



The transition to a sustainable system of drug development requires reformation of the regulatory and patent systems, and a shift of responsibility to open-access discovery and clinical evaluation of innovative drugs to the public sector.

Towards a sustainable system of drug development

Ellen H.M. Moors¹, Adam F. Cohen² and Huub Schellekens^{1,3}

¹ Innovation Studies, Copernicus Institute of Sustainable Development, Utrecht University, Heidelberglaan 2, Utrecht NL-3584 CS, The Netherlands

² Centre for Human Drug Research, Zernikedreef 10, Leiden NL-2333 CL, The Netherlands

³ Department of Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, Utrecht NL-3584 CG, The Netherlands

Drug development has become the exclusive activity of large pharmaceutical companies. However, the output of new drugs has been decreasing for the past decade and the prices of new drugs have risen steadily, leading to access problems for many patients. By analyzing the history of drug development and the pharmaceutical industry, we identified the main factors causing this system failure. Although many solutions have been suggested to fix the drug development system, we believe that a combination of reforms of the regulatory and patent systems is necessary to make drug development sustainable. These reforms must be combined with a larger, open-access role for public research institutes in the discovery, clinical evaluation and safety evaluation of new drugs.

Developing new medicines was traditionally a recession-proof activity, trusted to produce double-digit growth figures and continuing innovation that was marketable at high prices. Although the number of new medicines reaching the market picked up in 2011 from an all-time low of 26 medicines approved by the US Food and Drug Administration (FDA) in 2010 [1], the annual output of the pharmaceutical industry has effectively flat-lined for the past 10 years, whereas the processes for discovering and developing new products remain much the same. This means that the scientific productivity of the pharma industry has been poor for the past decade, because attrition rates in clinical trials have also climbed steeply [2,3], regulations are becoming more difficult [4] and market conditions are getting harsher [5,6]. The number of new molecular entities (NMEs) required to achieve one new drug approval is increasing at every stage of development. In 2007–2011, it took an average of 30.4 NMEs in preclinical development to obtain one approval, compared with just 12.4 NMEs in 2003–2007 [1]. All these developments make the costs per approved molecule unsustainably high, and require an adaptation of the current system for drug development.

Corresponding author: Moors, Ellen H.M. (e.h.m.moors@uu.nl)

Ellen Moors

is a professor of sustainable innovation at the Copernicus Institute of Utrecht University in the Netherlands. She studied biochemistry and biophysical chemistry at Radboud University, Nijmegen and received her PhD in technology management from Delft University of Technology in 2000. She teaches on health, sustainability and medical technology, and on the management of life sciences innovations. Her research focuses on smart regulation and governance of pharmaceutical innovations, new modes of governing pharmacovigilance and technology dynamics in the life sciences field, and responsible innovation. She has received various grants from the Netherlands Organization of Scientific Research on societal and governance aspects of life sciences research, including genomics and Alzheimer's disease.



Adam Cohen

graduated in pharmacy (DPharm) and medicine (MD) and obtained a PhD degree from Leiden University, the Netherlands. He is currently the director of the Centre for Human Drug Research, studying early drug development and proof-of-concept studies in healthy subjects and patients. He is also a professor of clinical pharmacology at Leiden University and Leiden University Medical Center. He is an editor of the *British Journal of Clinical Pharmacology* as well as a member of the Health Council and the Council for Medical Sciences of the Royal Academy of Sciences in the Netherlands. He has represented the Netherlands in Brussels and with the European Medicines Agency (EMA) regarding European Union clinical trial directive revisions, and advises investors and drug and food companies on drug development and organizational issues.



Huub Schellekens

is a professor of pharmaceutical biotechnology at Utrecht University, the Netherlands. He also teaches medical biotechnology at the Copernicus Institute and has a research position at the Faculty of Pharmaceutical Sciences. He studied medicine and received his PhD in medical microbiology from Erasmus University, Rotterdam in 1980. He works as a medical microbiologist on the preclinical development of biopharmaceuticals. He has published more than 350 papers in peer-reviewed international journals concerning many aspects of the development of therapeutic proteins. During the past few years, his work has included the immunogenicity of protein drugs and the problem of biosimilars. He has been a member of the Dutch Medicine Evaluation Board and National Expert of the European Medicines Agency.



Additionally, there appears to be a lack of added value over existing treatments for several of these new medicines [7]. Previously, pharmaceutical companies were able to develop drugs for health problems that had never been addressed before. Today, few such unaddressed categories remain, meaning that most newly developed drugs will be competing with existing ones. This has led to public policies to stimulate drug development, including incentives for novelty drugs [8,9]. However, during the current economic crisis, pharmaceutical companies have been rather cautious, which favors an incremental research focus on follow-on drugs that offer little additional efficacy [10] over more speculative high-risk and/or high-reward innovation strategies. Additionally, Olfson and Marcus [11] recently showed a significant decline in average difference in efficacy between active treatment and placebo. This supports new directions for comparative effectiveness research on drugs, including comparative studies on the safety, tolerability and cost of treatments with established efficacy.

In addition, drug prices are increasing at a rate that blocks access to essential drugs in the developing world, as well as in Europe and the USA [12]. Increasing costs of development [13,14], and medications going off patent, are eroding the financial position of major companies and their capacity to develop new drugs [15]. Some major and extensively publicized safety problems with new medicines have also led to early market withdrawals. As a result, the reputation of the pharmaceutical industry and public trust in the regulatory system has been damaged [16,17].

This previously unheard-of accumulation of negative facts is considered by some industry-watchers to herald the demise of the current system of drug development. The question is whether solutions can be found within the system to remedy this matter of great public concern, given that the need for effective treatments has in no way diminished.

In this review, we examine the most important impeding factors that have led to this system failure. We analyzed the impacts of the solutions offered to repair the system, and we suggest a model for sustainable drug development that is capable of providing affordable, safe, effective and innovative medicines, especially for unmet medical needs on a global scale.

The rise of the pharmaceutical industry

The industrial production of pharmaceuticals began during the 19th century, based on emerging technologies for the extraction, purification and modification of chemicals from natural sources. During the early 1800s, compounds such as morphine, atropine and colchicine were isolated and purified from plants, and the extraordinary potency of small amounts of these substances led to the rapid development of pharmacology as a scientific subject in the UK and Germany.

During the 19th century, the first drugs were chemically synthesized. Increasing insight into human physiology and pathology, and microorganisms helped to identify new compounds with biological activity and to screen for toxicity. Many chemical companies along the Rhine in Basel, Switzerland specialized in chemical dyes for the textile industry, and ventured into pharmaceuticals based on the possible use of these dyes as antimicrobial agents. These companies pioneered the basic discovery process for new drugs based on random screening of their collection of chemical compounds [18].

