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Drugs for Rare Diseases: Paying for Innovation

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1. Introduction

One of the most challenging problems for pharmaceutical policy is how to pay for very expensive new drugs for rare diseases, sometimes known as “orphan drugs”. There has been an increase in the number of such drugs over the last few years, as well as in the level of expense for certain drugs. At the top end, Genzyme is marketing some drugs with annual costs of over \$300,000 per patient. Given the increasing personalization of medicine, it is likely that the number of very expensive drugs for relatively rare conditions may increase substantially in the near future (Haffner, Whitley, and Moses, 2002). The provincial insurance plans (like other insurers worldwide) therefore need a way of deciding whether, and how much, to pay for such drugs. This paper argues that it is possible – and necessary – to develop a coherent rule concerning coverage for very expensive drugs. The rule has to balance two conflicting goals: having strong incentives to develop new therapies, and being able to afford those therapies without bankrupting drug insurance plans.

Nearly 7000 rare diseases and conditions have been identified, with hundreds of new pathologies described globally every year, most of which have a genetic origin.¹ Approximately two thirds of these rare diseases are serious, chronic, and debilitating, because of their genetic origin. Characteristics include early appearance before the age of two in two thirds of cases; chronic pain in one fifth of cases; motor, sensory, or intellectual deficiency in half of cases, and early death in many cases (Plan National Maladies Rares, 2005-2008). From a social perspective, therefore, the importance of rare diseases should not be underestimated, and particularly now that advances in the understanding of genetics makes it increasingly possible for cures or therapies to be developed.

Pharmaceutical researchers have naturally tended to focus on drugs for common diseases. There are a number of reasons for this. Drugs for a common disease offer much larger potential revenues, and lower production costs because of economies of scale. Testing and approval for orphan is hampered by the rarity of patients, since the number of patients in clinical trials may be below the normal expectation. Thus even if a firm develops a successful treatment for a rare disease, it may have difficulty in demonstrating safety and efficacy to the satisfaction of regulatory authorities. Many rare diseases are not diagnosed by doctors, so that even if a firm succeeds in developing and obtaining

¹ For a list of rare diseases with information on prevalence, see “Rare diseases in numbers: Preliminary report from an on-going bibliographic study initiated by Eurordis in partnership with Orphanet, available at http://www.orpha.net/actor/Orphanews/2005/doc/Rare_Diseases_in_Numbers.pdf, last accessed November 4 2005.

marketing approval for a drug, the number of patients it can reach is reduced below potential simply because of faulty diagnoses.

When drugs for rare diseases have been developed, therefore, firms often apply rather high price levels. Remicade, used for Crohn's Disease, costs approximately \$10,000 for a course of three infusions. Repeat infusions may be needed up to every eight weeks, implying costs of well over \$20,000 per year (Otley, Critch, and Butzner, 2004). Humira, another therapy for Crohn's, costs approximately \$17,000 per patient per year. Zavesca, a therapy for Gaucher's Disease, is priced at approximately \$117,000 per patient per year. Fabrazyme, for Fabre's Disease, costs about \$290,000 per patient per year, and Aldurazyme, for MPS1, costs about \$435,000 per patient per year.

None of the rare disease drugs, individually, would bankrupt provincial drug insurance plans: but collectively, they begin to impose a heavy toll. For example, it is estimated that there are between 50 and 100 MPS1 patients in Canada. Funding of Aldurazyme for all these patients would imply a total cost of approximately \$20m - \$40m annually. Not only is this beginning to be a substantial cost to the insurer, it suggests a disproportionate reward for the manufacturer, Genzyme. Given sales for all affected patients in other OECD countries at similar prices, revenue would amount to \$600m annually.² Fabrazyme, with perhaps 200 patients in Canada, could generate revenues of \$60m in Canada, and around \$2bn annually in OECD countries.

Recognizing the obstacles to the development of orphan drugs, governments in the US, the EU, and some other jurisdictions have adopted formal plans to incentivize the development of drugs for rare diseases. The US Orphan Drug Act, which was the first significant initiative to incentivize pharmaceutical development for rare diseases, offered tax incentives and special exclusivity protection for orphan drugs. In Canada, there is no special incentive system for orphan drugs, which are treated much the same as other drugs. This means that Canada's contribution to aiding the global fight on rare diseases is achieved through a willingness of provincial drug plans to pay high prices for orphan drugs. However, provincial drug plans have been hesitant to pay very high prices for drugs; even where the therapeutic effects are excellent, very high prices for orphan drugs may make them not cost-effective according to the usual trade-off between the number of life-years saved and the price. This paper focuses on this decision problem for provincial insurers.

