The Research-Based Pharmaceutical Industry and Society: What Is at Stake in the Future?

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ABSTRACT. The US House of Representatives passed the far-reaching Pharmaceutical Market Access Act in July of 2003. If this bill or any similar language becomes law, the provision of health care would be affected radically on a worldwide basis. The author discusses the implications of such a law for governments, society, the pharmaceutical industry, and consumers, touching on societal expectations for cures and diagnostic procedures, aims and results of government regulation of the pharmaceutical industry, individual responsibility for health, and the situation of research-based and biotech enterprises as shouldering both social and commercial responsibility for health care. The author also addresses the economic risks of research-based and biotech enterprises, the need for transparency in cost structure, the funding of R&D, marketing costs for new products, the parallel imports market, and the effects of government reimbursement decisions. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com>*

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PRE-ELECTORAL US LEGISLATION

With a bipartisan majority under the leadership of Republican Congressman Gil Gutknecht, the US House of Representatives passed the far-reaching Pharmaceutical Market Access Act of 2003 on July 24, 2003 (1). Should this bill or any similar language be confirmed also by a majority of the Senate and signed into law by the President, the provision of health care would be affected radically on a worldwide basis.

The bill provides for the reimportation of medicines from FDA-approved facilities in industrialized nations at prices enforced by government agencies of those countries. While the immediate focus of the political debate is mainly geared toward the importation of medicines from Canada, the bill, if enacted, would provide for the importation of the government-enforced pricing systems of some of the southern European states without much guarantee for US citizens to gain access to the price differential. Instead, the first and foremost beneficiary will be the parallel trader–a fact that can easily be observed within the European Union, where parallel trade for all industries is enforced following the "free movement of goods" principle.

As such a development in the US would dramatically impair the prospects of the pharmaceutical and biotech industry, the foreseeable result will be that the funding of research and development programs for new diagnostic technologies and therapeutic solutions eventually will have to come from government sources.

So far, and particularly throughout the last decade, private investors saw good reasons to spend billions (US$) annually with the expectation of being rewarded with a premium return on their high-risk investment.[1]

PHARMACEUTICAL INDUSTRY AND SOCIETY

Research-based pharmaceutical enterprises and the emerging biotech companies have in common that they are inescapably embedded and part of the social systems of the nation states in which they are operating.

The unprecedented advance of diagnostic and therapeutic solutions, in combination with the development of sophisticated instrumentation and operating procedures, has resulted in seemingly insatiable expectations of the various and, in many cultural and economic aspects, differing societies around the world.

> Current expectations are that for any disease there ought to be a cure available to as many people–ideally–free of charge.

Current expectations are that for any disease or abnormal condition there ought to be a cure; that the cure is most likely to be achieved by the application of diagnostic procedures and eventually a medicine; that, if no medicine is yet available for the purpose, then someone, somewhere, will discover one; and that, as soon as it is discovered and proved to be safe and effective, the medicine ought to be available to as many people as possible–preventive or to patients–and, where possible, free of charge.

These general expectations of the public at large, and particularly the people and governments in less-developed countries, are to a certain extent the result of the achievements of the research-based pharmaceutical enterprises. They have been further funnelled since the deciphering of the human genome, which has accelerated the growth of biotech enterprises promising the development of genetically engineered medicines or of other genetic health interventions.

Governments, however, have more often than not failed to appeal to their peoples' personal responsibility for securing and maintaining their health. Such an approach would require an informed patient or an individual being interested in the prevention of a disease before becoming a patient. Such an individual would take an interest in the environment and conditions for health care provision and also in his or her private health insurance coverage.[2] This, ideally, would allow for an individual negotiating the conditions of service packages starting from the basic health provision with or without a patient contribution up to an appropriate coverage for cases of potentially catastrophic events. The informed individual taking seriously his or her responsibility for his or her own health is surely a better solution than a dependence on government decisions with the possible effect of denial by oblivious rationing or otherwise access to appropriate medicines on the premise of national budget constraints, which is the unfortunate experience today even in some industrialized countries.[3]

Enticing responsible individuals into taking care of their own health–without neglecting the need for solidarity with those who cannot afford to do so–is further mandated because health interventions are today, and will be more so in the future, asked for not only on the basis of need but also on what is seen as fashionable.

