הביטאון לכלכלה ומדיניות תרופות
ISRAEL DRUG BULLETIN

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P H A Rx M A

כרך 14, ביטאון מס׳ 82 כסלו-טבת תשס״ח, דצמבר 2007-ינואר 2008

DRUG PRICING AND ITS REGULATION IN ISRAEL: ISSUES, PROBLEMS AND SUGGESTIONS FOR REFORM

בקיצור רב

- מחירה של תרופה הוא תוצאה של עלות קידום המכירות שלה ומדיניות אי-ההתערבות של ממשלות יותר משל עלות המו״פ או מההתקדמות הטיפולית שלה. חרף זאת, מחירי התרופות הגבוהים אינם על סדר היום הציבורי בישראל, שלא כמו במדינות אחרות. מאמר זה מתמקד בתמחור תרופות וברגולציה שלהן בישראל: איך זה עובד, מהן הבעיות, וכן הצעות לשיפור.
- שיטת ״ציטוט״ המחירים, המבוססת על מחירים (לבית-מרקחת) במדינות האיחוד האירופי, אינה מספקת בסיס איתן לפיקוח על מחירי מוצרים עם כניסתם לשוק, מאחר שבישראל התוצר (ההכנסה) לנפש נמוך יותר ומאחר שבכמה ממדינות הציטוט נהוגים מחירים גבוהים ולפעמים גם בלא פיקוח. מחיריהן של תרופות חדשות בישראל דומים לעיתים קרובות לאלה שנהוגים בבריטניה, למרות שבמדינה זו הם מהגבוהים ביותר באירופה.
- יש מקום להשגת תמורה הולמת יותר מההוצאות על תרופות, וזאת באמצעות הערכות של עלות-תועלת, כאשר שוקלים תהליכי תמחור וסבסוד ציבורי. זוהי גם הזדמנות להפוך תהליכים אלה לשקופים יותר מאשר הם כיום.
- כשהתרופה כבר בשוק, יש לעודד תוכניות ל״חלוקת-סיכון״ כגון תמחור על בסיס מספר המטופלים ותמחור על בסיס תוצאים, בעיקר לגבי טיפולים חדשים ויקרים מאוד.
- מחירי הרכישה של תרופות גנריות ע״י קופות החולים ובתי החולים נמוכים בדרך כלל, לפחות במקרים בהם הצריכה גבוהה והתחרות עזה. בישראל חל מע״מ בשיעור מלא על כל התרופות, כולל אלה שבסל, שלא כמו במדינות רבות, המפחיתות את המע״מ על תרופות אלה באופן חלקי או מלא. ראוי לציין כי עלויות ההפצה הישירות בישראל הן נמוכות יחסית, בשל חלקן המשמעותי של קופות החולים בהפצה ישירה.

Government regulation of drug pricing is both complex and a stranger to public awareness. So though it has been with us for years, it remains largely unknown or poorly understood by many affected by its operation. This opacity partly explains how it has flourished for so long despite being flawed. The key determinant of public spending on branded medicines, drug pricing regulation makes almost no attempt to circumscribe, review or otherwise "regulate" the price of individual products according to society's valuation of these treatments. This arbitrary pricing can lead subsequently to skewed assessments of cost-effectiveness and judgments of affordability when deciding which drugs should be added to the basket of health services.

In contrast to other countries, the high price of drugs is not part of the public debate in Israel.[1] This absence of debate is particularly noticeable whilst very expensive drugs (eg biological therapies) are being considered for inclusion in the basket, especially so as their very high price often means that other drugs are left out of the basket. Furthermore, once in the basket their high price continues to create a barrier to access, as manifested by demand-side measures embedded in subsequent Ministry of Health (MoH) guidelines, restrictions by sick funds, and prescription copayments.

The purpose of this article is to put the subject of drug prices on the public agenda in Israel and to help us understand what has gone wrong and what needs to change. Its focus is:

- Drug pricing and regulation in Israel: how it works and what are its flaws and problems;
- How to regulate drug prices better: suggestions for improvement.

