MEZIS
MEIN ESSEN ZAHL ICH SELBST

NACHRICHTEN
NR. 2/16

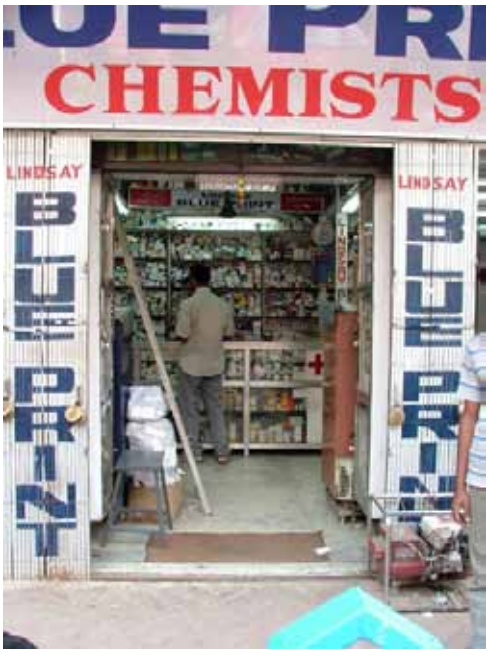
Editorial

While a lack to life-saving medicines has been a feature in the resource-constrained parts of the world for many decades, the global trend of escalating prices of pharmaceuticals has started to hinder access in rich industrialized countries as well. Monopolies caused by patents on new medicines or where there is only a single producer for an older off-patent neglected medicine, which is now used as a speciality medicine, are the most important reason for high prices and a lack of affordability and access to essential medicines. The costs of producing me-too medicines, which offer a marginal benefit over existing options, at best, also absorbs important research and development (R&D) resources, and potentially diminishes the incentives for real innovations which can benefit patients.

The articles draw a comparison between the Indian, German and South African situation, in order to show the global impact of highly priced medicines. It touches on the extent to which individual physicians and patients are influenced by high priced medicines. The process of developing treatment guidelines, which then guide the allocation of resources, is also open to influence. The articles discuss how these issues can best be tackled through changes in practice and policy on the individual, national and global level. As the global problem affects nearly all countries, the analysis and recommendations can be generalised to most contexts.

Christiane Fischer

Medicines in Germany...



„and in India

Essential medicines and "me-too" medicines

Essential medicines: According to the World Health Organization (WHO) "essential medicines are those that satisfy the priority health care needs of the population… Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.[1] The WHO Model List of Essential Medicines, last updated in 2015,[2] contains about 350 active agents essential for health care. They are "selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness".

"Me-too" medicines offer few, if any, benefits over existing medicines. From one perspective, they absorb important R&D resources as they diminish incentives for research and development (R&D) for real innovations that may benefit patients. However, from another perspective, if considered interchangeable with existing medicines, they can offer the potential for price competition, even before patent expiry and the launch of generic medicines. In the WHO Model List of Essential Medicines, the existence of such interchangeable options is indicated with a square box symbol.

Countries should develop policies to carefully manage the listing of me-too medicines, especially on health insurance reimbursement lists. A differential should not be paid for medicines which offer little or no advantage over lower-priced alternatives. However, where alternatives can be reimbursed at the same or very similar levels, competition can be used to drive down such prices. Where procurement is by means of a limited list and a competitive bidding process (tenders), use of the WHO square box notation can also assist in maximising competition and assuring the lowest possible prices.

THE ROLE OF THE PHARMACEUTICAL INDUSTRY

Global spending on medicines is expected to reach US$ 1.3 trillion by 2018, an increase of 30 % as compared to 2013. In 2013, the global sales figure was US$ 989 billion (about 1/3 in the US), and it is expected to reach US$ 1300 billion by 2018.[3] The 10 largest drugs companies (six in US and four in Europe) control over one-third of this market. They spend about one third of all sales revenue on marketing - roughly twice what they spend on R&D. R&D is predominantly directed at the development of new products for the most lucrative markets, of which a large share have been characterised as "me-too", or pseudo-innovative.[4] According to the profit imperative the first aim of any industrial product is to maximise the company's profit. As a result, market-driven products for the rich are prioritized over need-based medicines for the poor, who are unable to pay for them.[5]

Christiane Fischer, Andy Gray, Gopal Dabade

Contents

1 *World Health Organisation Information of the WHO relating to the Essential Medicines. Geneva. http://www.who.int/medicines/services/essmedicines_def/en/ [22.8.2016]*

2 *World Health Organisation (2015) 19th WHO Model Lists of Essential Medicines. Geneva. http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf?ua=1 [22.8.2016]*

3 *Gagnon, Lexchin (2008) The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the United States. PLoS Med, 5(1), http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050001 [22.8.2016]*

4 *Prescrire Int (2013) New drugs and indications in 2012. Sluggish progress, timid measures to protect patients. Prescrire Int; 22(137): S. 105-107, http://english.prescrire.org/en/115/447/48383/2591/2588/SubReportDetails.aspx [22.8.2016]*