Increasingly, a grey zone has been developing for the demand of health interventions, diagnostic as well as surgical procedures, including medications that fulfill individual or societal expectations of well-being. Requesting fashionable lifestyle products suggested by social trends in certain parts of the society, should, however, provoke acceptance of individual responsibility. The cost associated therewith should in no way impair the provision of health services to those in need.

NATION STATES AND THE INDUSTRY

Research-based pharmaceutical and biotech enterprises are fully dependent upon the various government controls of the nation states they are, and intend to continue, serving. Contrary to the worldwide trend of deregulation in other industries, research-based and biotech enterprises are now, and further becoming, the focus of various government agencies and their increasing efforts for–in some cases contradictory–regulations. Such government interventions occur at every conceivable level, starting with the encouragement (or the lack thereof) to search for new diagnostic methods and effective therapies and continuing during the processes of research, development, manufacture, and eventually marketing of a new diagnostic or therapeutic product. Through the entire process, nation states are actively and concurrently controlling–as multiple regulators, as duty and tax collectors, and also as customers–the conditions governing the enterprises' strategic and operating options for entrepreneurship.

While the authority to regulate is clearly mandated for the assurance of safety, quality, and efficacy of medical interventions, the nation states' influence on the economic parameters governing the enterprises' existence (e.g., prices, reimbursements, costs, and profits) without a clear understanding between the parties involved of the respective rules and responsibilities creates an overall element of uncertainty and resulting business risk.

> Research-based pharmaceutical and biotech enterprises are constantly torn between compassion and commerce.

Research-based pharmaceutical and biotech enterprises are constantly torn between compassion and commerce. While these enterprises are geared to provide solutions for those who are mentally and physically suffering from (life-threatening) diseases, they have to operate on a sound financial basis, just as any other privately financed company, to maintain their current investors' confidence and to encourage the engagement of potential investors.

Because of frequent misunderstandings about the research-based pharmaceutical and biotech enterprises' modus operandi and the complex net of external parameters that influence their ability for long-term and sustainable decision making, the author has provided in a separate publication a current perspective of the ethical pharmaceutical industry and its interdependencies, especially in the area of transfer pricing.[4]

WHOSE RESPONSIBILITY IS IT?

Enterprises are confronted with a lack of transparency as to the respective responsibilities of the nation states and the enterprises of the industry. While, in principle, nation states are supposed to provide for the health of their citizens, they do so with great variations. Even in the "united" market of the European Union, the principle of subsidiarity has maintained the nation states' autonomous approach toward health care.

> Enterprises are–with moral overtones and the quest for solidarity–drawn into a blurred environment of decision making.

The enterprises of the industry, aiming to operate as efficient health care providers in these nation states, are, however, with moral overtones and the quest for solidarity drawn into a blurred environment of decision making by government agencies as well as various interest groups. Some of the demands may be considered part of the business model of a research-based pharmaceutical or biotech enterprise and its potentially largest customer–the nation state. Yet others, whether based on principle or occurring haphazardly, are clearly outside the business environment that any other industry would be exposed to and be required to consider.

Concepts like solidarity, sympathy, compassion, social responsibility, and particularly ethical behavior influence the day-to-day decision making of research-based pharmaceutical and biotech enterprises. While all of these are, and should be, governing principles of individual behavior, the decision making of commercial transactions should also be guided by clear rules and a distinct definition of the respective parties' responsibilities.

> For governments it appears to be easier to develop measures for controlling the supply-side.