BACKGROUND

Most new medicines offer little benefit over existing medicines and in addition, many offer uncertainty over their safety, particularly in the long-term. The FDA estimates that only one-third of new drugs submitted to them are truly innovative, the remainder being little or no improvement on existing therapies.[2] In the absence of a real breakthrough the

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next best thing for a drug company to do is to make its drug seem like a breakthrough. Surveys described in the literature show prescribers are ignorant of costs and tend to underestimate those of expensive drugs.[3]

The cost of R&D of new drugs has long been the excuse for increasingly high drug prices demanded by industry. But the price of a drug is less related to the cost of R&D or to therapeutic advance (witness high prices for "me too" drugs) than to the rising cost of promotion[4] (see Box: Pricing of new drugs: promotion, {perceived} benefits and R&D costs), and the laissez-faire of policy-makers and organisations paying for medicines. The latter should ensure transparency of drug pricing and R&D costs. They should resist pressure from drug companies towards the maximum international price acceptable by rich countries.

GOVERNMENT PRICING

For decades government price controls in Israel involved a complex and opaque set of calculations based mainly on supplier cost inputs.[5] This mechanism changed substantially in 2000 when government, still ostensibly concerned with ensuring prices are fair and not excessive, nevertheless decided to benchmark to high-income European countries: Holland and thus indirectly to UK, Germany, France and Belgium, those countries to which Holland itself benchmarks. Furthermore, some of these countries have no price control (UK, Germany) and/or are first- or early- launch countries as well as having a powerful research-based drug industry (UK, Germany and France). Early launch in high-price countries establishes a benchmark for subsequent launches in other countries, such as Israel.

In early 2007 this generous benchmark was adjusted with the addition of two lower-income countries, Portugal and Hungary, and Spain. However, these countries tend to have later launches. The impact of this adjustment on prices of products in the market appears to have been marginal.[6] This appears also to apply to the prices of new products, probably because these three additional countries are also member states of the EU club where industry tries to keep to uniformly high prices, and also because pricing of new products in Israel may take place beforehand. Prices of new products in Israel are often at a similar level to that in the UK (price to pharmacy), even though ex-factory prices in the UK are one of the highest in EU[7] and elsewhere. Furthermore, prices of drugs are updated usually once or twice a year by the MoH, mainly reflecting changes in the shekel-euro exchange rate. In practice this usually means prices of most drugs are raised at least by 3% per update.

The role of government pricing controls in attaining the goal of cost containment has been limited in Israel. Government has rarely used price controls, such as across-the-board price freezes or general price reductions on existing products, for explicit cost-containment endeavours as is the case in other countries. Government price intervention has to balance wider policy goals, such as ensuring financial stability of the sick funds which, to no small extent, have come to rely both on revenues from prescription copayments and on extra state funding for new drugs; both of these revenue sources are based on the maximum prices set by government and not on the actual prices paid by the sick funds. In the case of copayments for generics and for drugs not in the basket this arrangement translates into actual profits for the sick funds. In contrast, in the case of some of the key European reference countries(eg Holland, UK, France), revenues from copayments are either marginal and/or are independent of drug prices, meaning their governments are not obliged to consider copayment policy as an input to drug pricing policy.

There is also implicit interest in a government list price that leaves plenty of margin for generic producers; the use of price freezes/ reductions could weaken the role of the domestic generic industry.

Government has preferred to use other policy levers in order to create the market conditions which encourage price competition. The effective monopoly life of a patented drug in Israel is often shortened due to relatively late market approval as well as a subsequently delayed and drawn-out reimbursement decision-making process. Also, at the other end of the product life cycle, generic versions of many leading drugs have become available in Israel some years earlier than in many other countries. Patent expiry of a drug in Israel usually occurs as soon as the first patent expiry worldwide.

Another policy reform was the introduction of parallel imports in 2001 after prolonged industry-wide opposition. A preliminary brief report of an assessment based on an opinion survey amongst senior personnel in the health system claims that this has contributed to lower drug prices.[8] Other reforms

have focused on deregulation in order to create wider distribution channels in the OTC market; there is no evidence to indicate that these have attained the declared goal of increasing price competition.

