



White Paper Series

CHANGING THE WAY WE THINK ABOUT DRUG PRICES: INSIGHTS FROM ECONOMICS

Audrey Laporte, Brian S. Ferguson

White Paper No: W15001

www.canadiancentreforhealtheconomics.ca

October 2015

*Canadian Centre for Health Economics
Centre canadien en économie de la santé
155 College Street
Toronto, Ontario*

CCHE/CCES White Paper No. W15001
October 2015

Changing the Way We Think About Drug Prices: Insights from Economics

Audrey Laporte^{a,b}, Brian S. Ferguson^{b,c}

^a*Institute of Health Policy, Management and Evaluation, University of Toronto*

^b*Canadian Centre for Health Economics, Toronto, Canada*

^c*Department of Economics, University of Guelph*

Funding This policy paper was funded under an agreement between Novartis Pharmaceuticals Canada Inc. and the Canadian Centre for Health Economics at the University of Toronto. Under the agreement the sponsor placed no restrictions or limitations on data, methods, or conclusions and had no control over the outcome of the research.

©Laporte & Ferguson

Executive summary

Pharmaceutical treatment has been growing in significance in Canadian health care over the years, with prescription drug spending rising as a percentage of total health expenditure from 6.3% in 1975 to 13.4% in 2014, while the hospital expenditure share fell from 44.7% to 29.6% and the physician expenditure share remained fairly constant at roughly 15%. The rate of increase in publicly funded pharmaceutical expenditure, which was greater than the rates of increase in spending on hospitals and physicians in the early 2000s, dropped to rough equality with the rates of growth in other sectors in 2009 and to virtually zero from 2012-2014¹.

The benefits of pharmaceuticals have also been growing: a 2013 Conference Board of Canada report, looking at spending on six classes of drugs, concluded that the province of Ontario gets back roughly twice as much in benefits as it spends on pharmaceutical treatment². Nevertheless, discussions of the role of pharmaceuticals in health care tend to focus solely on costs and in particular on the prices of individual pills. One common comparison is between the price charged for individual pills and the cost of the physical manufacture of a pill, with the interpretation always being that the research-based pharmaceutical companies are making unjustifiable profits on essential medications.

The public debate is likely to become more contentious as research continues to shift from traditional chemical drugs to biologics and as personalized medicine becomes more important. Recent developments in cancer immunotherapy are particularly relevant here since training the body's immune system to attack certain types of cancer involves both of these new fields.

Eventually we should be able to develop personalized medicine markers so that we will be able to tell which drugs will work on which patients, but until then we are facing considerable uncertainty about the likely effectiveness of a new drug once it moves from the clinical trial setting to the world of real medical practice. This sort of uncertainty has prompted the design of various types of Risk Sharing pricing schemes: we propose that these schemes should be looked at through the lens of the economic theory of insurance, and suggest that an insurance market could be developed to make Risk Sharing Schemes more effective.

This paper suggests that there has been a fundamental failure in the way the pricing of medication has been explained to the public and to politicians. We suggest that the most fruitful way to think about pills is not as individual inputs into the production (and cost) of medical care but as the equivalent of kilowatt hours of electricity: units of measurement which represent the flow of services generated by a production sector: in the case of electricity, when we pay for kilowatt hours of power we are paying for the services produced by the capital assets embodied in generating plants, and in the case of health care, when we pay for pills we are paying for the services produced by the intellectual capital embodied in the pharmaceutical R&D enterprise. From that perspective, expecting the price of a pill to be closely tied to the price of its physical manufacture is akin to expecting the price of a Kilowatt hour of electricity to be closely tied to the cost of manufacturing the wire over which it is delivered. Pharmaceutical R&D is a capital asset that incurs costs and yields benefits over time. The analysis of this asset is complicated by the fact that the time pattern

¹Canadian Institute for Health Information (2015): *Prescribed Drug Spending in Canada, 2013: A Focus on Public Drug Programs*

²Conference Board of Canada (2013): *Reducing the Health Care and Societal Costs of Disease: The Role of Pharmaceuticals*

of the costs is in general quite different from the time pattern of the benefits, but the net present value of the flows of costs and benefits can be used to value the original asset.

Seen as an asset, we can value pharmaceutical R&D from both the perspective of the firm and from the benefit of the payer. In the latter case the stream of benefits incorporates both the stream of health benefits produced by a new drug, as valued by the agency involved, and the stream of cost savings to the health care system overall. When we look at the original research enterprise as a capital asset, we can also see more clearly how to allow for the benefits to the health care system that will follow from a prescription drug going off patent. We argue that, since the generic copy would not exist had the original drug not been developed, the cost savings and health benefits of the post-patent period should be credited in part to the original research-based pharmaceutical company.

There has also been a failure to explain the basis on which drug prices are set in various countries. While drug companies are often accused of putting a dollar value on human life, in countries whose regulatory agencies use cost effectiveness analysis as part of the marketing approval process, it is in fact the regulatory agencies that set acceptable threshold values on a year of healthy life. While the academic literature tends to treat these threshold values as known, in practice there is considerable uncertainty about some of them. This has led to calls, most notably in the UK, for a more transparent approach to setting out the regulatory agencies willingness to pay for a year of healthy life.

Whether a drug is approved for sale in a particular market typically depends in part on its Cost Effectiveness, measured by an Incremental Cost Effectiveness Ratio (ICER) which is, in essence, dollars per unit of health generated by the pharmacological treatment. The public debate, on the other hand, is frequently framed in terms of dollar per pill. On a 'dollars per pill' basis, a wonder drug which could pack its cure into a single pill would come out as worse than a treatment which delivered an equal improvement in health at identical total cost but which required the patient to take several pills per day every day for a decade. Since it seems unlikely that the language of ICERs can be made accessible to public and political debate, it seems desirable to try and find a language that conveys the same type of information in a manner which is accessible to a wide audience.

We suggest that increased transparency in the assumptions underlying pricing decisions on both the firm and the regulatory sides of the market would at least improve the quality of public discourse about the drug price issue. After a discussion of some of the issues involved, we propose starting from a framework set out by Patricia Danzon and colleagues³ and building in explicit assumptions about uncertainty and the time pattern of revenues, including assumptions about the effect on prices of the originator drug going off patent.

We are not suggesting that looking at drugs as an asset will end all debate about the price of drugs. To take one example, there is, and will continue to be, considerable debate about what the true cost of pharmaceutical R&D is. Nevertheless, we suggest that taking an asset-based approach and incorporating ideas from the relevant economic literature will at least help clarify the debate and improve the light to heat ratio.

³Patricia Danzon, Adrian Towse, Jorge Mestre-Ferrandiz (2013): "Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context" *Health Economics* 24(3), 294-301, March.

I Introduction

The cost of pharmaceuticals has become a persistent theme of health policy discussion in Canada. Since 1975, expenditure on prescription drugs has risen from about 6% of total health expenditure to about 13% in 2014, while the share of physician expenditure has stayed roughly constant at about 15% and the hospital share has fallen from 45% to 30%. It is important not to exaggerate the information content of these numbers - because shares must add up to 100%, increases must be balanced by decreases even if there is no causal relation involved. Still, pharmaceuticals have become a much more important part of the Canadian health care system in recent years, as they have everywhere else⁴.

How important can perhaps be judged by the fact that, when Medicare was first introduced, drugs were not included. The exception was drugs dispensed to patients in hospital, and that was itself significant: there was a limited number of important drugs to be taken other than on an inpatient basis. In recent years, not only have all provinces introduced public drug plans to cover the pharmaceuticals costs of certain classes of patients and of diseases, but the provinces have proposed the establishment of a national drug plan and have called on the federal government to take the lead in designing it.

Much of the recent attention paid to pharmaceutical care has focused on drug prices. There is a widespread feeling that we are paying more and getting less and a suspicion that the research based pharmaceutical companies are more concerned with squeezing every cent they can out of existing drugs than they are in finding new, innovative drugs.

It is certainly true that the pace of drug development has slowed and the productivity of pharmaceutical R&D expenditure has declined sharply in recent years, although recent developments in cancer treatment have offered promise that this may only be a short run decline. Nevertheless, the research-based pharmaceutical sector is faced with what has been termed the patent cliff: the expiry of many blockbuster drug patents, with no drugs of similar importance ready to emerge from the pipeline⁵.

It is not clear why this might have happened. Sometimes, of course, a drug simply falls short of expectation. That would be the case if, for example, it had an effect in a large part of the patient population, but the effect was less than had been hoped. A price based on the expectation of a

⁴The costs of pharmaceuticals are often discussed, their benefits less so. Benefits include health gains to individual patients and also externalities to the system associated with the fact that being able to treat more patients on an ambulatory basis means that hospitals can focus on treating more severely ill patients. This change in concentration may, of course, increase hospital costs on an annual budgetary basis, something which is relatively easy to measure, but increase the productivity of the health care system overall in ways which are rather more difficult to measure. In this paper we will be dealing with costs and benefits at the level of the individual drug.

⁵In a report for Industry Canada, IMS-Brogan estimates the value of drugs going off patent for the period 2005 to 2016. The value of patent losses, measured in terms of sales in Canada of the drugs involved, was \$295 Million in 2005 and \$341M in 2006, then jumped to \$1,200M in 2007, \$1,000M in each of 2008 and 2009, \$1,800M in 2010, \$1,100M in 2011, an estimated \$2,460M in 2012, \$755M in 2013, \$964M in 2014, \$828M in 2015 and \$462M in 2016. It is presumably no coincidence that the CPI for prescribed medication actually started to fall in 2009 and continued to fall through 2015, as brand name drugs went off patent and were replaced by their generic counterparts. The All-Items CPI continued to rise. While the price drop was due to the shift to generic drugs, those generic drugs only exist because of their brand name counterparts. For the patent expiry data see *Canada's Pharmaceutical Industry and Prospects*, Industry Sector, Manufacturing & Life Sciences Branch, Industry Canada, Ottawa (2013). For the CPI for All items and for Prescribed Medicines see CANSIM table 326-0020.

greater effect than had been projected is hard to justify when the actual effect is weak.

In other cases the drug might prove effective in a subset of the population and ineffective in others. In that case the mean or median improvement shown in clinical trials might yield an Incremental Cost Effectiveness Ratio (ICER) above the threshold level, even if the drug proves to be highly effective in part of the population⁶.

The first of these two broad cases we may simply file under the heading “drug discovery is difficult”, and accept that compounds that look very promising in the lab can wash out when tried in human beings. The second case raises a different set of questions. While it might look as if we are dealing with a case of a broken drug, the advent of the concept of personalized medicine raises other possibilities that are worth considering.

The Rise of Personalized Medicine

Personalized medicine is the term used to refer to situations in which the genetic makeup of the patient affects the success of particular drug treatments. It can also encompass the case in which the genetic makeup of an invading agent affects treatment success - when there are different, but unidentified, strains of a disease that respond differently to different drugs. In that case the personalized element refers to the particular strain an individual happens to have been infected by.

In either case the success or failure of a drug differs across individuals for reasons which are systematic but which, in the current state of the science, happen not to be known. This is not a case of a broken drug, it is a case of a drug which works when matched with the right patient, but where we lack the ability at present to do the matching.

This situation represents a significant change from the circumstances that marked earlier post-WWII drug development. In the earlier years of the penicillin era, drug development tended to focus on battling invasive organisms, with the objective of finding a drug that would kill the invader without seriously harming or killing the patient. Success tended to be defined, quite reasonably, in terms of the recovery of a large segment of the patient population. There might be cases where a

⁶The ICER for a new drug (or other treatment) is the ratio of the change in total costs resulting from switching from the existing to the new treatment to the ratio of the change in total health measure (usually a measure of Quality Adjusted Life Years - QALYs) produced. The assumption is that the two treatments are mutually exclusive - this is the case even if the new drug is an add-on, where the old treatment is defined as the regimen without the new drug and the new treatment is defined as that with it included. The total cost of the old regimen is subtracted from the total cost of the new to give the incremental cost, and the total health outcome of the old treatment is similarly subtracted from that of the new to give the incremental QALYs, then incremental cost is divided by incremental outcome. Many countries' public drug approval agencies have a threshold ICER for drug approval. If the actual ICER exceeds the threshold the new treatment is judged too expensive, at the price proposed by the drug company, and not granted approval. If the actual ICER is at or below the threshold the new drug will typically be approved. It is important to note that the ICER is calculated on the basis of the treatment of a single patient, and the decision to approve often does not take account of the budgetary implications of the new drug. One issue with the use of ICERs in drug approval is that agencies frequently do not publish their thresholds. Presumably this is to discourage drug companies from gaming the system - putting resources into finding ways of raising the price of their product to the highest level consistent with the threshold ICER. It may also be a device for allowing the regulatory agency to vary the threshold - accept a higher cost per QALY for a drug whose incremental benefit was relatively small but whose mechanism of action was innovative and promising of future advances than it would accept in the case of a more conventional drug. While this gives the agency flexibility, it introduces uncertainty because of the subjectivity involved in judging innovativeness.

drug would not work on a particular patient - in earlier periods perhaps because of drug allergies, more recently in a more personalized medicine sense when the patient happens to have contracted a drug resistant strain, but the expectation was in terms of widespread success. One legacy of this period was a tendency to criticize drug companies for going after blockbusters, and ignoring smaller market drugs.