Until the Second World War, pharmaceutical developments occurred in regular companies that produced their goods using standardized procedures. At that time, the rise of the pharmaceutical industry was accelerated by the development of large-scale production methods for penicillin, which revolutionized the treatment of infectious diseases. However, penicillin was not protected by patents, and there were many entrants in the market. Competition was strong; the price for 100,000 units of a standard form of penicillin dropped from US\$20 in 1943 to 4.5 cents in 1950, and its production became ultimately unprofitable [19].

To be able to survive, pharmaceutical companies started to invest heavily in the discovery of new products, and took out patents to avoid a repeat of their experience with penicillin. The expansion of publicly funded biomedical research also provided a boost to the research and development of the industry. It was the beginning of the rise of the pharmaceutical industry, with many new, highly profitable drugs protected by patents and low tax or regulatory barriers. Between 1951 and 1961, 4562 new prescription products were brought to market. Approximately 10% of these products were new chemical entities, and analysts estimated that 70 cents of every dollar spent on drugs in 1961 went towards the purchase of drugs not available 10 years previously [20].

Stricter conditions for the marketing of new drugs began with the thalidomide disaster of 1961. The introduction of the Drug Price Competition and Patent Restoration Act, also known as the Hatch–Waxman Act, in the USA in 1984 enabled the introduction of generic pharmaceuticals, but did not influence the rise of the pharmaceutical industry, which had its golden years during the 1970s and 1980s [21]. Large public investments in biomedical research, leading to scientific discoveries that in turn provided the industry with targets and tools for new drugs, and increased protection of inventions by patents were important to the success of the pharmaceutical industry.

Patents

During the 17th and 18th centuries, the use of medicine became increasingly scientific. The results were shared and mentioned in pharmacopeias, generally after the results were evaluated by a committee of prominent physicians. Any financial interest in the development or use of the new medicinal products was considered unethical.

Subsequently, a new industry emerged in the USA, UK and the rest of Europe. Local and regional wholesalers dealt in both imported and indigenous botanical products. Small specialty manufacturers produced extracts and other goods made from basic ingredients. Distributors at the national, regional and local levels produced and sold a variety of medicinal and chemical goods, including botanicals, animal products and refined chemicals. These products were marketed directly to the public, with almost no oversight. Drugs were in demand, and their manufacture and distribution was considered completely acceptable as long as the products were not adulterated.

By the end of the 19th century, the German pharmaceutical industry started to market synthesized rather than isolated products, such as aspirin, sulfonal and phenacetin. Although these products were patented and trademarked, their medical advantages were so obvious that they were also used widely by US doctors even though they were not included in the *US Pharmacopeia*. In

addition, US companies started to patent processes, or to produce products by sublicensing methods patented by foreign companies.

Currently, the pharmaceutical industry holds patents covering the discovery process, the products themselves, and their production, formulation, delivery and indications. Consequently, the pharmaceutical sector is one of the main users of the existing patent system. The number of pharmaceutical-related patent applications to the European Patent Office (EPO) nearly doubled between 2000 and 2007. The industry is now the major filer of patents in the European Union (EU), with 17,006 filings in 2008, even higher than in the information and communication technology sector.

The patent system gives the inventor a monopoly, which enables the recovery of research and development costs with a premium as reward. Furthermore, it intends to stimulate innovation, because the publication of the patent gives others a basis for further developments. The monopoly offered by patents has resulted in high prices for drugs. In addition to the increasing cost of new drugs, the prices of existing drugs have increased faster than the rate of inflation. The high prices restrict access to drugs in less affluent parts of the world, and have led to inequalities in drug access in Europe and the USA. The problem with the patents is that they reward incremental low-risk innovation more than high-risk ground-breaking innovative research [22,23]. A strong fear of sharing intellectual property exists, even though collaboration could accommodate innovation opportunities [24]. A 2009 report by the European Commission on the use of patents within the pharmaceutical sector [25] shows that companies develop and practise defensive patenting strategies primarily to block the development of competing innovative products. A total removal of the patent system would make risk-based funding impossible and new solutions are required. The FDA recently responded to this problem by formulating guidance about novel, ground-breaking combination therapies, in which two or more novel agents are tested and co-developed together in a single development program [26]. This indicates a new paradigm for drug developers that emphasizes sharing of information and collaboration in testing combinations.

Regulatory system

The regulatory system of medicines has met with many criticisms over the years: it is bureaucratic, hampers innovation, is not science driven and keeps competition and new entrants out. It costs more than it yields, is too industry minded, delays the availability of new drugs, does not protect against unsafe drugs and lacks alignment with doctors [27,28].

One of the most striking observations regarding the drug regulatory system is the lack of research regarding its functioning and effectiveness, which makes it difficult to substantiate or rebuff the criticism. However, it also means that a scientific rationale for most of the demands of the regulatory system is lacking. Regulation of medicines must be more founded upon scientific principles [29].

The regulatory system is rather rigid, which does not enable a rapid adaptation to new scientific insights or technological advances. A drug development process takes an average of 10 years and, in principle, the same product coming from the same production process should be used throughout the development.

Also, modifications in the production methods and their use after marketing authorization are expensive and need regulatory approval. Therefore, manufacturers are locked into outdated technology for a considerable time period and are discouraged from using innovative methods for developing drugs.

The regulatory demands and number of guidelines is also expanding at an increasing rate and is considered to be the most important reason why the cost of introducing new drugs is increasing. These increasing costs have consequences for innovation: the barrier for small companies becomes higher. New companies have more difficulty in getting their drugs approved, although small companies might also be under a higher pressure and, therefore, more inclined to submit a request for marketing authorization prematurely. Higher costs also means companies are less willing to take risks and prefer developing follow-on products rather than drugs with a complete new mode of action.

Although there is evidence that the introduction of regulatory demands has led to a marked decline in new drugs, there are no data showing whether regulation has led to better drugs. It remains unclear whether current regulatory requirements are able to establish the optimal benefit:risk profile for drugs. Although, both in the USA and Europe, regulatory guidelines are introduced on the basis of a comprehensive public consultation, no detailed analysis of the cost effectiveness of new guidelines is being performed. There is also no evaluation afterwards to determine whether the goal of the guidelines has been achieved. Thus, although the guidelines and recommendations are increasing, they are rarely revoked.