THE ROLE OF THE SICK FUNDS

Capturing the benefits from market forces and the bargaining power of the sick funds has had a major impact on cost containment,[9] greater than any government pricing controls. With only four competing sick funds and with the largest, Clalit, having alone over 50% of the insurance market and over 60% of the prescription market (according to its former CEO it is the third largest drug purchaser worldwide), price competition for generic substitutes and therapeutic alternatives is high. Sick funds are able to negotiate with industry about discounts, rather than prices, and can determine market shares for substitutes. The size of discounts usually depends on the prescription volume of the product. In the case of therapeutic alternatives, market share may be crucially determined by the outcome of a balance of preferences and restrictions set by each sick fund for the various drugs in a therapeutic group.[10]

Negotiations between sick funds and manufacturers about rebates in return for preferred status on sick fund-specific formularies only makes sense as the former are able to oblige providers (physicians, pharmacies and hospitals), or create sufficient incentives for them, to use preferred prescription drugs. With Israeli sick funds able to selectively contract, they do not have a hard time to incentivise physicians to control expenditures, including prescribing. This capability has been facilitated by the widespread computerisation of clinics and physician practices, including prescribing. As a result, the sick funds are able to reduce to a substantial extent the share of prescription drugs that are more expensive than their therapeutic alternatives or generic substitutes.

However, with regard to patented drugs that have no clear therapeutic alternative (i.e. "stand-alone") and that are listed in the mandatory basket the sick funds have much less flexibility and thus leverage. As a result, discounts by manufacturers are miserly and approach zero in the case of life-saving/-extending drugs.

SUPPLY CHAIN: TAXES AND DISTRIBUTION COSTS

In Israel full value-added tax is applied to all medicines including those that are reimbursable. Many countries apply either reduced or zero VAT at least for reimbursable medicines.

Notwithstanding high taxation, direct distribution costs are quite low in Israel, due to the relatively limited involvement of retail and wholesale elements in the chain of supply. Much of the logistics of supply from manufacturer to patient are under the direct control of sick funds, in particular Clalit which has its own supply chain including warehouses and an extensive pharmacy network. Where retail distribution is involved, differential pharmacy margins are applied: between 17%-35% with lower margins for the more expensive products. Retail pharmacies contracted with the sick funds are also required to provide sick funds with a discount based on prescription turnover. Consignment-based supply arrangements between Clalit and retail pharmacy chains have extended that fund's relatively low distribution costs whilst offering its members improved access to retail pharmacy services. Consignment arrangements have also been established between some sick funds and selected hospitals for certain expensive drugs.

PRICING AND THE EFFECTIVENESS OF EXPENDITURES

The reliance on price benchmarking - external (other countries' prices) and internal (prices for other products considered comparable) - rather than economic assessment as a basis for establishing prices suggests there is scope to improve the effectiveness of pharmaceutical expenditures in Israel.

As there is also little use of cost-effectiveness analysis for determining the reimbursement status of new pharmaceuticals - new drugs added to the basket are not ranked according to their cost-effectiveness - companies are encouraged to price their new products at higher levels than otherwise would be the case. Often egged on by their main customers - the sick funds - manufacturers have few incentives to propose the lowest cost-effective price. Another limitation of the Israeli reimbursement system lies in the inability of the state to recoup overpayments (from sick funds) when later information shows that initial decisions on market-entry price and budgetary impact were incorrect. A policy initiative that could add to the efficiency of public subsidy would be the negotiation by government of a maximum reimbursement price *before* a coverage decision is made, and not subsequent to it, as is the procedure today, by sick

funds who often have little leverage then to negotiate a lower price.