While the sort of drug development which marked the earlier period is still important, especially in the effort to develop antibiotics to which bacteria are not resistant, the types of illness being targeted by more recent drug development fall into a different category. While some research still deals with fighting off invaders, much other research is focused on repairing things that have gone wrong in the functioning of the patient's body. It is in this type of condition that the individual patient's genetic make-up is more likely to play a role.

One key practical problem with this kind of research is that, while we might suspect that there are individual genetic factors which play a key role in determining whether a particular drug works on a particular patient, there are very few cases in which we can identify a particular factor, certainly not to the extent of being able to design a diagnostic tool which will let us identify the patients who will respond to a particular treatment.

This kind of uncertainty requires that we change the way we think about paying for drugs. It also requires that we face up to certain facts about drug development. As noted, drug companies have, in the past, been criticized by some for pursuing large market blockbusters and ignoring smaller market drugs, and it is certainly the case that drug development has tended to be directed towards cases where the return was in the first instance going to be a function of the size of the market. More recently drug companies have been criticized for trying to turn small market drugs into blockbusters by setting extremely high prices on their products. A key fact however is that small market drugs can easily be almost as expensive to develop as are large market drugs.

The primary costs of drug development arise from the requirements of clinical trials. Phase III trials in particular are expensive because of their size, and sometimes their duration. Their size is determined by the need to attain a certain amount of statistical power when it is suspected that the average amount of health improvement will be small. That is, trials must be powered to detect much smaller average effects on outcomes than has been the case in the past. This smaller effect could arise either from the drug working on a large part of the population but having less effect than might have been hoped, or it might be a reflection of the personalized medicine effect, where there are two subpopulations of the overall patient population; one large one in which the drug has no effect and a second, smaller one in which the drug is highly effective. Absent a marker that allows us to assign patients to subpopulations, we need large trials to ensure that we are not rejecting a drug that could prove very beneficial for a smaller population⁷.

Even in cases where we can identify the factors which will make a drug successful in a subset of the population we have cost problems. The clinical trials required to demonstrate the effectiveness of a small market drug will only be small if we can identify target patients accurately and if we have a reasonable expectation that the effect on that pre-determined population will be large. In that fortunate case, Phase III trials for a small market drug will require small trial populations and the costs of drug development will be correspondingly reduced; otherwise the cost of development

⁷See, for example Malorye Allison "Can cancer clinical trials be fixed?" *Nature Biotechnology* 29(1), January 2011.

for small market drugs will be every bit as high as that for large market drugs and the cost per pill can be expected to be much higher in the case of the small market drug. It is important to note that the development cost for any drug will depend on the expected effect size, not the size of the market. When we are only hypothesizing that there exists a patient (or disease) subset with favourable genetic characteristics the Phase III trial must be large enough to allow us to detect in the overall population an effect which is small on average even though large in a subgroup.

Whatever the reason, the prices of pills have been rising. The increase is made to seem particularly large in the public's eye because of a tendency to think that the price of a commodity should be based on the cost of physical production of that commodity. Most people have no idea how the price of an iPhone compares to the cost of producing it (and, interestingly enough, with only occasional exceptions, most people do not seem to begrudge Apple the profits it makes on assorted electronic equipment) but it is widely known that most pills cost very little to manufacture, especially compared with the prices reported to be charged for them.

We argue in this paper that it would be a useful contribution to public debate were we to stop thinking about pills as if they were individual entities but rather to think about them as the stream of output produced by a capital asset, the pharmaceutical R&D enterprise. With this in mind, we give an overview of some recent developments in the literature on the pricing of pharmaceuticals, and propose that adopting a capital asset perspective allows us to bring them together into a single unified framework in a way which would make pricing decisions much more transparent, and easier to explain to the press, the public and the politicians.

II Background

The issue with which we are dealing arises from a tendency to oversimplify the nature of the production process for medical care. If we define treatment outcome as the output of the production process, the inputs can be categorized broadly as labour, capital and materials. Pharmaceuticals are usually thought of as materials, on a par with bandages, and the implicit assumption is often made that materials should be priced at a moderate mark-up above their physical cost of production. In all cases, the price should be sufficient to keep the supply coming in the future, but the underlying idea, were it to be expressed clearly, would probably hold that something which was not costly to produce should not be costly to buy.

This would also, of course, imply that an input that was costly to produce could reasonably be costly to buy. The issue with pharmaceuticals, then, is in part a failure to think clearly about their production process. We should be thinking of pharmaceuticals not in the way we think about bandages but more along the lines of the way we think about electricity: as a stream of units embodying the stuff produced by a large, off-site production facility. The production of a certain amount of output requires a certain number of kilowatt hours (KWhs) of electricity: that electricity is purchased from an external production unit and each KWh is priced in a manner that reflects the costs of the generating station. Electricity is a produced input, and if we are to continue to be able to use it in upstream production processes, we must accept that its price will reflect the costs of production of the individual KWhs at the generating plant and further that the generating plant is a very capital intensive production unit.

Individual pills should be seen not so much as items in their own right but as embodiments of the intermediate output being produced by the pharmaceutical sector. This means that their cost must take account of the capital costs involved in their production. In the case of electricity generation the capital cost is visible - there is clearly a considerable amount of fixed capital equipment involved in the production of any given number of KWhs of a given energy form, whether hydro, solar, nuclear or any other. This capital is visible, clearly must be financed, and the sheer magnitude of the financing means that the capital cost will have to be recovered from the stream of revenue generated by selling the stream of output - KWhs - which the plant can produce. We can, in other words, relate the value of the stream of the plant's output to the production and operating costs of the generating plant itself.

We can make the same argument about pharmaceuticals, substituting R&D for the bulk of the fixed capital (although the production of the physical pills does involve the use of fixed production capital) - as Danzon and Towse (2003) put it:

“This large R&D expense complicates pricing for several reasons. First, R&D is a fixed, globally joint cost; that is, this cost is largely invariant to the number of patients or countries that ultimately use the drug and cannot be causally attributed to specific countries.”⁸

Danzon and Towse's reference to R&D as a joint cost merits a bit of explanation. 'Joint cost' is a term used by economists when the processes of production of a number of goods draw on a common input in a manner which makes it impossible to assign the costs of that particular input to the individual outputs. The common textbook examples are agricultural: hides and meat from the same animal, for example. It is possible to determine the labour cost involved in the production of each of those final outputs, but there is no definitive way of allocating the cost of the animal itself between the two outputs. The usual practice is to fall back on a rule of thumb - to assign joint costs in a manner proportional to the value of output, for example. The same issue arises in the case of a trading company that deals in multiple goods and has to own its own warehouse space. If it were able to rent warehouse space for each good as and when it needed it for that good, there would be no cost allocation problem - operating on a venture basis this way makes the bookkeeping easy and means that the trading company is not paying for empty warehouse space. If the company has to own its own warehouse space, which it uses to store its various goods as necessary, the warehouse costs, including the costs of maintaining the space when it is not being used, must be allocated across the various product lines in which the company deals. This is typically done according to some kind of accounting rule, on the grounds that it must be done and there are a variety of equally sensible ways of doing it. In many commercial cases tax considerations may play heavily into the choice of method. In health economics the most commonly cited example of cost allocation is probably the problem of allocating hospital fixed costs - heating, electricity etc., across the various patients in the facility in order to come up with some kind of an average cost per patient day figure or, in economic studies, in order to estimate a hospital cost function. Sometimes the issue goes the other way - estimating hospital inpatient care cost functions often involves coming up with a way of separating the costs of the inpatient departments from those of the outpatient department, which involves assigning joint costs of utilities and administration across the two broad categories of patient care.

⁸Danzon, Patricia and Adrian Towse (2003): "Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents" *International Journal of Health Care Finance and Economics*, 3: 183-205, quote from pg. 185.

In the case of pharmaceutical R&D, the nature of the joint cost is slightly different. The joint-ness here derives from the riskiness of the research enterprise. As we will discuss in a bit more detail below, the majority of drugs that are promising enough to be taken to the clinical trial stage of research do not make it to market. It is estimated that only about 17% of the drugs that reach the human trial stage survive through all three trial phases and reach market⁹. That figure is for what are called small molecule drugs. For vaccines the rate is reported to be closer to 7% (Plotkin et al. (2015)¹⁰). The others fail at various stages in between, often because the promise that they showed in the lab, or in animal testing, does not hold up when they are tested in humans. The incurred research costs of the remaining 83% do not simply vanish when their particular research alley proves to be a dead end. All of the chemists involved in that work have had to be paid.

We often see demands from lawmakers that pharmaceutical companies reveal the research costs of a particular drug. While in principle it would be reasonably straightforward to allocate direct research costs to individual drugs, that figure would be economically meaningless. What matters is the total amount spent on research and the total number of drugs which make it to market as a consequence of that research.

It is unnecessary to make the point that successful drugs are better both from the supplier's and the demander's point of view than are failed drugs. Drug companies do not deliberately spend money on drug projects that they know will fail. As we will also discuss in more detail, drug research is an economically risky way of trying to make a profit, and the riskiness of the investment increases the further the research moves away from well-mapped areas into the realm of previously neglected diseases or diseases like Alzheimer's which have stubbornly resisted any and all breakthroughs.

Clearly, though, there is a fundamental difference between physical capital and R&D. Physical capital is a visible asset, relatively easy to quantify, if not always to value. R&D is intellectual capital, difficult to identify, extremely difficult to measure and even more difficult to value. It is well known that considerable research goes into the development of new drugs, although there is often dispute about the details - in particular, how much is paid by the public sector and how much by the private, and what the true R&D cost of bringing a new drug to market is. The most commonly cited estimates of the costs of pharmaceutical R&D are those produced by the Tufts Center¹¹ which are often disputed, partly on the grounds that the Tufts Center is industry financed, partly on the grounds that it tends to work with data on a relatively small sample of new drugs which are not necessarily representative of the typical stream of output of new drugs, and partly because its estimates include a significant element of what economists call "opportunity cost of funds". Some authors, usually writing in the medical literature, reject the whole notion of "opportunity cost of funds" - i.e. the notion that the funds devoted to R&D should be valued in terms of what they could earn if they were put to alternative uses. Others, who accept the reality of the notion of opportunity costs, would be more likely to dispute the Tufts Center's choice of an interest rate to use in valuing the funds.

Still, while there might be some hesitation about agreeing with the Tufts Center's most recent

⁹See Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal (2014): "Clinical development success rates for investigational drugs" [*Nature Biotechnology* 32: 40-51, January.

¹⁰Stanley A. Plotkin, Adel A.F. Mahmoud, and Jeremy Farrar(2015): "Establishing a Global Vaccine-Development Fund" *New England Journal of Medicine* 373: 297-300.

¹¹See Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski (2003): "The price of innovation: new estimates of drug development costs" *Journal of Health Economics* 22: 151-185

estimate of roughly \$2 billion US to bring a new drug to market¹², their previous estimate, of between \$800,000,000 and \$1 billion does seem to hold up and has been found to be consistent with estimates produced using other methodologies¹³.

The paper by Plotkin et al. (2015) is interesting from this perspective in the way it represents a recognition of the costs of drug development. The authors note that the expense of drug development, which comes primarily from the cost of clinical trials, requires large sources of dedicated funding¹⁴. For vaccine development, they propose the establishment of a fund on the order of \$US 2 billion, which one of the authors has suggested in newspaper interviews¹⁵ might support research on four or five vaccines. Even if only one of the four or five were successful, that would still be a higher success rate than is normally found in vaccine development, and would bring the cost of the development of that one vaccine to somewhere in the ballpark of the Tufts Center's latest estimate for drugs.

There is a further difference between the physical capital of an electricity generating plant and the intellectual capital which underlies advances in pharmaceuticals. The capital cost of putting the electricity generating plant in place is largely front loaded, so the plant can be seen as starting to generate revenue pretty much as soon as it goes on stream. The intellectual capital invested in drug development is spread out over a longer period - through the various phases of drug trials - and there is a much longer gap between investment spending and the inception of a revenue stream. The drug development process is typically taken to span seven to ten years, once the drug enters the clinical stage, so that even if we are looking at funding on an individual research project basis, the period before the investment starts to bring in revenues is very long. If we combine that fact with the 17% (at best) success rate for individual drugs, and remember that we have not included any allowance for riskiness of the revenue stream once a drug makes it to market - it may simply not catch on to the degree hoped for, possibly because a competing drug makes it to market at about the same time - the process of development of a single drug is a very lengthy, very risky investment¹⁶.

While in principle drug development ventures could be funded through the financial markets, the risk of individual ventures combined with the length of time before payoff might begin would compel

¹²"Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion" Tufts Center for the Study of Drug Development news release, http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

¹³Christopher P. Adams and Van V. Brantner (2006): "Estimating The Cost Of New Drug Development: Is It Really \$802 Million?" *Health Affairs* 25(2): 420-428.