5 *World Health Organisation Pharmaceutical industry. Geneva. http://www.who.int/trade/glossary/story073/en/ [22.8.2016]*

The global situation of (lack of) access to medicines

Lack of access to medicines includes the extent essential drugs are not available and/or not affordable for patients who need them. The other side of the medal is that at the same time expensive pseudo-innovations, which do not provide any therapeutic progress as compared with the former standard of therapy, dominate largely the global market. The business strategy of firms is to focus only the wealthy part of the populations. Drugs will be developed in India for 100 million people only (out of a population of more than 1.27 billion). Therefore the impact of the influence of pharmaceutical marketing practices the rules of procedure in pricing drugs will be discussed in the analysis and recommendations are developed. The aim is to improve access to essential drugs and to help disappear pseudo-innovative drugs from the global market.

Equitable universal availability of and access to essential medicines at affordable prices is a fundamental human right.[1] However the reality is different: According to WHO estimates about 2.1 billion people globally cannot access even essential medicines. Those who lack access are particularly concentrated in Africa and India[2] but also in Eastern Europe, where about 90% of the population there pays for medicines through out-of-pocket payments.[3] Essential medicines such as warfarin, an oral anticoagulant used to prevent thrombosis, are not on the market in Albania[4] nor in Uganda[5]. Lack of access can be the result of medicines not existing. This is the situation with neglected diseases such as Dengue fever. The economic incentives to develop such medicines are lacking. Alternatively, where market-oriented research has led to the development of a needed medicine, they may be priced out of reach of those in need.

The price of specialty medicines, which usually target narrow markets, are generally very high. This has become a main driving factor for escalating costs in many national health systems, including that of Germany. One example is ivacaftor, a medicine used to treat cystic fibrosis, which costs € 25,504 per month. Patients on this medicine would need lifelong treatment. Another example is crizotinib, to treat lung cancer, which costs € 7277 per month.

PSEUDO-INNOVATIONS AS PART OF MARKET-DRIVEN R&D

Apart from "me-too" products, there are other forms of pseudo-innovation which can be considered to be part of a market-driven R&D, such as the creation of a market for a non-existing disease, also referred to as "disease-mongering". For example, the German pharmaceutical company Jenapharm contracted with a consulting organisation (Cramer Consulting GmbH) to create a new illness: the male menopause. The consulting firm showed on their website how the public's and patients' opinion had been changed over a three year period by advertising the "disease" to urologists, general practitioners and patients. A condition that previously was interpreted as a sign of a phase of life has been repositioned as either a sign of potential illness or something that should be treated medically. By this means, Jenapharm was able to realise increased revenues for an existing product.[6]

Promoting over-diagnosis of a real disease is the second method used to increase the use of an existing medicine. Asperger syndrome has in the past been described as part of the autism spectrum disorder, a rare and serious condition: However, there are large variances in reported prevalence rates, ranging from 0.03 to 4.84 per 1,000 population, due to differences in diagnostic criteria.[7] In Germany the most obvious secondary disease benefit for the parents of a child being diagnosed with Asperger syndrome is an additional educationist in school class, a so called "integration teacher". Additionally, atypical antipsychotic medications such as risperidone and olanzapine have been advertised to German doctors to reduce the associated symptoms of Asperger syndrome.[8] Risperidone is indicated only for the treatment of schizophrenia and for acute bipolar disorder. Increasing awareness of Asperger syndrome may result in over-diagnosis and over-prescribing, increasing the revenue from sales of inappropriate medicines.

An example of new agents with marginal benefits is provided by the new oral anticoagulants (NOACs). It may well be that older, affordable and well-chacterised medicines are replaced by newer, more expensive and potentially more dangerous medicines. Although warfarin continues to be the most widely used oral anticoagulants, sales of the NOACs (dabigatran etexilate, rivaroxaban and apixaban) are increasing. A great fanfare of advertisement has accompanied the introduction of the NOACs. However, as Ansell shows, although the NOACs offer some pharmacokinetic characteristics of interest, there are numerous risks which argue against the use of these agents as first-line therapy. The most serious problem is that, until recently, there has not

been the means to reverse the NOAcs and thus manage a major bleeding incident.[9] There is a controversary about the effectiveness of idarucizumab, in addition access to the dabigatran reversal agent, idarucizumab, is lagging behind that of the NOAC, potentially putting patients at risk. No similar agents are yet available for the other NOACs.

For any new medicines, their therapeutic value needs to be assessed by an independent commission before they are reimbursed by the health system or included on any essential medicines list. This assessment needs to inform measures to set and approve the price of the medicine.

PRICE OF MEDICINES NEITHER RELATED TO R&D NOR TO PRODUCTION COSTS

It is clear, therefore, that medicine prices can be seen as the heart of the pharmaceutical industry's revenue-maximising business model. Prices differ according to the willingness and ability to pay, and are independent of R&D and production costs. Pricing of medicines reflects neither the value of a medicine nor the R&D costs, but simply what the largely unregulated market can bear.