In the area of health care, it appears to be easier for governments to develop measures for controlling the supply-side, rather than to emphasize the demand-side. On the supply-side, governments control access (in some cases even after their own health authority has granted a marketing authorization), prices, volumes, costs, and profits by means of requiring the determination of the product's "clinical excellence," the approval of pharmacoeconomic (instead of health economic) studies, the demand of price reductions, paybacks, and budget limitations, the enforcement of reference pricing, tiered pricing, generic substitution, parallel imports, and limitations to certain levels of costs, reimbursements, and "allowable profits." On the other hand, influencing the demand-side would require governments to create totally new structures and rules of responsibilities for the nation state, its people, the patients, and the health care providers, as well as for the enterprises of the industry and those of the trade.

In the area of health care, there is an apparent lack of distinction between social and commercial responsibility. Research-based pharmaceutical and biotech enterprises clearly shoulder each type of responsibility, and the individuals working within the industry must, therefore, have a clear perspective of both. These enterprises operating as multinational groups on a worldwide basis are accustomed to regularly filing social responsibility reports that demonstrate their adherence to codes of good conduct particular to the industry and their good corporate citizenship in the respective nation states they serve. There are the opaque zones, though, where demands for social responsibility with moral overtones of solidarity are in conflict with the commercial responsibilities that the enterprises also have to respect. The lack of clarity and governments' constant moving of goal posts impede the transparent decision making for which the management of these enterprises is used to being held accountable.

> The overriding principle governing the enterprises' future existence must be their managements' ethical behavior.

The overriding principle governing the future existence of research-based pharmaceutical and biotech enterprises must be their managements' ethical behavior. Although, there is, of course, no claim that executives of the research-based pharmaceutical industry are a special breed of the human race, nor that the executives managing biotech enterprises have genetically coded ethics ingrained, the author is of the firm opinion that ethical behavior evidenced through transparent systems applied and reported on a consistent basis is an indispensable survival strategy for multinational groups of the research-based and biotech industry. They are confronted by their regular stakeholders as well as other privately or publicly organized interest groups from societies around the world with so many contentious issues that they simply cannot afford to conduct their business processes in anything but an upright, ethical, and transparent manner. It is for this reason, for instance, that the biotech company IDEC Pharmaceuticals (which completed a merger with Biogen, another US biotech enterprise, in 2003) states in the first line of its 2002 annual report: "Honesty, integrity and quality breed trust."[5] As much trust is needed by patients and their physicians to rely on the safety, quality, and efficacy of diagnostic and/or therapeutic products, all other stakeholders and many interest groups will want to be assured of the enterprises' ethical behavior and transparent systems applied on a consistent basis.

In its 2003 global 500 report about the world's largest corporations, *Fortune* magazine devotes a special section to "Balancing Profit and Principle, Redefining Corporate Value" and starts off with:

> When British pharmaceutical giant GlaxoSmithKline announced in April its decision to further reduce the not-for-profit prices of its HIV/AIDS medicines for the world's poorest countries by up to 47%, the move highlighted more than its long-standing strategy to improve health care in the developing world through preferential pricing. It demonstrates just how strong the corporate commitment is to taking a principled approach to doing business. (3)

How the effects of this and other related decisions are to be interpreted from the view point of sustainability as well as transfer pricing will require considerable further analysis and also wise political leadership and judgment.

RISKS PECULIAR TO THE INDUSTRY

Multinational enterprises are faced with major economic, regulatory, and pharmapolitical risks.

In addition to the overall level of uncertainty and the resultant business risk, research-based and biotech enterprises are faced with major economic, regulatory, and pharmapolitical risks particular to the industry. Peculiar economic risks of research-based and biotech enterprises are the result of their research and development programs being subjected to serendipity and fortuity rather than a positive correlation between funding and the outcome of new diagnostics and/or medicines. Such risks inherent to the industry are documented by research over the last three decades which shows that investors are expected to provide the financing of some US $1.7 billion for a new medical entity to become a possibility (4). Even if such a new product has been secured through all pharmacological and toxicological testing and various clinical trials, enterprises marketing a new medicine may be faced with the risk resulting from unexpected side effects to be seen only after launch with the broader use of the product under the conditions of daily life rather than within the controls of a clinic.

