenges threaten the industry even further. These challenges and the responses of the pharmaceutical industry will be the subject of the second installment of this series. But as for the industry's image, the tarnish is partly of their own making and partly the result of the difficult and unenviable balance that they must maintain between being a business and upholding a moral obligation to make the world a healthier place. Without profitability, the industry will not be able to reinvest in research, and no clear alternative pathway for discovering tomorrow's drugs has arisen. Yet, access to affordable drugs, especially new drugs that are priced high out of necessity, has become an issue that must be dealt with. It is hoped that a successful balance between these two apparently opposing needs can ultimately be reached so that the world can continue to enjoy the health benefits that pharmaceuticals provide.

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Notes

Having worked in research and development for many years, the authors are in receipt of an occupational pension from the pharmaceutical industry. However, the authors are not spokesmen for the pharmaceutical industry. The views expressed by the authors are entirely their own. The authors declare no competing financial interest.

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Magid Abou-Gharbia received his B.Sc. in Pharmacy and his M.Sc. in Medicinal Chemistry from Cairo University in 1971 and 1974, and his Ph.D. in Organic Chemistry from the University of Pennsylvania in 1979. Following an NIH postdoctoral fellowship at Temple University, Magid joined Wyeth Pharmaceuticals in 1982, where he was ultimately promoted to Senior Vice President of Chemical and Screening Sciences. His team's efforts led to the identification of eight marketed drugs and several clinical candidates. In 2008 Magid joined Temple University School of Pharmacy as Professor of Pharmaceutical Sciences, Associate Director of Research, and Director of the Molder Center for Drug Discovery Research. Magid serves on the Scientific Advisory Board of several companies and professional societies and has adjunct professor appointments at several universities.

Wayne E. Childers received his B.A. in chemistry from Vanderbilt University in 1975 and his Ph.D. in organic chemistry from the University of Georgia in 1984. While pursuing his Ph.D. studies, Wayne served as Assistant Adjunct Professor at Bucknell University from 1982 to 1984. Following a postdoctoral fellowship at Johns Hopkins University School of Medicine, Wayne joined Wyeth in 1987, where he led CNS-directed project teams that advanced four new chemical entities to clinical trials. In 2010 Wayne joined Temple University School of Pharmacy to serve as Associate Professor of Pharmaceutical Sciences and Associate Director of the Molder Center for Drug Discovery Research. Wayne's research interests involve the application of state-of-the-art techniques to the identification and development of new chemical entities for treating unmet medical needs.

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ABBREVIATIONS USED

ACT, artemisinin combination therapy; AD, Alzheimer's disease; AIDS, acquired immunodefficiency syndrome; ANDA, abbreviated new drug application; ART, antiretroviral therapy; B, billion; DTCA, direct-to-consumer-advertising; FDA, Food and Drug Administration; FTC, Federal Trade Commission; GSK, GlaxoSmithKline; HAART, highly affective antiretroviral therapy; HIV, human immunodeficiency virus; NCATS, National Center for Advancing Translational Sciences; OTC, over the counter; Pharma, pharmaceutical industry; R&D, research and development; REMS, risk evaluation mitigation strategies; TRIPS, trade-related aspects of intellectual property rights agreement; UN, United Nations; US, United States; WHO, World Health Organization

REFERENCES

(1) Angel, M. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*; Random House: New York, 2004.

(2) Brody, H. *Hooked: Ethics, the Medical Profession and the Pharmaceutical Industry*; Rowman & Littlefield Publishing: Lantham, MD, 2008.

(3) Goldacre, B. *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients*; First Estate: London, UK, 2012.

(4) Badcott, D. Big pharma: a former insider's view. *Med. Health Care Philos.* **2013**, *16* (2), 249−264. Published on-line February 16, 2012. Available at: http://link.springer.com/content/pdf/10.1007%2Fs11019-012-9388-6. Accessed on 04/26/2013.

(5) LaMattina, J. *Drug Truths: Dispelling the Myths About Pharma R&D*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009.

(6) LaMattina, J. *Devalued and Distrusted: Can the Pharmaceutical Industry Restore Its Broken Image?*; John Wiley & Sons, Inc.: Hoboken, NJ, 2013.

