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High Cost Medicines

P. Venkata Durga Seshu Priya*[1], Dr. P. Venkatesh[2], L. Manasa[3]

[1-3]*Department of Pharmacy, Jagans Institute of Phaarmaceutical Sciences, Jangala kandriga, Nellore, A.P.*

ABSTRACT

The healthcare expenditure is continuously growing at an unprecedented and unsustainable rate. With the shift to value-based care, healthcare organizations are expected to provide consistent high-quality, safe care while reducing healthcare costs. As reimbursements shrink, healthcare organization leadership and clinical providers must identify opportunities to minimize unnecessary practice variation while providing high-value healthcare. In recent years, the therapeutic landscape has changed with the proliferation of specialty drugs, which are used in the management of an array of medical conditions, including cancers, chronic infections, autoimmune disorders, transplantation, and bleeding disorders. Loosely defined based on their high costs, the need for special handling protocols, and close patient monitoring, specialty drugs are projected to account for 50% of the total medical expenditure by 2019. The biologic agents, which are produced or derived from a living organism, are the most rapidly growing class of specialty drugs, and hold promise to revolutionize the management of a range of chronic medical conditions. The challenge, however, is reconciling the potential therapeutic benefit with the high cost of these agents. Specialty drugs contribute significantly to the inpatient diagnosis-related group payment system, often with unproved benefits over less-expensive treatments.

Keywords: Healthcare expenditure, reimbursements shrink, high cost, protocol, biologic agents, medical conditions.

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Corresponding author
P. Venkata Durga Seshu Priya
Department of Pharmacy
Jagans Institute of Pharmaceutical Sciences
Jangala Kandriga, Nellore, A.P.

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1. Introduction

Global health care expenditures have been rising sharply, and drug costs are a major factor. The imatinib, a drug for chronic myeloid leukemia, which tripled in cost after the US Federal Drug Administration (FDA) allowed for a new indication. Novartis raised its price from $31,930 in 2005 to $118,000 per year in 2015 despite a huge increase in the volumes sold. The price hike occurred despite the fact that research costs for the new indication were included in the initial price. Also in the US, the list price of sofosbuvir (Sovaldi®) is $84,000 for a 12-week treatment, or $1,000 a pill, which has caused health plans to refuse routine coverage of this drug for hepatitis C virus (HCV) infection. Sovaldi® alone accounted for 64% of US HCV-related spending in 2014, which totaled $12.3 billion. Sovaldi® could be cost effective, since it prevents the ultimate need for a liver transplant, but the financial

impact is too high for US insurance companies to make it available for all patients with HCV infections. The cost of pyrimethamine (Daraprim®), a 60-year old drug, rose from $13.50 to $750 per pill (a 5455% raise) after Turing Pharmaceuticals acquired the distribution licence. This has further sparked public debate. Additional price hikes in Mylan's EpiPen® from $94 ten years ago to $609 for a pack of two have caused additional public backlash, protests and US Congressional hearings. Governments and health insurers are struggling with the dramatic increase in costs of new medications[1-9]. In December 2015, the US Senate issued a warning report on Sovaldi's escalating drug price and its impact on the US health care system. The committee report said the Gilead Sciences pharmaceutical company had set the price as a benchmark to "raise the price floor" for its future hepatitis C-drugs like Harvoni, thus knowingly reducing the number of eligible patients for these superior treatments to cure HCV[10-15].

Simultaneously, on the other side of the Atlantic, the UK cost gatekeeper, the National Institute for Health and Care Excellence (NICE), initially rejected reimbursement for two costly cancer immunotherapies—nivolumab (Opdivo®) and trastuzumab/emtansine (Kadcyla®)—despite fierce opposition by industry and patient groups. With a number of better targeted immunotherapies–that fit within highly promising precision medicine approaches–on their way to the market, the drug pricing and funding crisis is expected to deepen and reach a critical level for even the wealthiest countries. The German government is planning to curb companies' right to set launch-prices. Belgium, Luxembourg and the Netherlands are working together to seek a common approach to their price negotiations with drug firms. A January 2017 Lancet commentary co-authored by the Dutch Minister of Health Edith Schippers stated that: "We need meaningful efforts by both the pharmaceutical industry and governments to invest in new medicines, provide full transparency on costs, prices, and who pays what beforehand, and respect the legal space for governments to protect public health. If we don't succeed in these efforts, we cannot guarantee people's access to innovative and affordable medicines[16-21].

