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Research Article

New Approach to the R&D and the Consequences on Drug Pricing

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Abstract

Achievement of sustainable economic stability and growth in the last 15 years was influenced by the absence or inconsistence of structural reforms in the major world economies. Negative or zero growth trends in the country's GDP have significantly affected the Pharma industries, forcing them to shift and/or reduce the costs in all horizontal areas of business, affecting among the others, R&D costs. Along those trends a new paradigm of the so called "Circular and resource efficiency" economy is evolving. Optimization, sustainability, long term efficiency, customization are becoming widely acknowledged pillars of this new development Model. Pharmaceutical business is integral part of these systematic changes. Regulator, Funds, payers and patients are under growing pressure to adapt very fast to these new emerging needs. Old definitions and models for the pricing methodologies, constant "battling" between monopsony behaviour of the governments, pressure on the prices by the payers on one side, and the pharmaceutical companies investing in R&D to ensure a new patented drug and long-term financial sustainability on the other side, are creating an overall unsustainable result of lose- lose game. Only on first sight this price reduction seems to be beneficial for the patients, but in fact the numbers are proving that the patients are the biggest losers in mid and long term. In the eyes of the patients and other stakeholders, the pharmaceutical industry exists to discover new medicines that tend to become standard treatments. The faltering economics of R&D productivity are jeopardizing that mission: R&D expenditure is not delivering. Balance is needed. Consequently, absences of debates, clinical studies, HTA, pharmacoeconomic analysis are jointly creating "vicious circle" where no single player (in terms of institution) is ready to challenge the process by making a strategic move. Although number of facts are saying that now is the right time (maybe even the last chance) to institutionalize the process of the "holy trinity", R&D, HTA, reference pricing methodology, major dilemma is whether the approach should be driven by market forces or by regulations, or by mix.

Keywords: R&D; pharmacoeconomics; Reference pricing methodology; Drug costs; Methodology

Methodology

The referencing literature referring to R&D for this article were provided from the Pubmed, OECD, Embase and EconLit electronic databases, (18 articles with 35 unique cost estimates published in the period 2010-2022). In this analysis systematic literature review the author has included only literature in which the methodology used to collect the information and to estimate the R&D costs were clearly described. Average pre-launch R&D costs per NME are converted in the values to 2022 US dollars (US$) using the Gross Domestic Product (GDP) price deflator. Suitability of the R&D estimated costs were calculated considering how drugs' success rates and development time used for cost estimation were obtained, whether the study considered potential sources attributing to the variation in R&D costs and what the components of the cost estimation were. For the purpose of comparing results between studies, all cost estimates were adjusted to 2019 prices using the World Bank GDP deflator [1].

Discussion

Today's healthcare consumes 12% of global GDP, totaled US$ 8.5 trillion in 2019, more than double, in real terms, compared to the US$ 4.2 trillion spent in 2000 [2]. Spend is growing at average of 3.5% per annum, which will double expenditure in less than 20 years. Over the same period, global GDP increased by 74%, from US$ 50 trillion to US$ 86 trillion. Consequently, health spending as a share of global GDP rose from 8.5% to 9.8%. By 2080, estimated 50% of world GDP will be spend on health costs [3]. The health care system is under growing pressure as a result. Reduction on the reliance on market forces, growth in importance of emerging markets, need for control of costs and increase of performance levels must lead towards new agreement of delivering the services and products and covering the costs by third party payers. It is therefore important to find the right balance between global trends, funding and expenditure. By default, this requires intervention at short notice in a number of different domains [4]. Financial and staffing shortfalls are inevitable. To ensure that health care system is future proof, we need a new perspective that corresponds more closely to people personal experience.

Recent publications conclude that about 15% to 20% of clinical spend is wasted on efforts that are not valued by the key stakeholders [5]. To address this negative correlation, pharmacoeconomists need to focus on what really drives treatment decisions and what new data would be viewed as clinically meaningful for prescribers and value-creating for economic stakeholders. This requires 3 action points:

1. Continuing analysis, including assessment of the critical drivers of behavior for each stakeholder (prescriber, payor, and patient) based on advanced data infrastructure,
2. Detailed comparison of competitor labels and clinical data- to further inform which efficacy and safety endpoints matter most, and maps each of the brands against the stakeholder perception and
3. Understanding of how competitors are perceived by each stakeholder against the most critical factors, which can help identify the unmet needs.