Further, and only among other economic risks such as the financing of continuous R&D programs, the enterprise may be faced with no or a low return potential due to:

- The development and regulatory processes having lasted too long to be granted market access among the first entrants within a new class of products
- The competition having already established a significant market presence
- Being granted an indication that covers only a rare disease
- A high prevalence of a particular disease in an economically underdeveloped country
- Public opinion demands to provide products at “preferential,” “tiered,” or “equity” prices.

Various regulatory interventions provide for significant risks in research-based and biotech enterprises, as they are severely limiting enterprise managements’ ability to exercise entrepreneurship. Government interventions may preclude or limit the enterprises’ option to effectively use the marketing authorization granted, for example:

- Health economic or pharmacoeconomic studies not being accepted in support of sufficient market prices
- Public or professional bodies claiming that the medicine is not of "clinical excellence" and therefore not needed
- Pricing decisions[6] being impaired by government regulations and extended beyond any reasonableness and/or reimbursement status not being granted
- The additional burden of Phase IV (after launch) and pharmacovigilance studies
- Parallel imports
- Transfer pricing compliance programs, i.e., the documentary burden, the uncertainties due to the use of hindsight knowledge or secret comparables threatened to be used in audits with the exposure to double taxation, penalties, and litigation.

Government intervention into the determination of market prices, reimbursement levels, or even access to pharmaceutical products is sometimes justified by the fact that such governments are the principle customers of the industry or that their budgets are limited. In many countries, however, the cost of diagnostic and therapeutic products is only a small portion of the total cost of the health services, and insufficient consideration is given to the fact that early diagnosis and treatment by medicines may be effectively cheaper in many cases than other forms of treatment such as hospitalization. Economic reasoning suggests that instead of controlling the supply-side of pharmaceutical and biotech products, governments would be well advised to develop alternative structures for health care provision.

Research-based pharmaceutical and biotech enterprises are also faced with considerable pharmapolitical risks as a result of:

- An insufficient awareness and lack of appreciation for the complexities of the pharmaceutical and/or biotech R&D programs
- The continued and sometimes suddenly changing government control efforts
- The lack of political will to allow for more competitive market forces affecting the national structure of health care provision and therewith a greater transparency of respective responsibilities and accountability
- The contentious climate surrounding the pharmaceutical and biotech industry, with the consequence to lose and/or not to attract

the brightest minds as researchers for the development of needed diagnostic agents and therapeutic medicines
- Activities of nongovernment organizations and initiatives of institutional investors that severely affect the enterprises' business decisions.

It has to be kept in mind that such risks are shouldered by privately funded enterprises whose investments in R&D programs amounted to some US $50 billion in 2002.[7]

TRANSPARENCY AND COST STRUCTURE

Transparency is needed because of the interdependencies with societal interests, the often contentious climate created as a result thereof, and because of the often not fully understood facts and circumstances governing research-based pharmaceutical and biotech enterprises.

> Enterprises are faced with a lack of understanding of their cost structure.

One of the thorniest issues research-based pharmaceutical and biotech enterprises are faced with is a lack of understanding of their cost structure. To the amazement of the author, this unfortunate "innocence" applies not only to governments, NGOs, and the media but also to some of the professional consultants advising both governments and the management of the industry.

> There is an important task for universities to consider reorganizing their academic training.

There is a significant need unmet and therefore an important task for universities to consider reorganizing their academic training in this area. Students of various disciplines are still studying in isolation and leave their alma mater only as specialists of their respective fields. For research-based and biotech enterprises to effectively serve societies around the world, they need to attract the brightest minds whose demonstrated contributions within their areas of academic training provide for the sought-after advances. More so, however, these highly capable individuals should have an interest in and a solid grasp of the requirements and the

achievements of those other disciplines with which they will have an active interface. Such an intellectual preparedness and an appreciation of contributions from other disciplines are the elements conducive to an effective interdisciplinary decision making, without which highly integrated businesses would not be manageable on a worldwide basis.