Another incentive for manufacturers (with the support of sick funds) to over-bid when submitting a price proposal to the national reimbursement agency is the fact that applications and decisions remain confidential. In contrast in England & Wales, Roche was seen to cut its price of oncology drug Tarceva (erlotinib) by 28% while the national evaluation agency NICE considers an appeal by Roche against its recommendation to deny reimbursement.[11] (In the meantime in Israel the shekel price of this drug continues to rise following price list updates by the MoH). In Germany the NICE counterpart (Iqwig) ruled in 2005 that Lipitor (atorvastatin) offered insignificant clinical benefits compared with its off-patent rivals. It ordered reimbursement only at the cost of generic statins. In the USA, private insurers are becoming tougher: United Health, for instance, removed Nexium (esomeprazole) from its formulary effectively rejecting claims that the drug offered better value for money than the cheaper alternatives.[12]

Generic products are cost-effective – they represent a relatively high share of the market in terms of volume and a relatively small share of the market in terms of value. However, even if high brand-name prices make the Israeli market attractive for generics, generic price competition may still be limited in the case of less frequently prescribed medicines in what is overall a small pharmaceutical market. Furthermore, in Israel there are no incentives for patients to choose generic alternatives for prescription medicines. Incentives may need to be created for pharmacists and patients and not just for sick funds as now so that companies may launch generics with low sales volume on the Israeli market.

REGULATING PRICES OF DRUGS BETTER

International Price Benchmarking

There are two ways international price benchmarking could be improved:

- Choose reference countries with prices that are considered to be lower than in other developed countries e.g. Italy (price levels of reimbursed products are about 14% below the European average and 33% below the UK average[13]) and Australia (prices "are lower than those in much of the developed world."[12]).
- Reconsider the government's earlier proposal for a mechanism to link prices to national income (GDP per capita adjusted for PPP) as part of international price benchmarking. This was dropped following opposition by the pharmaceutical industry, leaving only the addition of three later-launch and EU countries to the list of reference countries.

In addition, the MoH's drug pricing unit should make available information and data on its activities and their impact on pricing and prices.

Pricing Based on Utilisation

Not only are the prices of new products artificially high[4] (see Box), but they are almost never reduced when new indications are granted, eg in autoimmune diseases indications for DMARDs extended to non-rheumatic disorders; broadening of indication for cancer therapies (eg Avastin); Mabthera (rituximab) in non-Hodgkin's lymphoma, and then extended to rheumatoid arthritis. The number of patients treated with Herceptin increased considerably as its initial indication for advanced breast cancer was extended later to adjuvant therapy, but its price is today even higher than at launch, presumably because of MoH price updates. Furthermore, these new biological therapies will remain completely insulated from threat of generic competition for several years, due to robust patent protection and a lack of a regulatory pathway suitable to support generic approvals of biologics.

By granting drug companies prices for their products that fail to reflect actual conditions of use, without regard for the greater public good, the health authorities continue to loose credibility. Prices should be adjusted according to the number of patients treated: government reimbursement could include price-volume agreements for new drugs that would compensate when a drug is approved for further indications and is then used by a far larger number of patients.

A proposal for an Israeli sick fund-based version of risk-sharing suggests that sick funds should be partially compensated by industry if there will be a significant deviation in the size of use of a new technology in the basket from that which has been predetermined.[14] However, it also proposes to continue the current practice of keeping any unused funds in reserve, ostensibly "for adding other drugs to the basket."

Sharing the risks of aggregate overspending of national public subsidies on medicines is another mechanism that has been developed in some countries (eg Hungary and Italy), with repayment by industry to the state or regional authorities of any excess over government spending targets.

Pricing Based on Results

Most medicines do not work in all patients. If that is the case in carefully designed and controlled clinical trials, it is even truer in clinical practice, where complications and poor compliance in taking drugs correctly lower efficacy still further. All patients suitable for treatment should have a chance to see if a new expensive drug works. If it does not work then the payer should not be charged or be given a rebate.[12,15]

Abroad, some companies have initiated risk-sharing schemes based on results i.e. outcomes. Facing rejection by NICE on grounds of excessive cost relative to the benefits, and rather than reducing its price, Janssen-Cilag has proposed to charge the NHS for Velcade (bortezomib) only if the patients show a complete or partial response. It will rebate the full cost of the drug for those who do not respond when treated in line with the drugs' indication.[12,15] This risk-sharing approach is part of a broader effort by health care systems around the world to introduce value-based pricing in an attempt to clamp down on rising medicine costs.