Academia and drug development

During the 18th and 19th centuries, there were impenetrable barriers between the drug industry and the medical and scientific world. These barriers started to crumble at the beginning of the 20th century, when the pharmaceutical industry, forced by the first laws regarding drugs and biological products, began hiring scientists to standardize drugs [30]. However, academics still treated pharmaceutical companies with suspicion. For example, industrial scientists were not allowed to join the American Society for Pharmacology and Experimental Therapeutics from its founding in 1908 until 1941 [31].

This negative academic attitude changed slowly. In 1923, the Amsterdam University Professor Laqueur was one of three founders of the Dutch pharmaceutical company Organon, and became a member of its board of directors [32]. His research group created strong alliances with Organon, which first appeared on the market in 1923 with the pancreatic hormone insulin. Insulin provided the credibility of a research-oriented pharmaceutical company, as expressed in its corporate slogan: 'Manufacturer of Organ Preparations on a Scientific Basis'.

In a decisive turn-around, academic researchers in need of the experience of large-scale production facilities actively began to solicit collaboration with the pharmaceutical industry. The most striking example was the search by Howard Florey during the Second World War for a pharmaceutical company willing to produce penicillin [33]. Florey could not find an interested British company, and instead found a partner in the USA.

After the Second World War, research expanded within both the pharmaceutical industry and publicly funded academia and

research institutes, leading to a gradual increase in collaboration. Publicly funded research still emphasized understanding the basic biological mechanisms in health and disease, which provided the pharmaceutical industry with the scientific insights needed for drug development. Academia also educated the many doctors and scientists needed in the pharmaceutical industry.

The partition of roles, with industry functioning as the commercial developer of drugs and academia as the provider of science and staff, started to disappear with the biotechnological revolution during the 1980s [34,35]. With the help of venture capitalists, academic researchers started their own companies to exploit their inventions and discoveries.

Furthermore, national and international organizations consider biomedical research essential for their economic growth. Most biomedical research funding is dependent on public-private partnerships, with an increasing influence of the pharmaceutical industry. For example, in the new Innovative Medicines Initiative program of the EU, pharmaceutical companies not only define the topics of interest, but also lead the public-private consortia of research groups [36].

However, the outcome of this commercialization of academic research has been poor, in terms of the number of new drugs. Many companies started by academics end in bankruptcy. The ones that survive by attracting investors or being taken over by pharmaceutical companies are those with products that are commercially attractive, regardless of their medical value. Finally, most university-initiated technology transfer units created to protect and sell academically generated intellectual property cost more than they earn [37].

The pharmaceutical industry: cruising altitude or free fall?

The success of the pharmaceutical industry is dependent on a pipeline with a continuous stream of new and commercially successful drugs. Over recent years, problems have been encountered in filling these pipelines. Many explanations have been offered for the recent dramatic drop in the introduction of new drugs to market [38–40]. The most frequent claim is that the low-hanging fruits have been picked, that is, most of the drugs for diseases that are easy to treat have been developed. However, this argument is difficult to reconcile with the data showing that 90% of all research efforts are directed at 10% of diseases [41]. Furthermore, there has been great scientific progress in understanding complex diseases, such as cancer. Some authors deny this and blame the organizational and profit-driven complexity of the pharmaceutical industry for its lack of innovative power [42].

There are still many unmet medical needs [43]. Many neglected diseases are most frequent in the developing world, which cannot afford expensive drugs and, therefore, is an unattractive commercial market. However, affluent parts of the world also have an urgent unfulfilled need for new drugs. Pharmaceutical innovation should also encompass unmet health needs of different populations and particular groups of patients, such as older patients, women and children, who have particular needs regarding products and dosages. More research is necessary on personalized medicine with specific patient groups who benefit most from particular therapies [44]. There is relatively little research activity for less common diseases, such as neglected and orphan diseases,

and pediatric indications, because of their low market potential [45,46].

New antibiotics are a case in point. There is an obvious need for new antibiotics because of increasing resistance to current drugs. Knowledge of the biology of microorganisms and development tools are amply available; however, although all of the necessary conditions are in place to support the development of new antibiotics, few have been produced [47]. Probably, the existence of cheap generic versions of many antibiotics to treat the most common infections contributes to this lack of development. A new antibiotic will become a second-line treatment, and such a restricted use of a new drug is not considered commercially attractive. Given the expiry of the patents of many widely used drugs, new drugs must increasingly compete with generic drugs. Mortality as a result of cardiovascular diseases has dropped considerably since the introduction of potent drugs to regulate blood pressure and reduce cholesterol levels. Generic versions of these drugs are increasingly being introduced and the pharmaceutical industry is clearly losing interest in developing new cardiovascular drugs [48]. Paradoxically, the high prices of patented medicines have caused the emergence of the generic drug industry. In contrast to other products that tend to become cheaper over time, medicines stay expensive and, in most cases, even increase in price, until the expiry of the patent.

The changing focus of the industry is also influencing the potential to develop innovative new drugs. Pharmaceutical companies are spending more on marketing than on research and development [49,50]. Obviously, it could be stated that all companies advertise to increase awareness of their product and increase sales, so that more money becomes available to spend on research and development. However, when this is overdone, marketing campaigns get aggressive and promotional practices become dubious. As seen for antidepressants, penalties have been steadily escalating with large fines as a result, as in the case of risperidone, an antipsychotic drug for use in older patients.

Mergers and acquisitions have become the main tool for companies to fill their pipelines. As a result, many large pharmaceutical companies are in a continuous state of reorganization, which does not favor stable research departments pursuing long-term scientific goals.

The consolidation of the industry has also resulted in the disappearance of medium-sized dedicated and specialized pharmaceutical companies and the rise of large pharmaceutical companies pursuing the same targets with the same technologies, which also erodes the innovative potential of the industry [51]. In many companies, greater attention to short-term shareholder value has affected investment in expensive research to develop the drugs that will provide profits over the coming decade. To mitigate the risks associated with drug development, large companies have diversified into areas such as diagnostics, medical devices and healthcare products, further reducing investment in drug research and development [52].

The vicious circle blocking innovation

From the 1960s to the 1990s, the pharmaceutical industry was successful in meeting many therapeutic needs. Evolving synthetic chemical technology made it progressively easier to produce new molecules with mechanisms of action similar to previous

molecules. Such chemically, but not therapeutically, innovative compounds were patentable. The long-term protection of patents allowed high prices to be asked, which in turn led to big increases in turnover and profitability throughout the industry, as well as to inevitable counterbalancing effects: the generic drug industry emerged, showing that it was possible to be profitable while selling drugs at relatively low prices. The introduction of generic drugs shortened the sales period of the patented drugs and put pressure on the pace of innovative developments. Chemical innovation was the easiest way to accomplish this.