R&D COSTS

Vital to an understanding of the cost structure of research-based pharmaceutical enterprises is the fact that up to a third of a particular enterprise's current costs are not directly attributable to the products currently sold in a particular country.

This is mainly due to the expenditures for research and development programs which, during the time frame of on average 12-14 years, may or may not lead to a successful launch of a new product. Bearing in mind the impossibility of predicting the outcome of research, the high proportion of R&D activities becoming abortive, and the length of time needed for successful R&D to bear fruit in the form of a marketable product, it is prudent and widely accepted both for statutory accounting purposes and by tax laws around the world to treat current R&D expenditures as sunk costs.

> R&D expenditures have to be funded continuously from current revenues of all products currently sold.

Nevertheless, such R&D expenditures have to be funded continuously from current revenues of all products currently sold. Because current R&D expenditures are investments for potentially positive inventions in the future yet simultaneously fund, inherently, the many abortive programs, these expenditures cannot in any conceivable way be directly allocated as costs to the products currently sold.

As can be observed from the experience of biotech enterprises, most of which are dependent on a positive conviction of venture capital funds to finance their ongoing R&D programs, it is extremely difficult for a significant number of such newly created enterprises to ensure the necessary liquidity to continue their operations.[8]

MARKETING COSTS

To safeguard most effectively the remaining time frame of patent protection in the various countries around the world, research-based pharmaceutical and biotech enterprises will have to launch newly developed products with initially high marketing expenditures to gain market share quickly and to establish and protect the needed franchise that potentially would allow them to continue with sales of the products even after patent protection has lapsed. Not all pharmaceutical or biotech groups are in a position to launch a new product concurrently in a number of countries around the world, nor would an independently operating distributor in a particular country have the resources, confidence, and thrust for such a high impact campaign. The emerging biotech enterprises often form alliances with multinationally operating pharmaceutical groups that have the experience and the infrastructure to embark on such a capital-intensive marketing strategy.

It is, however, not at all a matter solely of immense capital but a matter of professional experience with the medical profession's practice in each of those countries gained over a long period of time to conduct and control the value chain of product supply in the various countries with invariably differing regulatory requirements. Although the sales in most countries are conducted indirectly via wholesalers to pharmacists and other retail distribution outlets such as hospitals, the medical profession prescribing the products is still the main target audience for the dissemination of scientific literature detailing the diagnostic or medical advance of the product in question. In most countries, this marketing effort requires a very labor-intensive face-to-face communication through scientifically educated and highly trained sales representatives. It is the experience of the research-based enterprises that they have to engage in a vigorous campaign to quickly capture the attention of interested physicians and provide them with a high quality package of scientific and medical information–and possibly training–all of which provides the necessary comfort for the acceptance of the new product.

Competition is fierce, both from other multinationally operating enterprises and from indigenous national companies defending the use of their established remedies for ailments. To penetrate the market and gain a sufficient market share, therefore, enterprises commonly spend on marketing–the provision of scientific and medical information, selling, and other distribution activities–between 15% and, in the initial launch period, as much as 35%, of turnover.[9]

> Marketing expenditures are at least as significant as those for R&D, but the associated risks are of a different quality.

These expenditures are at least as significant as for research and development activities in any given period. The associated risks, however, are of a different quality. At the research and development stage, the risk is that the incurred expenditures are sunk costs and simply may not produce a marketable product at all. The enterprises' efforts in this context may be totally unavailing, regardless of how much money they spend on R&D.

By the time the new product has reached the market, there is still a significant risk, but this risk is that the enterprise will not succeed in persuading its customers of the new product's value and thus not be able to establish a satisfactory market share before other products begin to compete with it. However, at this stage there is a product, and the chances that the enterprise's marketing expenditures will make that product adequately profitable are higher than the chances at the R&D stage that any additional expenditures on R&D may produce a marketable, let alone an adequately profitable, product at all.

At the marketing stage the worst risk is past. The problem now is to ensure that the product succeeds. Although the current cost of doing so may in relative terms exceed even the cost of discovering and developing a new product, management is enabled to control the process of expenditure with greater stringency and with much shorter time lines to verify planned results.