¹⁴"These days, the development of just one new vaccine requires a capital investment ranging from \$500 million for the least complex to \$1 billion or more for the most complex, including construction of facilities for manufacture. Moreover, only about 7% of vaccine development projects that reach the preclinical development phase result in a licensed vaccine. With few exceptions, the scores of biotechnology companies and government and university laboratories engaged in vaccine discovery and development lack the necessary resources to carry candidate vaccines through early-stage clinical trials - let alone the costly phase 3 trials required for licensure." Plotkin et al. (2015) pp. 298-299.

¹⁵Carl Zimmer: "Heading Off the Next Epidemic" *New York Times* August 11, 2015.

¹⁶The argument that drug companies need high rates of return to compensate for the riskiness of their research investments is often disputed on the basis of the continuing profitability of many large drug companies. See, for example, the figures given in Stan Finkelstein and Peter Temin (2008): *Reasonable Rx: Solving the Drug Price Crisis* FT Press. We need to draw a distinction here between the profitability of a product (in this case drug research venture) and of a company. A company can be profitable even if the ventures it invests in are risky if it has a large enough portfolio of ventures. Similarly it is possible for a portfolio of individually very risky financial assets to be relatively safe if the assets are chosen carefully with an eye to the correlation across their returns. Diversification is a way of reducing risk, in both finance and drug development.

lenders to demand a high interest rate on any individual drug development venture. This underlies the fact that most drug development is funded from retained earnings of drug companies¹⁷ so that R&D cycles with the cycles in drug companies' gross profit streams.

We have, then, an industry whose contribution to the production of health outcomes involves very large expenditure on R&D capital, which must be funded internally, making the previous years' profitability more of a constraint on future investment than it would be in the case of an electricity generating plant, which is more likely to be funded out of funds borrowed against the expectation of a continuing stream of revenue, which stream can reasonably be expected to begin not too long after the borrowing is done and to continue for a longer period, since power plants don't face the issue of patent expiry.

There are other ways in which the pharmaceutical sector seen as a producer of inputs for the healthcare sector differs from other production sectors.

We have noted the heavy expenditure on R&D capital required for the production of pharmaceuticals. At the same time, as we noted earlier, pills are often attacked as overpriced because commentators tend to look at the average cost of the physical production of a pill. There are other industries in which potential entrants face high entry costs, usually in the form of initial investments in physical capital, combined with low and fairly flat marginal costs of production of the output. In the past, many utilities have been characterized by that sort of cost structure. Usually, in economic analysis, the large expenditure on capital which is required to get into the business acts as a barrier to entry by competitors, to the point that the first entrant can be regarded as a natural monopolist and is regulated accordingly.

The pharmaceutical sector differs in that the high cost of entry into a particular product line applies only to the first entrant. Pills are easy to reverse engineer, so once an effective medication has been discovered it is easy to take it apart and work out what the active ingredient is, meaning that the cost of entry by competing firms is in principle very low. The usual policy response to this is to grant a patent to the first firm to enter the research program. A patent confers a monopoly on that firm for a particular period of time and allows it to earn profits from its drug, with an eye to its recovering and earning a return on its development costs in order to encourage it and by example other firms to continue drug development. Drug patents are less protective than people tend to assume - drug companies face competition from other drugs aimed at treating the same condition, so long as the mechanism of action of those other drugs differs sufficiently from that of the first drug so as not to violate its patent¹⁸.

Even so, patents do create a problem of the balance between what economists refer to as static

¹⁷See, for example, Scherer, F. M. (2001): "The Link Between Gross Profitability And Pharmaceutical R&D Spending" *Health Affairs* September 20(5): 216-220.

¹⁸See Lichtenberg, F. R. and Tomas J. Philipson (2002): "The Dual Effects of Intellectual Property Regulations: Within- and Between- Patent Competition in the US Pharmaceuticals Industry" National Bureau of Economic Research, NBER Working Paper No. 9303, November. One often overlooked advantage of the patent system as a mechanism for encouraging and rewarding drug development is precisely the fact that new drugs can enter in competition with existing, on-patent ones, if their mechanism of action is sufficiently different that they do not violate the first entrant's patent. This is an advantage, since it is often the case that certain patients respond to some drugs and not to others, even though all of the drugs are intended to treat the same condition. The patent system encourages the development of a portfolio of drugs for treating individual conditions. This point tends to be neglected by analysts who regard multiple entrants into the market for the treatment of particular conditions as me-too drugs. Under a properly functioning patent system the only me-too drugs are generics.

and dynamic efficiency. Dynamic efficiency refers to the need to encourage research: without the stream of monopoly revenues yielded by the protected position given the firm by its patent it would not have the resources necessary to continue with drug development. Static efficiency, or better, inefficiency, concerns relate to the fact that the patent does create a monopoly position, at least for a limited amount of time (20 years from date of filing, which is generally very early in the drug development process), and that monopoly position creates economic inefficiency¹⁹. Indeed, much of the recent public debate about drug pricing can be seen as arguments over whether recent pricing decisions have meant that the static inefficiency has come to outweigh any dynamic efficiency gains. This is a significant policy question: while immediate users of a particular medication would benefit most were the price of their particular medication driven down to the level of the marginal cost of production, and the producer would benefit most from a very strong, long lasting monopoly, maximization of long term social welfare, which must take account of the benefits to future patients from future drug development as well as the immediate interests on the two sides of the market, calls for a delicate balance. Ideally, the length and strength of patent protection should be just sufficient to keep innovative drug development going, without making it so easy to live on the proceeds of past successes that there is no incentive to devote resources to ongoing research.

III Drugs as Assets

The way to think about pharmaceuticals when we are taking a societal or a payer perspective, is not as individual commodities in their own right but as units of account that allow us to measure the stream of services generated over time by the capital asset which is pharmaceutical R&D. This perspective is quite different from that of the individual physician or patient. From the latter perspective, pills should be thought of as individual inputs which are being bought as a necessary part of the process of producing medical treatment. The physician and the patient are interested in the marginal physical productivity of the individual pill in the production of an individual unit of care; i.e. in the extra health benefit that results from consumption of that pill. This difference in perspective helps explain disagreements among stakeholders on the demand side about the value of pills²⁰.

Looking at the pharmaceutical R&D enterprise as a capital asset means that we must consider the cost of production of that asset - the supply price of the research enterprise - and the stream

¹⁹Perhaps unexpectedly, economists do not regard the firm's monopoly profits as an element of that inefficiency. In economic models they simply represent a transfer from consumers to producers, with no welfare implications. The monopoly welfare loss comes from the fact that in order to take advantage of its monopoly by setting a price above its full costs of production the firm must restrict output. Alternatively we can look at this as saying that the high price reduces quantity demanded. In introductory analysis, the people who are discouraged by the monopoly price from buying a product are the ones who put a lower value on it than do the people who buy it. Once we get beyond the introductory textbook level we must recognize that many of these people have lower willingness to pay for the product because they have lower incomes, and further that the structure of insurance in the United States has historically had an inflationary bias built into it, exacerbating the issue.

²⁰As used in the literature the classification of perspective into societal, payer and individual probably fits the American system more cleanly than it does other countries'. Countries whose drug approval agencies require cost effectiveness analysis adopt mixed perspectives of various kinds. The calculation of the ICER requires an evaluation of the health gain from allowing the new drug on the market, and the agency must decide what monetary value to put on the gain. The incremental cost may or may not take account of costs beyond pharmaceutical costs, and virtually never considers cost savings, or cost impositions, which are unique to the family of the patient.

of benefit it yields. The price that the social payer pays for the output of that asset should not exceed some measure of the value it produces but must exceed the supply price of the asset if the pharmaceutical sector is to continue to invest in the production of the asset.

When we buy an asset, whether real, as in the sense of physical capital, or financial, we are looking at the cost of the particular amount of that asset which we plan to buy and the return it is expected to yield. This general notion underlies proposals for Value Based Pricing of pharmaceuticals, but there is still room for those proposals to be fleshed out. In particular we need to consider the nature of the return to the asset.

An asset is typically thought of as yielding a stream of returns over time. In the case of pharmaceuticals we can point to a couple of broad categories of return. One is in terms of the stream of health that will be enjoyed by the patient as a result of taking one pill versus another or versus receiving no treatment at all. In drug evaluations this stream is usually measured in terms of QALYs, Quality Adjusted Life Years. If a drug is an improvement over existing treatments, the patient can be expected to receive more QALYs as a result of being treated by that drug than he would on the standard treatment. This is referred to in the literature as the Incremental Effectiveness of the new drug over the old, and essentially compares the total of health outcomes that would follow from switching the patient to the new drug with the total that he would receive were he put on the existing treatment. Ideally, we would like to be able to value the stream of improved health which the individual will receive over time and use that in the calculation of the price of the pills. An asset that yields a longer stream of benefits will tend to have a higher price than one that yields a shorter stream.

Because we are looking at ways to price pills, we must look at how to measure health gains in dollars. The idea that we might be putting a dollar value on health has always been a stumbling block to the application of cost benefit analysis in health policy making, although standard drug pricing approval policies do exactly that. The usual process is to define a threshold ICER in terms of dollars per additional QALY gained, and then to judge whether a new drug meets the threshold value at the price that the manufacturer is proposing to charge for it. If the proposed price puts the cost of the additional QALYs gained too far above the threshold ICER value, the drug will typically not be approved for sale. This clearly amounts to putting a dollar value on health gains, and is essential given the need of health authorities to live within finite budgets.

Patricia Danzon, Adrian Towse and Jorge Mestre-Ferrandiz²¹ (hereafter DTM) propose a pricing rule for new drugs which would base the new product's price on the price of the comparator drug, the incremental health benefit it yields relative to the standard treatment and the difference in other treatment costs associated with shifting from the older to the newer drug. This approach involves treating the incremental cost of a new drug as the full change in the cost of treatment in the condition at which it is aimed, including non-drug costs, and therefore allows the pricing of a new drug to take account of any savings in things like hospitalization cost which might result from switching to the new drug. The QALY gain associated with the switch is valued at the threshold dollar-per-QALY amount used by the national drug approval agency²².

²¹Patricia Danzon, Adrian Towse and Jorge Mestre-Ferrandiz (2015): "Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context" *Health Economics* 24: 294-301.

²²Danzon and Towse's approach lets the firm set its own price, assuming that the drug plan can calculate differential QALY gains for different target groups of patients. Under that approach, if the firm sets a high price, the agency would restrict use of the drug to high QALY-gain subgroups of patients. On the issue of differential indications for a drug see also Karl Claxton, Mark Sculpher and Stuart Carrol (2011): "Value-based pricing for pharmaceuticals:

The DTM approach fits into the asset value view of drug pricing when we think in terms of both benefits and costs as being streams over time. The calculation of the net present value (NPV) of an investment project involves looking at the entire life of the proposed investment and in each period subtracting the costs from the returns, then discounting the stream of net returns back to yield a single present value. This approach recognizes that the time pattern of the stream of benefits might well differ significantly from the time pattern of the costs - in most investment projects the costs will be heavily loaded in the earlier years and the returns come later. For an individual investor looking at buying a unit of a financial asset at its going market price, the NPV value is an indicator of whether the acquisition is worth making. In a competitive stock market, it is generally assumed that the price of a share in a company will be bid up until it equals the expected present value of the share of the company's profits which would accrue to the owner of a unit of the stock. The DTM approach suggests that we think in similar terms about the price of pharmaceuticals.

Most proposals along these lines use the relevant national drug approval agency's ICER threshold as the value of each undiscounted QALY expected to be generated by the new treatment. This requires, of course, that such an ICER threshold exist. Absent that, as in the American case, we need some alternative dollar measure of health benefit. Lakdawalla et al. (2015)²³, drawing on the literature on the value of a statistical life year, use a value per QALY of US\$100,000 which, it should be noted, is well in excess of the threshold ICERs used by most countries drug price evaluation agencies. Lakdawalla et al. calculate what they call the Quality-Adjusted Cost of Care, in which they net out the monetary value of the health benefits gained from the use of a particular pharmaceutical from its price. Their approach is interesting, but on the whole it seems likely to be more fruitful to talk about the expected net present value of, in essence, buying a share in pharmaceutical R&D capital where the cost of acquisition to the purchaser - a public drug plan, for example - is represented by the stream of payments for the pills being taken by individual patients. The NPV approach also has the advantage that it allows us to break the asset's life into two segments, one prior to and the other after patent expiry. (DTM note that their approach of allowing the company to set its own price and the drug agency to limit use of the drug²⁴ to patients whose expected benefit made the drug cost-effective at that price would in principle allow the drug company to appropriate all of the net benefit of their product during the patent period, which would presumably serve as an incentive for the company to undertake further research investment.) Arguably, research-based drug companies do not receive enough credit for the fact that, at a certain point in the future, their drug will go off patent. While policy planners and consumers benefit from the availability of generics, there does seem to be a tendency to forget that, absent the original research investment there would be no generics. When we consider drug pricing from a NPV perspective, it might not seem unreasonable to allow the originator of a drug to benefit even after the drug has gone off patent by requiring generics manufacturers to make a small royalty payment to the originating company for each generic pill sold. This stream would last only so long as the active ingredient still had a market - once the active ingredient had been superseded so the market for generic copies had dried up, payments to the originating company would also cease²⁵.