Countries need to ensure that every means to exert downward pressure on medicine prices are used; this should include the provision for independent assessments of the value of any new medicine, provisions to allow for parallel importation (where appropriate), and for invoking the necessary means (such as compulsory licensing) to address monopolies that prevent access to affordable medicines. In addition, countries need to pay attention to cost increases that occur through the distribution chain, and to the role of co-payments in limiting access to essential medicines. The means to improve transparency regarding R&D costs and production costs need to be investigated and implemented.

Christiane Fischer, Andy Gray, Gopal Dabade

1 *United Nations (1966) International Covenant on Economic, Social and Cultural Rights. §§ 12 und 15. United Nations (2000) The right to the highest attainable standard of health: E/C.12/2000/4 (General Comments).*

2 *World Health Organisation (2004) The World Medicines Situation. Chapter 7. http://apps.who.int/medicinedocs/en/d/Js6160e/ [22.8.2016]*

3 *World Health Organisation Medicine Pricing and Financing. http://www.who.int/medicines/areas/access/en/ [22.8.2016]*

4 *Esmeralda KE (2015) Patients Pay Price for Albania's Drug Reform. Balkan Insight. http://www.balkaninsight.com/en/article/patients-pay-price-for-albania-s-drug-reform-09-23-2015 [22.8.2016]*

5 *Fischer C, Jenkes C, Kibara D (2014) Poor and Forgotten. Pharma Brief Spezial 1. http://www.en.bukopharma.de/uploads/file/Pharma-Brief/E2014_01_special_Uganda.pdf [22.8.2016]*

6 *Cramer Consulting GmbH (1995) www.cgc-pr.com/agentur/chronik/ [22.8.2016]*

7 *Autistic spectrum disorder Factsheets: Incidence of Asperger Syndrome. http://autism-help.org/asperger-syndrome-incidence.htm [22.8.2016]*

8 *McPartland J, Klin A (2006) "Asperger's syndrome". Adolesc Med Clin; 17/3, pp 771–788.*

9 *Ansell J (2012) Controversies in Cardiovascular Medicine- New Oral Anticoagulants Should Not Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation. American Heart Association; 125, pp 165-170. http://circ.ahajournals.org/content/125/1/165.long [22.8.2016]*

10 *Ansell J (2012) Controversies in Cardiovascular Medicine- New Oral Anticoagulants Should Not Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation. American Heart Association; 125, pp 165-170. http://circ.ahajournals.org/content/125/1/165.long [22.8.2016]*

Monopolies increase prices and limit access

Even after patents expire and generic entry is theoretically possible, sole producers of older medicines are in a position to charge any price for such a medicine. Such monopolies have a dramatic impact on access to medicines.

MONOPOLY POWER OVER OLDER, OFF-PATENT MEDICINES

Doxycycline, an antibiotic is sold in Germany for € 20.75 for 100 tablets. In Germany there are still four generic producers of doxycycline. In the US, where there is a sole producer, the price increased from US$ 20 for 100 tablets in October 2013 to US$ 1,849 in April 2014.

Cycloserine is a drug used to treat multidrug-resistant tuberculosis (MDR TB). The only producer of cycloserine increased the price from US$ 500 for 30 capsules to US$ 10,800. Much media attention has been paid to the case of ***pyrimethamine*** (Daraprim®), a 62-year-old medicine originally developed as an antimalarial, but now used mainly to treat toxoplasmosis in patients with HIV. In Germany, GSK sells 30 tablets for € 27.68. In the US the product was acquired in August 2015 by Turing Pharmaceuticals, who immediately raised the price from US$ 13.50 to US$ 750 per tablet. This means annual treatment costs per patient now reach hundreds of thousands of dollars.[1] ***Carmustine*** is a 40 year old cancer

treatment. After the producer had sold the licence, the new sole global producer tripled the price in January 2015.

As noted, there are no patent barriers to generic entry for these products. However, for each of them, the potential market size is limited. In addition, by tightly controlling distribution, sole producers can make it difficult for potential competitors to access the stock needed to perform bioequivalence tests. Old medicines can be transformed into high-priced speciality medicines by the power of these new monopolies. This type of market behaviour is also seen as a productive business strategy for firms which seek out old neglected medicines. Competition is key to the gains that can be obtained from generic medicines. Where a single producer has a monopoly on supply of an old medicine, country governments should provide incentives for generic entry, or should consider funding production by state laboratories or third parties. Where possible, parallel importation has the potential to reintroduce competition.

PATENTS - TIME BOUND MONOPOLIES

The World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) sets a minimum standard for protecting meaningful innovation. All WTO member states have to implement the minimum TRIPS standards into their national laws. Patents need to be granted on products which are new, industrially applicable and innovative. However the definition what has to be considered as innovative can be carefully defined in national law. To mitigate the impact of pharmaceutical patents on access to essential medicines TRIPS includes important flexibilities such as compulsory licences, parallel importation and exclusion of patentability. Section 3(d) of the Indian Patent Act explicitly excludes marginal innovations from patentability: "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process".[2] In other words, marginal innovations are not innovative enough to qualify for a patent.

