A Prescription for **New Drugs**

During the 20th century, the pharmaceutical industry made crucial strides in advancing drug development. In recent times, however, the sector has seen noticeable cost-related cutbacks in research activity. We urgently need new drugs for the treatment of cancer, dementia and many other diseases. In developing countries, the problem is a matter of life and death. Our author pleads for a radical rethinking of the drug development system, and for the involvement of basic research.

TEXT **PETER H. SEEBERGER**

Life expectancy in Germany has almost doubled since 1900, increasing from 70 to 80 years between 1960 and 1980 alone. Better hygiene and nutrition played a very big part in this development. Another factor is clearly the improvement in medical care. Growing numbers of new drugs have brought an end to our fear of dying from previously fatal conditions, such as bacterial infections. Vaccines now shield us from viral and bacterial diseases like polio. Even conditions that were considered fatal until recently, such as HIV/AIDS, today no longer carry an automatic death sentence.

Germany earned itself the moniker of "pharmacy to the world"

The pharmaceutical industry has driven the development of various drugs since the early 20th century. During this period, due to its role in the development of numerous drugs, Germany earned itself the moniker of "pharmacy to the world" and became a model for the sector in many other countries. However, considering the overall contribution of the pharmaceutical industry's products to the wellbeing of the population, it's surprising how unpopular the sector is. Surveys reveal that car manufacturers, for example, are held in much higher esteem.

The pharmaceutical industry is viewed as rich, powerful and devious. Admittedly, this reputation isn't entirely undeserved. Denouncing its transgressions and preventing future mistakes is clearly the right thing to do. However, criticism of Bayer, Sanofi and other companies must not cause us to lose sight of the bigger picture. The development of the pharmaceutical sector is a cause for concern.

At the global level, the pharmaceutical industry is in the throes of a huge crisis that has been under way for a decade. Though the pharmaceutical giants are still pulling in big profits, they are increasingly cannibalizing their own scientific substance. The question arises here, of course, as to whether the well-being of very profitable companies should really be of concern to society. But the fact is that work on the development of new drugs and vaccines is waning – a situation that is clearly a matter of concern for the general public.

The problem has its roots in the fact that drug development is an increasingly risky and therefore expensive business. The costs currently range between 500 million and 1.3 billion euros per drug or vaccine. There are many reasons for this explosion in costs. First, the "simple" drugs are already available on the

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We could be forgiven for believing that a pill already exists for every conceivable ill. Yet we urgently need new drugs for the treatment of cancer, dementia and other diseases. The problem is even more severe in developing countries.

market, and second, thanks to scientific progress, the drug development process has become more complicated. Moreover, the availability of better analytical methods means that the regulatory authorities exercise greater control over development and production processes.

This has serious impacts on company policies: pharmaceutical concerns currently concentrate on the development of blockbuster drugs – that is, drugs that earn them over one billion euros per year – mostly because they cure or alleviate very common conditions in rich industrialized countries. Such drugs alone enable the companies to achieve good returns within a matter of years – until the patent expires. The transformation of fatal conditions into chronic ones is popular with the companies, as patients are then forced to take a particular medication for a very long time.

Many important drugs remain unaffordable for the majority of people in developing countries

For reasons of cost, diseases like malaria, which affect and kill people mainly in newly industrialized and developing countries, aren't attractive for the pharmaceutical industry. The same applies to the marketing of expensive drugs in countries with less purchasing power. As a result, many important drugs remain unaffordable for the majority of people in developing countries.

A solution that is often called for (and that was implemented by the state in India) is to set aside existing patents and subsidize companies that produce cheap imitation products known as generics. This approach is entirely understandable from the perspective of governments like that of India. And it is very effective in the short term. However, the pharmaceutical companies in industrialized countries will be less likely to engage in costly research in the future if they know that the fruits of this research are going to be expropriated in some locations. The newly industrialized countries haven't yet spawned any innovative pharmaceutical companies that are developing new drugs aimed at solving the region's health problems. There is reason to hope that this situation will change at some stage. In the meantime, however, there is no other solution in sight apart from generics – and even these are often unavailable.

Cancer drugs are a good example of the gap that exists between industrialized and newly industrialized countries in this regard. In Europe, one in every three drugs introduced to the market is a cancer drug. "New" doesn't necessarily mean considerably better in this context; often what is involved is merely a minimal change over existing drugs. There are around half a million cancer patients in Germany each year whose treatment with these new products costs around 80,000 euros per patient per year.

This astonishing volume of new drugs – between 600 and 800 are estimated to be in development – is due, not to an increase in the number of cancer cases or the improvement in treatment methods, but quite simply to market forces. The market is the mechanism that controls pharmaceutical research, supply and production. Although cancer drugs account for just 2 percent of the medicines prescribed, they are responsible for 25 percent of health insurance companies' drug costs. This is the reason why there are a lot of new drugs on the market, even if, in many instances, they don't represent any fundamental progress in terms of cancer treatment.

