Fair pricing for new drugs: Does unbundling help?

Dr. Josef Probst
is Director General of the Main Association of Austrian Social Security Institutions.

Priv.-Doz. Dr. Claudia Wild
is Director of the Ludwig Boltzmann Institute for Health Technology Assessment (HTA).

Until just a few years ago, the term "access to medicines" was linked to the discussion about cheaper, partly generic, and vitally important medicines for developing countries. Today, medicines not available to everyone due to their high cost have the potential to drive a wedge between members of society. The term "social toxicity," derived from developmental psychology, succinctly sums up this issue. For some time, Western countries and institutions (OECD[1], the European Parliament[2, 3], and US institutions[4]) have been addressing "access to medicines" in numerous events and reports. The common goal of these initiatives is to counteract the unsustainable prices of medicines, which at the same time often have questionable additional benefits for patients, with new, future-oriented solutions. In 2017, a group of experts from the European Commission dealt with internationally discussed solutions and their potential impact. The Expert Commission's proposals primarily include regulatory approaches that should lead to better, innovative, medicines and socially acceptable prices in the medium term.[5] Particular attention in the report is given to the role of research and development (R&D): R&D expenditure, including investment risk, is mostly used as a justification to disguise the actual motivation of profit maximisation. The Gilead case shows the business matter in an unconcealed way.[6] In fact, pharmaceutical companies spend twice as much on marketing and sales as on R&D. Nonetheless, it is emphasized by the pharmaceutical companies that it is the research expenditure that particularly causes the high prices.

Public research effort and "public return on investment"

Resource-intensive and high-risk basic research predominantly takes place in the public sector, at universities and the corresponding publicly funded research institutions. Exact figures for public financing have not been available up to now. One recent study looked at the share of funding from the American National Institute of Health (NIH). The study examined the financing of all 210 drugs approved by the FDA between 2010 and 2016.[7] The authors found that more than $ 100 billion of NIH research funding was spent on basic research of the later approved 210 new molecular entities (NMEs). That was about 20% of total NIH research spending. Basic research for 84 of the 210 first-in-class drugs alone received $ 64 billion in NIH research funding. That means each of these drugs received the funding of $ 760 million on average. Similar studies linking European biomedical research expenditure to later drug approvals are not available for Europe. Nevertheless, the call in Europe, as in the US and Canada, for public return on investment is

getting increasingly louder.[8, 9] The demand is that publicly funded research must result in free use and broad access to affordable medicines.[10]

Recently, a lawsuit against the patent holders of Nusinersen, brand name Spinraza©, was considered in the US. The drug was further developed by Ionis Pharmaceuticals and marketed by Biogen with annual treatment costs of $ 750,000 for the first year of therapy and $ 375,000 for subsequent years. Basic research for this was largely funded by NIH research funds. Since this was not appropriately declared in the patenting, it may lead to a revocation of the patent protection under US law. However, this legal procedure is obviously not being pursued.[11, 12] Based on publicly available FDA-compliant documents, Knowledge Ecology International (KEI) calculated the development costs of Nusinersen's pivotal trials (ten Phase 1-3 trials involving a total of 437 patients) at $ 17.8 million. With a tax exemption of 50% due to orphan drug status, costs decreased to $ 8.9 million and, after capitalizing the risk of failure, amounted to $ 35 million.

Actual R&D costs remain completely non-transparent: the Tufts Center, which is closely affiliated with the pharmaceutical industry, calculated R&D costs of $ 2,558 million per drug.[13] The Open Innovation Initiative of Product Development Partnerships (PDP) for Neglected Diseases reports development costs of $ 50 million for repurposing and combination therapies and up to $ 170 million for the entire R&D[14] to bring a drug to market. These calculations do not include capital costs.

Delinkage and unbundling in the pharmaceutical industry

The existing business models in the given multinational, European, and national legal frameworks have led to suboptimal results in some areas. Particularly in recent years, the possible framework has been excessively exploited and profit maximisation has been the key driving force behind the pharmaceutical companies. Publicly funded health systems have been pushed to the limits of financing. Moreover, the instrument of extensive patent protection has partially failed to stimulate necessary innovation.

Meanwhile, the demand for delinkage and unbundling of individual production stages is being discussed for the pharmaceutical industry. In the telecommunications and rail sectors, the separation of the high-investment routing and rail lines from use was effectively implemented across Europe with the keyword unbundling. This turned out to be a real paradigm shift that has resulted in a completely new regulation of industries. The guiding ideas of these new business models should be critically examined for their applicability in the drug industry. The phases of the drug development process are shown in Figure 1; the post-marketing phase would still have to be added.