PARALLEL IMPORTS

The well-intended policy of "free movement of goods and services" aims to strengthen market forces throughout a whole region, such as within common markets like the European Union, the three neighboring countries having signed the North Atlantic Free Trade Agreement (NAFTA) and possibly soon also in South America within the Mercosur.[10] This is intended to benefit the ultimate consumer but has severely negative implications for research-based pharmaceutical and biotech enterprises.

Parallel imports are possible when the price level of a multinational group's patent-protected and branded product is lower in Country A than in Country B. Frequently, this price differentiation occurs because of government price impositions in either or both of these countries.

Parallel imports normally occur when a wholesaler buys products from the multinational group's subsidiary in Country A and there is sufficient difference between the prices in Country A and Country B for it to be worthwhile, after taking into account transport and other costs, for the wholesaler to bring them into Country B. There he would sell to wholesalers and/or retailers at lower prices than those they would have to pay for supplies of the same product bought directly from the multinational group's subsidiary in that country.

Parallel imports already have a considerable effect on the market share of multinational groups' sales of the same medicine in some European countries, particularly the UK and Germany. Increasingly now, the cross-border traffic of medicines between Canada and the US has alarmed government agencies, lawmakers, insurers, and especially the (mostly elderly) public in need of chronic medications.

Economic reasoning supports the free movement of goods concept as it ideally strengthens market forces to the benefit of the consumer. So far, this is only evidenced by products of enterprises that are free of price controls or any other government interventions.

> Parallel imports are the recurrent source of profits only to the nonproductive trader, the no-risk-taking arbitrageur.

However, government-authorized activities of parallel traders endanger the research-based pharmaceutical and biotech enterprises' return on their investments. Parallel imports are the recurrent source of profits only to the nonproductive trader, the no-risk-taking arbitrageur.

Available evidence suggests that these imports are conducted fully at the expense of the originators' enterprises and, to a considerable extent, the public at large because parallel traders do not, as expected, pass their advantage on to the ultimate consumer, the payer (5). These may, ultimately, realize savings only due to the originators being forced to reduce their prices. Parallel importers have no incentive or obligation to forgo retention of the full price differential and usually let only their sellers and buyers partially participate in their advantage.

> Parallel imports completely distort the revenue and cost structure of the affected enterprises.

Parallel imports not only have a negative impact on the overall profitability of a multinationally operating group, but they also completely distort the revenue and cost structure of the affected enterprises within

the group. A group company based in a country with government-enforced low prices, such as Greece in the EU or Canada within NAFTA–where parallel imports are, or may soon be, enabled to redirect products into a higher price country–will show disproportionately higher sales compared to its cost structure. The group company's marketing expenditures have been negotiated with the originator of the product on the basis of that country's needs. A significant diversion of products to other markets would completely pervert the affected group companies' analysis efforts for providing meaningful and transparent data in support of their gross margins.

Parallel imports have also become part of the emotional health policy debate resulting from the 2001/2002 South African AIDS/HIV access-to-medicines crisis. Instead–as in cases of an epidemic–of the imperative action by the World Health Organization (WHO), this has fortunately led to UN General Secretary Kofi Annan himself accepting responsibility for the global health crisis with his personal authority and that of the supranational organization he represents. Upon his initiative, the Global Fund to Fight Aids, Malaria and Tuberculosis was created.

The initial acceptance of responsibility on a supranational level was subsequently followed by the 2002 WTO compromise formula of Doha. Apart from the Doha proposal for nation states to allow least-developed nations to demand compulsory licences for the manufacture of medicines for three diseases (HIV/AIDS, malaria, tuberculosis), responsibility was further shifted upon ethical pharmaceutical enterprises with the demand to apply "tiered," "differential," or "equity" pricing for their medicines to be sold in those nations. This is without any consideration for who other than the enterprises should foot the bill–and also without considering the consequences for both their pricing of products in other markets and the resulting transfer pricing between enterprises within the same multinational group.