The exact opposite situation prevails in the newly industrialized and developing countries. As is the case in the industrialized countries, breast and cervical cancer are the most common forms of cancer in women there. The treatment options and drugs available in the industrialized nations are good. In Africa, in contrast, being diagnosed with one of these cancers is tantamount to being handed a death sentence. Following diagnosis, if one is made at all, patients live for only around four months on average – and they don't receive any kind of treatment. Very few patients in African countries can afford the cancer drugs available in the industrialized world.

A similar situation may be observed in China and Vietnam, where, due to improving living conditions and healthcare, people are living longer and there has been a sharp rise in the number of people developing cancer. Here, too, the market controls the volume of pharmaceutical products available. As almost nobody can afford the expensive drugs available in the industrialized countries, and there are also no health insurance companies, there are few cancer drugs on offer in these countries.

The idea that the market will regulate everything is thus both right and wrong. The market is, indeed,

the mechanism that regulates the pharmaceutical sector, but this type of regulation isn't always good from an overall systemic perspective. A minimum level of cancer drug supplies for developing and newly industrialized countries would be extremely useful. However, this would require the availability of extremely cheap cancer drugs. Such drugs aren't being developed by the pharmaceutical companies in the industrialized countries, as cheap drugs don't have high profit margins.

Malaria drugs, which are produced from the active ingredient and plant extract artemisinin, are also effective against cancer. Artemisinin-based malaria therapy costs around one euro. Clinical studies have been available for around ten years now that show that artemisinin is similarly effective at treating many types of cancer as current cancer drugs.

However, none of the pharmaceutical companies have set about licensing artemisinin derivatives as cancer drugs because the manufacturer would have to bear the high cost of the clinical licensing phases, but wouldn't ultimately be able to file an effective patent, given that the active ingredient is already licensed as a malaria drug.

The market economy logic thus hinders the researching and licensing of a cancer drug that would be suitable for use in large numbers of patients in Africa, Asia and, ultimately, industrialized countries as well.

This dysfunction isn't the result of the sinister machinations of evil people working in greedy pharmaceutical concerns. Nevertheless, it isn't enough to simply acknowledge the existence of such anomalies with a shrug of the shoulders. The identification of innovative solutions to this problem requires political and scientific intelligence. One possible conclusion is that very different approaches and solutions are needed for different societal conditions. It may be assumed that the pharmaceutical industry with a uniform research system aimed at meeting the needs of the entire world isn't the best solution.

To return to the situation in the industrialized countries, a process of consolidation may also be observed as another effect of the high drug development costs combined with the pressure of the financial markets. Bigger and bigger pharmaceutical groups have emerged with a view to exploiting the synergies between companies: Bayer swallowed up Schering AG, and Sanofi and Aventis merged, while Aventis itself was the result of the merger between Hoechst and Rhône-Poulenc. As the size of the conglomerates and their market values have risen, so, too, has the importance of shareholder value in the pharmaceutical industry.

Many companies were optimized with an eye to the balance sheets: from an economic perspective, research on new drugs is a risk that must be minimized. This could be achieved, for example, by transferring almost all segments of the drug development value chain to low-wage countries. Yes, that saved on costs. But it was a Pyrrhic victory, as it also resulted in the large-scale loss of highly skilled employees in industrialized countries.

Admittedly, cutting research budgets, for example closing central laboratories, is the least conspicuous measure in the short term. In the long term, however, this strategy threatens the very survival of the firms. For some time now, companies like Pfizer haven't launched any new drugs and have been living entirely off their acquisitions, as their own development pipelines were empty. Nothing ventured, nothing gained! In an ideal world, a pharmaceutical company should be more than a bank with an R&D department.

The fact that many pharmaceutical concerns continue to rake in the sales is mainly due to the assimilation of successful products through the takeover of other companies. This conceals the major underlying trend, which is that the outlook for the entire sector is precarious. Germany's "pharmacy to the world" is closing down. Generics are being produced cheaply abroad, and tens of thousands of highly skilled jobs have already been lost – in Europe and the US, too – for example at Merck, Pfizer, AstraZeneca and almost every other pharmaceutical company.

Products that have few expectations riding on them often achieve huge commercial success

Of course, the management boards of most large pharmaceutical concerns recognize the enormous challenges they face, and are trying to counteract the trends and find ways to operate profitably in the long term. However, the circumstances are anything but simple: as demonstrated by various failed attempts in the past decade, it's extremely difficult to develop new drugs with high sales while simultaneously sat-

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isfying the expectations of the financial markets. The pharmaceutical giants also tend to obey a kind of herd instinct and follow certain fashions.

For example, over the past decade, several companies invested billions in RNAi technology, which, following great initial hopes, has, as yet, yielded no success. And products that have few expectations riding on them often achieve huge commercial success. Whereas, up to the year 2000, the rule of thumb was that, despite being an effective resource on the level of national economies, vaccines could yield little corporate profit, this thinking changed when annual sales of around five million US dollars came in from Pfizer's pneumococcal vaccine Prevnar (developed by Wyeth). Suddenly, other vaccines became commercially viable products if they targeted wealthy customers. Several vaccine companies have therefore been acquired by larger pharmaceutical concerns in the past five years.