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This process needs to consider several game changers. First, it needs to abandon the prevailing biomedical model which focuses on sickness and to replace it with policy actions on preventions that will outpace the policies of dealing with sickness and its consequences on personal wellbeing and social roles. Introduction of the concept of "positive health", in which actions are guided by the desires, values and preferences of the individual needs, is to become a focal point. Next, actions of all involved participants must be focused on the notion of QUALY (quality of adjusted life years) that should replace the limited approach of what someone with an illness is still capable of. Finally, to focus on "positive health" means to redefine the approach in the analysis on how the person perceives his quality of life while participating with his actions in society. Crucial element in implementation of the concept of positive health is to understand the variations between individuals: variations in norms, values and goals, but also in lifestyle, behaviour, environment, genetic disposition, and above all in the body's response to healthy and pathogenic stimuli.

New R&D funded from a complex mix of private and public sources and clinical trials required to gain market approval largely funded by industry must embrace those new changes and redefine the approach of the companies while defining their pricing policies and market access. Typically, R&D process goes throughout four main stages: Early Drug Discovery, Pre-Clinical Phase, Clinical Phases, and Regulatory Approval. This lengthy process ultimately aims to protect the patients while launching on the market only medicines that pass the rigorous selection. As shown in Figure 1, in the last 20 years number of medicines in the pipeline is constantly growing YOY, almost tripling in 2019 compared to 2001 [6]. However only very limited and small number reaches market launch.

Average levels of new drugs approved by FDI in decade 2000-2010 from 20 almost doubled in the last decade, reaching a peak in 2018 with 59 new approved drugs (Figure 2). These tendencies are even more noticeable in the group of the so called "first class drugs", (ones that use a new and unique mechanism of action for treating a medical condition) [7]. Average absolute number of first-class drugs in period 1999-2010 was 6 and it skyrocketed to 26 in period 2010-2020 with participation of 35% in total approved drugs. This is the essence of the R&D and the perspective. More efficient the R&D, more applications, more approvals, higher number of new first-class drugs, better the ROI.

Next element of the analysis is based on constant complains of high R&D estimated at approximately USD 151 billion across OECD countries, with nearly two-thirds in the United States, followed by Europe, Japan and China. Figure 3 shows that R&D costs per medicine

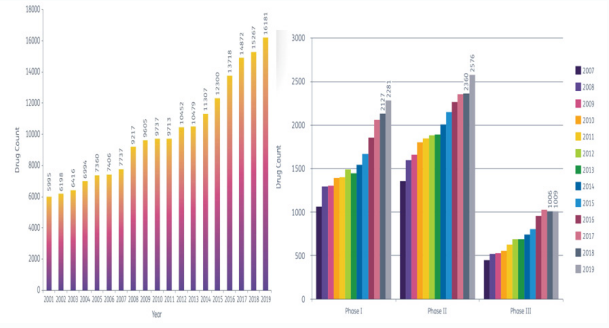

Figure 1: Total size of R&D in pipeline and by clinical phase 2001-19. Source: Pharmaprojects, January 2019.

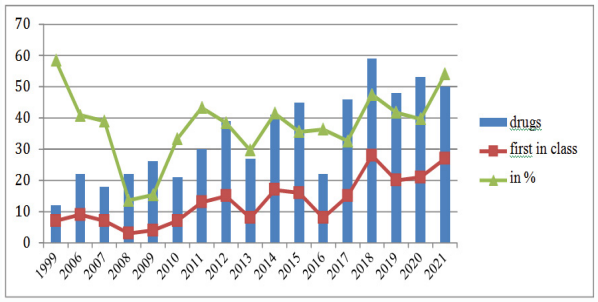

Figure 2: Number of FDI approved drugs (1999-2021). Source: Author based on FDA annual reports 1999-2022.