(7) Bartfai, T.; Lees, G. *Drug Discovery: From Bedside to Wall Street*; Academic Press: Waltham, MA, 2006.

(8) Bartfai, T.; Lees, G. *The Future of Drug Discovery: Who Decides Which Diseases to Treat?*; Adacemic Press: Waltham, MA, 2013.

(9) Gagnon, M.-A.; Lexchin, J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLOS Med.* **2008**, *5*, 0029−0033. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050001. Accessed on 04/26/2013.

(10) Barfett, J.; Lanting, B.; Lee, J.; Lee, M.; Ng, V.; Simkhovitch, P. Pharmaceutical marketing to medical students: the student perspective. *McGill J. Med.* **2004**, *8*, 21−27. Additional details available at: www.nofreelunch.org/slide/htm.

(11) Buckley, J. Pharmaceutical marketing − time for a change. *Electronic Journal of Business Ethics and Organization Studies (EJBO)* **2004**, *9*, 4−11.

(12) Steinman, M.; Bero, L.; Chren, M.-M.; Landerfeld, C. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann. Intern. Med.* **2006**, *145*, 284−293.

(13) Brauser, D. APA answers criticism of Pharma-influenced bias in DSM-5. www.medscape.com. Published January 4, 2013. Accessed on January 9, 2013 at: www.medscape.com/viewaritcle/777132. Accessed on 04/26/2013.

(14) Olsen, G. *Confessions of an Rx Drug Pusher*; iUniverse: Bloomington, IN, 2005.

(15) Liu, K.; Zhang, M.; Nagappan, G. New small molecule drug discovery for Alzheimer's disease. In *Alzheimer's Disease: Targets for New Clinical, Diagnostic, and Therapeutic Strategies*; Wegrzyn, R.; Rudolph, A., Eds.; CRC Press: Boca Raton, FL, 2012; Chapt. 5, pp 164−189.

(16) Hargreaves, R. It ain't over 'til it's over" − the search for treatments and cures for Alzheimer's disease. *ACS Med. Chem. Lett.* **2012**, *3*, 862−866.

(17) Barton, J.; Emanuel, E. The patents-based pharmaceutical development process. *JAMA, J. Am. Med. Assoc.* **2005**, *294*, 2075−2082.

(18) The Express Scripts Research & New Solutions Lab, Drug Trent Quarterly, published November 28, 2012; available at: http://digital.turn-page.com/i/95262. Accessed on 04/26/2013.

(19) Battelle Technology Partnership Practice and PhRMA. The US biopharmaceuticals sector: economic contribution to the nation, 2011; available at: http://www.phrma.org/sites/default/files/159/2011_battelle_report_on_economic_impact.pdf. Accessed on 04/26/2013.

(20) Ward, S.; Jones, M.; Pandor, A.; Holmes, M.; Ara, R.; Ryan, A.; Yeo, W.; Payne, N. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol. Assess.* **2007**, *11*, 1−160.

(21) Government Printing Office, PUB.L. 111−148, 124 Stat. 119; available at: http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/html/PLAW-111publ148.htm. Accessed on 04/26/2013.

(22) Keyhani, S.; Diener-West, M.; Prow, N. Do drug prices reflect development time and government investment? *Med. Care* **2005**, *43*, 753−762.

(23) Harper, M. The truly staggering cost of inventing new drugs. In *Forbes Business*, published February 10, 2012; available at: http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/. Accessed on 04/26/2013.

(24) Manhattan Institute Center for Legal, Policy Trial Lawyers, Inc.: Health care. The lawsuit industry's effect on American Health, 2005. Available at: http://www.triallawyersinc.com/healthcare/hc01.html. Accessed on 04/26/2013.

(25) KPMG International: Issues Monitor. The rising costs of litigation in the pharmaceutical industry, 2011, Vol. *9*. Available at: http://www.kpmg.com/Global/en/IssuesAndInsights/ArticlesPublications/Issues-monitor-pharmaceuticals/Documents/issues-monitor-pharmaceuticals-june-2011.pdf. Accessed on 04/26/2013.