Niche medicines which target especially narrow markets are generally extremely expensive. For example, the cystic fibrosis drug ivacaftore (Kalydeco®) is sold in Germany for € 25,504 per month per patient. Such pricing behaviour has raised important ethical questions. If, for instance, a potentially life-saving treatment for hepatitis C or cancer is unaffordable, are the consequences of this lack of access ethically acceptable in the light of the human right to the highest attainable standard of health?

Where a viable market exists, and competition can be engendered, the benefits of price cuts can enable a morally-acceptable and ethical outcome. This has been the experience in relation to HIV. Since 2003 the price for combination antiretroviral therapy has been reduced from over US$ 10,000 per patient per year to around US$ 100, predominantly because of generic production in India.[3] As patents for the TKI-based cancer treatments will expire within the next five years, a dramatic price decrease is expected through generic production. However, that price drop will only be achieved in the case of a viable generic market being created. The alternative scenario would see a post-patent sole supplier still enjoying the power of a monopoly.

Ever-greening of patents, such as in case of a new indication, also pose challenges to generic competition. Until 2012 alemtuzumab (sold as MacCampath®) was used to treat patients with chronic B cell lymphatic leukaemia. No alternative existed. In spite of this Genzyme took alemtuzumab off the global market in 2012.[4] In 2013 Genzyme re-released the medicine in many countries with a new patent for the new indication of multiple sclerosis. The new product, sold as Lemtrada®, is 44 times more expensive per milligramme. In Germany alone there are 120,000 patients with multiple sclerosis[5], but only 7300 with chronic B cell lymphatic leukaemia.[6] The multiple sclerosis market therefore is far more profitable. As the German patent law allows for ever-greening patents in case of a new indication, an un-

necessary monopoly situation with extremely high prices is created.

The current system of incentivising innovation by means of patent protection results in a time-bound monopoly situation, which can lead to unacceptably high prices. It also does not stimulate necessary innovation, but rewards those who can take advantage of lucrative markets.

ACCESS TO SOFOSBUVIR – AN ETHICAL QUESTION

Chronic hepatitis C affects about 130-180 million people globally. Half a million people die from it each year. Additionally, chronic hepatitis C infection can develop into liver cirrhosis or liver cancer. The disease is prevalent in high- and lower-income countries. In India alone around 12-18 million and in the European region 15 million patients are estimated to be infected.[7,8]

Although extremely effective, as part of a combination regimen, sofosbuvir did not qualify for a patent in India early in 2015 as being only a marginal innovation.[9]

However in May 2016 the Indian patent office reversed course and granted a patent on sofosbuvir, to Gilead Sciences[10], stating now that the drug is „novel and inventive".[11] The decision reflects the growing pressure on the Indian government to bolster protection of intellectual property.

While the price for a three month treatment in US is nominally US$ 84,000 and € 43,500 in Germany, the generic sofosbuvir and ledipasvir fixed-dose combination price for a 12 weeks treatment in India is US$ 500.[12] More patent challenges were filed in Europe (by Doctors of the World), in Argentina, Brazil, China, Russia and Ukraine. Patents have not been granted yet in Argentina, Brazil and Ukraine. The price of Gilead`s branded sofosbuvir (Sovaldi®) in India is almost the same as that of the generics.[13]

Branded sofosbuvir has been available in Germany since January 2014. In an early benefit assessment done under AMNOG by the German Institute for Quality and Efficiency in Health Care (IQWiG), an added benefit in comparison with the appropriate comparator therapy war clearly found for non-pretreated patients infected with genotype 2 virus.[14] These new hepatitis C medicines have the potential, in appropriate combinations, to cure hepatitis C in a substantially higher proportion of patients than was previously possible. In 2015 the World Health Organization added several new direct acting antiviral medicines for hepatitis C (sofosbuvir, daclatasvir, ledipasvir plus sofosbuvir, ombitasvir plus paritaprevir plus ritonavir with or without dasabuvir, simeprevir) to the Model List of Essential Medicines.[15]

Christiane Fischer, Andy Gray, Gopal Dabade

1 *Pollak A (2015) Drug Goes From $13.50 a Tablet to $750, Overnight. New York Times 20.9.2015. www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html [22.8.2016]*

2 *Indian Patents Amendment Act (2005) Section 3d. http://ipindia.nic.in/ipr/patent/patent_2005.pdf [22.8.2016]*

3 *MSF (2014) Untangling the web of antiretroviral price reductions. 17th ed. www.msfaccess.org/sites/default/files/MSF_UTW_17th_Edition_4_b.pdf [22.8.2016]*

4 *Genzyme (2012) Marktrücknahme von MabCampath®. Informationsschreiben von Genzyme, einem Unternehmen der Sanofi Gruppe.*