Risk-sharing offers advantages to companies that can show their drugs provide important extra value to patients. However, they will need to provide data, and any price reduction implemented in one country is likely to be rapidly imposed in others.[12] Defining and agreeing on what is a sufficient response will be a crucial issue in such arrangements.[15] Who will define it – clinicians, the sick funds or the government? What type of evidence should be used?

Tracking the true costs and benefits of drugs after launch is also likely to be expensive and not always easy to do. It may be feasible for Velcade, given the infrastructure already in place to monitor patients with myeloma closely. It will prove difficult for many other treatments, as the UK experience with its earlier pioneering risk-sharing agreement in 2002 for multiple sclerosis treatments indicates.[12]

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PRICING OF NEW DRUGS: PROMOTION, (PERCEIVED) BENEFITS AND R&D COSTS

For most drugs there is a spectrum of benefit with some people gaining major net benefit and larger numbers of people gaining less benefit. If a drug is only available at a high price then it is only worth that price for the small group who gains major benefit.[4]

Drug promotion can persuade people to pay higher prices for drugs than they would otherwise by increasing the perceived benefit. Higher drug prices give companies an incentive to do more promotion because they will get more return on their investment in promotion. A high price can also increase the income that companies receive so that they have more money to invest in drug promotion.[4]

The **real ceiling** price is the threshold at which the product provides no more benefit for the buyer than the benefit that would be gained from spending the money on the best alternative i.e. the opportunity cost for the buyer. The **perceived ceiling price** is the highest price that the buyer is willing to pay based on the buyer's estimate of the benefit to be expected from the product. Drug promotion increases the perceived benefit of drugs and thus increases the perceived ceiling price. A high **offer price** can itself also contribute to increasing the perceived ceiling price.[4]

A **highest possible price strategy** is one that involves a seller accepting lower sales as a trade off for higher profits per unit sold ("skimming the market"). High price strategies are made profitable for drug companies selling original drugs by patent monopoly protection. The reduction in competition caused by patents makes persuasive promotion more profitable. In competitive markets (as sometimes is the case of generic drugs), promotion may increase use of all similar drugs, with the company who paid for the promotion only getting a particular share of the increased sales. Without competition, the company promoting a patented drug gets all the sales increase that results from persuasive promotion.[4]

It is often claimed that drug companies selling new drugs must charge high prices to recoup their R&D costs. If that was the only cause of high prices then companies would lower the price for every drug as soon as their income from that drug was enough to cover the R&D costs for that drug. But no company lowers its price for that reason.[4]

Rather than saying that large R&D expenditures causes high prices it is more correct to say that high prices causes large R&D expenditures. Drug companies really charge high prices for new drugs because they are more profitable than low prices. They are willing to invest more money in R&D because they get high

prices. Higher prices also reward and provide the funding for more spending on promotion which in turn can persuade people to accept even higher prices. Drug companies usually spend more on promotion than they do on R&D because promotion provides higher return on investment.[4]

Of course, prices and profits must be sufficiently high to foster a thriving industry and to fund R&D of new treatments. Tax revenues of drug companies show that the bulk of their revenues are not allocated to research. The lion's share goes to marketing and administration, followed closely by returns to shareholders.[2] Compared to most other industries, research-based drug companies spend more on promotion, on staff and on returns for shareholders. Furthermore, much of the companies' R&D investment is on "me too" drugs which have little or no advantage over other drugs already on the market. It has been suggested that in countries where governments are third party payers they could achieve more R&D and greater social benefit by paying lower drug prices and investing some of the savings into R&D directly via competitive tender.[16]

Many third party payers are now using economic evaluations to estimate the **real ceiling prices** so as to avoid the error of paying above the ceiling price; many of them then pay the estimated ceiling price. Even when the drug is as good as estimated there is no consumer surplus because the benefit is cancelled out by the cost of the drug. If the drug is not as beneficial as expected then there will be a consumer deficit – the benefit from the drug will be less than the opportunity cost so purchasing the drug will do more harm than good. Third party payers could achieve more consumer surplus, and funds available for other more cost effective forms of health care, by using their market power to negotiate lower prices to as close to the seller's **floor price** as possible. .[4] (P.S)

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PHARMA Drug Bulletin is a Member of the International Society of Drug Bulletins