The political consequences of necessary enforcement have not been sufficiently considered either. The so-called "Ramsey pricing strategy," i.e., considerably reduced prices in nations with lower ability to pay and/or higher elasticity of demand than in wealthy nations, requires parallel imports to be prohibited from such low income nations. As compliance with such a mandate cannot be assured, the political debate is still ongoing. With the September 2003 WTO Ministerial Conference in Cancun having failed to secure a sustainable agreement, the research-based pharmaceutical and biotech enterprises continue to struggle with their decision making in that opaque zone of unclear responsibility and accountability.

Re- and parallel imports are the result of price discrepancies in inefficient markets. Parallel importers, as arbitrageurs, exploit these price discrepancies for as long as they exist without being burdened by any of the risks associated with the product development, the preparation of dossiers for regulatory approval, etc. They have grown into a formidable market force by founding their own trade organization. In the words of one of its founders: "Parallel imports will last, as water is flowing to the lowest level, as long as prices will not have been equalized, throughout the European Union, at the lowest level."

Should governments continue to insist on their existing level of government interventions, respectively, invent new forms of regulation for privately funded businesses, and at the same time allow this market inefficiency to continue, this may lead eventually to full government financing of medicinal research. Both the intended US legislation and the ten additional members acceding the European Union in 2004 are factors reinforcing such a development.

The requests from NGOs for "tiered" or "equity" prices have already created negative implications beyond the discussed problems within a common market. Internationally operating traders, exploiting the opportunities of electronic commerce, illegally use the price differential between price-controlled markets.

> Even the United States has not yet geared up to the potential health hazards and commercial consequences resulting from parallel imports.

Even the United States has not yet sufficiently geared up to the potential health hazards that may be the result of the importation of products assumed to be identical with those sold in the US market.

Lawmakers in fear of their constituents' electoral demands appear to have succumbed to opportunistic and short-term decisions. Even in the US, support for the protection of enterprises that have originated the products and have taken the risks to market them under the conditions required by the respective nation state appears to be dwindling:

> Support for a law allowing consumers to buy American-made drugs that sell for lower prices in other countries has been rising among lawmakers anxious to address high drug prices . . . . . Specifically, the bill would allow the reimportation of prescription drugs approved by the Food and Drug Administration [FDA] manufactured in FDA-approved plants in 25 industrialised countries.

> A main source of imports would likely be Canada, where many elderly Americans living near the border already travel to fill their prescriptions. (6)

The commercial consequences for the research-based pharmaceutical and biotech industry, and subsequently for the budgets of nation states around the world, of the US allowing the import of government-enforced prices from countries without any research base will be beyond current imagination. Private investors would have to withdraw from that sector altogether, venture capital would not be forthcoming, and nation states would themselves have to organize and provide funding for the research and development of desired remedies for their peoples' health.

Dr. Mark McClellan, the Harvard-trained medical scientist and economist, on leave from Stanford University as Commissioner of the US Food and Drug Administration (FDA), recognized the long-term negative consequences for societies around the world. He voiced his concern in his first international speech and offered a thought for international discussion: ". . . to aim for worldwide drug prices in proportion to a nation's income" (7).

THE ALL-OR-NOTHING IMPEDIMENT

Research-based pharmaceutical and biotech enterprises–during their research and development programs–are continuously confronted with the challenge of whether their original invention will live up to the expectation of becoming useful without significant side effects, but various other and comparable challenges are at stake even after marketing authorization has been gained. So far, at least, potential sales are created in major markets through the positive outcome of pharmacoeconomic or health economic studies, the product's registration on a positive rather than a negative list, the gaining of a reimbursement status, and the support of rather than a denial from an access-controlling government agency such as the National Institute of Clinical Health (NICE) in the United Kingdom. A negative outcome of any of those challenges would, indeed, ridicule the whole development process, as no product sales would be the consequence.

> There is no other industry subjected to such a dilemma.