Its role, specification and prospects in a newly devolved NHS", Centre for Health Economics Research Paper 60, University of York, York, UK.

²³Darius Lakdawalla, Jason Shafrin, Claudio Lucarelli, Sean Nicholson, Zeba M. Khan and Tomas J. Philipson (2015): "Quality-Adjusted Cost of Care: A Meaningful Way To Measure Growth In Innovation Cost Versus The Value of Health Gains" *Health Affairs* 34(4): 555-561.

²⁴This could be done if the public agency were to cover the cost of the drug only for patients whose expected benefit was greater or equal to the cut-off chosen by the agency.

²⁵Yang Lu, John R. Penrod, Neeraj Sood, Sarah Woodby, and Tomas Philipson (2012) "Dynamic Cost-Effectiveness

It might be easier to appreciate the drugs as assets approach to pricing if we consider a drug which has garnered a lot of press coverage recently: Sovaldi, Gilead Pharmaceutical's drug for Genotype 1 Hepatitis C. Sovaldi is a cure for Genotype I Hepatitis C, the most common form of Hepatitis C. A twelve week course taking one pill a day (in combination with interferon) is priced in the US at \$US 84,000, or \$1000 a pill. Expressed that way the pricing of the treatment has outraged many, prompted questions in Congress, including demands that Gilead tell it what Sovaldi's R&D costs were²⁶. When looked at as an asset, however, the picture alters somewhat.

The costs of a course of treatment with Sovaldi are predictable - \$1,000 a day for 84 days. That can be seen as the cost of undertaking the investment. The return on the investment can be seen as the cost savings that might arise from using Sovaldi as opposed to older, much less successful treatment regimens. The stream of returns itself is uncertain. In roughly 20% of people who contract Hepatitis C the body cleans the virus out by itself, with no need for treatment. In the remaining 80%, the progression of the disease is variable. In some cases it progresses slowly, never reaching the stage of doing serious damage, so that patients die with it rather than of it. In others it is much more virulent, causing liver cirrhosis and possibly requiring a liver transplant to treat. Thus the cost of treating a case of Hepatitis C could range between virtually nothing, and several hundred thousand dollars, and the timing of the expenditure would depend on the rate of progression of the disease. If a patient is on Sovaldi, there is no need for other treatments, and the disease is resolved quickly. We can regard the return on the investment as the reduction in the cost of other treatments that have been made unnecessary by the development of Sovaldi²⁷.

In terms of the pricing of Sovaldi, we are looking at a decision which set the price per pill in developed countries at a level which would, one suspects, allow Gilead to realize the expected economic benefits of the drug while it is under patent, on the assumption that no other Hepatitis C

of Oncology Drugs" *The American Journal of Managed Care* 18(11) supplement, November, S249-S256 have made an argument for retrospective cost effectiveness of drugs, taking account of factors which would not have been known at the time the original CEA was being done - precise detail on effectiveness including the discovery of new indications for which the drug could be used, for example. While this approach would give a detailed picture of how a drug development investment program had actually panned out, it would not be applicable to trying to set the price of a new drug. Kimberly Tran and Brett J. Skinner "Economic value of the utility-expansion for new cancer drugs approved in Canada from 2004-2014", *Canadian Health Policy* 2 October, 2015, Toronto: Canadian Health Policy Institute, perform a similar analysis for cancer drugs in Canada, looking at cases where cancer drugs have sequentially been approved for multiple indications over time.

²⁶See Robert Pear: "White House Is Pressed to Help Widen Access to Hepatitis C Drugs via Medicaid" *New York Times* August 26, 2015. One individual quoted in the *New York Times* article observed that the furor about Sovaldi was hard to understand - if we could cure breast cancer for the price of Sovaldi, no one would complain about the cost. Two recent cost effectiveness analyses have found Sovaldi to have an Incremental Cost Effectiveness Ratio (ICER) of close to \$50,000 per QALY. See David B. Rien et al. (2015): "The Cost-effectiveness, Health Benefits, and Financial Costs of New Antiviral Treatments for Hepatitis C Virus" *Clinical Infectious Diseases* 61(2), 157-68; and Jagpreet Chhatwal et al. (2015): "Cost-Effectiveness and Budget Impact of Hepatitis C Virus Treatment With Sofosbuvir and Ledipasvir in the United States" *Annals of Internal Medicine* 162(6), 17 March, 379-406. An ICER of \$50,000 per QALY is typically taken in the literature as the threshold for acceptability, in the sense that ICERS below this are taken as cost-effective. No one seems quite sure where this figure comes from: See Scott D. Gross (2008): "Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold" *Expert Reviews, Pharmacoeconomics Outcomes Research* 8(2), 165-178. For a critical review of the literature, including an argument to the effect that the long run cost savings will not make up for the high up front cost, see Leora Schiff (2015): "Finding Truth in a World Full of Spin: Myth-Busting in the Case of Sovaldi" *Clinical Therapeutics* 37(5), 1092-1112.

²⁷This actually underestimates the benefits of Sovaldi, since the fact that one would no longer need a liver transplant must be seen as generating additional QALYs for a subset of the Hepatitis C patient population.

drugs enter at competitive prices²⁸. Once it is off patent, so long as the market for generic Sovaldi is sufficiently competitive, the benefits will accrue to the patient. Thus Gilead's monopoly profits are definitely time limited.

The pricing of Sovaldi, then, can be seen as a case of Danzon-Towse pricing with the addition of the time dimension and the fact that there is a statistical distribution of potential cost savings across the patient population, rather than a single cost per patient. The Sovaldi case illustrates the Danzon-Towse approach in other ways, as well. Gilead has entered into agreements with Indian generic drug firms, licensing the Indian firms to sell Sovaldi in certain low-income countries at a price that is almost certainly not much different to the marginal cost of production. This amounts to a recognition that the threshold cost per QALY will be much lower in low income than in higher income countries²⁹.

In the United States there has been considerable upset about the impact of Sovaldi on the budgets of state Medicaid programs and state and federal prison systems. These arguments can be used to illustrate a number of issues with regards to drug pricing which are often conflated in public debate.

The first thing to note about the budgetary impact of Sovaldi in these cases is that there is at present a large unmet need for treatment for Hepatitis C from a large number of patients at various stages of disease progression. Once that need has been met, the demand for Sovaldi will settle down at an equilibrium level based on the new inflow of cases each year. The budgetary impact of treating those patients will be much smaller than the impact of treating the current backlog.

The second is the issue of silo-ing in the healthcare system. When we look at a drug like Sovaldi as an asset, taking a health system perspective, we define the return on the asset as the cost saving associated with replacing other forms of treatment by a 12-week course of Sovaldi. When we look at it from the perspective not of the system but of the budgetary units within the system, we must recognize that the budget which bears the cost of Sovaldi and the budget which experiences the saving from not having to fund liver transplants, will not necessarily be the same budget. This is not a new issue, but it is one that needs to be kept in mind. The development of a drug that saves patients from needing hospital in-patient treatment will impose a cost on a public drug plan and a saving on the hospital system budget. If the drug plan is operating at full financial capacity, as is generally the case, adding a new drug to the public formulary could force the removal of some other drug from that formulary, even in the case of a drug whose return takes the form of net cost savings for the system as a whole. Normally, when we are looking at the decision to undertake an investment, we can be sure that the individual bearing the cost of the investment will also reap the benefit and will make their investment decision on that basis. This is not necessarily the case in health care. Further, requiring the savings to be transferred to the budget that is incurring the extra cost is an option which will meet considerable resistance, if only because the hospitals (in the case which we are considering) will have a list of additional, socially beneficial, things which they could do with the monies they are saving. (Even in the UK, where drugs, physician care and hospital care are all part of the NHS budget, decisions by the National Institute for Clinical

²⁸An assumption that is already questionable, since one other Hepatitis C drug treatment has recently been brought to market, and another is expected to come to market soon.

²⁹There have been newspaper articles citing complaints about the international pricing of Sovaldi: these deal with middle income countries, not low income ones. Here the threshold cost per QALY will be lower than in richer countries, but the actual level has not been established.

Excellence (NICE) to require that new drugs be covered can be controversial because they force NHS regional authorities to make decisions about what other items to cut back on in order to satisfy the new mandates.)

The response to the introduction of Sovaldi in the US illustrates another aspect of the DTM argument. It has been reported³⁰ that different agencies have been making different decisions about which patients should be treated with Sovaldi, with some state Medicaid plans reserving the drug for more severe cases than others. DTM argued that if we let the drug company set the price for its product and treat the payer's threshold ICER as the policy variable, some payers (DTM were thinking in terms of different countries) might set a higher benefit threshold for treatment than others³¹. This is essentially what is being observed across states in the United States with the ICER threshold depending on the budgetary impact, and hence opportunity cost, of equally priced pills across states.

Some medical authorities quoted in Pear (2015) suggested that deciding to reserve the use of Sovaldi for the more serious cases was not consistent with medical ethics, and that the drug should be made available to all patients who contracted Hepatitis C. To the economist, this argument neglects two basic principles.

The first is the principle of diminishing marginal benefit that, as applied to this instance, says that patients should receive treatment in order from those for whom it will be most beneficial to those for whom it will be least beneficial. There will be some individuals for whom Sovaldi yields no benefit at all (Trivially, people who do not have Hepatitis C, or patients with a Hepatitis C genotype on which Sovaldi does not work) and we would never plan to give them Sovaldi. We should expand the distribution of Sovaldi up to the point where the value of the benefit to the last patient treated just equals the cost of the treatment. If the patient population has been properly ordered, then for every patient up to that margin the value of the treatment exceeds the cost of the treatment.

The other area of economic theory that applies here is another aspect of investment theory, known as real option theory³². Real option theory deals with the case where an investment program can be defined as having stages, at the end of each of which the investor has the options of: proceeding to the next stage, cancelling the project altogether, or waiting until new information has been collected. Real option theory has a great deal in common with Decision Tree Analysis, which is widely used in medical decision making³³. In the case of Sovaldi we can define nodes, starting with the point at which the patient is first diagnosed, at which the physician could decide either to treat

³⁰See Robert Pear: "White House Is Pressed to Help Widen Access to Hepatitis C Drugs via Medicaid" New York Times August 26, 2015

³¹There is also a relation here to the work of Jeffrey S. Hoch, Andrew H. Briggs and Andrew R. Willan (2002): "Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis" *Health Economics* 11(5): 415-430.

³²Or, as Nancy L. Stokey titled her book on stochastic control and Real Option theory The Economics of Inaction Princeton: Princeton University Press. 2009. It is highly unlikely that the formal math of real options could be easily applied here. We are simply suggesting that we should look at the drug pricing decision through a similar conceptual lens.

³³Decision Tree analysis is, of course, used in drug evaluation now. We are proposing that some of the ideas that are part of this framework be made more explicit components of the pricing decision. Similarly, Markov Modeling is widely used in modeling cost effectiveness, and deals with the same issues as we are discussing here - uncertainty about the future and the need to discount future costs and benefits. We would argue that most of this literature is not accessible to many participants in the public debate. In many ways we are arguing for a change in the approach to what is sometimes referred to as Knowledge Translation, not a fundamental change in the way the more technical analysis is done.

the patient with Sovaldi or wait until the next optimal decision time, in the meantime observing the patient, basically collecting additional information which will determine the action she takes at the next decision point.

Rational use of scarce resources under uncertainty often calls for an application of real option, or decision tree theory. This approach to optimization under uncertainty is now widely used in the analysis of long term investment in physical capital, including how uncertainty about the returns to an investment affect the decision as to whether to proceed with an investment project. It has also been applied to the analysis of R&D decisions from the perspective of the firm doing the investment³⁴, and it seems likely that it could be used to put a logical framework on the decision of a drug approval agency or insurer about the how the value of the cost savings and health gains from a new drug should translate into the appropriate price of the asset and the price of the pills which embody the services of that asset.

IV Value Based Pricing of Pharmaceuticals

Pharmaceuticals, in the sense of individual drugs, should be regarded as units embodying the output of the capital-intensive enterprise that is the pharmaceutical sector. This means that when we think about the pricing of individual pills, we should be thinking in terms of a stream of revenue that pays for the capital asset underlying the pills. As Danzon and Towse (2003) note, the joint nature of this capital makes it very difficult to assign cost shares to different users of its output. We would in general expect this allocation to depend on the quantity used and on the value that individual users of the product derived from that use. That concept, however, is much easier to state than to apply.

In general we can say that the stream of revenue generated by the capital asset in question will be bounded by the supply price of the asset and the monetary value which users of its product place on that use. This is simply an application of basic demand and supply theory: in a static setting, for any given quantity of output, the price of a product cannot lie below its supply price³⁵ and will not lie above its demand price³⁶. In a perfectly competitive static market, the actual market price will be at the intersection of the demand and supply curves, meaning that the market price will equal the supply price and also equal the demand price. The market for pharmaceuticals, of course, is not perfectly competitive, especially while a drug is still under patent. Once the patent expires there is no particular need to worry about price from a social welfare perspective³⁷ so long as the

³⁴See, for example, Eduardo S. Schwartz (2003): “*Patents and R&D as Real Options*” National Bureau of Economic Research Working Paper No. 10114 November.