The prescription drug price controversy is not new. In the 1990s, there were comparable heated debates on the high prices for interferons, paclitaxel (Taxol®) and HIV/AIDS medication.Though the prices of these drugs were much lower than current new drug price levels, the fact that taxpayers had helped to pay for developing those innovative therapies at the time, generated public debate on fair pricing. In LMIC, where the need for HIV/AIDS medication was the highest, the fair-pricing issue was even more pressing, particularly with regard to the problematic availability of essential HIV medicines. Pharmaceutical expenditures are based on two factors: price and volume. This means that regulation can either aim to lower drug prices, or reduce usage. On the one hand, there is a growing life expectancy (and aging population worldwide), while there are increasing medical options for disease control. Therefore, following drug innovation expectations and usage growth statistics, it is likely that costs will continue to rise. Many countries are striving towards universal health coverage, with guidance from the global public community, to reduce individual catastrophic spending. Although these countries are preventing individual catastrophic spending by pooling risks and costs, a sustainable solution to the problem of fast-rising drug costs is still necessary. The solution will require unprecedented measures to prevent health care costs from spiraling out of control. Though specifics can vary wildly, the general shape of the curve of investments during the drug development phase, exponential growth of sales after registration and decline through competition and patent term expiration is valid for most drugs. Drug life cycles generally have four stages. First, there is a testing and approval trajectory. Second, after the drug is introduced there is market expansion, and the product is accompanied by growing expectations and drug indication extension. Next, drug maturity with a high sales volume is accompanied by rising criticism and disappointment regarding drug effectiveness and side-effects. Finally, there is contracting use and limited drug application. In most cases, this is a gradual process that involves the documentation of less favorable experiences and reports of the drug's effectiveness and adverse reactions in everyday practice. Thus, a drug's benefit-risk assessment and the resulting safety profile is under constant revision. Over time, newer and presumably better alternatives gain attention[22-26]. This is part of an evolutionary process of selection and adaptation. Most brand-name medicines continue their careers as generics after their patents expire. On average this results in a 20–25 year therapeutic life-time in 'the doctor's bag'–the portfolio of drugs available to a doctor–due to therapeutic substitution and competition between branded drugs and generics.

Types of prescription drugs

This article refers to prescription drug prices, but there are distinct types of prescription drugs and this requires clarification. First, there are drugs that are under patent, with an exclusive producer and no direct competition. Then, there are generic drugs with an expired patent that allows for production by other manufacturers.

Biological drugs follow the life-cycle patterns of small molecules or conventional drugs, but higher prices are accepted and specific regulation of generic competition is in place. Oncological drugs are a separate category, because high prices are historically more common, expected to rise, and more acceptable given the severity of the indications. Laws are in place to incentivize the development and marketing of orphan drugs, which means they follow market dynamics that differ from conventional drugs. Finally, when the patent runs out, and other

producers can manufacture the same drug, generics are introduced. In the case of biologicals, biosimilars compete with the innovator while following a specific set of regulations[27-29].

Patents and registration

The pharmaceutical industry is often characterized as a competitive sector in a free market, where the total supply and demand determine market price. However, according to business analysts, in a truly free and competitive market without patent regulation, it would be difficult to profit from new drug development. This is why governments protect companies from competition during the life of a patent.

This can be extended to 25 years. In addition, in the US, the FDA can grant exclusive marketing rights upon a drug's approval, which is generally concurrent with the length of a patent. The FDA usually grants new drug exclusivity for between seven years for orphan drugs and five years for new chemicals, with an additional period of six months of exclusivity following pediatric approval. Patents are also granted for new chemical entities. This allows companies to charge high prices once the drug is ready for marketing. Patents then become public, which gives other producers the chance to further improve and develop the drug. Patent timelines are limited, which provides an incentive for companies to shorten the drug development phase or look for disease areas with less stringent trial requirements.

For example, there is more research in drugs for late-stage cancer than early-stage cancer, because of the less demanding and shorter trial trajectories. The number of patents a company files, or alternatively the research and development (R&D) costs per patent filed, are often used as an output measure for the efficiency of drug development and the future of a firm. Since most patented molecules do not make it to the market as an actual medicine, both datasets are incomplete representations of productivity. In debating the patent system, some analysts state that basic human rights like health and access to essential medicines should be equitable and should not be limited by property rights.

Developmental phase

Pharmaceutical companies must register new drugs, which requires clinical studies and safety tests. This is a high-risk, high-cost and low-output endeavor. The odds of having a drug approved varies from approximately 24% (for systemic anti-infective drugs) to less than 10% (for drugs used to treat cardiovascular, gastrointestinal or metabolic disorders). On average, it takes a company ten years to register a drug. Thus, companies have to decide on projects that have a good chance of becoming registered drugs several years in the future. The drug development process requires investments, estimated at between $60 million to $2.6 billion, most estimations are close to $800 million from bench research to prescription medicine. The wide range of cost estimates is due to the lack of clear data and various methods of calculation, and depends on the type of drug and the trial data required, as well as the size of the company developing the drug. Development costs are highest for large companies due to their relatively high overhead and marketing costs. Historic examples illustrate what happens when the demonstration of medicine safety during development is not adequately regulated. An exemplary case is the thalidomide drug disaster that took place between 1958 and 1962[30-31].

