The basis of the discovery process for a new pharmaceutical product

Abstract: The history of pharmaceutical industry (and pharmacy) is measured from one discovery of an innovative drug or approach to treatment of a particular disease to the next one. The basis of the discovery process for a new pharmaceutical product is in understanding the mechanism of action of a particular disease or processes in the organism related to the disease and/or its symptoms. The essence of a pharmaceutical is in the active ingredient capable of affecting processes within the organism beneficially.

Key words: Pharmaceutical market, New drug development, Pricing Regulations, The cost of pharmaceutical products

INTRODUCTION

Management logic require a certain level of certainty and measure time in terminal units, whereas scientific research process is conducted with flexible timing in terms of milestones determining: the beginning of particular activities, the need for corrective actions, or the completion of particular processes. As a specific feature of biotechnology sector (but also applicable to numerous innovative pharmaceuticals), states high risk level, which '…confronts levels of risk and uncertainty well beyond what is entailed in "normal" R&D.' In pharmacy, especially biotechnology, problems in R/D often raise new questions and a need to conduct further research so as to find appropriate solutions, and more often than not research ends in a conclusion that there is no technically feasible solution, or that the solution is inadequate by one criterion or another, which prevents the commercialization of the product. Objectively, both specific features stem from the 'conflict' between business logic and scientific research approach and are related to high risk levels and long innovation cycles. Pharmaceutical industry's decision to channel R&D, in search of blockbusters, to drugs for chronic conditions, has result in the need to observe drug safety over a long period, in view of the fact that these therapies are long-term or life-long. The process of creating a new pharmaceutical begins with the process of discovering an active ingredient with pharmacological attributes, followed by a long development period, where the active ingredient acquires the formulation and form of final pharmaceutical product, and paralleled by the commercial development process, which is supposed to place the innovative scientific side of the discovery and development into a pragmatic framework of unmet or inadequately met market needs [1] [2][3]. Although the discovery and development processes follow a time sequence, it is important to note the simultaneously conducted commercial development process, aimed at channeling scientific research towards commercially attractive goals. In addition to innovative pharmaceuticals, by the active ingredient's level of novelty, the following can also be regarded as new products:

- a new salt of a drug which is already approved for sale; it is a chemical derivative of an existing drug;
- a new formulation of a drug already on sale, such as a new quantity of the active ingredient (strength), new method of administration *etc*.;

- a new combination of two or several drugs already on sale;
- a drug already on sale, a new manufacturer's bioequivalent drug, such as generic products;
- a new indication is a moment when the manufacturer of a drug already on sale proves the therapeutic value of the given product in other situations, i.e. in other diseases, and this also includes transferring drugs from the ethical into OTC drug category. [4] [5] [6].

THE DISCOVERY PROCESS

'The main business of the pharmaceutical industry is to provide drugs that save and extend lives, cure diseases, and alleviate the burden of sickness or age.' The history of pharmaceutical industry (and pharmacy) is measured from one discovery of an innovative drug or approach to treatment of a particular disease to the next one. The basis of the discovery process for a new pharmaceutical product is in understanding the mechanism of action of a particular disease or processes in the organism related to the disease and/or its symptoms. The essence of a pharmaceutical is in the active ingredient capable of affecting processes within the organism beneficially [7][8]. The discovery process includes a particular sequence of activities of various profiles of experts, about which various authors agree. After selecting the disease, i.e. target identification, the subsequent steps are:

- target validation, where a set of preliminary experiments aims to confirm therole of the selected target and its significance in disease causation, symptomsand treatment;
- a process called High Throughput Screening (HTS), wherein numerous chemical compounds are tested in relation to the biological target (computing technology enables testing hundreds of thousands of compounds towards a single biological target), with the aim to discover the lead compound that has the desired effect on the selected target; at this stage it is important to view the chemical characteristics such as the simplicity of compound synthesis, solubility, reactions with other substances *etc*.,) as well as biological characteristics (such as selectivity of impact, toxicity, activity in living organisms *etc*.);
- the next stage after identifying the lead compound is creating a lead series of compounds similar to the lead molecule or compound with a justifiable potential of having a pharmacological effect on the selected target;
- before entering the development stage, i.e. pre-clinical studies, the preceding step is lead compound optimization, aimed at selecting (from the lead series) the molecule or compound with the highest potential of developing into a successful innovative pharmaceutical product, and this stage, practically, marks the definition of the molecule or compound which is the potential future drug; compounds from the lead series are subjected to a set of in vitro and in vivo tests on animals, so as to establish the initial therapeutic activity and toxicity, i.e. safety and efficiency. In addition to this molecule or compound, the pharmaceutical company may select several 'substitute' compounds (from the same or different lead series). [9] [10] [11].

At a certain point during the discovery process, the pharmaceutical company that has identified the lead series of molecules/compounds must protect its discovery with a patent, either as a new chemical entity (NCE) or a new molecular entity (NME), or the patent protection may refer to the process of compound production. The development stage is aimed at developing the 'ideal profile' of the active ingredient – indications, formulation and other attributes of the new drug with a task to create the product's clinical, and therefore market values. In practice, achieving the ideal profile results in adopting the new drug as the 'gold standard', acknowledged as the best available therapy for a particular disease. From the business development aspect, the choice of disease is defined by the company's specialization in a particular therapeutic area, potential market size, but also the assumed existence of significant advance in the treatment of the disease (which is related with subsequent possible differentiation of the product in relation to competitors). The complexity of defining the potential market size once again confirms the significance of a time gap between the discovery and the launch of an innovative pharmaceutical, as projections are made for a product which still does not exist on the market, or it is simply about forecasting potential markets after 8 or 12 years, that it takes to develop (which raises the issue of the structure of the competitive environment at the moment of product launch). An innovative pharmaceutical may be the result of work of a pharmaceutical company's in-house R&D team, may come as the result of work of scientists and experts at universities, or be acquired from other companies in various development stages[12][13].

As the source of the innovative pharmaceutical product is within the R&D process, this leads to the conflict between the logics of scientific work and business, manifested as (Pisano, 2006a):

- problems related to patenting certain primary discoveries; and/or
- the fact that scientific norms highlight sharing discoveries, publishing scientific work and knowledge diffusion, while business logic rests on the positions of protecting patent rights and limiting information diffusion to enable capitalization on the scientific discovery.

Confrontation of two different logics significantly impacts the pharmaceutical discovery and development processes [14] [15].

NEW PHARMACEUTICAL PRODUCT DEVELOPMENT

New drug development is defined as a '... set of interdependent tasks with the intended purpose of marketing a new chemical or biological entity...', i.e. a new active ingredient. The development stage comprises preclinical and clinical studies of compounds/molecules with a reasonable potential of becoming a new successful pharmaceutical product. Developing a new pharmaceutical product is a time-consuming process, engaging a considerable share of the pharmaceutical company's resources. [16].

Pre-clinical studies are the initial stage of new pharmaceutical product development. First of all, it is necessary to establish the pharmacological profile of a future new drug by gathering information on the pharmacokinetic and pharmacodynamic properties. Pharmacokinetic properties are usually tested through ADME tests, designed to establish: the path and degree of drug absorption; the drug's distributions through liquids and