5 *Hein T, Hopfenmüller W (2000) Hochrechnung der Zahl an Multiple Sklerose erkrankten Patienten in Deutschland. Der Nervenarzt; 4, S. 288–294.*

6 *Nennecke A, Wienecck A, K. Kraywinkel (2014) Inzidenz und Überleben bei Leukämien in Deutschland nach aktuellen standardisierten Kategorien. RKI; 57, S. 93–102. http://edoc.rki.de/oa/articles/remvy9Qwtu5so/PDF/26tbuKMx9Pbs6.pdf [22.8.2016]*

7 *Robert Koch Institut (2016) GBE Themenheft Hepatitis C. http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsT/hepatitis_c.pdf?__blob=publicationFile [22.8.2016]*

8 *WHO (2016) Fact Sheet. http://www.who.int/mediacentre/factsheets/fs164/en/ [22.8.2016]*

9 *Silverman E (2015) Gilead gets a big win as India uphold a Sovalsi patent, after all. www.statnews.com/pharmalot/2016/05/10/gilead-hepatitis-patents-drug-pricing/ [22.8.2016]*

10 *Indian Patents Act (2016) Section 25(1) read with Rule 55. Patent Application No. 6087/DELNP/2005. http://freepdfhosting.com/a03fe3f626.pdf [22.8.2016]*

11 *Pricing and availability of generic Indian Ledipasvir and Sofosbuvir co-formulation as on 26 April 2016. http://hepcasia.com/2016/05/03/pricing-and-availability-of-generic-indian-ledipasvir-and-sofosbuvir-co-formulation-as-on-26-april-2016/ [22.8.2016]*

12 *WHO (2016) Fact Sheet. http://www.who.int/mediacentre/factsheets/fs164/en/ [22.8.2016]*

13 *Silverman E (2015) High Price for Gilead Sciences Hep C Drug Prompts Patent Challenges. 2015. Wall Street Journal. http://blogs.wsj.com/pharmalot/2015/05/20/high-price-for-gilead-sciences-hep-c-drug-prompts-patent-challenges/ [22.8.2016]*

14 *IQWiG (2014) Sofosbuvir: indication of added benefit for specific patients. www.iqwig.de/en/press/press-releases/press-releases/sofosbuvir-indication-of-added-benefit-for-specific-patients.6099.html [22.8.2016]*

15 *WHO (2015) WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers. Press release. www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/ [22.8.2016]*

The German situation

In Germany, prescription medicines are reimbursed by the public health insurance schemes. Medicine prices of for prescription drugs are not paid by individual patients through out-of-pocket payment, but by the insurance scheme, and in case of universal health insurance coverage, in the end by all tax payers. According to the Arzneiverordnungsreport, which evaluates prescribing behaviour each year, the amount spent on medicines increased by 9.9% from € 33.3 billion in 2013 to € 35.43 billion in 2014. The increase in expenditure was mainly due to patented medicines, where the price increase was 15.1% and the public health insurance paid 25% more than in 2013. Eight new drugs had a price/packet cost of more than € 10,000.[1]

After being launched on the market for one year pharmaceutical companies in Germany are forced to subject their new products to evaluation of their additional therapeutic benefit. The results of such an evaluation are the precondition for new medicines being reimbursed by the public health insurance schemes and for the prices paid for these medicines in Germany. This is regulated in the Act on the Reform of the Market for Medical Products (Arzneimittelmarkt-Neuordnungsgesetz – AMNOG) of 22 December 2010. If it is not possible to demonstrate any additional benefit in comparison to the standard therapy, the new medicine is allocated to a reference price group for reimbursement by the public health insurance. If there is no such reference price group, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) negotiates with the pharmaceutical company on a refund rate. If an additional benefit is proven to exist, GKV-Spitzenverband negotiates a supplement with the pharmaceutical company on top of the price of the former standard therapy.[2]

The high price policy of the industry is not mitigated by AMNOG within the first year of marketing, when neither the cost effectiveness nor the comparative efficacy of new medicines is evaluated. In other words during the first year companies can charge any price they wish for a new medicine. This has dramatic consequences for the health system. Dimethyl fumarate (Tecfidera®) is a new medicine used to treat multiple sclerosis (MS). In 2014 expenditure for MS patients on this medicine alone increased by 163%. After the AMNOG evaluation for cost effectiveness and efficacy ended with the result "nothing new", the company (Biogen) had to decrease the price by 42%. The excess expenditure on this product in the first year amounted to million € 100 million in 2014. Instead of "only" € 140 million, a total of € 240 million was spent.[3]

New medicines need to be evaluated for their therapeutic value and cost effectiveness at the time of marketing authorisation, based on the data used for registration. Maximum prices must be decided upon, based on this assessed value, and then only adjusted if additional evidence is generated.