The increased societal concern with safety of medicines led to ever-increasing regulatory requirements, adding to the burden of developing new medicines [53]. A 2011 survey with senior executives from the life sciences industry showed that the top three barriers for pharmaceutical innovation were directly related to their regulatory environment: (i) costs of drug development; (ii) time involved in drug development; and (iii) regulatory restrictions [54].

Aggressive marketing was required to sell expensive medications that were only marginally different from already-existing treatments, which further eroded the reputation of the industry and hampered industry efforts to find well-trained scientists and maintain good relations with universities. In addition, the universities started to patent their own innovations, effectively becoming competitors rather than partners. The current regulative system in the developed western world, both regarding market approval and patent regulation, led to medicines becoming more expensive. This high cost created severe access problems, mainly in the developing world, further decreasing the reputation of the industry. Accordingly, the responsibility for resolving problems regarding too expensive, unavailable or unaffordable medicines lies with many actors in the entire healthcare system, one of which is the pharmaceutical industry producing the drugs [55].

Pharmaceutical companies responded by increasing their size, and thereby market control, through mergers and acquisitions. They also started an intense lobby to extend patent duration and keep drug prices high. The end result was a vicious circle of negative trends that amplified each other (Fig. 1). An unpopular pharmaceutical industry has emerged that is highly attentive to marketing, and whose ability to develop real innovative products with added medical value is eroding. The question is how this situation can be remedied.

A model for sustainable drug development

There is a general awareness that the current system of drug development is in crisis. However, there appears to be little consensus about the cause of the problems and, therefore, how to solve them. We have tabulated the major reforms suggested in recent literature (Table 1) and analyzed the impact of these suggestions on the future sustainability of drug development. We considered the following impact parameters: effects on the risks of drug development, on innovation, on societal costs of new drugs and on access to drugs. We defined innovation as the development of real new drugs with added medical value and access. Affordability for the entire world population and medical need then function as drivers for innovation, independent of the market for individual drugs. We define societal costs of new drugs as the contribution to drug development by supporting biomedical

research, as well as drug prices. We have clustered the reforms into five broad categories: (i) technological and organizational changes; (ii) changes in the patent system; (iii) changes in the regulatory system; (iv) changes in reimbursement; and (v) social and/or political changes.

Technological and organizational changes

The main goal of rationalizing drug development is to reduce the attrition rate [5]. Rational drug development has the potential to identify failures early during the development process, thereby reducing the risks of late-stage failures and facilitating innovation, because companies can concentrate their resources on the most-promising drug candidates [56]. However, these changes will not make medicines cheaper, neither will they improve the access of developing countries and communities to drugs.

Finding new indications for existing drugs (i.e. repurposing) would be cheaper than developing new drugs [57,58]; however, it would substantially increase costs [59] and does not fit our definition of innovation. Besides, medicalization of pharmaceutical research could improve innovativeness but at higher risks of development [60]. The most drastic organizational change drug companies have executed is the increase of size and market share through mergers and acquisitions [61]. Theoretically, such a move should lead to economy of scale. Unfortunately, mergers and acquisitions appear to be managed by cost reduction only, which inevitably leads to reduced investment in research and development and reduced innovation potential. A second deleterious consequence of mergers is a reduction of competition between companies, which can result in upward pressure on drug prices.

Other organizational changes include public–private collaboration [56,62–64], precompetitive collaboration between companies [65] and open-access innovation networks [24,38,61,66,67]. These types of collaborative research and development effort have more innovative potential than the individual partners and spread the risks among the partners. However, they do not reduce the risks of developing new drugs. In our analysis, concentrating drug discovery in noncommercial, publicly funded organizations, such as universities, would have a major effect on access problems [12,37,68,69]. The main motivation of researchers in these institutes will be medical need, rather than the market potential of their new drugs.

Changing the patent system

The proposed modifications of the patent and data protection systems are wide ranging, and not always consistent. Both shortening and lengthening the duration of protection of intellectual property have been advocated [70,71]. As long as companies are able to set their own prices, these changes in the system will not result in reduced costs. Companies confronted with a shortened period of product protection will increase their prices to maintain income, whereas there is no incentive to reduce prices when this period of exclusivity is lengthened.

Although a relaxed patent system for developing countries would certainly increase access to drugs in underdeveloped parts of the world by introducing local generic drugs [12,72], it would not affect the other parameters of sustainable drug development. Restricting the ability of pharmaceutical companies to pay their