A preliminary question, addressed in the next section, is whether it is ever suitable for government-funded drug insurance plans to offer coverage for very expensive rare-disease drugs whose price makes them not cost-effective under standard analyses. The process used by the provinces to determine inclusion in provincial insurance plans requires a cost-effectiveness analysis to be submitted to the Common Drug Review.³ Drugs for very rare diseases are apt to fail this test because of high prices. This does, however, raise the question of whether there are mitigating circumstances – such as a

² In fact, sales of this product have been much lower than that globally, owing to slow take-up of the product given its extremely high price. The sales in the last quarter were approximately US\$20m (double that of a year before). (Biomarin Pharmaceutical Inc 10-Q SEC Filing, 11/03/2005) Given that drug sales typically increase substantially in the first five years after marketing authorization is granted, it seems possible that global Aldurazyme sales may increase to perhaps US\$200-US\$300m annually.

³ The Common Drug Review makes a recommendation which is not binding and provinces ultimately have to decide whether to cover drugs or not. Quebec does not participate in this process.

preference for equity in health outcomes, or the value of innovation – which might lead to a different standard for drugs for rare diseases and conditions.

The second point I address in this paper is what rule should be used to determine when to offer coverage of orphan drugs, and what price point should be acceptable. The benefit of having an explicit rule is that it permits drug firms to anticipate the return they can earn on their investment, reducing their risks and thus increasing incentives for orphan drug development; and it offers provincial insurers a reasonable justification for covering or not covering specific drugs.

2. Paying extra for rarity

An important preliminary question is whether it can ever make sense to pay extra for expensive drugs for rare diseases. Currently most provinces use some form of explicit cost-effectiveness evaluation under the Common Drug Review process to determine which drugs will be covered. The justification for using such an approach is that with a limited budget, hard decisions have to be made, and the best strategy is therefore to pay only for the drugs with the greatest impact. Given this approach, many orphan drugs will not be covered because of their high prices. For example, Aldurazyme, a maintenance therapy for people with MPS-1, has a cost per Quality-Adjusted Life Year (QALY) well over \$500,000, which makes it relatively expensive per QALY. McCabe, Claxton and Tsuchiya (2005) argue that to pay high prices for rare disease drugs is discriminatory against people who suffer from non-rare diseases, because the expensive drugs disproportionately use up limited resources. They discuss a hypothetical situation in which two groups of individuals have similar diseases, J and K. Disease K is ten times more common than disease J, but disease J costs ten times as much to treat. Finally, they assume a fixed budget large enough to treat one individual with J or ten individuals with K:

Then the real choice posed by orphan status is between treating 1 individual with J or 10 individuals with K. To argue that the patient with J should get treatment implies that that health gain of individuals with J should be valued 10 times higher than those with K. The idea that decisions should be made based on valuing health outcomes more highly for no other reason than rarity of the condition seems unsustainable and incompatible with other equity principles and theories of justice. Why should one's health be valued less simply because the condition is not rare?

McCabe, Claxton and Tsuchiya's argument ignores the issue of innovation, and simply assumes that treatment is possible. Second, the argument treats the prices as fixed, while in reality drug prices are normally set not at some unalterable cost of manufacturing but at a level designed to make the greatest profit for shareholders. Ultimately the price is the product of a balance between the buyers' willingness to pay, the seller's willingness to supply, and relative bargaining positions. Thus we observe that prices for drugs vary substantially between countries and even within countries depending on the buyer's characteristics (Hollis and Ibbott, 2006). When price is not necessarily fixed, one can see

that a decision to share the budget between the diseases allows for the insurer to provide different levels of incentive for innovation.

It is essential to consider the impact on innovation when considering whether to pay for orphan drugs, since without innovation no treatment may be available. Consider the example of diseases J and K above. It is likely that common disease K, which has 10 times as many patients, will be able to attract commercial drug development, even with only moderate prices paid for the drug. Rare disease J, however, will not be an attractive commercial target unless the innovator can sell its drug at very high prices. Thus, one might wish to split the budget between J and K, even if it means that some patients with K will suffer. Alternatively, the government might fund only J, and let the K sufferers pay for their own drug. (In effect, this is expanding the budget by shifting responsibility for paying for drugs away from the government.) Or the insurer might wish to pay for both drugs, but at a lower price point, recognizing that the cost of treatment is not fixed by divine fiat, but is arrived at through bargaining.