Christiane Fischer

Christiane Fischer

1 *GKV-Spitzenverband (2015) AMNOG - evaluation of new pharmaceutical. https://www.gkv-spitzenverband.de/english/statutory_health_insurance/amnog___evaluation_of_new_pharmaceutical/amnog___evaluation_of_new_pharmaceutical_1.jsp [22.8. 2016]*

2 *IQWiG (2014) Dimethylfumarat bei MS: Zusatznutzen ist nicht belegt. https://www.iqwig.de/de/presse/pressemitteilungen/pressemitteilungen/dimethylfumarat-bei-ms-zusatznutzen-ist-nicht-belegt.6230.html [22.8. 2016]*

3 *Schwabe U, Pfaffrath D (2015) Arzneiverordnungsreport. Berlin: Springer.*

The Indian situation

The Indian generic drug industry has scaled great heights and achieved success. According to government of India the Indian drug industry has registered spectacular growth over the last two decades and currently occupies the 3rd position in the world in terms of volume and 10th in value. So much so that India is often referred to as the 'Pharmacy of the Developing World'. The pharmaceutical exports are valued at over US$ 14 billion. The Indian Pharmaceutical industry has been a dominant player in manufacturing generic drugs.[1] This success has no doubt attracted the wrath of the multinational big companies including the major threat coming from USA and EU, especially upon the Indian intellectual property policies; as much of the success of the Indian generic drug industry is due to the Indian Patent act of 1970. As US president Barack Obama and Indian prime minister Narendra Modi met in New York on 28th September 2015, Doctors Without Borders (MSF) warned that US pressure on India to change its intellectual property policies could result in millions of people around the world losing their lifeline of affordable medicines. The international medical humanitarian organization MSF, which relies on affordable generic medicines produced in India to run its medical programs in more than 60 countries, urged Modi to stand strong and protect India's role as the "pharmacy of the developing world".[2]

This is not the first time that the Indian industry has been targeted by the USA & EU multinational drug companies. Given the above facts one would wonder about the situation of healthcare and access to medicines in the Indian context.

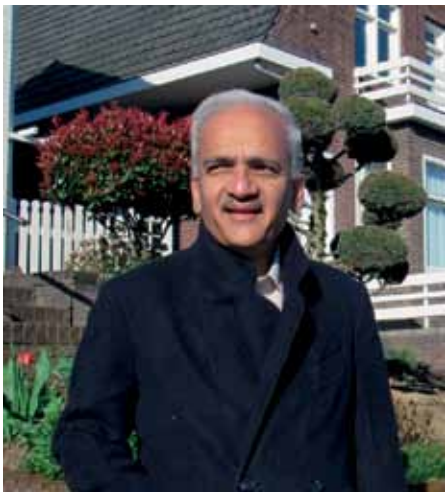
OUT-OF-POCKET EXPENSES

As per World Bank statistics, in India, the out of pocket (OOP) health expenditure as a percentage of private expenditure on health has remained in the range of 80%–90% for more than 10 years and as of 2013 it stands at 85.9%.[3] According to WHO this is perhaps the highest in this region. A comparative OOP of neighboring and other countries makes this clear.[4]

Out-Of-Pocket expenses 2013		
	Country	*OOP*
1	*India*	*85.9%*
2	*Nepal*	*81.4%*
3	*Thailand*	*80.4%*
4	*Malaysia*	*79.9%*
5	*China*	*76.7%*
6	*Indonesia*	*75.1%*
7	*Saudi Arabia*	*55.3%*
8	*South Africa*	*23.2%*

Does cost of a drug matter much in the Indian context? Yes, it does just take at this example. The drug 'Sorafenib' sold under its trade name 'Nexavar' manufactured by the German based multinational drug company Bayer costs Indian Rupees 208,000 (€ 3739 per month for a person, whereas exactly the same drug when manufactured by the Hyderabad based Indian generic drug company Natco Pharma Limited, sold under its trade name 'Sorafenib' costs Indian Rupees 8,800 (€ 880) per month for a person. A huge price difference of 97 %! It should be noted here that the Indian generic company is also making a good profit.

The news that medicines can be made available at such affordable price has spread far and wide. Much credit for this effort should go



Gopal Dabade

to the Indian generic industry. People were delighted that medicines can now be made easily available and thus more lives could be saved. But the joy was short lived because Bayer was perceptibly upset. Its chief executive officer (CEO), Marijn Dekkers, issued a statement that stunned the world. He said, "We did not develop this medicine (Nexavar) for Indians," adding, "We developed it for western patients who can afford it".[5] Dekkers further called the Indian regulator's action as "essentially theft".[6]

This statement of Bayer chief was shot down by Doctors Without Borders by saying that it summed up everything that was wrong with the multinational pharmaceutical industry.

Not only Bayer but all the multinational drug companies of Europe and America stood up and brought pressure on the American government to trouble Indian government with regard to India's Intellectual Property Laws. Just look at this: The US International Trade Commission (USITC) has launched an investigation to examine a wide range of Indian policies that discriminate against US trade and invest-

ment. This investigation on 'Trade, investment and industrial policies in India: Effects on the US Economy,' was requested jointly by the Senate committee on finance.