This drug for morning sickness resulted in malformations in the extremities (phocomelia syndrome) of thousands of babies born to women who had taken thalidomide during pregnancy. Regulatory reaction to drug safety alerts often involves the introduction of more stringent regulations requiring more safety and efficacy studies, which leads to more dropouts in the development process and an increase in invested time and costs. Regulatory agencies are criticized by many parties for being either too stringent (delaying innovation and increasing costs) or not stringent enough (allowing dangerous drugs to be marketed). Arthur Daemmrich, a US historian, discussed this tension between safety management and drug innovation and was the first to use the term 'double bind trade-off phenomenon'.

The imperative of regulation makes it more difficult for smaller companies to register drugs, thus limiting the number of firms with the critical mass and financial means to invest in drug research. This situation limits viable competition from smaller companies for Big Pharma—the collective sector of large pharmaceutical companies. That is why most new drugs that received a positive reaction from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) between 2010 and 2012 were filed by large (59%) or intermediate-sized (28%) companies[32-35].

Small enterprises are important during early phases of development. However, in later phases, if the success of a new chemical entity developed by a small company is likely, a large pharma company will often buy the small company or purchase the licence for the new medicine. Higher investments, however, will not necessarily fill R&D pipelines with new promising drug compounds. R&D has recently yielded fewer drugs than in years past, since low-hanging fruits have already been harvested. Furthermore, there are many drugs with promising results in phase II settings that have not made it to phase III settings. Regulatory agencies allow drugs to be released to the market based on safety and effectivity, but not with reference to price or cost-effectiveness. This means the price and reimbursement of a drug are determined only

after registration approval and insurance company and/or government negotiation.

Post registration and reimbursement

Once a drug is registered for a specific disease indication, manufacturers can apply for reimbursement. Many public health care systems allow the government to control drug prices. Some base the acceptability of a price on the Incremental Cost Effectiveness Ratio (ICER) and budget impact.

This means companies have to assess the volume of sales and the price at which they are reimbursed, and then offer a price based on that estimate. Then, negotiations take place between the company and the reimbursing agent or government to determine an acceptable price for each stakeholder.

A drug's reimbursed price can be lower than the pharmacy retail price or list price. This makes patients aware of drug prices, since they will have to pay for the difference out of pocket. Such pricing and reimbursement schemes can be a tool to make patients switch to cheaper or generic drugs, and make manufacturers of high-priced drugs lower their prices to prevent patients from making this switch.

Manufacturers argue that patient co-payments can cause adherence problems, especially for expensive and psychiatric drugs. This means physicians and patients prefer drugs without co-payments. To circumvent this situation, producers have implemented patient-assistance programs, which are discussed in paragraph 5.6. Companies want to make the highest possible profits in each country by differentiating prices, but they also want their prices to be similar across countries and close to competitors to reduce the incentive for parallel importation. Governments worldwide want innovative new drugs to be available as quickly as possible, so their population can profit from them. High drug prices may incentivize companies to develop and launch their new drugs faster. On the other hand governments also want to have affordable drugs for everyone at the lowest possible price, to reduce healthcare spending.

In Europe, marketing to doctors and pharmacists is permitted, if it is medically substantiated. This requires more expensive studies, and careful wording of the marketing message. Still, marketing is a large part of the pharmaceutical industry's expenses. In fact, more money is spent on marketing than on R&D. To market drugs to doctors and circumvent this regulation, trials are sometimes used as a marketing tool. 'Seeding trials' are designed to 'seed' the use of a drug among patients and physicians, while they often offer no scientific purpose.

Mature phase

During a drug's patent life, doctors and pharmacists play a crucial role in the choice for one drug over another. These professionals need to inform the patient about their pharmaceutical options, and a drug's effectiveness and costs. This is why advertising aimed at brand recognition continues during the mature phase of a drug's life cycle.

Several studies have shown that if there are financial incentives for doctors to choose one drug over another, the one that is most beneficial to the doctor's finances is most likely to be prescribed. In the US, where Medicare and Medicaid reimbursement is based on a 6% mark-up of the price of cancer drugs, doctors have an incentive to select the more expensive option. This is another explanation for the high prices for drugs in the US. In order to help patient and doctors, the European Society for Medical Oncology and the American Society of Clinical Oncology have developed frameworks to assess the value of new cancer drugs.