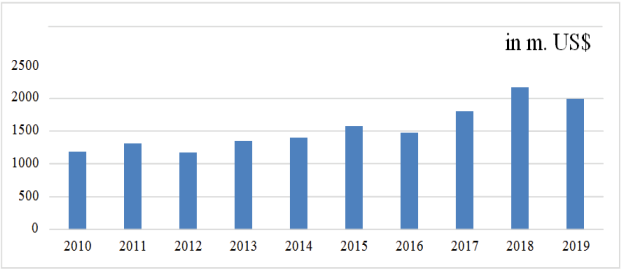

Figure 3: Average cost to bring drug to the market. Source: Ten years on-Measuring the return from pharmaceutical innovation 2019, Global data, Deloitte.

since 2010 increased for 67%, reaching almost US$ 2billion in 2018.

The known fact is that the pharmaceutical industry is highly R&D intensive. On average across OECD countries, the industry spent nearly 12% of its gross value added on R&D. However, forecast peak sales per asset 2010-2021 have more than halved since 2010 (Figure 4).

Today, only 30 percent of drugs launched earn an acceptable rate of return a rate that is likely to deteriorate further given the increasing demands of payors and access agencies that want more value for their money. To cover the costs, pharmaceutical manufacturers traditionally rely on a few "top sellers" to make up for the underperformers. In other words, producers need mass markets (economies of scale) and longer patent protection to cover the costs. Obviously, there is geo-disbalance. According to IMS data, [8] 62% of sales of new medicines launched during the period 2007-2017 were on the US market, compared with 18% on the European market. Reason for this is the fragmentation of the European markets. Sale numbers on new markets such as China and Brazil have registered two-digit growth,

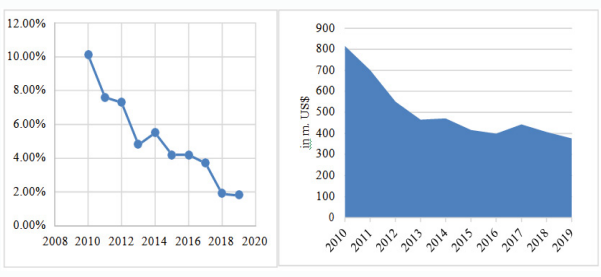

Figure 4: R&D returns of 12 large Pharma companies and peak sales per asset 2010-2021. Source: Ten years on | Measuring the return from pharmaceutical innovation 2019, Global data, Deloitte.

projected to surpass European markets, in 2023 (Figure 5).

Given the increase in R&D expenditure and the number of approvals per inflation-adjusted, R&D spending efficiency has declined steadily. This may lead to conclusion that those R&D costs are inflated, too much of company budgets go toward marketing and legal defense, including to protect patents. Major shift in the approach to the R&D is necessary.

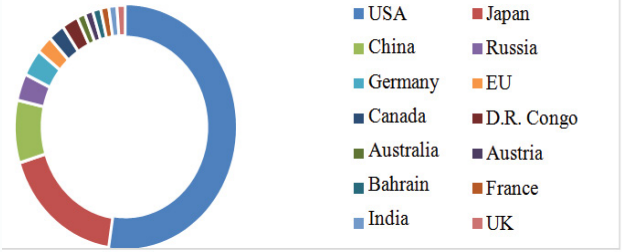

Figure 5: Countries of first launch. Source: NAS supplement infographic 2021.

New R&D Model

R&D costs are clearly influenced by costs of discovery and pre-clinical development, costs of clinical development, cost of capital, company and product profile. A few studies have broken down total costs and showed that clinical development accounts for 50%-58% of R&D costs per new medicine.

To calculate the efficiency of R&D, Companies need to consider the following input elements:

1. Relationship between firms' risk, Cost of Equity (CoE), Cost of Capital (CoC) and the intensity of R&D
2. Ratio of R&D to total revenues.
3. Cash flows and the discount rate which is directly linked to higher risk.