tissues; successive transformation through metabolic processes; as well as its elimination and accumulation in the organism. Pharmacodynamic studies refer to the drug's biochemical effects, the mechanism of its activity in the organism (how it acts), as well as the relation between the concentrations and effects of the drug, which also affects the development of drug formulation. Drug formulation refers to the drug's dosage and appearance, primarily the administration route. An integral part of pre-clinical studies also implies studying the toxicity of the future drug. The final stage of pre-clinical studies is submitting applications for permission to test the new chemical or molecular entity on human population. Test results in terms of the drug's pharmacological properties and toxicity are supposed to justify the initiation of therapeutic application, first on a group of healthy individuals. Pharmaceutical companies have developed numerous, mostly formalized methods for the commercial evaluation of the potential new product. Entering the development stage also implies escalating costs, so that it is understandable that there is a high degree of caution before the company decides to take that step. At this point of the new drug discovery and development process, legitimate decisions imply the continuation of pre-clinical studies or giving up the development of the given product due the lack of its compatibility with the company's aims (where one of the solutions may be to license this product), or the decision to formally enter the clinical trial study stage. Of about 250 compounds entering the pre-clinical study phase, five on the average meet the criteria qualifying them for clinical tests. 'Clinical drug study is the study conducted on humans with the aim of establishing and confirming the clinical, pharmacological and pharmacodynamic actions of (a) studied drug(s), identifying each side-effect of the studied drug(s), and studying the resorption, distribution, metabolism and discharge of the drug(s) with the purpose of establishing its safety and efficiency (Article 49 of the Law on Drugs and Medical Devices of the Republic of Serbia, 2004). [17] [18].

STRATEGIC POSITION ANALYSIS

Stage 1 of clinical studies of the new pharmaceutical is supposed to prove that the new drug is safe for human use, and which dose is considered to be safe for human use. As a rule, this stage is conducted on a small group of healthy volunteers, usually 20 to 100 respondents. The law precisely regulates the rules of conducting clinical studies, which are usually limited on young, healthy, adult males. Studies are conducted under strictly controlled conditions, and each respondent is observed immediately upon drug administration, over an appropriate time period ranging from a few hours to a few days. The use of the drug on the healthy population and the results of the first stage of clinical trials are a precondition for the first use of the innovative drug on people with the disease/condition/indications for which the drug is being studies. [19]

Stage 2 of clinical studies is a small-scale study conducted on a smaller population of 100 to 500 patients. This stage should confirm that the innovative drug on trial really has the desired effect on given indications, the so-called proof of concept (POC). Proof of concept is established upon the completion of drug safety and efficiency trials, determination of minimum and maximum efficient drug doses, and monitoring the possible side effects [20].

Stage 3 of clinical studies is a significant step for the pharmaceutical companies, as this is the longest, and also the costliest stage of clinical development. Stage 3 includes

studies on a large group of patients, from 1000 to 5000 persons. Impartiality of studies, resulting in objective evidence of the drug's efficiency and safety, is based on '... randomized, blinded, placebo-controlled...') trials. According to PhRMA publication, clinical studies at this stage include:

- Placebo controlled trials: a group of respondents/patients receives the new drug under development, while another group is given placebo, or, in some cases, recognized available therapy for the given indication;
- Randomization : respondents are divided by random sample method into a group receiving the innovative therapy and the group receiving placebo. So as to avoid the risk of jeopardizing reproductive health in women. cases when this would pose a risk for the patient's health, alternative therapy), which provides having the tested and control group with equal representation of respondents with varying stages of the disease; and
- Blind (ed) tests, which can be single-blind(ed), when the respondents do not know whether they are taking innovative therapy or placebo, and double blind (ed), when not even the testers (physicians) participating in the clinical trial do not know which patients are being given therapy or placebo [21].

Basically, of clinical studies is a large-scale game, which is to result in statistically significant evidence of drug efficiency and safety. The decision by relevant authorities to approve the sale of an innovative drug depends, in essence, on the results that the innovative therapy has shown during clinical trials, especially the final stage. The results of clinical studies are intended to help balance the beneficial and side-effects of the drug. Clinical studies will also shape the market lifespan of the pharmaceutical product, and it will be placed on the market as a therapy for those conditions/diseases for which the clinical trials have proven to be influenced beneficially.After launching the new drug on the market, most pharmaceutical companies continue to monitor the drug on the market in order to obtain additional information regarding the drug's safety and efficiency, its impact on the quality of patients' lives, but also in search of new indications. [22]