³⁵The supply price of a unit of a product is the minimum price for that unit which will just be sufficient to persuade the producer to produce it. If the price offered lies below the supply price for a unit, that unit will not be offered for sale.

³⁶The demand price for a unit of a product is the highest price the consumer will be willing to pay for that unit. It depends on factors such as the consumer’s income and the price and availability of other commodities. Essentially, when she is deciding whether or not to buy a unit of a product, the consumer is, in the back of her mind, comparing the benefit she expects to get from consuming that unit of that commodity against the benefit she would get if she spent the same chunk of her income on other commodities. In economists’ terms, the true price of a commodity to the consumer is its opportunity cost. Money is just a convenient way of keeping the accounts. In a country where there is not much to buy, money is not worth much.

³⁷This implicitly assumes that the patent length has been chosen optimally.

market for generic copies of the drug is reasonably competitive. Introductory economics textbooks suggest that for a market to be competitive requires a very large number of suppliers. Practical experience suggests that, barring the formation of a sellers' cartel, results virtually equivalent to those of a perfectly competitive market can be attained with free entry and four or more regular suppliers of roughly similar size. When the number of suppliers falls below this, there will be a tendency for the price to rise from a competitive to an oligopolistic level. Popular discussion of the role of generic drugs has tended not to appreciate this point. As a result, especially in the US, recent sharp increases in the prices of generic drugs have come as something of a shock to the public, commentators and politicians³⁸. The key to understanding these increases is to realize that generic drug companies are, like the research-based drug companies, in business to make a profit. The generic companies acquired a virtuous halo in the past as a result of competition among them keeping the price of generics down. This halo translated into a piece of conventional wisdom; that generic drugs were somehow automatically cheaper than brand name drugs. Politicians may try to devise regulations that keep generics' prices down, but in fact the only thing which will keep prices down is active competition in the market. American lawmakers should keep in mind that the fact that generic prices have been much higher in Canada than in the US was an unintended consequence of Canadian price regulations.

Danzon and Towse (2003) make another point that is worth noting here. Pharmaceuticals are sold worldwide, so the issue of allocating the joint research costs is not just applicable to consumers in a single country but applies across countries, rich and poor. While research-based drug companies are often accused of wanting to use patent protection to raise prices in poor countries to near-rich country levels, this would not be a profit maximizing strategy unless it led to international agencies agreeing to pay the difference between the upper and lower prices. Absent subsidies, it is unlikely that the profit-maximizing price in most poorer countries would be much above the marginal cost of the physical production of the pills. Any higher price would reduce quantity demanded to a point where the cost of shipping and selling would wipe out any possible profits. Similarly, generic manufacturers from, most notably, Brazil and India, have been lauded for going into poorer country markets. It should be noted, though, that, given that the research-based companies would have no hope of recovering any part of their development costs from sales in poorer countries, and would therefore base their pricing strictly on costs of production, their profit-maximizing prices would be the same as those of the Indian and Brazilian companies³⁹.

The research based companies' issue with poorer countries is not the price they would be able to sell their products for in those countries, it is the issue of re-exportation. This gets into a standard piece of basic microeconomic theory, dealing with differential pricing in different markets. It is often the case that a commodity will tend to sell for a higher price in higher than in lower income markets. This is simply a reflection of the fact that consumers in higher income countries are likely to have lower opportunity costs and hence higher willingness to pay than consumers in lower income countries. For a high income country consumer the marginal good which must be sacrificed to pay for another good may well be a luxury good, whereas in a lower income country it is much more likely to be a necessity. When the commodity is freely tradable what is known as the law of one

³⁸See, for example Elisabeth Rosenthal New York Times 24 November, 2014 "Lawmakers Look For Ways to Provide Relief for Rising Costs of Generic Drugs" <http://www.nytimes.com/2014/11/25/us/lawmakers-look-for-ways-to-provide-relief-for-rising-cost-of-generic-drugs.html>

³⁹This story was somewhat complicated by the fact that it was discovered that quality control on some Indian-made generics being sold in poorer countries was much weaker than quality control on generics being shipped to richer markets.

price tends to apply - tradable commodities will flow from low price to high price markets. The price differential is most easily seen in the case of non-tradables, such as housing across high and low income communities in Canada. Even if the price of timber is the same in low and high income communities the price of housing will tend to be higher where incomes are in general higher - this can be thought of simply as the builders' way of getting a share of a richer pie.

Pharmaceuticals are clearly tradables. The research-based pharmaceutical companies' issue with lower prices for their product in poorer countries is that those drugs tend not to remain in the poorer countries but to be re-exported to richer countries. The Brazilian and Indian generic manufacturers would have no objection to their product being re-exported from, say, South Africa to Europe, since they have no development capital to pay for and would simply regard it as an expansion of demand for their product.

Re-exportation is not simply an issue for the lowest income countries. Even before its current economic crisis, Greece suffered chronic shortages of pharmaceuticals, despite the fact that the drug companies were shipping supplies quite sufficient for the Greek market. Greece was, among European countries, a low price country. Under the single market, and given European regulations about the extinguishing of property rights on first sale of a commodity, drugs which were shipped into Greece were shipped out again almost immediately to be sold in higher income European countries. The only cost to doing this was the re-packaging which sometimes had to be done. Re-exporters from Greece could undercut wholesalers in richer European countries in supplying pharmacies in those countries, and those higher-income countries public drug plans did not draw any distinction with regard to where product came from so long as it satisfied local packaging rules.

As we noted above, willingness to pay will tend to be higher in high than in low income countries. This ties into the issue of what is known as value based pricing if we take value as being a demand side measure. We are using the term value here not in a moral sense, although there is an underlying notion of the value of life and health. Instead we are dealing with the way that underlying value relates to a willingness to give up other things in order to acquire commodities which are beneficial to life and health; i.e. with what we have referred to above as opportunity cost.

Demand-side notions of value based pricing have been discussed in the literature, but are difficult to implement because of the difficulty of measuring demand side value. Philipson and Jenna (2005), for example⁴⁰ argue that the social surplus from the development of drugs for HIV/AIDS came to \$1.38 Trillion, of which, they argue, drug companies captured only about 5%. The gist of their argument is that future drug development is put at risk because drug companies capture only a small part of the total social value of the products they develop. The argument rests on assumptions about the value of a life-year, and in particular the value of life that might otherwise be lost. The general notion is valid, although the measurement issues which would be involved in trying to use these calculations as the basis for demand-side value based pricing are formidable, to put it mildly.

Further, it would be misleading to take this argument as evidence that pharmaceuticals are qualitatively different from any other commodities in this regard. For all commodities it is the case that the majority of consumers derive more benefit from the consumption of the commodities than

⁴⁰Philipson, Tomas J and Anupam B. Jena (2005): Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs National Bureau of Economic Research Working Paper 11810, December. See also Tomas J. Philipson and Anupam B. Jena (2006): Surplus Appropriation from R&D and Health Care Technology Assessment Procedures NBER Working Paper No. 12016, February.

they sacrifice in order to obtain them. Economists refer to this as consumer surplus, and while maximizing welfare does not require maximizing consumer surplus, most economists tend to look somewhat askance on efforts to transfer consumer surplus away from consumers. When the latter is done on large scale we are looking at what is known as a rent-seeking system, and rent seeking systems tend not to display much economic growth and rent-seeking tends to be prejudicial to the well-being of the mass of the population over the long run.

Further, in virtually all markets in healthy economies producers capture relatively small shares of the total social welfare produced by their commodities. Nordhaus (2004), for example, argues that:

“only a minuscule fraction of the social returns from technological advances over the 1948-2001 period was captured by producers, indicating that most of the benefits of technological change are passed on to consumers rather than captured by producers.”⁴¹

The reason consumers capture the bulk of the social returns is, in essence, competition. Nordhaus is dealing with the Schumpeterian process of creative destruction, by which new products and techniques displace old ones. This process underlies most economic growth. In brief, when a company develops a disruptive product or technique, i.e. one which is both successful and fundamentally different from the way things have been done in the past, the innovator will displace older companies and will reap an extra-normal profit in the process, often under the protection of patent laws. Eventually, however, the monopoly position which comes from being first entrant, ends and other firms enter, producing products which are very close competitors for the first entrant's product. This competition drives down the price of the product, and it is this price competition that distributes the bulk of the social welfare across the mass of consumers, away from producers. This is the same process as applies to pharmaceuticals when a new drug is protected under patent for the first part of its existence, then faces generic competition⁴². One can make a good case that brand name drug companies do not get enough credit for the benefits to consumers yielded by generic copies of their original drugs and that this should be credited to them in any calculation of the social benefit produced by their product. But while it is essential that the research-based sector (although not necessarily any particular individual firms in that sector) reap enough extra-normal profit in the short run to encourage the sector to keep the research enterprise going, attempts to define pricing rules based on estimates of the total consumer surplus produced by their products seem unlikely to be of practical value.

Philipson and Jena define value in terms of the total social welfare produced by pharmaceuticals. This is an approach that is consistent with economic theory, and is what one would like to be able to do for purposes of performing cost-benefit analysis of pharmaceuticals, but cost-benefit analysis has never been particularly easy to apply in any field.

⁴¹Nordhaus, William J. (2004): “Schumpeterian Profits in the American Economy: Theory and Measurement” NBER Working Paper No. 10433, April.

⁴²Subject to the qualification noted earlier about the need for a workable degree of competition among the generics firms.

V Risk Sharing Schemes

One subcategory of Value Based Pricing schemes is what are referred to as Risk Sharing Schemes (RSS). As in other cases to which we have referred, RSS are relevant for cases where the effectiveness of a drug is not sufficient to pass the regulator's cost effectiveness analysis at the price which the supplier proposes to charge for it, in the sense that the drug's ICER falls short of whatever threshold the regulator is using. Normally falling short of the ICER threshold would result in the drug not being approved for market, unless the drug company was willing to bring the price down to a level that would meet the threshold (clearly we are assuming that the drug has a certain degree of clinical effectiveness, just not enough to justify the proposed price). Risk Sharing Schemes build on this starting point, but do not require that the price be cut immediately. Instead, if the company has enough confidence in the effectiveness of its product, it may reach an agreement with the regulator that would allow the drug to enter the market at the company's proposed price, on the condition that certain patient outcome targets be met within a certain period of time. If those targets are not met, the company must reimburse the insurance agency an amount that would bring the agency's cost per QALY down to the pre-determined threshold level.

One of the best known examples of RSS relates to the use of Beta Interferon and Glatiramer for the treatment of multiple sclerosis in the UK (See Buxton, M. J.(2006)⁴³ . After a lengthy review process, NICE concluded that neither drug was cost effective - Buxton(2006) reports that depending on the model being used the ICER ranges between £35,000 and £104,000 with a mean value of £70,000⁴⁴. Normally this would be sufficient for the drugs not to be covered under the NHS. In this case, however, presumably because of its sense of the importance of finding a treatment for MS, the Department of Health proposed a Risk Sharing Scheme under which the drugs would in fact be used in the treatment of MS patients, but if the measured progress of the patients receiving the treatment was not sufficient to bring the ICER down to £36,000, the NHS would receive a rebate on what it had paid for the drugs.

Initially the results of the MS RSS were unfavourable to the drugs, with the treatment group not only not achieving the outcome target but actually seeming to do worse than the historical data used in place of a control group. Raftery (2010)⁴⁵ referred to the RSS as a costly failure and McCabe et al. (2010)⁴⁶ argued that the RSS should be halted. More recent evaluations⁴⁷ look more favourable for the drugs involved.

One of the issues involved in the MS RSS was that, at the end of the first evaluation, the scientific advisory group decided not to recommend that the reimbursement payments be triggered⁴⁸ on the

⁴³See Buxton, M. J.(2006): "Economic Evaluation and Decision Making in the UK" *Pharmacoeconomics* 24(11): 1133-1142. Andrea Messori: "Outcome based schemes are more common than you think" *British Medical Journal* 341(7763) pg. 62, lists a number of Italian RSSs.

⁴⁴On general modeling issues, see Chilcot et al. (2003): "Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis" *British Medical Journal* 326, 8 March, 522-525.

⁴⁵Raftery, J. (2010): "Multiple sclerosis risk sharing scheme: a costly failure" *British Medical Journal* 340(7759) 12 June, 1282-1284.

⁴⁶McCabe et al. (2010): "Continuing the scheme is unjustified" *British Medical Journal* 340(7759) 12 June 2010, 1285-1288.

⁴⁷Palace et al. (2015): "Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator" *Lancet Neurology* 14, 497-505.

⁴⁸McMillan, S (2010): "UK NHS haemorrhages money over patient access scheme" *Pharmacoeconomics & Out-*

grounds that issues with the study design⁴⁹ made it impossible to tell whether the ICER threshold had been met⁵⁰.