Why was all this happening? To get an answer to this question we need to know about Bayer and the drug Nexavar®. Bayer has its presence in almost every country all over the world. Its financial powers are just beyond anyone's imagination. In fiscal year 2012, Bayer employed 110,000 people and had sales of € 39.7 billion. The medicine Sorafenib has been found to be useful in treating cancer of kidney and liver. The drug was discovered by Bayer and has been patented in most countries all over the world including India in the year 2008. So Bayer held the absolute power to dictate the price of the drug till 2020.[7] But on March 9, 2013 the government of India's patent office at Chennai (IPAB – Intellectual Property Appellate Board) issued Compulsory Licensing (CL) thus breaking the monopoly of Bayer.[8]

This meant that drug could be manufactured by another company even though Bayer had patents. It is this grant of Compulsory Licensing that has annoyed Bayer. Is it wrong for India to do this? An emphatic "No" says an article in the prestigious medical magazine Lancet of February 2014 titled, "The political origins of health inequity: prospects for change". It says, "The Sorafenib® case is not only a story of one drug and one country's patent law, but also a flashpoint in a long-running global political contest over how certain types of health-related knowledge are produced, and who benefits. Even countries that traditionally embrace strong intellectual property rights at times use the threat of a compulsory license, as the USA did in 2001 for drugs against anthrax."[9]

Both the USA and EU should stop undermining the very Indian generic drug industry that, by providing quality medicines at an affordable cost, makes the global health initiatives a successful one.[10] They should stop defending the profit interests of the multinational drug companies. And above all they should respect the democratic processes of India and other countries. Nothing short of a global cry against the injustice will halt this ruthless process.

Gopal Dabade

1 *Indian Goverment, NPPA - National Pharmaceutical Pricing Authority.*

2 *MSF (2015) At Obama-Modi Meeting in New York, MSF Urges India to Protect Affordable Medicines for Millions. www.doctorswithoutborders.org/article/obama-modi-meeting-new-york-msf-urges-india-protect-affordable-medicines-millions [22.8.2016]*

3 *MSF (2010) The Truth Behind the Spin: How the Europe-India Free Trade Agreement Will Harm Access to Medicines. www.doctorswithoutborders.org/news-stories/briefing-document/truth-behind-spin-how-europe-india-free-trade-agreement-will-harm [22.8.2016]*

4 *Frederick M (2013) The Judgment In Novartis v. India: What The Supreme Court Of India Said. IP Watch. http://www.ip-watch.org/2013/04/04/the-judgment-in-novartis-v-india-what-the-supreme-court-of-india-said/ [22.8.2016]*

5 *The World Bank (2015) Out-of-pocket health expenditure (% of private expenditure on health). http://data.worldbank.org/indicator/SH.XPD.OOPC.ZS/countries/1W-IN?display=default [22.8.2016]*

6 *World Health Organization (2013) Health Financing Out of Pocket Expenditure on health as a percentage of private expenditure on health. http://gamapserver.who.int/gho/interactive_charts/health_financing/atlas.html?indicator=i2 [22.8.2016]*

7 *The World Bank (2015) Out-of-pocket health expenditure (% of private expenditure on health). http://data.worldbank.org/indicator/SH.XPD.OOPC.ZS/countries/1W-IN?display=default [22.8.2016]*

8 *KEI (2014) Bayer CEO Marijn Dekkers explains: Nexavar cancer drug is for "western patients who can afford it". http://keionline.org/node/1910 [22.8.2016]*

9 *Peck A (2014) Pharmaceutical CEO: Cancer Drug Is Only For Westerners Who Can Afford It. http://thinkprogress.org/health/2014/01/26/3205861/pharmaceutical-ceo-cancer-drug-westerners-afford/ [22.8.2016]*

10 *La Mattina J (2013) Does Pharma Only Develop Drugs For Those Who Can Pay. www.forbes.com/sites/johnlamattina/2013/12/05/does-pharma-only-develop-drugs-for-those-who-can-pay/ [22.8.2016]*

11 *IP India (2011) Compulsory License Application. www.ipindia.nic.in/ipoNew/compulsory_License_12032012.pdf [22.8.2016]*

12 *Ottersen OP, Dasgupta J, Blouin C, Buss P, Chongsuvivatwong V et al. (2014) The political origins of health inequity: Prospects for change. The Lancet; 383 (9917): p 630-667. http://www.thelancet.com/action/showFullTextImages?pii=S0140-6736%2813%2962407-1 [22.8.2016]*

13 *United States International Trade Commission (2014) Trade, investment and industrial policies in India: Effects on the US Economy, Publication Number: 4501, Investigation Number: 332-543. https://www.usitc.gov/publications/332/pub4501_2.pdf [22.8.2016]*

The South African situation

In South Africa, the majority of the population are dependent on the public sector for health services. These are provided free of charge at primary care facilities, including the provision of medicines that are included on the Essential Medicines List/Standard Treatment Guidelines. Means-tested user fees are applied at higher level of the health system, such as at hospitals. Medicines procured for the public sector are mostly older, off-patent and thus generic. A local competitive bidding (tender) process is used to ensure access to affordable prices. However, even within the public sector, tertiary and quaternary services are having to deal with the challenge of new, high-priced and on-patent medicines, particularly for cancer and rare conditions. Even though the number of patients requiring such treatment, such as enzyme replacement for inherited disorders like Pompe disease, may be small, the budget impact may be large. South Africa operates the world's largest antiretroviral treatment programme, with more than 3 million patients on treatment. This number is expected to increase further as the country applies a test-and-treat policy, in accordance with WHO guidance. The country has used its buying power to achieve some of the lowest prices for antiretroviral medicines, based on access to voluntarily licensed generics.