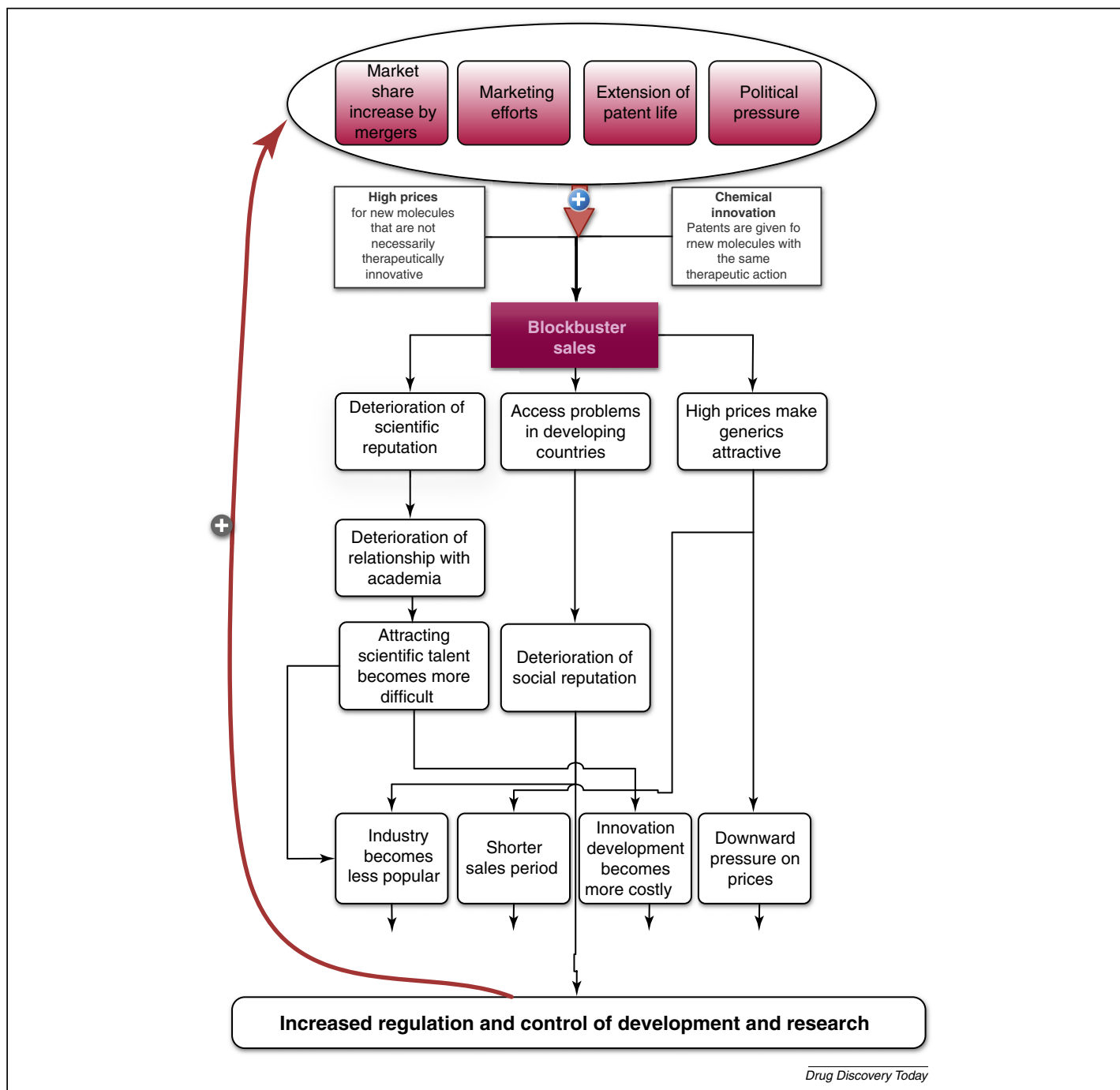


FIGURE 1

The vicious circle of trends in drug development.

generic competitors to delay the introduction of their products would make generic drugs available sooner and reduce costs [73].

As a result of patents, price competition is rare in the pharmaceutical industry. Patenting only substantial innovations would effectively end the development and intense marketing of follow-on drugs and promote innovation, because such developments would become much less lucrative compared with the development of drugs with new modes of action. However, the development of more innovative drugs would be risky, because of their intrinsic higher failure rate during development and after market introduction. The higher risk and the lack of competition by follow-on drugs

would inevitably lead to high prices of drugs, which makes them unaffordable and inaccessible for many patients [74–76].

Both sharing in patent pools by companies [75] and refraining from patenting by publicly funded research institutes [37] would promote innovation and access, because drugs would be developed for a wider spectrum of diseases. However, these approaches would not diminish the risks of drug development.

Regulatory solutions

The recommended changes in the regulatory system are contradictory. Both relaxing and increasing the regulatory burden have

TABLE 1

The impact of reform measures on sustainable drug development: a literature study

Reforms	Measures	Impact parameters ^a				Refs
		Effects on risk of drug development	Effects on innovation	Effects on costs for society	Effects on access to drugs	
Technological changes	Rationalizing drug development	↓	↑	–	–	[5,56]
	Repurposing	↓	–	↑↑	↓↓	[57–59]
	Medicalizing pharmaceutical research within industry	↑	↑	–	–	[60]
Organizational changes	Mergers and acquisitions	–	↓↓	↑↑	↓↓	[61]
	Break up pharmaceutical research units	–	↑	–	–	[15]
	Public–private collaboration	–	↑	–	–	[56,62–64]
	Precompetitive research	–	↑	–	–	[65]
	Open-access drug development	–	↑↑	–	–	[24,38,61,66,67]
	Drug development within academia and/or research institutes	–	↑	–	↑↑	[12,37,68,69]
Changes in patent system	Increased length of patent and/or data protection	–	–	↑↑	↓↓	[70,71]
	Reduced length of patent protection	–	–	–	↓	[70,71]
	Relaxed patent rules in developing world	–	–	–	↑↑	[12,72]
	Restrict pay for delay	↑	↓	↓	↑	[73]
	Restrict patents to substantial innovation	↑↑	↑↑	↑↑	↓↓	[74–76]
	No intellectual property protections for public research	–	↑↑	↓	↑	[37]
Changes in regulatory system	Patent pools	–	↑	–	↑	[75]
	Earlier approval	↑	–	↑	↑	[12,44,77,78]
	Include evaluation of value in marketing authorization	↑↑	↑↑	↑↑	↓↓	[12,77,80]
	Stricter marketing rules	↑	↑	↑↑	↓	[77]
	More self-regulation	↑↑	↑	–	–	[81]
Changes in reimbursement and/or access	Price controls	↑	↓	↓	↑	[12,81]
	Innovation rewards (buy-out pricing)	↑↑	↑↑	↑↑	↑	[12,38,69]
	Tiered global pricing	–	–	↓	↑	[12]
	Disease burden incentive system	↓	↑↑	–	↑↑	[12]
	Advanced market commitment	–	↑	–	↑↑	[69]
Social and/or political changes	More emphasis on care than cure and/or on prevention	↑↑	↓	↑	–	[82]
	Optimize drug use	–	–	↓	–	[83]

^a–, no effect; ↑ or ↓ some positive or negative effect; ↑↑ or ↓↓ substantial positive or negative effect; ↑↑↑ or ↓↓↓ maximal positive/negative effect.

been suggested. Earlier drug approval, before the full clinical benefit has been demonstrated, is being promoted by both industry and policy makers as a way to foster innovation [12,77,78]. Carefully designed regulatory and pharmacovigilance strategies to optimize risk management by taking a case-by-case approach should determine an optimal toolkit to establish adequately the benefit:risk profile of innovative drugs, such as biopharmaceuticals [79]. Furthermore, developments such as real-life data utilizing electronic health records are regarded as innovative methods to compare and evaluate the performance of new medicines after market approval. These methods could shorten the time needed to bring a drug to the market, while ensuring safety through active post-marketing surveillance [44]. However, earlier approval would not affect the risks of drug development, and would lengthen the exclusive marketing period (and, therefore, the costs) of such drugs.

Developments such as the Affordable Care Act in the USA can have a huge impact on the pharmaceutical sector, because with this shift from unit-pricing to value-based purchasing, new drugs will be priced based on the value healthcare payers give to them. There are many advocates for including the value of new drugs compared with existing therapies in the marketing authorization procedure [12,77,80]. This strategy would not only provide a major incentive to develop innovative drugs that meet this demand, but would also increase the risks of development because their authorization is less certain, inevitably leading to higher prices and reduced access. Stricter marketing rules would reduce the use of new drugs, increase prices and reduce access.

Self-regulation by itself would not reduce the required safety, efficacy and quality evaluations, and would make pharmaceutical companies more vulnerable to legal action regarding adverse effects [81]. The risks of drug development would increase and

innovation would suffer because companies would avoid developing drugs with an unpredictable safety profile.