Stage 4 of new drug study is voluntary, but in practice, regulatory bodies may request its conduct. Monitoring the drug's performance in real-life environment over a long period of time is gaining significance. makes a distinction between the efficiency and effectiveness of therapy, referring to efficiency as the degree of success of the therapy in ideal conditions (such as those in clinical trials), while effectiveness is the measure of its success in real life. Gathering continuous data on the use of the drug in real-life environment requires patient registers which are '...an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose(s).'[21]. The success of generic drug manufacturers does not depend on developed R&D capacities. Their key strategy is successful imitation – proven through drug bioequivalence – as the proof that a generic drug is '…comparable in dosage, form, strength, route of administration, quality, performance characteristics, and intended use as the original drug.' Due to the burdened budgets of healthcare payers, generics become 'instant hits' and easily find the way to drug formularies or preferential status when

therapy is prescribed. To sum up, R&D process in pharmaceutical industry is characterized by long time horizons, high capital intensity, and high risk levels, especially from the aspect of the drug's pharmacological effectiveness and efficiency, and its safety of use, and qualify the circumstances around innovation in pharmaceutical industry as extreme. point to escalating investment requirements (or development costs) of a successful pharmaceutical, from its discovery to launch. The long R&D process in pharmaceutical industry must also be viewed from the aspect of lost days of sale, although not a precise measurement. Each day of delayed launch of a potential blockbuster may cost the company up to several million dollars (e.g. according to data given for Prilosec it is 11.2 million US dollars, while daily sales of Zocor amounted to nearly 8 million USD). Cteristics of scientific research, but its objective is to launch a successful new product [14]. 'Ideally, marketing is involved and provides a commercial perspective early in the discovery and development process. In this context, its mission is to marketplace – and to spotlight important product characteristics and differentiated attributes that should be evaluated during trials.' From the commercial development aspect, the impact of economic logic on pharmacy is manifested through the allocation of the organization's resources through '...three key decisions...'

- which drugs to develop (portfolio management);
- the best development path/method through development process design; and
- planned product price (pricing strategy)

The role of marketing in R&D in pharmaceutical industry differs from its role in consumer goods industry. Key differences stem from:

1.different roles in understanding consumer needs, which do not depend on culture, fashion or taste, but are medical or health-related;

2.the nature of innovation, which is a result of scientific research, which puts the role of marketing as information source into perspective, in terms of proposing new products or specifying the attributes of future products;

3.direct participation of marketing in pharmaceutical R&D is limited; once again it is about the complexity of R&D and high uncertainty levels – '...marketing can diminish market uncertainty, its powers in dealing with technical uncertainty are clearly limited.'.

4.testing new pharmaceuticals is possible only at later development stages, and even then they are conducted under controlled conditions and by experts, while in the consumer goods industry this is normally the task of marketing; and

5.limited sales forecasts for innovative pharmaceuticals affect marketing's ability to validly assist in selecting development projects by forecasting sales at the point of transition from discovery to development phase[10].Instead of looking for the widest possible target market, with the objective problem of confirming the drug's efficiency and safety, the author proposes gradual development (expansion) of target market from a very narrow, specific group of patients. With respect to various authors conclusions on the place and role of marketing in R&D, as well as the specific features of the market and the product, we can draw the following conclusions:

1. The influence of marketing on pharmaceutical R&D has a strategic dimension; assessing the market and the company's inner potential result in decisions on which research paths are considered to be compatible with the company's business (market) objectives, which, in turn, results in the decision to support particular products in further

development, prepare some for licensing, and abandon the others. This task also requires assessing the future drug's market potential [17].
2. The complex nature of R&D itself limits the role of marketing to conditionally advisory; marketing may propose elements of 'design' (including the effect) of a drug that stakeholders are interested in, but it is up to R&D to evaluate the justifiability of these claims from the aspect of available know-how and possibilities [13].
3. The role of marketing is strengthened at later stages of clinical development, notably for the purpose of informing the expert public on the potentials of the innovative drug, which should enable a fast diffusion of therapy in proportion with its therapeutic superiority in comparison with existing therapies [12].
Economic justifiability is not the only criterion for developing innovative pharmaceuticals. First of all, this refers to rare diseases affecting proportionately low percentage of population. For instance, the USA offers pharmaceutical companies various benefits for developing orphan drugs, in an attempt to encourage research and development in the areas without commercially justifiable investment logic. Typical diseases of developing countries are another example, where morbidity statistics are totally different from economically developed countries. A special significance belongs to the 'relocation' of R&D from highly developed Western countries to Eastern Europe, China, India, Latin America *etc*., as pharmaceutical houses want to exploit lower costs not only in the production process, butalso in R&D.A top academic medical centre in India charges between 1500 and 2000 USD per clinical study report related to a single patent, while at the same time a 'secondclass' centre in the US charges 20,000 USD for the same job. [11].

PRICING (COST)

The cost of pharmaceutical products is one of the key causes of controversy related to this industry. Numerous cultures have proverbs expressing the opinion that health is priceless or that health is the greatest wealth. What if health does have a price? One of the basic premises of marketing is that price should reflect consumer value. How can one measure the value of keeping good health or gaining it back? The objective need for health does exist. 'It's not like buying a Lexus-it's not something where you have a choice. People get angry because this is something that is critical, that they need, and companies are raising the prices so much.' The value of a pharmaceutical product is a complex category exceeding the level of physiological needs, although it stems from maintaining or re-establishing the organism's normal functions. Moreover, not only does humanity's need to keep good health and extend their own lifespan exceed the resources that an individual or society can allocate, but also the quantum of human knowledge about the 'mystery of life' does not suffice to safeguard people from biological vulnerability and impermanence. The controversial issue is that there is no price we would not pay to stay (or become) healthy, as opposed to the fact that any price a company charges for its pharmaceutical product is excessive. Why? Because '…particularly in the case of health-care sector, where many persons consider access to health care a right of citizenship rather than an ordinary service (health service themselves) or an ordinary commodity (pharmaceuticals and medical devices).' Between the objective R&D cost of innovative pharmaceutical products and the subjective

perception of their value and the company's right to make a profit on them stands the pharmaceutical product's market price. Marketing has the responsibility to capitalize on the newly discovered knowledge translated into an innovative product, enable future R&D and achieve the pharmaceutical company's business objectives, bearing in mind the availability of the pharmaceutical and the public opinion (which is not favorably disposed to pharmaceutical industry's pricing policies). 'Drug costs (and change in drug costs) are visible to naked eye; identification of drug benefits requires careful analysis of good data.' Advances in the quality of life, extended life expectancy and medical/therapeutic advances are undoubtedly evidence pro industry, but there is also the evident critical attitude to '… monopolistic pricing and high profits…'[3]. Pharmaceutical industry and its products are an inseparable part of the healthcare system in which they function. In the opinion of the past few decades of discourse on healthcare system are marked by three key issues: quality, cost and availability. The price of pharmaceuticals makes a direct impact on all three. The apparent logical response is to control prices of pharmaceuticals, i.e. to lower them. However, such a response is only a part of a complex equation which is supposed to provide a wide range and adequate quantities of pharmaceuticals, which requires maintaining the economic logic in their production, and at the same time, certain advances in finding more efficient, safer (and why not more agreeable) therapies. Such a requirement is objectively feasible in encouraging R&D within pharmaceutical industry. Most authors propose the unequivocal position that the past decades have seen a rise in the share of pharmaceutical costs in the total healthcare system. The rise in the total expenditure on pharmaceuticals results from the introduction of more effective (therapeutically superior) products and increased use of drugs

- for diseases for which adequate/appropriate therapy did not exist; and
- preventive therapies.