The MS RSS episode illustrates two key issues with risk sharing plans in practice. One is the amount of uncertainty that can enter into the modeling exercise. As Thompson et al. (2013) note: “Several cost-effectiveness models of disease-modifying treatments (DMTs) for multiple sclerosis (MS) have been developed for different populations and different countries. Vast differences in the approaches and discrepancies in the results give rise to heated discussions and limit the use of these models.”⁵¹. The other is the need to define the target and payment triggers very carefully. Too much uncertainty in that regard can be expected to lead to legal disputes and the incurring of costs that could better be spent on treatment of at least some patients.

It is also necessary to consider when RSS plans make sense. In the MS case, the issue in broad terms was reasonably easily defined - would treatment with the drugs under review produce ICERs below NICE’s threshold for approval⁵². Since price was controllable, the uncertainty arose with regards to the outcome - the number of QALYs generated - by the use of the drugs. The MS case was complicated by the lack of an RCT with a control group: the comparison was done against Canadian historical data⁵³. If uncertainty about the outcome of a trial is sufficiently large - confidence in the result is weak - it may be difficult to justify using a particular ICER threshold for approval purposes. In this case an RSS, so long as the target outcomes are sufficiently clearly defined, could presumably reduce the likelihood of denying market access to a drug that might possibly benefit a certain part of the patient population.

In effect, an RSS could be used to add rigor to post-marketing surveillance, sometimes referred to as a Phase IV trial. A drug which clearly does not produce negative health effects (this was one of the problems with the early analysis of interferon beta) but whose positive health effects have sufficient uncertainty attached to them could be allowed onto the market sooner than might otherwise be the case. (In some cases, extended clinical trial requirements might mean that even a drug which was ultimately successful might have a very limited amount of patent life left by the time it reached the market - the likelihood of such a case might conceivably lead to a company choosing to drop the drug from its trial program.) Some authors have suggested that drug evaluation should be limited to safety, with effectiveness left entirely to market evaluation. The Japanese experience in

comes *News* 26 June 2010, No. 606

⁴⁹See Boggild, M. et al. (2009): “Multiple Sclerosis Risk Sharing scheme: two year results of clinical cohort study with historical comparator” *British Medical Journal* 339 (7734): 1359-1363.

⁵⁰The chair of the scientific committee responded in Lilford, R. J. (2010): “Response from chair of scientific advisory committee” *British Medical Journal* 341 (7763) 10 July 2010, pg. 61.

⁵¹Thompson, Joel P., Amir Abdolahi and Katia Noyes (2013): “Modelling the Cost Effectiveness of Disease-Modifying Treatments for Multiple Sclerosis” *PharmacoEconomics* 31: 455-469.

⁵²On debates about NICE’s ICER thresholds, and whether NICE should be setting thresholds, see McCabe C, Claxton K, Culyer AJ (2008): “The NICE cost-effectiveness threshold: what it is and what that means” *Pharmacoeconomics* 26(9):733-44, and Culyer A, McCabe C, Briggs A, Claxton K, Buxton M, Akehurst R, Sculpher M, Brazier J. (2007): “Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence” *Journal of Health Services Research and Policy* 12(1):56-58. See also Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M. (2015) “Methods for the estimation of the NICE cost effectiveness threshold.” *Health Technology Assessment*;19(14).

⁵³Trial design is an ongoing problem - while European regulators approved the use of Alemtuzumab for MS, the FDA as of March 2014 had refused approval on the grounds that in trials against interferon beta 1a patients were not blinded as to which drug they were receiving, and that in one group, 12.6% of the control group dropped out as against 2.3% in the trial group. See Mullard, Asher (2014): “FDA’s rejection of alemtuzumab divides neurologists” *The Lancet* 383, March 8, 2014, p. 859.

the recent past suggests that this would not be a desirable route to follow: having drug approval rules along these lines are reported to have resulted in there being on the Japanese market a number of things like “heart tonics” which provided no clinical benefit but were profitable⁵⁴. That has also been adduced as part of the explanation as to why Japanese drug companies have tended not to have played a major role in the world pharmaceutical market.

While RSS’s are often looked on as risky for public budgets, that risk can be mitigated if the triggers for repayment from the drug companies are sufficiently clear. They would also provide some indication of the degree of confidence that drug companies have in their products.

From the perspective of the economist, RSS’s have another interesting feature - properly designed, they are likely to be insurable. RSSs act to shift much of the risk that a drug will ultimately not live up to expectations from the public insurer to the pharmaceutical company. At present, once a drug has been approved, it is politically extremely difficult to de-list it. This means that, even if it is not effective, the tendency of individuals to assign what might be a random improvement in their health status to whatever medication they happen to be on means that, even in the face of clinical evidence raising doubt about the effectiveness of a drug, a certain number of people will continue to take it. This lies behind the fact that certain cold remedies, which have no solid clinical support, continue to have a loyal following in the market, and, so long as we are talking about OTC cold remedies which people are paying for out of pocket, and so long as there is no evidence that they are harmful, there is no real problem. With prescription drugs, however, even if there is no evidence of harm, unsupported loyalty can translate into an appreciable impact on a public plan’s drug budget.

From the perspective of the firm, one interesting characteristic of a well-designed RSS is that it should be commercially insurable. In a sense it becomes possible to write an insurance policy, or design a derivative, based on whether the firm is going to be required to repay an appreciable amount of its revenue from one drug to the public plan⁵⁵. The insurance payment would be triggered, in essence, if the drug proved to be a washout. The premium the pharmaceutical company would have to pay to insure a drug would depend on its ability to convince an insurer about the likelihood that the drug would fail to meet its targets. The level of the premiums it would have to pay, as compared with what it was willing to pay, would provide the company with at least some external evaluation of its evidence, in addition to that which it would have received from the drug evaluation body.

It might be argued that the ability to insure against a drug eventually proving to have an unsatisfactory ICER would reduce the amount of skin a pharmaceutical company had in the game. Should the drug in question prove a washout, the cost, in the form of reimbursement payments to the drug plan, would be passed back to the insurer. On the other hand, since the premiums it would have to pay on any individual drug would depend in part on the evidence it provided its insurer in support of that drug and in part on its track record, which would be a matter of public record, the degree of moral hazard could probably be controlled. And while we argued earlier that

⁵⁴See F. M. Scherer (2000): “The Pharmaceutical Industry” Chapter 25 in *Handbook of Health Economics, Volume 1*, Edited by A.J. Culyer and J.P Newhouse, Elsevier, and the references cited therein.

⁵⁵Again, this depends on the trigger conditions in the RSS being clear - in this regard, designing an insurance policy for a RSS would raise issues similar to those which arise in designing catastrophe bonds to be issued by hurricane prone jurisdictions. See, for example, Howard Kunreuther and Geoffrey Heal (2012): “*Managing Catastrophic Risk*” National Bureau of Economic Research Working Paper No. 18136, June.

drug development has to be funded out of retained earnings because its unattractiveness to the finance sector, insurance has the advantage that payouts by the pharmaceutical company in the event of a drug being a washout would not further reduce the funds available for research. In the absence of such insurance, drug companies might feel pressure to reduce the riskiness of their drug development portfolios by sticking to low-risk research. Some form of insurance might reduce the pressure which the RSS policy option might create for focusing on me-too drugs.

VI The Pricing of Treatments and Cures

We sometimes hear the claim made that drug companies do not want to discover cures for diseases, that they would rather turn fatal illnesses into chronic conditions, and find treatments to ameliorate, rather than cure, chronic illnesses, the argument being that both of these approaches would generate permanent streams of profit, whereas a cure would yield a one-shot payment. Looking at this argument through a financial asset lens makes it clear that it does not hold up. We can think of the on-going stream of profit from drugs that control but do not cure a chronic condition as the counterpart of a financial annuity. Finance theory tells us how to price an annuity in the sense of finding a lump-sum up-front payment that would be equivalent to the stream of payments. Basically we are asking what lump-sum price would just be sufficient to persuade the owner of the profit stream to sell it. The same principle would apply to curative drugs: there will be a price for the curative drug which would just be sufficient to persuade a drug company to market it rather than the ameliorative drug (assuming that the same company would be producing both). Furthermore, unless the drug company and the payment agency discount future payments at very different rates, it seems unlikely that the payer would prefer maintenance to cure.

The argument that drug companies do not want to find cures also neglects the role of patents in the drug sector. Financial annuities are typically priced on the assumption that they will yield a stream of fixed annual payments over a very long horizon. In the case of profits from maintenance drugs, the brand name company will receive the profit stream up to the point at which its patent expires: after that the payments will go to a generic manufacturer. While it is also true that eventually the revenue from a drug that cures the disease will go to generic manufacturers, the relatively short duration of the profit stream from a drug that ameliorates but does not cure should make it easier to price the cure at a level that makes it more attractive than the alternative.

While the up-front payment for a cure might have the same present value as the stream of payments associated with continuous treatment, it may well look different from the point of view of the budget of the paying agency. If there is a significant backlog of existing cases at the time at which the cure is discovered, curing all of those cases might require additional funding. Over the longer run, though, the rate of inflow of new cases will presumably be constant, at a rate determined by the incidence of the disease, and there should be a transition to an equilibrium at which the savings each year from not having to pay the continuous costs of treatment of chronic patients are sufficient to cover the costs of curing the newly diagnosed cases each year. Making this kind of calculation explicit and public would go a long way towards helping the public understand the pricing of new drugs.

The cost saving to the payer, of course, would depend on the price that generic manufacturers would charge for their after-patent version of the ameliorative drug. We noted earlier that there

is a tendency among politicians and the public simply to assume that generics will be cheaper than brand name drugs. Recent experience in the US has made it clear that that is not the case. Canadian experience with generic price regulation should be sufficient to demonstrate just how easy it is for a price ceiling to become a price floor. When monopoly power results in the price of a generic being well above the unit cost of production of the physical pill, part of the benefit to the patients of the drug is going to a firm which in many cases is not incurring research costs and for which the extra is pure gravy (some generic manufacturers are moving into drug development: given that pharmaceutical R&D is primarily financed from retained earnings, starting as a profitable generics manufacturer might be a sensible part of a long run strategy to become a research-based company).

VII New Challenges: The example of Cancer Immunotherapy

Most of our discussion in this paper has implicitly assumed that we are dealing with traditional small molecule drugs. There are new research programs underway which have the potential to end the research drought, at least with regards to certain conditions, but which will also pose significant challenges for the drug pricing and evaluation.

One such area is cancer immunotherapy, a broad term for an approach which involves stimulating the body's immune system to fight cancer⁵⁶. They have been used with great promise⁵⁷ in the treatment of metastatic melanoma and lung types of cancer, as well as childhood acute lymphoblastic leukemia⁵⁸. In cases where chimeric antigen receptor modified T cells (CAR T cells) have been used to treat chronic lymphocytic leukemia⁵⁹, the T cells which have been modified to attack certain types of cancer seem to persist in the body, able to respond to a recurrence of the relevant tumor.

CAR T cells and other cancer immunotherapies bring together a number of issues which will have to be met on both sides in the process of making decisions about drug pricing approval⁶⁰. They hold the promise of long run treatment and possibly cure of at least certain types of cancers, which means that the Health Technology Assessment process will have to take a long run perspective both of cost savings from other forms of treatment and of the value of a life year used in the

⁵⁶See Jennifer Couzin-Frankel: "Cancer Immunotherapy" *Science* Vol. 342, pp. 1432-1433, 20 December 2013.

⁵⁷See Diana Fine Maron "Cancer Immunotherapy Pioneer Nets Major Prize" *Scientific American* 8 September 2015

⁵⁸Persis J. Amrolia and Martin Pule (2014): "Chimeric antigen receptor T cells for ALL" *The Lancet* 385, 7 February; Alfred L. Garfall et al. "Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma" *New England Journal of Medicine* 373(11), 10 September, 2015; Shannon L. Maude et al. (2014) "Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia" *New England Journal of Medicine* 371 (16), 16 October; and, at a less technical level, Matthew Herper (2014): "Is This How We'll Cure Cancer" *Forbes* 26 May; and Andrew Ward (2015): "Groundbreaking cancer drug given NHS approval" *Financial Times* 7 Sept.

⁵⁹Porter et al. (2015): "Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia" *Science Translational Medicine* 7(303), 2 September.

⁶⁰For one overview see Kudrin, Alex (2012): "Reimbursement challenges with cancer immunotherapeutics" *Human Vaccines and Immunotherapeutics* 8(9), September, 1326-1334. On issues in the cost of cancer drugs generally see Mustaqeem Siddiqui and S. Vincent Rajkumar (2012): "The High Cost of Cancer Drugs and What We Can Do About It" *Mayo Clinic Proc* October 2012, 87(10), 935-943

cost effectiveness assessment process⁶¹. They are biologics and, because they generally involve using the patient's own T cells to stimulate the patient's immune system, fall under the heading of personalized medicine⁶². For both of these reasons they will be more costly to manufacture than are traditional drugs⁶³, and because of the particular issues involved in the manufacture of biologics, eventual entry of generic copies - biosimilars - is likely to be much less rapid than is the case for small molecule drugs. Price competition will emerge, but is likely primarily to take the form of competition among brand-name suppliers, both before and after particular drugs come off patent, and production is likely to occur mainly in plants owned by brand name companies. The cost of production will come down over time, as the techniques involved are themselves refined, but the process is likely to be relatively slow. The research process itself is likely to prove costly, in part because of the need to control for the side effects which this type of therapy can produce, but the promise both of success against at least some cancers and the size of the potential market should encourage entry, so long as the pricing process is handled rationally. The prices currently being proposed for this class of therapy will make them among the most expensive drugs on the market, which means that calculation of long run cost savings and health benefits will have to be made quite explicit and the payment system will have to be designed in such a way that competition among suppliers will bring prices down over time.