The key point is that without substantial government funding for drugs for rare diseases, those drugs are unlikely to be developed; over time, of course, patent protection will expire and the cost of the drugs will fall, enabling treatment at lower cost. But sufferers of rare diseases will continue to suffer indefinitely without a commitment to funding drugs for those diseases at a rate higher than government funding for common diseases. Paying high prices today for rare disease drugs enables future low prices on the same drugs, following patent expiry (or perhaps after the insurer has paid a reasonable share of innovation costs). Those expensive drugs will become less expensive in the future – but only if they are developed. Thus there is a benefit to paying for expensive drugs today not considered by McCabe, Claxton and Tsuchiya: it stimulates the development of innovative drugs which become less expensive in the future.

An interesting analogue to the logic used by McCabe, Claxton and Tsuchiya is given by the following. Suppose, in the same hypothetical world they used, that treating an individual with a generically available drug costs only \$100. However, if government is willing to pay up to \$1000 for a new and improved treatment, it will be developed. Further, suppose that a new patented drug would offer survival rates somewhat higher than the older generically available one. What should we do with our limited budget? If we commit to paying for the new and improved drug, it will be developed, but there won't be enough money for everyone to be treated. But if we don't commit any money to paying for the new drug, it will not be developed. Looking forward, we might well make the decision to use some of the budget to fund expensive new drugs in order to provide an incentive for new drug development. It is only when one starts to consider the importance of having a robust incentive mechanism in place that it makes sense to pay extra for drugs which are new or used only for rare diseases. State insurers should be willing to pay more for rare-disease drugs than for common-disease drugs for exactly the same reason as we support the patent system – to encourage valuable innovation. Drugs will not be developed for rare diseases without a commitment to paying for them. To be sure, there is a limit to how much we are willing to spend to support innovation: it is the purpose of this paper to develop a rule for how much a reasonable insurer should pay, and how to relate price to rarity.

If more money is dedicated to orphan drugs, that may, of course, lead to less money for common-disease drugs. One might therefore worry that faster innovation for

orphan drugs could lead to slower innovation in other drug categories. However, the reduction in incentive for other drugs is very small, since the total amount of the budget dedicated to rare disease drugs is simply not that large. This means that the most likely negative effect is a slight slow-down in the rate of innovation in common-disease drugs. However, a failure to fund rare-disease drugs leads to them being unavailable permanently. Once a rare-disease drug is developed, it need not qualify for very high prices forever; so the period in which a rare-disease drug will not be cost-effective is limited.

Another justification for paying high prices for rare-disease drugs is equity in patient care across people with different illnesses. McCabe, Claxton and Tsuchiya essentially argue that efficiency requires that governments allocate their scarce resources to the most valuable uses. However, a different approach could be that it is unjust not to provide basic care for people with rare diseases just because the basic care is expensive. (For more on this, see the NICE Citizen Council report, 2005, and Gericke, Riesberg and Busse, 2005; and Hughes, Tunnage and Yeo, 2005.) This argument is reasonable, up to a point, but it provides no guidance on how much extra one should be willing to pay to provide a reasonable level of health to a given individual. In addition, the equity argument cuts both ways: one can try to achieve equity in health outcomes or equity in health spending.

3. The necessity of an explicit policy on orphan drugs

In the previous section, I have argued that one benefit from paying for expensive drugs for rare diseases is that it stimulates valuable innovation. The importance of innovation is not normally included in cost-effectiveness analyses. But this innovation argument only takes us so far. The question then arises: how much extra should a state drug insurance plan be willing to pay for orphan drugs? In this section, I begin to address this question by focusing on the necessity to have an explicit policy.

There is no well-established basis for determining how much to pay for a product for which there is no competition and which is important for the health, well-being, and perhaps survival of a few members of society. Once a drug has been developed, the drug company is in a position comparable, in one sense, to that of hostage-takers: pay this much, or the child will die. (This is not to pretend that their activities are similar in any sense to hostage-takers – after all, they save, not take life –, but in the determination of price they are in a comparable position.) The expectation of a for-profit company with a valuable product is that it will be sold for the price that maximizes the profits of the company – to do anything less is to rob the shareholders. But most for-profit companies do not have a product which is the only way of saving the life of an individual, nor is their product generally paid for by the government. In the case of hostage-takers, the government typically refuses to pay a ransom, not because it does not value the life of the hostage, but because it does not want to encourage more hostage-taking. But governments do want to encourage the development of orphan drugs, and so they willingly pay for such drugs. The problem, however, is that the greater the willingness of the government to pay, the higher the price the firm should charge. But when is a price, in such a circumstance, too high?

