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PERSPECTIVE

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Patients not patents: Drug research and development as a public enterprise

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1 | INTRODUCTION

The current system for drug innovation and usage has generally failed public health. Only 11 (1%) of 1032 new drugs approved in France between 2005 and 2014 were considered real advances, and 54 of the 87 analysed drugs or indications in 2014 were no better or actually worse than existing treatment options.[1] Drug harms are so prevalent that studies in high-income countries have shown that drugs are the third leading cause of death, after heart disease and cancer.[2-11]

The European Commission has estimated that adverse reactions kill about 200 000 EU citizens annually at a cost of €79 billion.[11] Many of these deaths are avoidable. Our for-profit system encourages overprescribing, and many patients could have fared well without the drug that killed them, for example a nonsteroidal anti-inflammatory agent or a psychoactive drug.[2,12] Meanwhile, many important health problems do not receive the attention they deserve, for example to address antimicrobial resistance.

The main problem is that the current system is based on patents and monopolies, which allow companies to set their price as they want. This system is unethical, as people may die if they cannot get access to the drug they need. It is also inefficient, as research knowledge is not shared, for example about toxicology and failed projects. Furthermore, the TRIPS-plus provisions prohibit generic manufacturers from using clinical trial data submitted by brand manufacturers.[13]

I propose a radically different approach in which the current drive of profit maximization via patents is replaced by a public interest-driven system that is not for profit. I hope this paper can be a starting point for a much-needed discussion.

2 | COUNTERING MYTHS ABOUT PATENTS AND EFFECTIVE MEDICAL INNOVATION

Patents are ill-suited to stimulate needed and effective innovation in health care. They stifle innovation because researchers cannot share their ideas freely, and the system encourages large-scale waste.[13] Indeed, it seems that stronger patent protection has led to a reduction in innovation.[13] As patents expire, drug companies often file court cases against competitors to prevent them from launching cheap generics. The European Commission estimated in 2008 that these legal tactics had cost the EU €3 billion in just 8 years.[14]

The drug industry spends only 1%-2% of gross revenues, net of taxpayer subsidies, on basic research to discover new molecules.[15] Most of the basic knowledge to develop treatment advances comes from publicly funded laboratories and institutions.[16-18] In its drive to maximize profits, the industry tends to focus on drugs to treat chronic conditions that affect many people, often making minor, patentable variations to existing drugs with no added therapeutic value, which, however, is rarely a hindrance to selling them in large volumes at prices that can be 10 or 20 times more expensive than off-patent drugs.[2,12] To achieve this, the industry spends much more on marketing than on research and development.[2]

The current system provides little incentives to study and develop less expensive nondrug interventions, although they may often be preferable. Some of our largest expenditures are for drugs to treat type 2 diabetes, hypertension and high cholesterol, which are largely attributable to poor diet and lack of exercise. Worthwhile interventions might include stricter regulations of food and soft drinks, subsidized school lunches and courses in the preparation of healthy, affordable meals that can make people lose weight so that they no longer need drugs.[19-21] Another example is the high and increasing usage of psychiatric drugs, which has been accompanied by an increase in disability pensions in all countries where this relationship has been investigated.[22] In most situations, psychotherapy should be the preferred option,[12] and in contrast to drugs, it reduces the risk of suicide.[23]

The industry's justification for patents and high drug prices is that patents are needed to recoup the high costs of drug development and thus ensure a needed supply of new drugs. Around 15 years ago, the industry narrative put the cost of developing a new drug at about US $1 billion,[18,24] while independent analysts arrived at a figure that was 10% of this.[25] Currently, the Drugs for Neglected Diseases initiative (DNDi) estimates that it can develop a new drug for between $110 million and $170 million, which includes a theoretical cost of failed projects.[26] In reality, the prices of drugs do not reflect research and development costs but what heavily subsidized "markets" are willing to pay.

3 | COUNTERING MYTHS ABOUT DRUG REGULATION

In recent years, drug agencies have gradually relaxed their standards for approval and drug companies pay a fee, which gives them leverage in the regulatory system.[27] The drug industry contributes 83% of the entire budget for the European Medicines Agency (EMA)[28] although nobody receiving 83% of a salary from industry would be admitted to any drug evaluation committee. With less rigorous regulatory standards, more drugs have been withdrawn from the market or have received serious safety warnings.[29-33]

The regulatory requirements are particularly low in cancer, and many hugely expensive cancer drugs have been approved without the existence of a single randomized trial[34,35] and with only surrogate outcomes, for example disease-free survival instead of longer life. New cancer drugs are generally no better than existing ones[2] or increase survival by 1 or 2 months only.[36,37]

The standards for approval continue to fall, most recently illustrated by the EMA's introduction of adaptive pathways, which will allow drugs to be approved based on observational data only.[38] Some patient groups support the industry's demands for faster approvals that will give them rapid access to the latest drugs. However, it is a myth that the current system benefits patients, and as most patient advocacy groups accept drug company funding, they generally cannot speak publicly on behalf of patients about regulatory issues.[39,40]