Perhaps we need financing models based on public funding bodies or state-guaranteed loans

Companies are currently trying to reduce their own research activities to a minimum to keep costs and risks low, the idea being that the discovery of innovative therapeutic and diagnostic concepts should take place in research institutes and small companies. The plan consists in purchasing promising compounds and technologies when the risks are manageable. This means that the price will be higher, but the pharmaceutical concerns can exploit their strengths: experience in clinical trials and drug development – but no longer in drug discovery.

The enormous costs of the late development phase can be borne only by large companies with deep pockets. The risks associated with this approach are, of course, the lack of control over the early development phase and the danger of paying too much in the competition for the best projects.

Action is urgently called for: what we need are new drugs for the treatment of cancer, dementia and many other diseases. It's a matter of life or death in developing countries: they need vaccines mainly for malaria, HIV/AIDS and bacterial diseases. It has long been accepted that, contrary to the cynical view, a good healthcare system helps prevent overpopulation.

Private initiatives like the Bill & Melinda Gates Foundation offer a very promising approach. The support of such foundations provides companies with an incentive to work on drugs that would never be developed without funding. However, such patronage isn't enough to solve the basic problem: the market-driven model of drug development as currently practiced is the best one I know – but it isn't good enough.

We will all have to do a radical rethink: the aim of profit maximization will have to give way to that of "health maximization." We would then develop drugs in a completely different way. There's no lack of expert knowledge in companies and research institutes. My Max Planck research group alone is currently working on the development of five new vaccines, including vaccines for tropical diseases that still claim hundreds of thousands of lives each year. Basic research and applied academic biomedical research are stronger than ever in western industrialized nations.

At the same time, the pharmaceutical companies that (still) exist (still) have considerable experience in guiding new products through the test phases to the point of market readiness. Moreover, there is no lack of efforts to bridge the gap – which experts refer to as a "valley of death" – between academic research and industrial development. However, the successes remain limited because the market structures aren't suitable. So the question arises as to what kinds of political tools could be used to set new and better incentives.

I'm not pushing for the control of drug development by a state body, but society must become more involved in drug development. Pharmaceutical companies must receive financial support to develop drugs for the treatment of smaller diseases. Perhaps we need financing models based on public funding bodies or state-guaranteed loans. In this case, however, the taxpayer must share not only the risk but also the profits.

It would appear that we have enough money to do this. The taxpayers' money spent on saving a single bank would have been sufficient to develop ten or more new vaccines capable of saving the lives of hundreds of thousands of people. It would also have generated innovative impetus for the creation of many highly skilled jobs.

So how can the Max Planck Society contribute? It is our task to carry out cutting-edge work on the

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level of basic research – and not to engage in a targeted quest for practical solutions to the plight of the pharmaceutical sector. Truly fundamental breakthroughs in the chemical, biological and medical sciences often involve completely new approaches to diagnostics, vaccines and drug treatments. While this kind of research doesn't provide specialized, tailor-made solutions to specific problems, the scope of the fundamental progress it achieves is all the more extensive.

Knowledge of the possible applications and current challenges through active discourse with industry and the willingness to allow science to become an application often forces us out of our scientific comfort zone. A few approaches already exist for the further development of systematic results from basic research with a view to translating them into applications.

Further efforts are needed from both sides – both the Max Planck Society and the pharmaceutical sector – to ensure that we make the most of the discoveries as fair partners. Max Planck researchers aren't a cheap "extended workbench" or a tax-funded source of ideas. Fair and effective ways must be found to organize the linking of knowledge and application in a way that ensures that society as a whole benefits, and not just a few individuals.

The pharmaceutical industry must get used to the idea that there are other values besides share values

Basic research at the Max Planck institutes has yielded important products, also for the healthcare market. In far too many cases, however, that fact is virtually unknown. I would like to see a future in which Max Planck researchers devise new solutions and realize their essential features through greater problem awareness. In this way, we can offer society a return on its investment that goes far beyond the monetary value of the funding we receive.

The topic of new drugs must be put on society's agenda. We must get used to the idea of ensuring the survival of our pharmaceutical sector, which merely gives the impression of being booming. And the pharmaceutical industry must get used to the idea that there are other values besides shareholder value. ◀

THE AUTHOR

Prof. Peter H. Seeberger was born in 1966. He studied chemistry at the University of Erlangen-Nürnberg and completed a doctorate in biochemistry at the University of Colorado. He has held the posts of Assistant Professor and Firmenich Associate Professor at the Massachusetts Institute of Technology in Cambridge, USA, and professor at ETH Zurich. He has been Director at the Max Planck Institute of Colloids and Interfaces and professor at the Freie Universität Berlin since 2009. Prof. Seeberger has published over 350 peer-reviewed articles, holds more than 30 patents, and has been awarded over 25 international prizes. Several spin-off companies have emerged from his laboratory. As a co-founder of the Tesfa-Ilg Hope for Africa Foundation, he supports the improvement of healthcare in Ethiopia.

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