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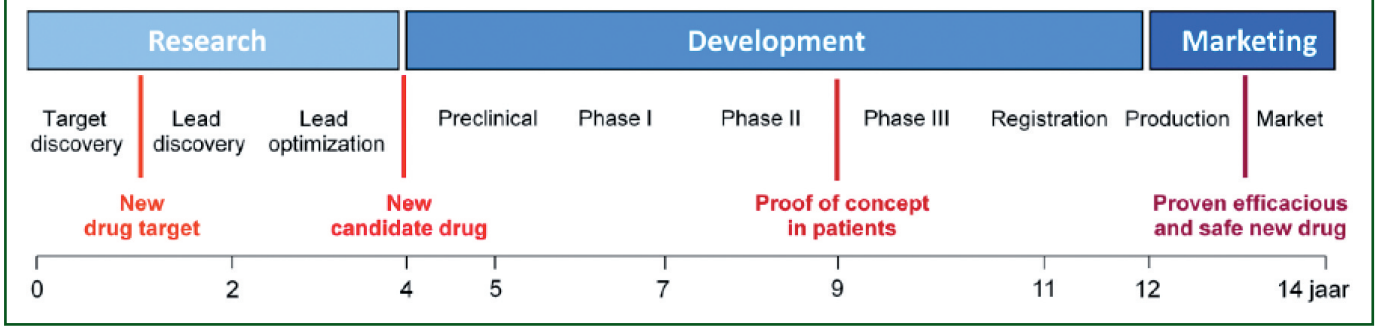
The UN High Level Panel on Access to Medicines has also called for the unbundling of R&D costs from the final price of health technologies in general[16]. A recently published expert report by the European Commission has gone one step further, discussing a complete decoupling of the working steps in the value chain.[5] A decoupling of the individual work stages has since long been executed in the pharmaceutical industry.[17]

Research partnerships with public research organisations and small biotech start-ups are common in the industry. The commissioning of Contract Research Organisations (CROs) to outsource development and clinical trials is increasingly being implemented in low-cost countries. Major pharmaceutical companies are sending out drug hunters and patent scouts to buy promising developments. These are paid according to defined milestones (asset transfer agreements). The approval and market introduction are then carried out by the global pharmaceutical companies. An example from Austria shows the pattern: basic research is conducted in the public sector with high public funding, followed by further development at biotech companies paid by large

Figure 1: Phases of the development of a drug[15]



Basic research is predominantly financed by the public sector.

pharmaceutical companies for reaching milestones (see box on denosumab).

In any case, civil society's call for transparency of the costs incurred in the various phases of drug development is justified, because the funds used for R&D and later for the purchase of medicines have been raised by the public and the community of solidarity.

The RANKL inhibitor denosumab (Prolia©, Xgeva©) inhibits bone resorption and is approved for the treatment of osteoporosis (Prolia©) and skeletal-related complications in adults with bone metastases due to solid tumours (Xgeva©). In 2018, the EMA (European Medicines Agency) is to expand the indication to patients experiencing degeneration in bone mass as a result of a cortisone treatment. Basic diseases for cortisone treatment include COPD, asthma, multiple sclerosis or rheumatic diseases.

Over the past 15 years, Josef Penninger built up the IMBA (Institute of Molecular Biotechnology) at the ÖAW (Austrian Academy of Sciences) to gain new insights into osteoporosis and oncological diseases. Denosumab was researched in the 1990s by Josef Penninger's research group in Toronto and subsequently in the 2000s at the IMBA of the ÖAW in Vienna. The research results were taken over by Amgen and the active substance was approved by the EMA as Prolia© in 2010, and as Xgeva© in 2011. The turnover development was enormous.[18] In 2017, the annual cost of treatment for denosumab in Austria amounted to between 430 EUR and 4,335 EUR. In 2017, denosumab's 100,000 prescriptions generated social security costs of € 28 million.

The Viennese start-up biotech company Apeiron, established in 2003 as an agency to exploit basic research results, was also founded by Josef Penninger. Among other sponsors, the company is supported by grants from the Austrian Research Promotion Agency, the Austrian Federal Economic Chamber, the Vienna Business Agency, the Austrian Wirtschaftsservice, the European Investment Bank and direct subsidies from the City of Vienna. Apeiron further developed the monoclonal antibody dinutuximab to market maturity and this drug was approved in 2017. Dinutuximab is used in the treatment of neuroblastoma. Other products are currently in the pipeline. The basic research was carried out in all cases at the IMBA. At Apeiron, the research results are utilized, brought to product maturity, and profits are made: Apeiron is working with the capital from Glaxo Smith Kline, Paladin, Medison, and Dexcel Pharma.

Paradigm shift? Innovative models of development and approval

Nobel laureate Joseph Stiglitz warned some time ago that price policy could lead to an implosion of the entire pharmaceutical system. As an alternative, he proposes a much more active role for communities of states in drug development and testing.[23] Both the Belgian HTA Institute KCE (Belgium Health Care Knowledge Center)[19] and the Dutch "Council for Public Health and Society"[15] concerned themselves with alternative models of drug development. One-off payments for genuine innovations could replace long patent terms. Submitting tenders for conducting clinical trials for new drugs with subsequent "generic" prices is also conceivable. The prices would have to include production costs, marketing expenditure, and profits, but the research effort would no longer be paid pill by pill. The first initiatives on patent pools and research platforms have shown that it is also possible to manufacture medicines outside the corporate world[20].

Research effort should not be paid pill by pill.

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It is essential to reconsider the contracting of public research organisations for the sale of research results in order to ensure that taxpayers' funds also benefit patients in an appropriate form. Health policy at all levels is called to explicitly express its priorities in research programmes in national institutions and within the European framework of research funding. It would be a worthwhile task for the EU to define concrete research investments in the next budget period. The use of funds, the outcome, as well as the patient benefits would have to be communicated transparently. The benefits of EU projects must directly prove advantageous to European citizens and taxpayers, unlike the € 5.7 billion Innovative Medicines Initiative (IMI) project.[21, 22]

In-depth analyses of the issue of "unbundling" are required in order to prevent the "social toxicity" of the current funding mechanisms.

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