The most successful pharmaceutical companies operate globally, so that it is logical to expect that they will encounter different attitudes of both regulatory bodies and the general public to their product pricing. The analysis of various factors influencing prices and pharmaceutical companies' pricing policies must always be viewed from the aspect of seemingly conflicting positions of different stakeholders [3].

SPECIFIC PRICING FACTOR

At the same time, pharmaceutical marketers try to appreciate the internal factors, notably marketing objectives, the appropriateness of pricing policies in relation to the total marketing mix, and, of course, the aspect of costs. A significant factor determining any discourse on the nature and movement of pharmaceutical prices is the issue whether they are patent protected innovative drugs or generic medicaments. The domination of external factors demands that the prime attention be paid to them , but in view of the fact that the influence of individual factors is not linear and unambiguous, we shall attempt to encompass the key aspects of the complex mutual influences [12][19].

Pricing Regulations

Pharmaceutical product pricing depends primarily on whether they are placed on markets with legislatively **regulated prices** in one form or another, such as the markets of the EU, including Serbia, or markets where prices are formed freely, with the US as a relatively isolated example. The basic idea of legislative bodies is to prevent the prices of pharmaceuticals growing above the rise in prices of consumption goods, the so-called zero real pharmaceutical price inflation Discussion on pricing regulations primarily refers to branded, patent protected drugs, although the impact on the generic drug market is also evident. ...where one must bear in mind that it is the most significant pharmaceutical market, consuming almost a half of the world's total sales of drugs, and the fact that the USA is a leading country in terms of pharmaceutical companies' investment in R&D [15] [16]. Attempts to control the prices of pharmaceuticals may be interpreted as efforts to substitute for monophony, where the state (or one of its bodies) acts as the only or exclusive buyer, for the relatively monopolistic position of innovative drug manufacturers. Pricing regulations on a national market are aimed at accomplishing the social objective of availability of adequate quantities of safe and effective drugs, while, on the other hand, one finds the objectives of pharmaceutical industry .Efforts to assess the efficiency of pharmaceutical pricing control systems from the aspect of accomplishing the goals of both society and industry have produced a voluminous body of research. Sources are dominated by authors advocating the position that long-term pricing regulations are a sub-optimum strategy for accomplishing the desired goals view the difference between the two systems, free (unregulated) pricing and externally (government) regulated pricing in relation to two key determinants: the system's ability (or perhaps eligibility) to reward investment in innovative pharmaceutical R&D, and the role of pricing as a market competition tool. Point to the opinion that free pricing does not satisfy the social aspect, but Vogel also argues that government control can be equally unsuccessful in their accomplishment. Pharmaceutical patent protection can also be regarded as a specific form of government intervention, as the state legislation provides relative monopolistic position for a certain period, as some kind of compensation for resources invested in R&D. However, 'patents do not guarantee profits' and unless consumers recognize product value, it is hard to expect that they will be willing to pay any price [8]. Methods of controlling public expenditure on pharmaceuticals can be divided into two basic groups:

1.methods focused on the pharmaceutical supply side:

- directly controlled prices of individual products;
- reference prices, where prices are set based on the prices of the same or
- similar products on reference markets;
- average pricing;
- curbing the margins of wholesale and retail pharmacies; and
- positive and negative drug lists (where the payer, i.e. the state, defines
- which drugs are to be dispensed at the cost of the healthcare system).

2.methods focused on the pharmaceutical demand side:

- patient co-payment levels when purchasing drugs;
- advice and guidelines for prescribing physicians and limited budgets; and

- even
- parallel imports; and
- moving drugs from the ethical to the OTC product category.