While it is clearly not possible to forecast all of the costs and benefits from cancer immunotherapy with precision, the general outline of the market sector and the way it is likely to evolve can be modeled, and this sort of model should be used to test the HTA and CEA processes to see how well the current approaches are likely to work in the case of new, expensive curative therapies and whether those processes are going to need significant modification, either at the level of theoretical modeling or at the level of practical application, to ensure that the economics of drug coverage keep up with the science of drug development.

VIII Conclusion

The thrust of the argument that we are making in this paper is that pills should be thought of not as individual inputs in the production function for medical care but as embodiments of the services of an asset, pharmaceutical R&D, which should be thought of as a form of joint capital good entering into the production of a wide variety of types of care⁶⁴.

Pricing of new drugs should be based in the first instance on any measurable cost savings which can be expected from shifting from a previous treatment technology to a new one, and the treatment technology should be defined in terms of all of its inputs, so that we are not just looking at savings on the drug budget. The calculation should be done on the basis of an entire course of treatment so that the fact that costs and returns are likely to be streams over time is taken proper account of, as are any elements of uncertainty about the effectiveness of or need for treatment. If a course of treatment can be characterized as decision tree analysis (or, in economists' terms, as a real option

⁶¹It is not clear that the public realizes that cost effectiveness review involves putting a dollar value on a year of life in good health.

⁶²In many cases they seem to work in some but not all patients.

⁶³For a discussion of some of the relevant production issues see Kaiser A. D. et al. (2015): "Towards a commercial process for the manufacture of genetically modified T cells for therapy" *Cancer Gene Therapy* 22, 72-78.

⁶⁴We include a technical appendix which provides a diagrammatic analysis of the issues raised in the paper.

problem) these tools should be used in the determination of the price of a drug as well as in the determination of effectiveness.

When a new drug can be expected to yield additional health benefits, this should be recognized along with any cost savings that it might yield. The question of how to value health gains is one which is already faced in cost effectiveness analysis and in the recommendations of the Patent Medicines Price Review Board in Canada, and the general practice in the theoretical literature of using the threshold ICER to give the valuation of QALYs produced seems as good a place to start as any. The Value Based Pricing literature includes suggestions that QALYs should be adjusted to reflect other social values - weighted by the age of the patient population, for example with the usual assumption being that drugs aimed at treating diseases of younger populations would receive more weight. It is not clear that this would be necessary if we were to analyze pharmaceuticals in terms of Net Present Value, since younger populations would presumably experience a longer stream of returns than would an older population. Much of the relevant literature here stems from a report by the Office of Fair Trading (OFT) in the UK on the scheme being used by the British health care system to regulate the prices of drugs. The UK was using a system of profit regulation rather than direct price regulation, and the OFT recommended that the prices of drugs should more directly reflect the benefits of drugs to British patients. Initially this seemed likely to lead to changes to NICE's system of evaluation of drugs, with QALYs being weighted to reflect non-health social values. Ultimately NICE seems to have settled for incorporating a broader range of social values into its cost effectiveness analyses, without going as far as the OFT report was widely seen to be recommending. It is not entirely clear how much difference this will make to NICE decisions in practice, since, rather than having a single threshold value for a QALY which it used to make its recommendations, NICE had a lower ICER ratio, below which a drug would definitely be approved, and upper ICER above which a drug would be rejected, and an intermediate range which allowed other considerations, not always clearly articulated to play into the approval decision by letting NICE approve some drugs with higher ICERs than it would permit others. Among other considerations proposed are innovativeness, and the degree to which a drug is aimed at an underserved patient segment. Both of these are commonly factored into a range of countries drug approval programs.

There are practical problems here, in particular with the possibility that the critical ICER for approval of a price might be indication specific. It is already very difficult for drug companies to justify charging different prices when the same drug is used for the treatment of different conditions, even if the benefit can clearly be shown to be greater for one indication than another. Indication-based pricing would be a form of what economists refer to as price discrimination, and one of the requirements for price discrimination is that it be possible to separate the relevant markets strictly. The ability of physicians to prescribe drugs for off-label use would seem to make indication specific pricing an unsustainable form of price discrimination, and attempts to enforce it would probably cause a great deal of political unhappiness.

Risk sharing can be incorporated into the asset based system, although if the stream of returns incorporates a factor for the uncertainty of the benefit it is not clear that this would be an advance. While there is clear cause for unhappiness on the part of a payer who is paying for pills which do not work on a significant number of patients, perhaps because of personalized medicine and genetic considerations, uncertainty about the probability that a drug will be effective on any given patient is likely to be an intrinsic part of the drug development process. Awareness of personalized medicine issues - the way the genetic make-up of the patient might influence the effectiveness of a

particular drug - should play a larger role in drug trials in future. If we are to take personalized medicine seriously we should design trials so that they are powered to give a reasonable indication of whether the trial groups should be regarded as a mixture of populations (for example, one larger one on whom the test drug has no effect and a much smaller one on whom it is highly effective, we which assume we do not know a priori) rather than as a single population. If we do this, though, and discover that the drug does work well on a subset of the population, for whom it would then be prescribed on a regular basis, the price paid for the drug would have to reflect the cost of having been able to discover it. Ensuring that drugs are paid for only in the case where the patient actually benefits from them may simply mean going from widespread use of a drug at a relatively low price per patient to more restricted use at a higher price since, while it is true that we do not want to be paying for ineffective drugs (and certainly we do not want people taking drugs which do not work for them since that is where anti-biotic resistance came from) it is also true that any pricing mechanism we adopt must yield enough revenue to the drug industry to keep the drug development enterprise going.

The issue of which countries should pay higher prices for drugs, and therefore make the larger contributions to the costs of drug development can also be tackled in the asset framework. It is generally thought reasonable that richer countries should contribute more than poorer ones to the cost of the development of drugs which will benefit both groups. If we base pricing on cost savings from new drugs, this consideration will in fact tend to be built into the price, since the cost savings will be based on the prices of the resources saved and those prices will tend to be higher in richer countries. Similarly, if we include a health gain element in the stream of returns we would expect the threshold ICER value to reflect the level of income in the country in question, creating a tendency for richer countries to pay more towards the joint capital than do poorer ones.

Popular attitudes towards the prices of pills can be thought of as having taken shape in the prime of the antibiotic development area and not much altered to reflect the realities of more recent drug development. In recent years the objective has switched from destroying invading organisms to finding drugs that can repair failures in the body itself. It is not unreasonable to believe that this would be a more complicated task than the first. Progress against the new targets will by the nature of the problem then necessarily be made in smaller increments than was progress against bacterial invaders. Whatever the technical issues involved, we would suggest that conceptualizing of pharmaceuticals as streams of costs and payoffs derived from an underlying asset may well help clarify the issues in the policy debate about pricing pharmaceuticals.

Our proposed framework for drug pricing is closely related to the DTM framework. We argue, though, that making explicit use of an asset-pricing framework allows us to encompass, in the same analysis, a number of key characteristics of pharmaceuticals. It lets us take account of the fact that costs and returns are both spread over time, that the time pattern of costs can differ dramatically from the time pattern of returns, that returns can include both health gains and cost savings, including savings in budgets other than the budget of the drug plan, and that it lets us incorporate uncertainty about the pattern of returns and the progression of the disease. Indeed it does more than allow us to consider all of these factors; it forces us to consider them. We suggest that extending the basic DTM framework explicitly in this direction, and doing it within a cost-effectiveness/drug approval/drug price approval setting, would eliminate a great deal of the confusion about drug pricing and substitute light where there is at present heat in much policy debate.

Appendix: Cost Effectiveness Analysis and the Problem of Cost Per Pill

The standard method of assessing the cost-effectiveness of a new drug is to calculate its Incremental Cost Effectiveness Ratio (ICER). We can illustrate the concept of the ICER with a graph drawn from an area of economic theory known as activity analysis.

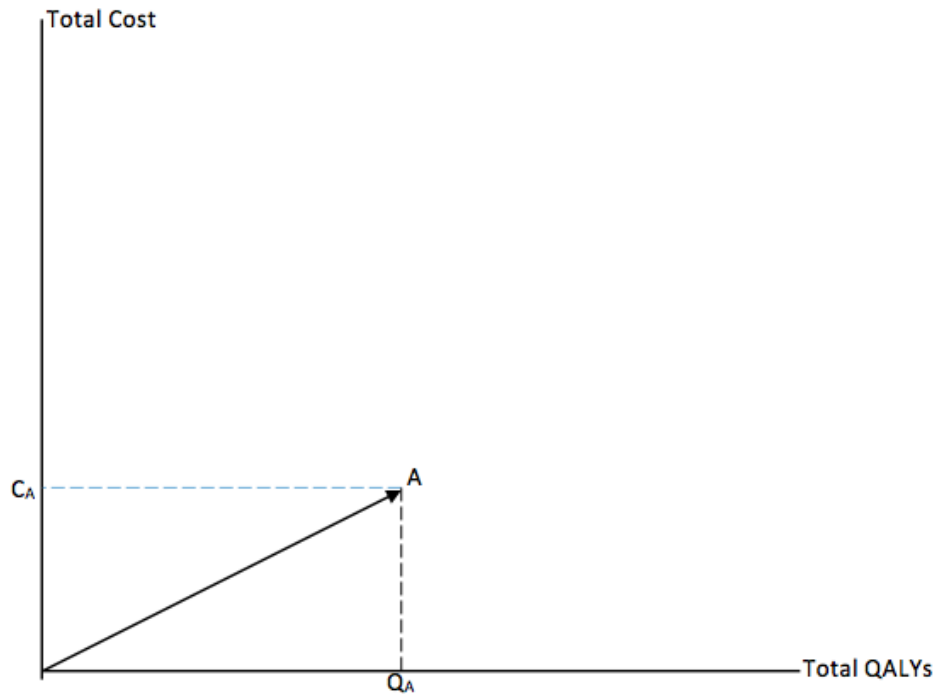


Figure 1

In Figure 1 above we assume that there is initially only one drug treatment for the condition in question, producing Q_A Quality Adjusted Life Years (QALYs) at a total cost of C_A . In this diagram the cost per QALY of treatment A is represented by the slope of the ray from the origin to point A. The diagram is usually implicitly drawn for a single patient - since the production and cost functions for this treatment are assumed to be linear, looking at the aggregate figures simply involves scaling the ray up.

Now assume that a new treatment is developed which produces more QALYs but at a higher cost per QALY, as in Figure 2 below:

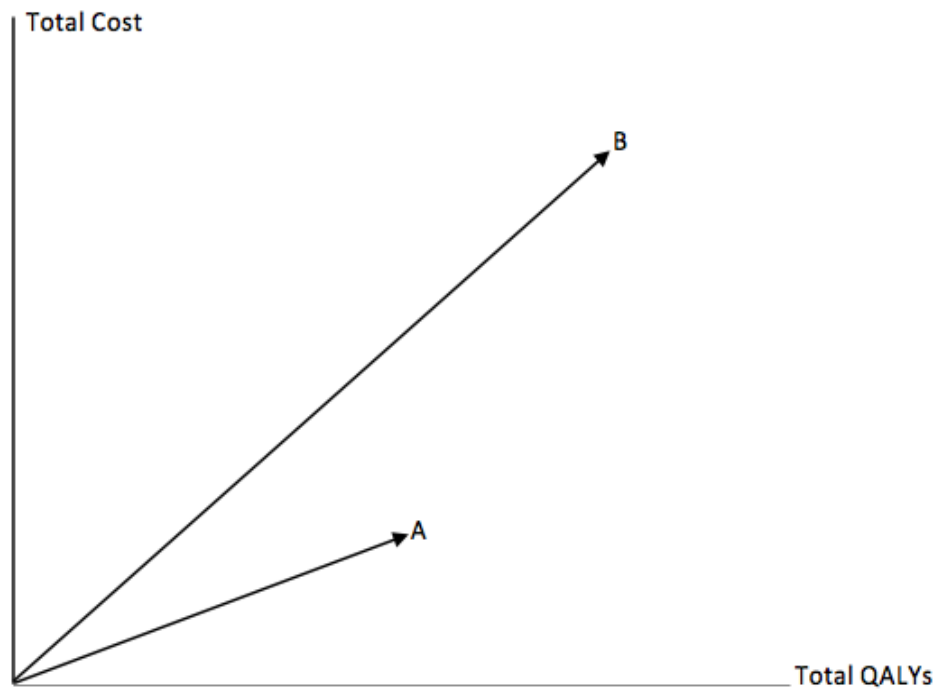


Figure 2

In Figure 2 it is clear that treatment B has a higher cost per QALY than has treatment A, since the slope of its ray from the origin is steeper, but this is not the basis on which it is judged relative to treatment A. Rather, we look at the ICER - the increase in total cost relative to the increase in total QALYs which would result if we shifted all patients from Treatment A to Treatment B. To see the ICER on the diagram, because we want to compare the gain in QALYs with the increase in cost associated with switching treatments, we draw a new pair of axes with origin at point A, as in Figure 3 below.