There is no other industry subjected to such a dilemma. Assume, for instance, that a so far independently operating biotech enterprise, which

is relying on its ability to create an effective and safe product, negotiates a license with a multinationally experienced marketing group to sell products on a worldwide basis. Such license terms would usually entail advance and staggered lump sum payments on the basis of certain milestones achieved such as the positive passing of Phase II and Phase III clinical studies and ultimately the marketing authorization in a particular country. If, however, the subsequent price or reimbursement negotiations are not successfully secured or a medical supervisory body such as NICE in the UK would hand down a decision that such a product–although it has been granted marketing authorization–should actually not be prescribed by the medical community, the licensee of the product would have to write down its lump sum royalty payments, as the licensor would surely not be agreeable to renegotiating the license terms.

A negotiated royalty–regularly directly related to net sales–usually implies an acceptance by the licensor of the licensee's bargaining power for gaining approval to sell the product and for achieving a reasonable market price. This would determine, within the given time frame of having secured marketing authorization in the various countries, revenues for the licensee and therewith royalty income for the licensor. A denial, though, of reimbursement status or frankly the disapproval of the product's prescription as best practice constitutes an absolute negation of income irrespective of the large costs incurred in advance of the expected launch of the new product. While the licensor, as the inventor, should be able to rely on the expertise and negotiation intelligence of the licensee in the respective markets, it would be inconceivable–as no third party would be agreeable to renegotiating the license terms–that the licensee would be enabled to reclaim his advances on royalties paid in case the licensee has failed to gain support from government agencies for pricing, reimbursement, and access.

In addition to initial lump sum payments based on certain milestones, license agreements usually entail minimum royalties on expected volumes sold during the expected life of the product. Licensors would therefore be loath to even consider granting a license if the potential licensee would attempt to structure the royalties, including lump sum payments, conditional on the outcome of access, price, and/or reimbursement negotiations and the potential of parallel imports to occur in any particular country.

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NOTES

1. In 2002, the top 30 pharmaceutical groups operating on a worldwide basis spent US $42 billion on research and development programs.

2. For an elaboration of this issue, refer to: Danzon P. Health insurance and the growth in pharmaceutical expenditures. *J Law Economics*. 2002; 45(Oct):587-613.

3. Health care costs are currently heavily debated throughout the world also in relation to the demographic structures of societies together with the related expectations and the need to fund another social cost: old-age pensions. The affordability of pensions directly reverts back to affordable medicines and therewith the pharmaceutical/biotech industry's inescapably being drawn into financing decisions that are regularly beyond those of other privately funded enterprises.

4. This article documents mostly additional data and literature references not cited and footnoted in Reference 2.

5. See: IDEC Pharmaceuticals 2002 Annual Report. *Care*. 2003; 2(2):1. IDEC Pharmaceuticals and Biogen merged in 2003 (market capitalization US $6.8 billion) and represent now, after Amgen and Genentech, the third largest biotech company in the US.

6. The negative influence of governments' price interventions on the ability of pharmaceutical enterprises to introduce new products swiftly to all markets–especially within the environment of potential parallel imports–has been thoroughly researched and reported in: Danzon PM, Wang YR, Wang L. The impact of price regulations on the launch delay of new drugs–Evidence from twenty-five major markets in the 1990s. Working Paper 9874. Cambridge, MA: National Bureau of Economic Research; July 2003.

7. The top 30 multinationally operating enterprises of the research-based pharmaceutical and biotech industry have together provided funding of US $42 billion in 2002 for research and development programs.

8. "Declining R&D productivity, rising costs of commercialization, increasing payor influence and shorter exclusivity periods have driven up the average cost per successful launch to $1.7 billion . . ." and reduced average expected returns on new investments to ". . . just 5 percent–significantly lower than the industry's risk-adjusted cost of capital" (4).

9. Biotech enterprises in their initial phase of development may not have sales, and when they do have sales or have royalty income, marketing expenditures for a new product may outweigh their revenues.

10. A common market among Argentina, Brazil, Paraguay, and Uruguay, soon to be joined by Chile.

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