In this phase, companies often attempt to have their drug registered for additional indications, thus increasing the number of patients, to increase their sales volume. A larger patient base would logically make the cost per treatment lower, but this is often not the case[36].

Declining phase

Several countries around the world have implemented preference policies, aimed at generic substitution. This policy requires physicians to prescribe and pharmacists to dispense the cheapest available version of a drug, often generic, unless a more expensive one is medically necessary. This can be the case for drugs with a very small therapeutic window, like Tegretol® (containing generically available carbamazepine) for the treatment of epileptic seizures.[127] For these drugs, the preference policy implies that new patients start on a generic drug, but those who have already reacted well to a branded version do not have to switch. The potential substitution rate differs per indication group. Some drug brands are so strong that, even after the loss of market exclusivity, doctors and patients continue to privilege them over generic drugs. Examples include brands like Viagra®, Prozac® and Aspirin®. For over-the-counter medicines, in particular, branding is a relevant mechanism to maintain market share, since consumer name recognition is a more important factor in product choice when there is no medical professional role.

Drug pricing and profitability

Drug life cycle analysis indicates a trend of shortening life cycles and pharmaceutical companies experiencing more difficulty achieving high, sustainable sale volumes during the past two decades than before. Since a company's income is based on volumes multiplied by price (equals value), the first strategy to maintain high revenues is to increase price. Despite regulated pricing, this practice results in drug spending growth matching overall medical spending growth. On average, the top ten pharmaceutical companies have a profit margin of 20%; those noted in the S&P 1500 have a net profit margin of 16%, compared to 7% for all other companies in the index. This means that even

though companies experience more difficulty in achieving long-term high-volume prescription drug sales, the higher drug prices compensate for the lower product turnover and safeguard Big Pharma's high-profit profile. This is not surprising, because pharmaceutical companies are for-profit entities that wish to maximize their profits and increase share-holder value without breaking the law.[37,38]

However, this approach means they may not automatically do what is best for society. Critics argue that more regulation is needed to counterbalance Big Pharma's only-for-profit motive and force them to do what is best for all stakeholders. Through a number of interventions (some more effective than others) governments and their regulators have tried to direct either the price of drugs or the availability of innovations. Government interventions to stimulate or curtail the pharmaceutical markets and the introduction of new procedural measures concerning drug patent licences and drug registration licences are discussed in the next chapter.

Drug pricing interventions

As stated previously, though the pharmaceutical market is often portrayed as a competitive market, it is not truly a free market. In addition to the patent system, skewed economic dynamics create further complexities. In free markets, a consumer decides on, buys, pays for and uses a product, whereas in healthcare, a doctor decides and the pharmacy or hospital pharmacy provides, the insurance company or government pays and the patient uses the product. Financial incentives are not aligned with consumption, so companies' pricing power is not related to how consumers value the products.

Orphan and priority drug regulations and potential consequences: The first option is to speed up innovation and regulatory approval, so that companies have less waiting time before marketing a drug and thus enjoy a longer profit-generating post-marketing patent life. One way to do this is to accept surrogate parameters as trial endpoints to prove efficacy, which saves time. Another innovative option is to harmonize regulation between countries, so companies only have to prove efficacy once.

FDA's unapproved drugs initiative and consequences

The FDA states that it uses a risk-based enforcement program in order to focus on products that pose the highest threat to public health and "without imposing undue burdens on consumers, or unnecessarily disrupting the market". However, the program has had unintended consequences. If a product is not officially approved by the FDA, the agency can require a New Drug Application from the manufacturer, which is reviewed to determine if the drug meets FDA standards. Inexpensive generic drugs that have been on the market for decades are studied anew, drug applications are filed and exclusive patent rights to sell the drug are given to the first manufacturer who meets the new FDA effectiveness standard. This manufacturer can then decide what to charge with no competition[39].

Possible drug-pricing measures

There are many ways to reduce spending on drugs. However, all are based on one of four general intervention options:

1. Shift from expensive to cheap drugs, within the same class,
2. Shift costs towards patients or insurers,
3. Reduce drug prices,
4. Reduce total drug uses.

Pharmacists in price reduction programs

As stated previously, physicians and pharmacists have a central role in determining which patient receives which medicine, and whether the use of expensive drugs is beneficial for specific patients. Programs that provide financial incentives for prescribers to save on costs incentivize physicians to be cognizant of drug prices and have the potential to reduce pharmaceutical expenditure gradually and permanently, by either rewarding when expenses are low or enforcing penalties when expenses exceed indicative or earlier budgets. After the implementation of such programs, doctors are more inclined to believe that medical costs are a relevant consideration in drug usage.