(26) Felland, L.; Reschovsky, J. More nonelderly Americans face problems affording prescription drugs. Robert Wood Johnson Foundation Center for Studying Health System Change, Tracking Report 22, 2009. Available at: http://www.rwjf.org/content/dam/web-assets/2009/01/more-nonelderly-americans-face-problems-affording-prescription-d. Accessed on 04/26/2013.

(27) Kneller, R. The importance of new companies for drug discovery: origins of a decade of new drugs. *Nat. Rev. Drug Discovery* **2010**, *9*, 867−882.

(28) Bloom, J.; Torreele, E.Should patents on pharmaceuticals be extended to encourage innovation? In *The Wall Street Journal*, January 23, 2012; available at ProQuest Newspapers: http://online.wsj.com/article/SB10001424052970204542404577156993191655000.html. Accessed on 04/26/2013.

(29) *Value-based pricing for pharmaceuticals: implications of the shift from volume to value*; Deloitte Center for Health Solutions, Deloitte Touche Tohmatsu, Ltd.: New York, 2012; available at: http://www.deloitte.com/view/en_US/us/Insights/centers/center-for-health-solutions/f604ae4d278b7310VgnVCM1000001956f00aRCRD.htm. Accessed on 04/26/2013.

(30) Yadav, P. *Differential pricing: review of current knowledge, new findings and ideas for action*; World Health Organization Geneva, 2010, available at: http://apps.who.int/medicinedocs/en/m/abstract/Js18390en/. Accessed on 04/26/2013.

(31) Yadav, P.; Cohen, J.; Alphs, S.; Arkedias, J.; Larson, P.; Massaga, J.; Sabot, O. Trends in availability and prices of subsidized ACT over the first year of the AMFm: evidence from remote regions of Tanzania. *Malar. J.* **2012**, 11. Published online at: http://www.malariajournal.com/content/11/1/299. Accessed on 04/26/2013.

(32) Jaruzelski, B.; Loehr, J.; Holman, R. *2012 global innovation study 1000: making ideas work*; Booz & Company: New York. Available at: http://www.booz.com/media/uploads/BoozCo_The-2012-Global-Innovation-1000-Study.pdf. Accessed on 04/26/2013.

(33) The pharmaceutical industry in figures, edition 2012, European Federation of Pharmaceutical Industries and Associations; available at: http://www.efpia.eu/pharmaceutical-industry-figures-edition-2012. Accessed on 04/26/2013.

(34) Source: PhRMA Chart Pack; available at: http://www.phrma.org/sites/default/files/159/phrma_chart_pack.pdf. Accessed on 04/26/2013.

(35) Gagnon, M.-A.; Lexchin, J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Med.* **2008**, *5*, e1. doi: 10.1371/journal.pmed0050001. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050001. Accessed on 04/26/2013.

(36) Source: Key industry facts about PhRMA, Pharmaceutical Research and Manufacturing Association; available at: http://www.phrma.org/about/key-industry-facts-about-phrma. Accessed on 04/26/2013.

(37) 2011 R&D budgets taken from 2011 annual reports of the following six generic pharmaceutical companies: Teva, Mylan, Watson, Sandoz, Hospira, and Actavas. These reports are freely available from the respective company's websites.