With other products, the price is held down by the ability or willingness of the individual to pay for the product; if prices are too high, the firm will not make much

profits. The same does not apply when the consumer is not paying. Instead, it is the willingness of the insurer to pay which is relevant. When the insurer is the government the problems are compounded, partly because the government has very deep pockets, and because the government has a particular responsibility not shared by private insurers (Hollis, 2002). Note that it is not good enough, in these circumstances, for the government simply to declare that it will cover drugs no matter what the cost: that will simply lead to the suppliers charging higher and higher prices. A declared willingness to foot the bill no matter how high is just a way to ask firms to charge very high prices. It is this which explains the extraordinarily high prices observed for certain drugs: not that the companies expect that the people afflicted with a particular disease will pay for the necessary drugs, but that some other interested individual – in this case a state insurance plan with very large financial ability – will pay to save the sick person.

There are, for some medicines, some limits to the high prices, because of the Patented Medicines Price Review Board (PMPRB), although in such circumstances the limits imposed by the PMPRB may not be binding, since the limits set are determined by comparing Canadian prices to foreign prices, which are affected by the same influences abroad as in Canada.⁴ For unpatented drugs, the external limits are imposed by the possibility of competition, which is again not usually very relevant for drugs for rare diseases since the costs of developing a generic version may not be prohibitive when considering the likely profitability of competing in a very small market.

The result of this is that the incentive is for firms to set the highest price which will enable widespread use of their product within the affected population. For a small population, this may be a very high price, as the total bill to the insurer will not be large. The insurer has limited options at this stage: if it requires co-payments to reduce its costs, it knows that some patients will suffer as a result, since they will choose to forgo the expensive medicine or be unable to afford it. If the insurer denies coverage because a given drug is too expensive then of course those with the disease will, for the most part, simply be unable to purchase the drug.⁵ Both these options entail poor outcomes for the insurer, the supplier, the patient, and politicians. If the insurer offers coverage at the very high price, the drug may create a substantial financial burden.

Thus, it is important in this situation for the insurer to have a rule about how much it will pay. As described above, if the alternative rule is "pay for any medicine of value" then that simply invites unreasonably high prices. The high prices, in turn, result in some medicines being unaffordable and insurance coverage being unavailable. That is to say, the "pay for anything" rule, ironically, will lead to some medicines not being covered because prices are too high. Unfortunately, the only way firms can figure out how high they can price their drugs under such a rule is to speculatively increase prices as new drugs are introduced. This means that looking forward, firms are uncertain as to whether innovative drugs will be covered under government insurance – there is inevitably randomness in the coverage decision, even if the product is effective, since the very high prices the firm will seek may result in no coverage.

⁴ Even if a drug cost \$20m per dose, the PMPRB is unlikely to find the firm in violation provided the price was comparable in the reference countries.

⁵ Failure to cover suitable medication, when the condition or disease is serious or life-threatening, is not only morally objectionable, it is politically very difficult to sustain. However, about 85% of orphan drugs are for serious or life-threatening conditions (Haffner, Whitley and Moses, 2002).

What would be preferred, then, is a coverage rule which allows firms to reliably estimate how much they can charge, and then expect coverage at that price. Firms will want their products to be covered, and so will price accordingly, except where the required Canadian price is far below that which can be obtained in other OECD countries. (Given the reference pricing mechanisms used, if the Canadian price is too low, it will harm the ability of the firm to generate revenues in other countries, and the product may not be offered in Canada.)

4. What can be used as a basis for payment

The above discussion suggests that it is important to have a rule. The question is then how the rule should be determined? As a starting point, consider the items which could possibly be included. These include:

- (a) The incremental therapeutic effect per patient
- (b) The cost of innovation
- (c) The cost of manufacturing, marketing and administration
- (d) The number of patients who could benefit from the drug globally and in Canada

We will examine each item in turn to see how it can be used. The essential idea is to determine whether and how any observable item should contribute to the price the insurer should pay for a drug.