Changes in reimbursement

Creative solutions have been suggested to increase access to medicines in both the developed and the developing world. Price controls, whether enacted directly or indirectly by restricting reimbursement per quality-adjusted life year, are not accepted on ideological grounds (e.g. in the USA), or are difficult to implement because of differences in national health systems (e.g. in Europe) [12,81]. Although they would reduce costs, they would have a negative effect on the other parameters of a sustainable drug development system.

A tiered pricing system would affect access in the developing world [12], but would have no influence on the risks associated with drug development or on innovation. Awarding a prize for innovation [12,38,69] as an alternative to a patent would make useful new drugs widely available and be an incentive for innovation. However, because of uncertainty regarding whether a new drug would be given an award, drug development would remain a risky enterprise.

Schemes that restrict reimbursement if a drug is effective in individual cases or reward manufacturers on the basis of reduction of disease burden in a population [12] would not reduce the risks involved in development or the costs of the drugs, but would positively influence innovation and access. The most interesting reimbursement system has been introduced by the Melissa and Bill Gates Foundation, which guarantees markets for specific new vaccines and drugs, particularly in the developing world [69]. This system would provide access to specific drugs and vaccines for specified populations, but would not lead to a sustainable system of drug development.

Social and/or political changes

The final group of reforms considered was social and political changes, including more emphasis on prevention [82], lowering the expectation of a cure for everything in the future, or optimizing the use of existing drugs [83]. However, the notion that prevention is cheaper than cure might be true for specific interventions, such as vaccinations, but cannot be generalized. If not all types or levels of cure were accepted, the risk of developing new drugs would increase, innovation would decrease and the fewer accepted drugs would be more expensive. Optimizing the use of existing drugs might reduce costs, but implies a status with no risks but also no innovation.

We conclude that all of the suggested changes only mitigate the symptoms of the failure of the current system of drug development. None of them provide a permanent cure for all of the root problems inherent in the current system (i.e. lack of innovation, high prices, inequalities in access and over-regulation). These problems are strongly interrelated. Regulations make drug development expensive and risky and only allow large pharmaceutical companies to develop new drugs. This monopoly enables companies to charge high prices. Pharmaceutical companies have become increasingly dependent on high prices for their survival because of the lack of new drugs in their development pipelines. Finally, the consequences

are excessive incentives towards developing follow-on drugs, and inequalities in access, especially in the developing world.

Putting it all together

There appears to be no reform that would have a substantial positive effect on either the societal costs of drugs or the risks of drug development by itself. Only a balanced combination of the reforms suggested would lead to a sustainable system of drug development. In our view, the decisive actions leading to the failure of the current system were: (i) the start of drug patenting by pharmaceutical companies during the mid-20th century; (ii) the introduction of comprehensive and strict regulatory systems following the thalidomide tragedy in 1961; (iii) and the introduction of data protection by the Hatch–Waxman Act of 1984. These mechanisms were the basis of the decades-long, exclusive, successful position of the pharmaceutical industry in drug development. However, this monopoly should be reconsidered now that the golden age of the pharmaceutical industry is over. We believe that the transition to a sustainable system of drug development requires reformation of the regulatory and patent systems, and a shift of responsibility for the discovery and clinical evaluation of new drugs to the public sector.

Given that more payers are founding their reimbursement policies on the evaluation of the effectiveness of a drug, the evaluation of the clinical effects of a new drug for marketing authorizations, as done by the European Medicines Agency and the FDA should become complementary. In 2004, Taylor *et al.* discussed the inclusion of cost-effectiveness as a fourth hurdle in licensing requirements [84]. A recent WHO study on priority medicines for Europe and the world indicates that the systems for market authorization and reimbursement decisions not only have different roles and involve various institutions, but are also closely interlinked. In combination, these systems have to function in such a way that they balance the need for new ‘safe’, ‘effective’ and ‘affordable’ medicines and innovations needed in these related areas. Thus, instead of a single-market authorization or a single reimbursement decisions, multiple decisions over time might be necessary to respond to new knowledge produced, using real-life data. Thus, new methods for evidence generation, benefit:risk assessment and regulatory dialog are needed to support regulatory policy [44]. Drug regulatory systems should concentrate on quality issues, manufacturing and distribution, which can be considered the weakest link in the chain from invention to patients. In 2008, more than 3600 incidents in manufacturing were reported to the FDA [85]. A less expensive marketing authorization process would result in fewer entry barriers for small companies, and would lead to more competition. The possibilities for patenting drugs should be as restricted as possible to protect intellectual property associated with substantive innovations, but should also allow competition. By curtailing the exclusivity of the pharmaceutical industry, a more free market for drugs would be created. Herein, pharmaceutical companies would compete at the level of production and distribution, as is the case in the generic drug industry, with less incentive for patenting because products would be sold at the manufacturing price. The patent system would no longer be interesting to the pharmaceutical industry. This transformation would secure the lowest possible prices for all

drugs, would save the world hundreds of billions of dollars, and would enormously increase access to drugs.

In our sustainable system, a structural reform would take place; the medical and scientific community in universities and other public research institutions would have a larger responsibility for the discovery, development and evaluation of the efficacy and safety of new drugs. Scientific research should be funded by public money, and all results should be made publicly available. The biomedical world already has the resources to take on this responsibility, as shown in other areas of medical intervention. In fact, new innovative surgical procedures are now being developed and tested in patients after the trials have been approved by ethical committees and their efficacy is published in the scientific literature. Professional bodies make the guidelines in which the best treatments are recommended, without patents being involved in novel surgical procedures. Why should the situation with new drugs be any different? More than the pharmaceutical industry, the scientific community will concentrate exclusively on drugs with a potential added value. This reform would also bring medical problems central to the development process, a precondition for the development of affordable personalized medicine, which is the biggest promise of new scientific developments.

The current system of drug development rewards fast improvements on the short term, which leads to risk-avoiding incremental innovation behavior of pharmaceutical companies. Currently, the academic institutions themselves are not (yet) capable of developing radical ground-breaking pharmaceutical innovations

on their own. Therefore, public–private partnerships are becoming increasingly important. Pharmaceutical companies have to put more effort in to collaborating with academia, governmental and nongovernmental organizations, fellow life sciences companies and other stakeholders, such as regulators and patient groups, to tackle precompetitive challenges collectively [1]. Indeed a world-wide growth of public–private partnerships is visible, focusing on early, translational and product development research with successes, such as the European Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [44].