4 | DRUG RESEARCH AND DEVELOPMENT AS A PUBLIC ENTERPRISE

A radically new approach is needed to stimulate innovation in the public interest and to reduce drug expenditure substantially. Marketing is not needed to persuade doctors to use good medicines and the patient-focused system I propose will prohibit industry strategies for disseminating misleading drug information such as industry-sponsored education of doctors and patient groups, detailing of doctors, drug ads (including those in medical journals for prescription drugs) and seeding trials of no scientific value.[2]

A European Institute of Public Health could have the overall responsibility for developing drugs and bringing them to the market, in collaboration with a network of institutions, which could themselves develop drugs or contribute to the various parts of drug development. Excellent examples of nonprofit institutes that have proved highly useful include the Mario Negri Institute,[41] the DNDi and Institut Pasteur. A public institute developed along these lines would have a transparent governance structure that is accountable to the people and would hold regular priority discussions, with public participation. For-profit companies could bid for contracts to contribute expertise and deliver specialized services, such as animal studies or drug manufacture.

Substantial funds will be needed initially, in the transition phase to the new system, to develop the necessary public infrastructure and to pay for public drug development. Several models already exist, one of which is taxation. The Italian drug agency requires drug companies to contribute 5% of their promotional expenses, apart from salaries, which has created a large fund used partly for independent clinical research,[42,43] and Spain has a similar initiative.[43] A tax on sales would create a much greater income but most importantly, the new system will avoid the huge waste we currently have. It has been estimated that the savings in the new system will be 5-10 times greater than the amount the drug industry currently spends on research and development.[13] Vastly more public money is therefore being poured into the current system than what will be needed in future.

To stimulate innovation, inventors could be awarded a "finder's fee," for example 10% of the potential savings for

1 year. Such innovations need not be limited to new interventions but could be studies that demonstrate that a currently used diagnostic test, intervention, dose or treatment length is no better than a cheaper one—a kind of study the industry has no interest in carrying out.

In the not-for-profit model, the price of drugs will be set low enough—using the manufacturing cost plus a small margin—that also third-world countries could afford to buy the drugs. This would improve the health of their citizens and increase international trade and prosperity.

5 | THE TRANSITION TOWARDS THE NEW SYSTEM

Some of the necessary changes can be introduced quickly; for others, a transition phase is needed that includes legislation, public education and research on needs.

5.1 | Patents, patent laws and trade agreements

Once fully implemented, the new system will abolish the patenting of drugs and devices. In the transition period, all regulations that impede the introduction of generic medicines and biosimilars to the market should be removed, and new patents for minor changes, for example the removal of the inactive part in a stereoisomer, should not be allowed. The bar for launching lawsuits against generic competitors with claims that they have broken a patent should be raised substantially, and the time limits for lawsuits and patent exclusivity shortened. Companies that launch frivolous lawsuits should be subject to stiff penalties, as the mere threat of such lawsuits often stifles innovation in start-up companies.[13]

In the transition period towards public drug development, compulsory licensing and government use of patents can ensure the availability of life-saving drugs and drugs that may prevent serious disability. These mechanisms, which are available under international law but underused, allow a third party (eg a generic company or government-owned facility) to produce cheaper copies of a drug, in return for a small fee to the patent holder. This interim measure would allow competition right from the start.

International trade agreements that emphasize secrecy and commercial confidentiality are a real threat to what I propose. Our politicians will therefore need to ensure that such agreements do not become obstacles for improvements in public health, equity and savings in our national economies. Existing agreements such as TRIPS (trade-related aspects of intellectual property rights) will need to be revamped.

5.2 | De-linking, prizes and pricing

In the transition phase, when drug companies still have new drugs under development, they could be offered a buyout of their patent, like a prize, commensurate with the benefits and harms of the drug, as documented in publicly conducted trials with relevant comparators and outcomes. The use of a prize system is consistent with proposals in the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPoA) of May 2008, and the EU Council Conclusions on Global Health in May 2010. Both called for needs-driven innovation and for further exploration of innovation models that de-link the postulated cost of research and development from the price of medicines.[44] Similar thoughts were expressed in the US Senate Bill 1137.[24]

Countries should collaborate on price negotiations with companies and use their powers to refuse to reimburse too expensive drugs and to impose pricing practices that take into account the public research investments and the fact that pharmaceuticals are public goods (as opposed to the currently promoted value-based pricing approach, which puts a monetary value on life).

5.3 | Public education and research on needs

To engage the public in the profound change to the new system, a programme of education and myth busting will be undertaken to combat the widespread erroneous beliefs that sustain the current system.

Important educational initiatives already exist to help the public think critically about the harms of inappropriate and excessive drug use and to recognize the many nondrug strategies for preventing disease and improving health.[45,46] These programmes have gained support among public health advocates internationally; they can be expanded and adapted, raising public awareness about the enormous inefficiencies that make the current system financially and morally unsustainable.

Like any drug development endeavour, the new system will have to manage the risk of aborted projects. Taxpayers may view such failures as a poor use of their money unless they understand the realities of scientific research, including the rarity of research breakthroughs. Continuous education of the public and the politicians, with trustworthy and transparent figures for the costs of research and development, will be needed.