(38) Paul, S.; Mytelka, D.; Dundiddie, C.; Persinger, C.; Munos, B.; Lindborg, S.; Schacht, A. How to improve R&D: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discovery* **2010**, *9*, 203−214.
(39) *The use of medicines in the United States: review of 2011*; IMS Institute for Healthcare Informatics: Norwalk, CT, April 2012; available at: http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf. Accessed on 04/26/2013.
(40) Higgins, M.; Graham, S. Balancing innovation and access: patent challenges tip the scales. *Science* **2009**, *326*, 370−371.
(41) Source: Paragraph four explained: why generic drug companies challenge patents. Parry Ashfold, Inc., Exton, PA, 2012, available at: http://www.paragraphfour.com/explained.html. Accessed on 04/26/2013.
(42) Source: Lipitor Sales Data, Drugs.com, available at: http://www.drugs.com/stats/lipitor. Accessed on 04/26/2013.
(43) Hitchings, A.; Baker, E.; Khong, T. Making medicines evergreen. *Br. Med. J.* **2012**, *345*, e7941 http://www.bmj.com/content/345/bmj.e7941.pdf%2Bhtml, accessed on 04/26/2013.
(44) Miller, C.; Ullrich, J. A consideration of the patentability of enantiomers in the pharmaceutical industry in the United States. *Chirality* **2008**, *20*, 762−770.
(45) Rouhi, A. Chirality at work. *Chem. Eng. News* **2003**, *81*, 56−61. Available at: http://www.usm.edu/phillipsgroup/CHE255_S10/chapter5/Chirality_at_work.pdf. Accessed on 04/26/2013.
(46) Rai, A. Use patents, carve-outs, and incentives − a new battle in the drug-patent wars. *N. Engl. J. Med.* **2012**, *376*, 491−493.
(47) Authorized generic drugs: short-term effects and long-term impact. A report of the Federal Trade Commission, 2011; available at: http://www.ftc.gov/os/2011/08/2011genericdrugreport.pdf. Accessed on 04/26/2013.
(48) Harrington, P.; Shepherd, M. Analysis of the movement of prescription drugs to over-the-counter status. *J. Managed Care Pharm.* **2002**, *8*, 499−508.
(49) Agreements filed with the Federal Trade Commision under the Medicare Prescription Drug, Improvement and Moderinization Act of 2003: overview of agreements filed filed in FY 2012, a report by the Bureau of Competition. Federal Trade Commission, January 17, 2013; available at: http://www.ftc.gov/os/2013/01/130117mmareport.pdf. Accessed on 04/26/2013.
(50) Driving biomedical innovation: initiatives to improve products for patients. A report by the U. S. Food and Drug Administration, 2011; available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm. Accessed on 04/26/2013.
(51) Taylor, D. Importing a headache for which there's no medicine: why drug reimportation should and will fail. *J. Law Policy* **2007**, *15*, 1421−1468.
(52) Bhosle, M.; Balkrishnan, R. Drug reimportation practices in the United States. *Ther. Clin. Risk Manage.* **2007**, *3*, 41−46.
(53) Lucchini, S.; Cisse, B.; Duran, S.; de Cenival, M.; Comiti, C.; Gaudry, M.; Moatti, J.-P. Decreases in prices of antiretroviral drugs for developing countries: from political "philanthropy" to regulated markets? 2003 World Health Organization Report; available at: http://apps.who.int/medicinedocs/en/d/Js18253en/. Accessed on 04/26/2013.
(54) Progress on global access to HIV antiretroviral therapy: a report on "3 x 5" and beyond, World Health Organization, 2006; available at: http://www.who.int/hiv/fullreport_en_highres.pdf. Accessed on 04/26/2013.
(55) Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011. World Health Organization, 2011; available at: http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf. Accessed on 04/26/2013.
(56) First WHO report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases. World Health Organization, 2010; available at: http://whqlibdoc.who.int/publications/2010/9789241564090_eng.pdf. Accessed on 04/26/2013.
(57) Gustavsen, K.; Bradley, M.; Wright, A. GlaxoSmithKline and Merck: private-sector collaboration for the elimination of lymphatic filariasis. *Ann. Trop. Med. Parasitol.* **2009**, *103* (Suppl. 1), Sl1−S15.
(58) Available at: http://www.accesstomedicineindex.org/. Accessed on 04/26/2013. The 2008, 2010, and 2012 issues of the Access to Medicine Index are available on this website.
(59) DiMasi, J.; Hansen, R.; Grabowski, H. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **2003**, *22*, 151−185.
(60) Kneller, R. The importance of new companies for drug discovery: origins of a decade of new drugs. *Nat. Rev. Drug Discovery* **2010**, *9*, 867−882.
(61) Stevens, A.; Jensen, J.; Wyller, K.; Kilgore, P.; Chatterjee, S.; Rohrbaugh, M. The role of public-sector research in the discovery of drugs and vaccines. *New Eng. J. Med.* **2011**, *364*, 535−541.