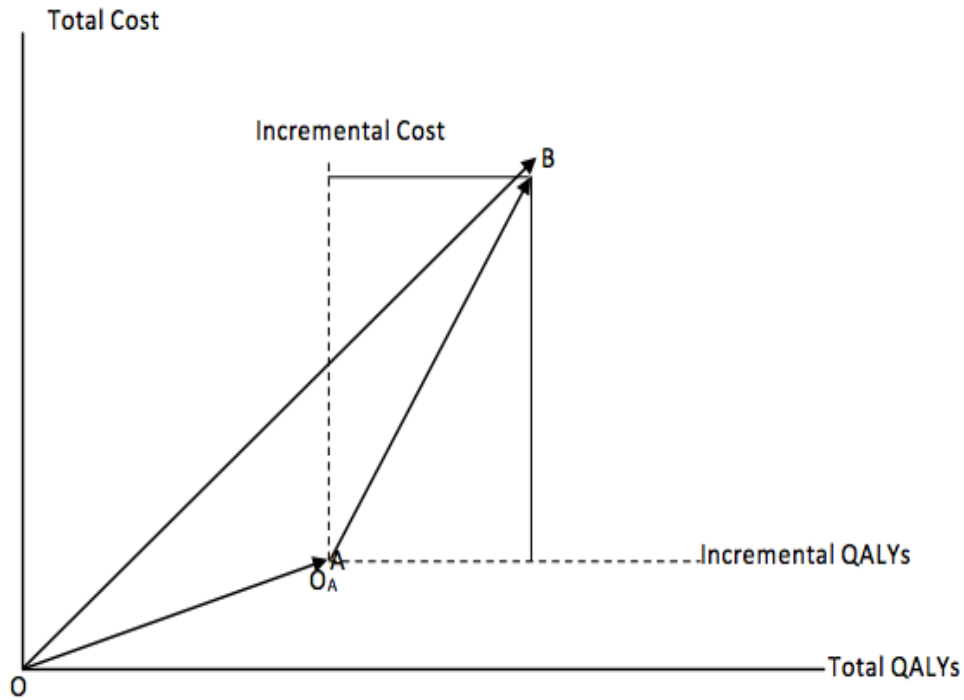


Figure 3

In Figure 3, the ICER for Treatment B relative to Treatment A is represented by the slope of the ray from A to B, measured against the dashed axes which originate at point A. Cost Effectiveness decisions are made, in broad terms, by comparing the slope of this ray with some threshold value, which could also be represented by a ray out of A: if the ICER ray is flatter than the threshold ray, the new treatment is cost effective and if the ICER is steeper than the threshold ray the new treatment is not cost effective. If there is no comparator treatment, the slope of the ray to A is compared with the threshold ray. It is important to remember that this analysis is being done on the assumption that the choice between the two treatments is an either-or choice: we must opt entirely for one or the other.

In Figure 4 below, we have added a threshold ray to the diagram, with a slope such that Treatment B's ICER is not cost effective:

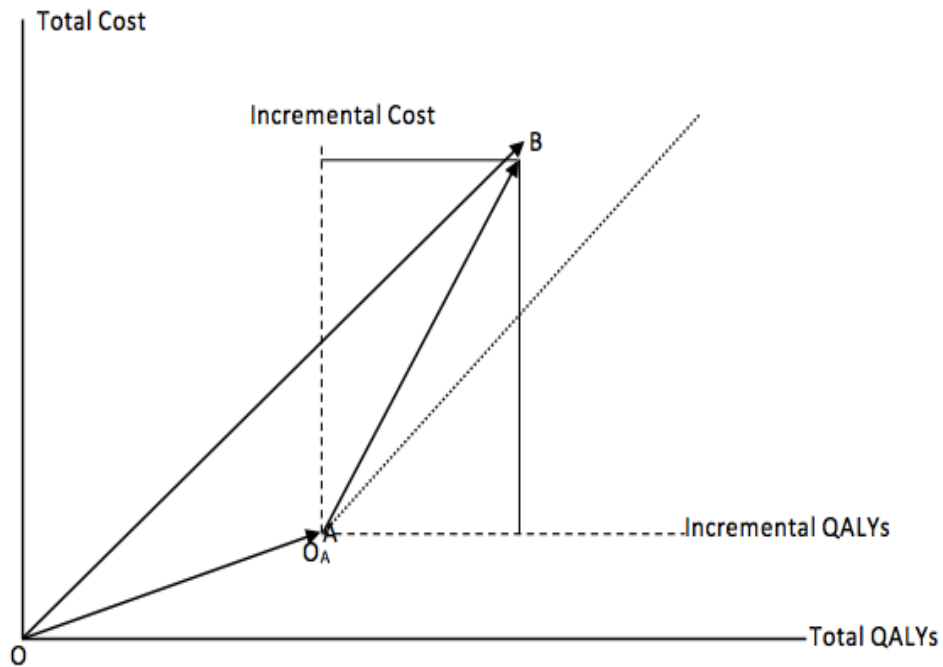


Figure 4

To this point we have been assuming that all of the cost of the new treatment falls entirely on the drug budget. Suppose, however, that while the ray which we have labelled B continues to represent the additional cost to the drug budget of introducing Treatment B, this new treatment can also reduce hospital (or other system) costs in a way which Treatment A cannot. We assume that the cost of Treatment A continues to fall entirely on the drug budget. Now we have two perspectives to consider. The perspective of the drug plan continues to be as in Figure 4 above. The perspective of the health care system, however, subtracts the hospital savings from the costs of Treatment B, reducing its overall cost per QALY:

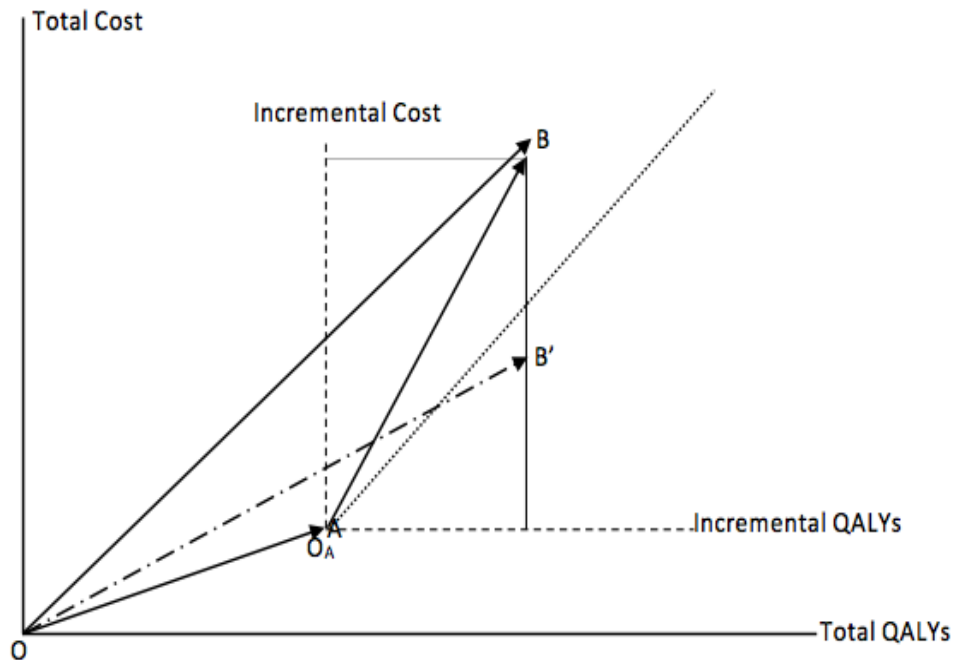


Figure 5

In Figure 5, the ray from the origin to point B continues to reflect the drug plan's perspective, but the dashed line from the origin to B' reflects the perspective of the health care system as a whole. It is clear that the ray from A to B' will be flatter than the Threshold ray, and that from the perspective of the system treatment B is cost effective. Whether this is recognized in the drug approval process is the issue of Siloing: whether the drug approval process is looked at only from the perspective of the drug program. If the drug budget is not to receive a transfer from the hospital budget, the drug budget winds up bearing the impact of what is a cost saving for the hospital budget and, assuming the drug plan has a hard budget ceiling, the drug program will have to cut back on its coverage of other drugs if it is to stay inside its budget ceiling.

In addition to the issue of Siloing, we can use the activity analysis diagram to get an understanding of the issues which arise in public and political, as opposed to technical, discussions about the cost of new drugs. The communications issue is that while CEA is undertaken in terms of ICERs, public discussion tends to take place in terms of cost per pill.

Figure 6 below is what is known in economic analysis, for obvious reasons, as a four-quadrant diagram. The upper left quadrant is the activity analysis diagram from our previous discussion:

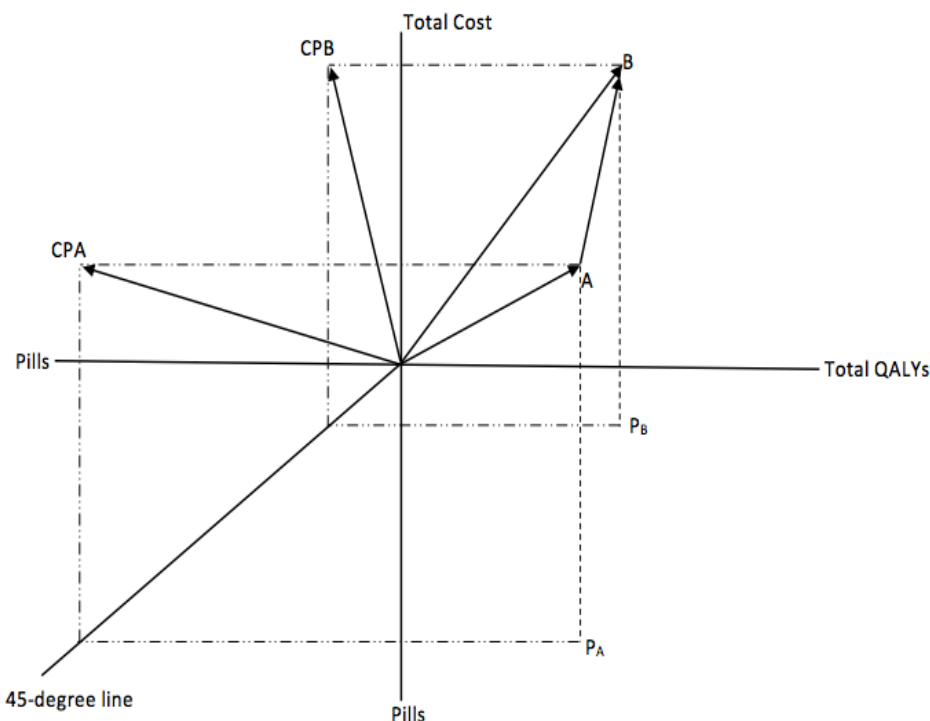


Figure 6

In Figure 6, in order to reduce the clutter on the diagram slightly, we shall assume that treatment B has a favourable ICER and not draw the threshold line. The bottom right quadrant of Figure 6 shows the number of pills associated with Treatments A and B, at P_A and P_B respectively. Note that Treatment A involves swallowing more pills than does Treatment B. The bottom left quadrant of Figure 6 contains what is known as a 45-degree line: this line has the property that any point on it has vertical coordinate identical to its horizontal coordinate, so it allows us to reflect from the downward pointing Pills axis to the leftward pointing one, which is also measured in Pills.

In the top left quadrant, the point CPB has as its vertical coordinate the total cost coordinate of Treatment B and as its horizontal coordinate the Pills coordinate of Treatment B - the number of pills which an individual on Treatment B must take. Similarly the point CPA in the upper left quadrant shows the total cost of Treatment A against the number of pills taken by a patient on Treatment A. the slopes of the rays from the origin to CPB and CPA show the cost per pill of Treatments B and A respectively. We note that the ray for Treatment B is steeper than that for Treatment A.

Now assume that Treatment B is such that a single pill suffices to deliver all of its health benefits. Even if B's ICER is highly favourable, its cost per pill would be extremely high, and it is this number which would dominate the public and political debate. In terms of our diagram, technical Cost Effectiveness Analysis, which is the basis for drug marketing approval (or insurance coverage) in many countries focuses on the slope of the ray from A to B in the upper right quadrant of the diagram while public and political debate focuses on the slopes of the individual rays in the

upper left quadrant, usually comparing them to a value presumed to represent the cost of physical production of the pill. It is hardly surprising that the two spheres of debate do not seem to overlap, to the point which even a wonder drug, which could cure cancer and which would be found highly cost effective on an ICER basis, would be the subject of much adverse comment if the treatment were capable of being contained in a single pill.