To move from a supply- and profit-driven to a demand-driven system, the needs of patients and of society will be identified, taking into account epidemiological data, public expenditures, mortality statistics and patient-relevant outcomes.[47]

5.4 | Needed changes at the European Medicines Agency and other drug agencies

In the new system, drug agencies are fully publicly funded and have much more focus on drug harms. Trials submitted for obtaining marketing authorization should be large enough and run for sufficient lengths of time to capture rare but lethal harms, particularly because promises of post-marketing studies are often not fulfilled.[42,48]

The most critical change to be adopted is to request the demonstration of a minimal clinically relevant effect by meeting criteria established in advance. This effect should be shown in independent trials in the appropriate patient population with full transparency on methodology and results, and taking into account all studies—not just those that showed benefit, which is the current regulatory standard. Current efficacy standards allow drugs to come on the market based on effects that are not clinically meaningful. The effect of newer antipsychotic drugs and antidepressants, for example, fall considerably below the threshold psychiatrists have established for minimal clinical relevance.[12]

Drugs should not be approved based on surrogate outcomes (eg blood glucose rather than complications to diabetes) except when they are validated to correlate with patient-relevant outcomes, which is very rarely the case.[49-51] Noninferiority and equivalence trials are also usually misleading[52-54] and should rarely be accepted. The norm should be to establish benefit in superiority trials compared to the best available interventions.

A new, well-funded section completely separate and independent from the section that approves drugs should be established to make decisions about drug withdrawal for safety reasons.

5.5 | Improving clinical trials

Clinical trials of drugs and devices will be performed independently from the industry by nonprofit public health-focused institutions, which will prepare the protocol, conduct and monitor the trials, and ensure that no one involved with the trials has conflict of interests in relation to drug companies. Additional safeguards, such as blinding data analysis and writing of manuscripts, will be put in place.[55]

Publicly conducted drug trials will ensure that new drugs are being compared with old cheap drugs in a fair manner and also with nondrug interventions. They will also be vastly cheaper than drug industry-conducted trials. The European Society of Cardiology has estimated that university centres can perform drug trials for about one-tenth to one-twentieth the cost of industry trials where there are numerous for-profit middlemen who tack a hefty surcharge.[56]

To improve the usefulness of trials for patients, draft trial protocols will be publicly available on a website to allow patients and others to comment on them. All information related to the trials will be publicly accessible, from the preplanned outcomes to the raw, anonymized patient data, allowing others to conduct their own analyses. The trial reports will be published in open-access journals or on the web so that everyone, including the patients who volunteered for the trials, can access them without charge. Preclinical studies (eg animal toxicology studies), including the raw data, will also be made available.

5.6 | Creating attractive job positions in the new system

Politicians often see the drug industry as a motor for economic growth that contributes to job opportunities, trade balance and the knowledge economy, a perception that the industry promotes. In 2013, according to the European pharmaceutical industry association, the industry directly employed more than 690,000 people in Europe and generated three to four times more jobs indirectly.[57] However, many of these jobs are in sales and legal departments, and ultimately paid for by all of us through high drug prices, and the intensive marketing causes many unnecessary deaths and is harmful to our national economies.

Many people working in the pharmaceutical industry have invaluable expertise, which they might prefer to use in a nonprofit environment. Psychological research has shown that inventing or contributing to something that is genuinely helpful to people can be a very strong motivator. Therefore, there will be no lack of incentives for useful innovations. In fact, it seems that high-risk, bold investments that led to technological revolutions were sparked by public sector institutions.[58]

In the beginning, there may be a scarcity of publicly employed researchers with the detailed know-how about conducting such tasks as long-term animal toxicology studies and randomized trials that meet the standards for drug approval. Training programmes can be developed to teach people the necessary skills.

I acknowledge that this vision of a better future requires much discussion and political will but also expect that details of the necessary new structures will be agreed upon over time, as we have no other choice than to change the current system radically.

CONTRIBUTORS AND SOURCES

This paper is the result of my participation in a consultative and deliberative process, initiated by the Belgian Health Care Knowledge Centre and the Dutch Health Care

Institute, to explore, in an unfettered way, potential solutions to the complex societal challenge of high drug prices and medical innovation. The project had the ambition to elaborate creative scenarios and to explore novel, more sustainable ways to ensure patient access to safe and effective drugs, while maintaining strong incentives for innovation and focusing on real health needs. The project benefited from the contribution of a carefully selected group of 30 experts and stakeholders from Europe and North America, including patient representatives, industry leaders, academics, regulators, payers and government representatives. Based on in-depth interviews of these experts, followed by two two-day workshops in Amsterdam in March and April 2016, four coherent scenarios were developed.[59,60] These scenarios were presented to a wider audience in the context of the Dutch EU presidency in June 2016. I encourage politicians, researchers, patients and other citizens to support the suggestions I have presented here, which provide the most radical of the four scenarios. I invite debate about this proposal, assessing its merits in relation to other possible change scenarios. I coined the idea of a future without patents and with public development of drugs. I am experienced in the areas of clinical trials and public health and I am a guarantor.

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COMPETING INTERESTS

I have no relevant interests to declare.

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