The market exclusivity offered by patents and data exclusivity is claimed by the pharmaceutical industry to be necessary for companies to recoup their large investments in research and development. In a world without drug patents, the research and development would be performed by public funds and would be accessible to all parties, and so these investments by industry would no longer be necessary.

To realize a transition to such a sustainable model of drug development, various activities in the current drug development system must be transformed. A sustainable drug innovation system requires novel forms of cooperation within and across the value chain, an open exchange of information, and innovation through various global knowledge networks without any patent restrictions. Drug development should be guided by expectations, research outcomes and policy targets, instead of by commercial gains alone.

References

- PWC (2012) *From Vision to Decision. Pharma 2020 Report*. Price Waterhouse Coopers
- Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–715
- Arrowsmith, J. and Miller, P. (2013) Trial watch: Phase II and Phase III attrition rates 2011–2012. *Nat. Rev. Drug Discov.* 12, 569
- Munos, B. (2009) Lessons from 60 years of pharmaceutical innovation. *Nat. Rev. Drug Discov.* 8, 959–968
- Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214
- Pammolli, F. *et al.* (2011) The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discov.* 10, 428–438
- The Congress of the United States Congressional Budget Office (2006) *Research and Development in the Pharmaceutical Industry*. United States Congressional Budget Office
- Wood, A.J. (2006) A proposal for radical changes in the drug-approval process. *N. Engl. J. Med.* 355, 618–623
- Grootendorst, P. *et al.* (2011) New approaches to rewarding pharmaceutical innovation. *CMAJ* 183, 681–685
- DiMasi, J.A. *et al.* (2004) The economics of follow-on drug development: trends in entry rates and the timing of development. *Pharmacoeconomics* 22, 1–14
- Olfson, M. and Marcus, S.C. (2013) Decline in placebo-controlled trial results suggests new directions for comparative effectiveness research. *Health Affairs* 32, 1116–1125
- Barton, J.H. and Emmanuel, E.J. (2005) The patent-based pharmaceutical development process. *JAMA* 26, 2075–2082
- Morgan, S. *et al.* (2011) The costs of drug development: a systematic review. *Health Policy* 100, 4–17
- Göttsche, C. (2013) Developing a new drug costs less than \$100m, not \$900m. *BMJ* 246, 398
- Garnier, J.P. (2008) Rebuilding the R&D engine in big pharma. *Harv. Bus. Rev.* 86, 68–70
- Friedman, M. *et al.* (1999) The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 281, 1728–1734
- Bauchner, H. and Fontanarosa, P.B. (2013) Restoring confidence in the pharmaceutical industry. *JAMA* 309, 607–609
- Sepkowitz, K.A. (2011) History of Medicine: one hundred years of Salvarsan. *N. Engl. J. Med.* 365, 291–293
- Federal Trade Commission (1958) *Economic Report on Antibiotics Manufacture*. Federal Trade Commission
- Comanor, W. (1964) Research and competitive product differentiation in the pharmaceutical industry in the United States. *Economica* 31, 372–384
- Hawtorn, F. (2005) *The Merck Druggernaut: The Inside Story of a Pharmaceutical Giant*. Wiley
- Mahlich, J.C. (2010) Patents and performance in the Japanese pharmaceutical industry: an institution-based view. *Asia Pac. J. Manag.* 27, 99–113
- Gold, E.R. *et al.* (2009) Are patents impeding medical care and innovation? *PLoS Med.* 7, e1000208
- Munos, B. (2010) Can open-source drug R&D repower pharmaceutical innovation? *Clin. Pharmacol. Ther.* 87, 534–536
- European Commission (2009) *Pharmaceutical Sector Inquiry Final Report. DG Competition*. European Commission
- Woodcock, J. *et al.* (2011) Development of novel combination therapies. *N. Engl. J. Med.* 364, 985–987
- Ebbers, H.C. *et al.* (2012) Effective pharmaceutical regulation needs alignment with doctors. *Drug Discov. Today* 17, 100–103
- Forda, S.R. *et al.* (2013) Priorities for improving drug research, development and regulation. *Nat. Rev. Drug Discov.* 12, 247–248
- Breckenridge, A. *et al.* (2013) Evolution of regulatory frameworks. *Nat. Rev. Drug Discov.* 10, 3–4
- Tansey, E.M. (2002) Medicines and men: Burroughs, Wellcome & Co, and the British drug industry before the Second World War. *J. R. Soc. Med.* 95, 411–416
- Gabriel, J.M. (2009) A thing patented is a thing divulged: Francis E. Stewart, George S. Davis, and the legitimization of intellectual property rights in pharmaceutical manufacturing, 1879–1911. *J. Hist. Med. Allied Sci.* 64, 135–172
- Oudshoorn, N. (1993) United we stand: the pharmaceutical industry, laboratory and clinic in the development of sex hormones into scientific drugs. *Sci. Technol. Hum. Val.* 18, 5–24