Value-based pricing measures

The ideal pricing model should include the health and socio-economic benefits of a drug by deploying sophisticated out-come based compensation models. The price of a drug should be proportionate to the added value in terms of quality of life, life years saved or tumor shrinkage. This would improve the value per monetary unit spent on health care, and increase innovation in relevant areas. A major reason for this is the lack of standardization in the practice of value-based pricing. Which factors are included and which are not varies, so value-based pricing is currently more of an art than a science. Data about the effect of such schemes are contradictory. One factor is that this policy has given a perverse incentive to drug companies to set high drug prices for the new generation of innovator medicines that are in line with the cost-effectiveness threshold (mostly in terms of quality-adjusted life year [QALY] and/or incremental cost-effectiveness ratio [ICER] terms) that a country is willing to pay. This also explains the differences in prices in individual countries, because cost-effectiveness thresholds differ across countries.

Setting price and profit ceilings

Another method of controlling drug pricing is to set price ceilings in various forms. For example, to combat the high prices of generic drugs in Canada, the government has recently negotiated a fixed price ceiling for six of the most used generic drugs. This one-size-fits-all approach might still result in overpricing for some of the six, and be too low to supply the entire market for others. A lower price could probably be negotiated through alternative tactics, like an open-tender invitation, but the several Canadian states failed to agree on an alliance for bulk purchasing.

Transnational licensing and pricing frameworks

To increase access to drugs that are on patent and expensive, but necessary in LMIC, these countries' authorities can choose to issue compulsory licences as allowed by the World Health Organization (WHO). This means that the authorities recognize the drug patents, but are allowed to have local generic manufacturers produce the same drugs, without fearing claims of patent infringement, or they can import the drug from another generic manufacturer. This reduces the costs of a new drug dramatically, though other options like international procurement seem to offer a better discount. Unfortunately, this approach is also administratively cumbersome, since in general, it applies to one drug at a time, and could result in other innovators withdrawing their drug from the market. However, compulsory licensing can be used successfully as part of a strategy to reduce prices offered by the originator.

International procurement is based on collective price negotiations between an innovative company and a union of LMIC. This approach leads to lower prices and more accessibility than compulsory licensing. Lower prices can be achieved through voluntary out-licensing, wherein the originator allows a generic manufacturer to produce the drug at reduced costs in exchange for a royalty. One example is the out-licensing of Harvoni® (containing sofosbuvir and ledipasvir), which Gilead Sciences gave to an Indian manufacturer to produce for 91 LMIC, against a royalty of 7%. High-income countries can also benefit from forming a union to increase bargaining power. For example, The Netherlands and Belgium recently signed an agreement to negotiate process for orphan drugs as a block. Several EU-countries have followed this example and joined the agreement, and some pharmaceutical companies have indicated their willingness to cooperate.

Patient-assistance programs and list prices

Companies that raise prices often defend their actions by stating that patients who cannot afford the drugs are offered assistance in the form of patient assistance programs programmes in Western countries. These programs allow patients to apply for the drugs at reduced or no cost, if they are uninsured and live below a certain income level. The income level is set so that many patients on normal wages don't qualify, so that drug prices can result in catastrophic spending. Furthermore, patient-assistance programs increase the workload for general practitioners' assistants, since they often require many forms. The costs to the healthcare system are still unnecessarily large, and are shifted from patients to insurance companies.

2. Conclusion

The more rise in drug prices worldwide is making healthcare unaffordable even in high-income countries. Apart from historic changes in the drug life cycle dynamics, price-volume proportions, and a transition from "one-size-fits-all" to more stratified precision medicine approaches, this problem is due to patent-induced monopoly positions, unintended consequences of drug and reimbursement policies and competitive market failure. This situation threatens to disturb the fragile compromise between the basic human right for affordable access to healthcare and the utilitarian protection of inventions to incentivize innovation. The current pricing spiral will only stop through well-designed regulatory interventions and measures around drug pricing on a national and transnational levels. Reduced healthcare spending is thought to reduce incentives for innovation, but given the current double-digit profit margins, industrial incomes could be lower without harming the industry's outlooks. Public-private partnerships, in which charity funds are used to sponsor research in exchange for lower prices, could significantly help direct spending decisions on research away from primarily financial motives towards what is best for society. Value-based pricing is a promising but also risky option that is already being used by some countries to reduce costs. The rise in drug prices is caused by uncontrolled market dynamics, changes in life-cycle dynamics and unanticipated policy side-effects.

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