Analysis that covers those elements may result with two options: cut the time and consequently cut the costs or, implies diversification of the risks. Process between discovering, validation and clinical development/going to sale can be time shortened by use of modern designs tools, such as advanced statistical methodology, modeling and simulation, mapping of the Real World Data. Ultimately this will define a cost benefit/risk ratio, and confirm the optimal dose for the identified target patient population in which the drug is effective. Second option is that Companies typically pursue portfolio optimization through diversification of their projects across development phases, therapeutic areas, and internal and external R&D. Portfolio optimization is highly sensitive to the valuation of specific projects, which is largely driven by the CoC, i.e. RoR (Rate of Return) that an investment in a project would be expected to earn in an alternative investment of equivalent risk. The introducing of the so-called "Pragmatic trials" diversification is in contrast to trials focusing on achieving regulatory approval that are typically performed with relatively small sample sizes, using experienced investigators, and carefully selected participants. The pragmatic RWE trial has potential challenges including recruitment of study participants that are similar to those who receive the intervention as part of usual care, recruitment of investigators that reflect health care professionals working in the community as opposed to academic centers, interventions delivered in a manner that is outside standard practice, the potential impact of obtrusive follow-up, and end-points that may not be important to patients (Ford & Norrie, 2016). But the carefully constructed and executed pragmatic trial provides the bridge between researches performed for the development of treatments to the evaluation of the effectiveness of treatments in practice.

Figure 6 presents the size of the factors that influence IRR (internal rate of return) of the R&D investments in the period of 7 years. IRR is decreasing by more than 50% in the period of 7 years mainly driven by the so-called commercial factors (cost to launch new drug on the market). This is clear evidence that future R&D with a goal to bring more value to the Pharma sector including all market players, should focus on optimization of commercial factors.

Let's analyze the targets. If the IRR>CoC (Cash-on-Cash Return, calculate the RoI by taking annual net cash flow from the R&D investment and divide by the investment's down payment) then this is a solid playfield for any market player regardless of its size. When a company has a project on market, the CoC usually is already close to a large pharmaceutical company discount rate, i.e. between 8% and 10% [9]. Start-up or a company that is still in discovery stage i.e. in preclinical or clinical faces a high CoC of over 20%. Reducing the cost margin in the R&D activities can raise the IRR (profitability of investment) on an average from 7.5% to about 13%. This would raise the RoI to between 14%-15%, from between 9%-10% currently. As a result of the minimal use of debt finance by most firms (cost of capital is expected to rise from currently 5.3%), the WACC and equity capital will be approximately equal to the CoE (Cost of Equity). Companies will invest large part of profits into R&D. Conclusion is to bring down the cost margins of debt or equity capital paid for commercial factors that will consequently increase IRR, RoI and finally, final price of new medicine [10-13].

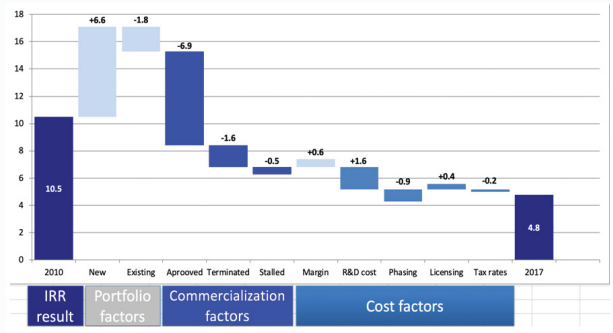

Figure 6: Drivers of change in IRR- Composition of costs in R&D. Source: Deloitte &Thomson Reuters-Measuring the return from pharmaceutical innovation 2019.

High costs produce high investments in R&D while marketability of products is lengthy and risky. Therefore, this process requires addressing of the reference pricing systems in the initial phase and preclinical modelling of the R&D cost of the pharmaceutical products. Sustainability in economic terms means forced necessity for counterbalancing of the 10%-12% reduction of the prices of drugs on main markets, compound rate that was recorded in the last 15 years. This new general approach to the R&D will define new pattern of behavior of all key players alongside the product curve (Figure 7).