In South Africa's private sector, factory gate prices are regulated as "single exit prices", which are subject to maximal annual percentage increases.[1] In addition, the distribution chain costs are controlled, with a maximal professional fee set for all dispensers. However, there is no way as yet to impact on the launch prices of new medicines. The submission of pharmacoeconomic data is voluntary at this stage. In time, it is hoped that the planned National Health Insurance will incorporate value judgements into its reimbursement decisions. The means to implement such a system pose significant challenges for a resource-constrained country. In addition, the country faces considerable challenges with regard to patent law.

The existing Patent Act includes measures that go beyond the minima set by TRIPS, and needs urgent reform. A system of effective patent examination, with enhanced standards for patentability, is also in planning but not yet implemented.

Andy Gray

Andy Gray

1 *Gray A, Suleman F (2015) Pharmaceutical pricing in South Africa. In: Babar Z (ed) Pharmaceutical Prices in the 21st Century. Springer International Publishing, Cham.*

2 *Dark Government (2014) Bayer Pharmaceutical: "New Cancer Drug Not for Indians" http://www.darkgovernment.com/news/bayer-pharmaceutical-new-cancer-drug-not-for-indians/ [22.8.2016]*

Conclusion

Independent trials are a necessary pre-condition to distinguish between effective (essential, rational) and insufficiently or ineffective (pseudo-innovative) products. As shown in this commentary, unaffordable high prices affect access to potentially life-saving essential medicines. Monopolies are a problem, both for newer on-patent medicines and for older single-source medicines. These problems face both resource-constrained and industrialised countries. They affect both those who pay out-of-pocket and national/social health insurance systems. Any medicine, which is covered or subsidized by the national health system, needs an appraisal of cost–effectiveness and budget impact.[1,2] This appraisal will allow for the determination, in a transparent way, of the initial appropriate price in a particular setting.

A number of key medicines have become exemplars to both types of problems. Sofosbuvir and pyrimethamine are but two of such exemplars.

The ethical question is therefore whether it is possible to justify denying access to highly effective medicines purely on the basis of their price. A human rights informed approach would argue otherwise: Prices on medicines limit access both in poor and in rich countries. Monopolies caused by patents (such as in the case of sofosbuvir) or by a single producer (such as in case of pyrimethamine) lead to unacceptably high prices. Access to more affordable essential medicines is a global problem, requiring global answers. However, action on a variety of levels is possible.

Christiane Fischer, Andy Gray, Gopal Dabade

Dr. Christiane Fischer is the medical manager of the German Initiative of Incorruptible Doctors MEZIS.

Conflict of interests (COI): She is member of the German Ethical Council and the Palliative Foundation. She has received remuneration for MEZIS lectures.

Andy Gray is Senior Lecturer at the Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa

COI: Member of the South African Medicines Control Council, South African National Essential Medicines List Committee

Gopal Dabade is President of the Drug Action Forum – Karnataka and co founder of No Free Lunch India

COI: None

1 *Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ (2009) Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. JAMA; 302(13): 1437–1443. http://dx.doi.org/10.1001/jama.2009.1409 [22.8.2016]*

2 *Hill RS, Bero L, Geoff McColl G, Roughead E (2015) Expensive medicines: ensuring objective appraisal and equitable access. Bull World Health Organ; 93: 4. http://www.who.int/bulletin/volumes/93/1/14-148924/en/ [22.8.2016]*

IMPRINT

MEZIS Mein Essen zahl' ich selbst!
Initiative of incorruptible doctors

www.mezis.de, info@mezis.de

ISSN: 2194-1440

Correspondence to:
Praxis Dr. Eckhard Schreiber-Weber, Parkstr. 48, 32105 Bad Salzuflen, Tel.: 05222 61901

Editors: M. Dannenberg, S. Habermann-Tal, H. Neumann, T. Mayer, J. Salzmann, N. Schurig

Chief Editor: C. Fischer

Translation: A. Mayr-Isenberg

Layout: K.-U. Dosch

Publication frequency: three times a year

Free for members

CONFLICTS OF INTEREST

All authors fill the revised questionnaire for the MN AG „conflicts of interest in medicine" (Dtsch Arztebl 2011; 108 (6)) form.

FUNDED BY AKTION SELBSTBESTEUERUNG E.V.