The normal practice is to regulate markets with a combination of the above methods rather than just one measure. Reviewing pharmaceutical prices in Europe, give an overview of approaches to their formation. The regulatory body in Serbia provides that the reference markets are those of Croatia, Slovenia and Italy [3] [8].
In the case of markets without external price level control, price levels are practically defined by the supply/demand ratio on the given market. On the other hand, pharmaceutical supply is also a category with high uncertainty levels, accompanied by the nature of discovery of new knowledge in the entire scientific nexus surrounding the industry. In the case of pharmaceuticals, the above mentioned consumers' willingness to pay for an innovative product refers to attempts to predict consumers' willingness to pay for a product that will appear on the market following at least eight to ten years of clinical studies [3][8]. As public pressure has turned healthcare costs, and therefore pharmaceutical costs, into a political issue, there is a permanent dilemma whether it is better to regulate drug prices or let them form freely on the market. Practically, it is about social welfare on the one and the issue of pharmaceutical industry development on the other side. The advocates of pharmaceutical pricing control system highlight the issue of drug availability and criticize the industry for high profits, often assailing marketing budgets as well. Opponents of price control argue that pharmaceutical pricing control systems are short-term strategies. 'Lower drug prices today will unequivocally improve access to currently developed medicines and this will improve public health.' Of course, no less important is the question how much these lower drug prices will cost society. Considering this simplified model in which only monopoly or full competition exists, any intervention by the government in a market mechanism would result in welfare loss. In case of pharmaceutical products, three theoretical assumptions can be made:

- Any form of monopoly pricing, as opposed to competitive pricing, will result in a reduction of output, at a higher price, and will engender a loss in consumer surplus, and thus a welfare loss.
- Society grants a monopoly to the inventor of a pharmaceutical for a limite amount of time, willingly sacrificing short run welfare, expecting that, after patent expires, new knowledge will contribute to greater welfare gain (above experienced short time loss).
- Price controls generate welfare losses in the short run as well as the long run.
- Taxes (income, sales, or property) that are used to pay for publicly financed health care (acute care, long-term care, or pharmaceutical care) generate welfare losses in the short run as well as the long run, trough detrimental distortions in economic active[12][14].

CONCLUSION

Led by economic logic and in the absence of imposed pricing limitations, pharmaceutical companies allocate their resources to projects with the 'highest risk-adjusted expected

rate of return'. Imposing external pricing controls is a direct threat to R&D investment in pharmaceutical industry, on at least three grounds:

- External pricing control reduces the expected rate of return on investment, which also means that projects become less attractive, and there is a real threat of losing funding sources.
- External pricing control and the need to negotiate the inclusion of drugs into drug formularies with various government bodies, and also negotiations on drug prices, may delay market launch of drugs.
- Reduced pharmaceutical prices impact on reductions in future cash flow, and long pharmaceutical development periods and high risk levels result in the fact that pharmaceutical companies are especially sensitive to funding sources, as their own funds have lower capital costs than external ones.

One of the central ideas of marketing is channeling resources into the production of products in demand on the market. The prices of given products are formed on the market. The price should reflect the value comprised in the given product, and a market with freely formed prices also provides feedback on the price that consumers are willing to pay for the given product. Deems it unfeasible to make an analysis that would enable an objective determination of pharmaceutical product prices by third parties (such as regulatory bodies, governments *etc*.):

1. Application of value-based principle is impossible due to the fact that the regulatory body's interest is to keep prices down, and assessing the value of medicaments is left to the regulatory body itself, with the assumption that it is capable of assessing product value more objectively than users or prescribing physicians.

2. Pharmaceutical R&D costs are incurred much earlier than the product's utility appears, and the real 'medical and economic benefits' of the drug can only be viewed in post-launch studies, when the drug has been on the market for a period of time.

Authors who dispute pricing controls argue that without free formation of market prices resources will not be employed appropriately, which will primarily threat future R&D, and the consumers will be deprived of innovative therapies. Pricing control positions, on the other hand, are defended with the accomplishment of the social goal – availability of therapies to a wide circle of users [3][8].

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