New curve is flatter as result of faster and broader market access facilitated by more efficient data exchange and improved regulations. Revenues are generated at early stage of the process which releases

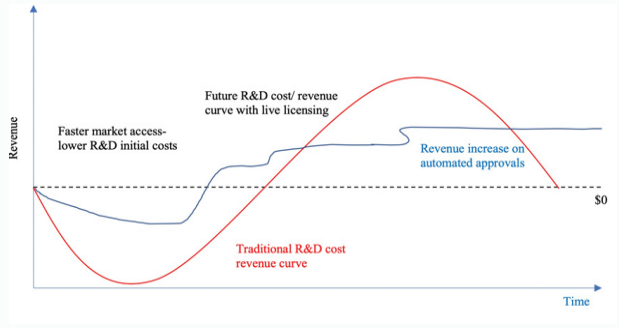

Figure 7: How the R&D cost/revenue curve might look by 2030. Source: Author.

more capital for future R&D and stimulates investments. R&D process will not be reserved only to the big Companies and can be easily outsourced while limiting the risks of failure [13-18].

This is a global effort that will change fundamentally Pharma R&D and deliveries. Setting up trans-institutional initiatives requires breaking down obstructive conventional barriers between disciplines and sources of financing. On the other hand, this will explore the potential for co-creation with patients, companies and other stakeholders who are not normally invited to participate. Balancing of the investments in prevention-related research to the total cost of care should also impact the design and financing of research programs. Finally, this complex and multidisciplinary approach will generate new forms of cooperation and integration between sources of financing. Government support mainly focused in early-stage research through direct budget allocations, research grants, publicly owned research institutions and higher education institutions will inevitably penetrate the R&D in the Clinical trials required to gain market approval stage, which is currently funded by the pharmaceutical companies [19,20].

Conclusion

Today's R&D is investment demanding, lengthy, cost inefficient process producing low RoI. With limited access to markets and geo-disbalance, launching 50-60 medicines in one year makes the process reserved only for big Pharma players. To make R&D process time and cost benefit efficient, new research methods and outcome measures that will focus on valid and sensitive measures for many disorders, that allow us to track and predict outcomes to supplement existing methodologies, are needed.

The new scientific outlook on prevention, treatment and care should impact the design and financing of research programs. At times, that may require us to change the rules, for example so that insurers can also invest in research. Shortening or reduction of the development cycles owning to a faster recruitment of patients from a larger pool looks like optimal solution. When this is complemented with policies of targeted clinical differentiation against the standard of care then drug's future commercial success is guaranteed.

Establishment of a common denominator with a clear 'value proposition' needs to be at the core of pricing and re-imbursement submissions when negotiating prices and market access between companies and regulator. Incremental costs need to consider potential incremental revenues from priority markets (price, positive formulary place, time-to-market) and the potential downside risk of unfavorable comparisons with alternative treatments. One option is simplification of the regulatory requirements/local presence for market access and for acceleration of the drug approval. Local R&D helps in building relationship with the governments and regulatory bodies while providing a market access in a timely way/direct exposure. New Model should also consider outsourcing the R&D to the more efficient, focused, equipped companies. Including the local trials companies will reduce the current time delay between launching the drugs on different markets. Company applies patient outcomes cost- efficiency and economic milestone early in development, that is, before they initiate more expensive late-stage. The essence of this approach is similar to the TQM process.

Combination of shortening of the timing between discovering, validation and clinical development and use of modern designs tools will limit the R&D costs, make them more efficient and leave governments enough maneuver space to succeed in definition of the new reference pricing methodology. New Model will also push the efforts for producing a more relevant pharmacoeconomic studies, increasing both their quality and quantity. New research methods and outcome measures will focus on valid and sensitive measures for many disorders that allow us to track and predict outcomes to supplement existing methodology. What is vital for future R&D is a broad, interdisciplinary approach in which the public/patients, organizations and co-funding bodies also play an important role mainly by investing in sickness prevention and apply the concept of personalized prevention. Data-related infrastructure, access, thinking and expertise based on an advanced data infrastructure consisting of existing and new studies and documentation will also be positioned in the core of the process. Research must also reveal what is needed to implement and scale up interventions on a structural basis and how to make lasting improvements to care processes. Regardless of how personalized medicine and prevention will be organized technology and Health Technology Assessment will play an essential role. To this extend the methods that are used to evaluate technology and determine its effectiveness and cost-effectiveness will need to be updated to keep up with changes in the supply of and demand for health care.

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