- 33 Ligon, B.L. (2004) Penicillin: its discovery and early development. *Semin. Pediatr. Infect. Dis.* 15, 52–57
- 34 Zucker, L.G. and Darby, M.R. (1996) Star scientists and institutional transformation: patterns of invention and innovation in the formation of the biotechnology industry. *Proc. Natl. Acad. Sci. U. S. A.* 93, 1270–1271
- 35 Hopkins, M.M. *et al.* (2013) Buying big into biotech: scale, financing, and the industrial dynamics of UK biotech, 1980–2009. *Indust. Corp. Change* 22, 903–952
- 36 IMI (2013) Available from http://www.imi.europa.eu/index_en.html (accessed 10.09.13)
- 37 Frangioni, J.V. (2008) The impact of greed on academic medicine and patient care. *Nat. Biotechnol.* 26, 503–507
- 38 FitzGerald, G.A. (2010) Perestroika in pharma: evolution or revolution in drug development? *Mt. Sinai J. Med.* 77, 327–332
- 39 Ardal, C. *et al.* (2011) Common characteristics of open source software development and applicability for drug discovery: a systematic review. *Health Res. Policy Syst.* 9, 36
- 40 Kesselheim, A.S. (2011) An empirical review of major legislation affecting drug development: past experiences, effects, and unintended consequences. *Milbank Q.* 89, 450–502
- 41 Schmid, E.F. and Smith, D.A. (2007) Pharmaceutical R&D in the spotlight: why is there still unmet medical need? *Drug Discov. Today* 12, 998–1006
- 42 Cuatrecasas, P. (2006) Drug discovery in jeopardy. *J. Clin. Invest.* 116, 2837–2842
- 43 O'Connell (2007) Neglected diseases. *Nature* 449, 157
- 44 Kaplan, W. *et al.* (2013) *Priority Medicines for Europe and the World 2013 Update*. World Health Organization
- 45 Moors, E.H.M. and Faber, J. (2007) Orphan drugs: unmet societal need for non-profitably privately supplied new products. *Research Policy* 36, 336–354
- 46 Heemstra, H.E. *et al.* (2008) Orphan drug development across Europe: bottlenecks and opportunities. *Drug Discov. Today* 13, 670–676
- 47 Thomson, C.J. *et al.* (2004) Antibacterial research and development in the 21st century – an industry perspective of the challenges. *Curr. Opin. Microbiol.* 7, 445–450
- 48 Garber, A.M. (2009) An uncertain future for cardiovascular drug development. *N. Engl. J. Med.* 360, 1170–1171
- 49 Donohue, J.M. *et al.* (2007) A decade of direct-to-consumer advertising of prescription drugs. *N. Engl. J. Med.* 357, 673–681
- 50 Smith, R. (2005) Curbing the influence of the drug industry. A British view. *PLoS Med.* 2, 821–823
- 51 Rafols, I. *et al.* (2014) Big Pharma, little science? A bibliometric perspective on Big Pharma's R&D decline. *Technol. Forecast. Social Change* 81, 22–38
- 52 Hill, W.L. and Gary, C.S. (1991) A longitudinal study of the cause and consequences of changes in diversification in the US pharmaceutical industry 1977–1986. *Strategic Manage. J.* 12, 187–199
- 53 Eichler, H.G. *et al.* (2009) Safe drugs and the cost of good intentions. *N. Engl. J. Med.* 360, 1378–1380
- 54 Economist Intelligence Unit (2011) *Reinventing Biopharma: Strategies for an Evolving Marketplace. The Innovation Imperative in Biopharma. An Economist Intelligence Unit Report*. Economist Intelligence Unit
- 55 Hogerzeil, H.V. (2013) Big pharma and social responsibility – the Access to Medicine Index. *N. Engl. J. Med.* 369, 896–899
- 56 Kaitin, K.I. (2010) Deconstructing the drug development process: the new face of innovation. *Clin. Pharmacol. Ther.* 87, 356–361
- 57 Boguski, M.S. *et al.* (2009) Repurposing with a difference. *Science* 324, 1394–1395
- 58 Novac, N. (2013) Challenges and opportunities of drug repositioning. *Trends Pharm. Sci.* 34, 267–272
- 59 Grody, W.W. and Getzug, T. (2010) Colchicine's other indication – effect of FDA action. *N. Engl. J. Med.* 363, 2267–2268
- 60 Kitsis, E.A. (2009) Rx for the pharmaceutical industry: call your doctors. *Hasting Center Rep.* 39, 18–21
- 61 LaMattina, J.L. (2011) The impact of mergers on pharmaceutical R&D. *Nat. Rev. Drug Discov.* 10, 559–560
- 62 Samarasekera, I.V. (2009) Universities need a new social contract. *Nature* 462, 160–161
- 63 Tralau-Stewart, C.J. *et al.* (2009) Drug discovery: new models for industry-academic partnerships. *Drug Discov. Today* 14, 95–101
- 64 Valance, P. *et al.* (2010) The future is much closer collaboration between the pharmaceutical industry and academic medical centers. *Clin. Pharmacol. Ther.* 87, 525–527
- 65 Woodcock, J. (2010) Precompetitive research: a new prescription for drug development? *Clin. Pharmacol. Ther.* 87, 521–523
- 66 FitzGerald, G.A. (2008) Drugs, industry, and academia. *Science* 320, 1563
- 67 Schuhmacher, A. *et al.* (2013) Models for open innovation in the pharmaceutical industry. *Drug Discov. Today* In: <http://dx.doi.org/10.1016/j.drudis.2013.07.013>
- 68 Bergman, L. *et al.* (2010) Investigator-initiated trials of targeted oncology agents: why independent research is at risk? *Ann. Oncol.* 21, 1573–1578
- 69 Dimasi, J.A. and Grabowski, H.G. (2007) Should the patent system for new medicines be abolished? *Clin. Pharmacol. Ther.* 82, 488–490
- 70 Higgins, M.J. and Graham, S.J.H. (2009) Balancing innovation and access: patent challenges tip the scales. *Science* 326, 370–371
- 71 Knowles, S.M. (2010) Intellectual property. Fixing the legal framework for pharmaceutical research. *Science* 327, 1083–1084
- 72 Kesselheim, A.S. (2007) Intellectual property policy in the pharmaceutical sciences: the effect of inappropriate patents and market exclusivity extensions on the health care system. *AAPS J.* 9, E306–E311
- 73 Musselwhite, L.W. and Andrews, J. (2010) Protect pharmaceutical innovation. *Science* 328, 1354
- 74 Yancey, A. and Stewart, C.N. (2010) Patent reform in the US: what's at stake for pharmaceutical innovation? *Expert Opin. Ther. Pat.* 20, 603–608
- 75 Gold, E.R. *et al.* (2010) Are patents impeding medical care and innovation? *PLoS Med.* 7, e1000208
- 76 Boldrin, M. and Levine, D.K. (2008) *Against Intellectual Monopoly*. Cambridge University Press
- 77 Breckenridge, A. (2010) Regulatory challenges, reimbursement, and risk-benefit assessment. *Clin. Pharmacol. Ther.* 88, 153–154
- 78 Boon, W.P.C. *et al.* (2010) Conditional approval and approval under exceptional circumstances as regulatory instruments for stimulating responsible drug innovation in Europe. *Clin. Pharmacol. Ther.* 88, 848–853
- 79 Ebbers, H.C. *et al.* (2011) Today's challenges in pharmacovigilance: what can we learn from epoetins? *Drug Saf.* 34, 273–287
- 80 Russo, M.J. and Balekdjian, D. (2008) Weighing the outcomes. *Nat. Biotechnol.* 26, 173–182
- 81 Miller, H.I. and Henderson, D.R. (2007) Governmental influences on drug development: striking a better balance. *Nat. Rev. Drug Discov.* 6, 532–539
- 82 Cohen, J.T. *et al.* (2008) Does preventive care save money? *N. Engl. J. Med.* 358, 661–663
- 83 Liaw, S.T. and Petersen, G. (2009) Doctor and pharmacist – back to the apothecary. *Aust. Health Rev.* 33, 268–278
- 84 Taylor, R.S. *et al.* (2004) Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. *BMJ* 329, 972–975
- 85 Orkie, S. (2009) Multinational medicines. Ensuring drug safety in an era of global manufacturing. *N. Engl. J. Med.* 361, 737–740