(a) The incremental therapeutic effect per patient

In principle, it is highly desirable to relate the price paid for a medicine to its value. Of course, value is a difficult thing to measure, and in the textbook economics situation, we measure value not by what people say a thing is worth to them, but by the amount they actually pay for it. However, even in a perfectly competitive market, without externalities and with full information on the part of both buyers and sellers, the value of a product is unknown, although we can put a lower bound on value to buyers by the amount people are willing to pay for it. In a market such as pharmaceuticals, none of the standard conditions of well-functioning markets holds, and it is very difficult to extract good information about value from a market plagued with these problems.

However, while the market may not yield much useful information about the value of pharmaceuticals, it is possible to obtain some sense of value by considering the effect of pharmaceuticals directly on health outcomes, at least a measure of value relative to other pharmaceuticals and medical products whose primary purpose is improving human health. This perspective is sometimes called an “extra-welfarist” approach (Drummond *et al* 2005). This requires direct observation of the health outcomes created by a drug. There are valid objections to this approach, but in the absence of better measures of value which the market fails to create, direct measurements of therapeutic effect are arguably the best measure of value that is available.

To obtain some measure of the relative value of one pharmaceutical over another, it is necessary to go through two steps: identifying the effect on health outcomes of each drug, and then measuring the health outcome within a standard measure of health such as QALYs (Quality-Adjusted Life Years).

The first step requires measurement of the average effect of an appropriately prescribed pharmaceutical on a range of health outcomes. Health is multi-faceted: for

example, a drug might relieve the pain and increase the mobility of arthritis sufferers, while also increasing their risk of a heart attack. Regulatory authorities such as Health Canada require observation of these effects both in pre-approval clinical testing and sometimes in post-approval epidemiological studies. In general, the decision to approve the marketing (and to permit the continued sale) of a drug is based mainly on the drug's effects on health outcomes. It is well known that the approval process is imperfect, and it must certainly be the case that the observer can only imperfectly measure the effects of a drug on health outcomes. This problem is even more acute in the case of many orphan drugs, which have small numbers of users and do not typically have extensive clinical testing.

The second step in this process is to aggregate health outcomes into a single measure. This is not a trivial step since it requires the observer to balance the merits of different health states and the outcomes of different people. The kinds of difficulties encountered here are formidable: Is it equally valuable to extend the life of a ninety-year old and a five-year old by one year? How should we treat gains in health status which will occur in the distant future? How should disability be treated, without discounting the value of life of a disabled person? How should we value a reduction in the probability of death compared to an increase in nausea and dizziness? Using a variety of hedonic estimates and “willingness to pay” studies, health researchers have attempted to sort out the relative values of different health states. Not everyone has the same valuations, and the problems inherent in hedonic estimation are well known. However, it is possible to obtain a standardized measure of the health impact of a drug treatment, denominated in terms of QALYs or a similar measure. And it is worth remembering that even the price system has difficulties in making these relative valuations.

Ultimately, this kind of approach typically obtains a measure of cost per QALY created by a drug. The insurer would then make a judgment as to whether to cover given drugs, based in part on this cost-effectiveness analysis.⁶ The Common Drug Review in Canada, as in other jurisdictions, relies on pharmaco-economic evaluations using QALYs and similar aggregate health outcome measures, when offering its recommendations. There is very extensive experience with evaluating QALYs related to drug treatments, since a large number of governments and other insurers all over the world use such an approach to determine inclusion of drugs on formularies, but this does not mean that the approach has been perfected, by any means. Drug companies have also used QALY-type analysis themselves in order to demonstrate economic effectiveness of treatments (Davidoff, 2001).

Within the context of state funded drug insurance, there is typically a fixed budget which must be allocated. The cost-effectiveness methodology (generically) is the only reasonable way for determining which drugs will be covered by the insurers. In principle, in this approach, drugs can be ranked according to their cost-effectiveness, and then only the highest ranking drugs included, with the cut-off determined by some budgetary limitation.

⁶ There are a variety of types of analysis available here, including “cost-effectiveness analysis”, “cost-utility analysis” and willingness-to-pay analysis. The particular approach used is not really relevant to the analysis of orphan drugs in this paper.

Since, as discussed above, orphan drugs are likely to be not cost-effective according to the usual standards, which do not account for the value of innovation, one could consider paying higher prices today in order to ensure a continuing stream of valuable innovations. But how much extra should the insurer be willing to pay, over other drugs with comparable effects? At most, the insurer should compensate the firm for its costs of innovation, production, marketing and administration. I discuss these points next.

(b) The cost of innovation

Manufacturers often justify high prices by pointing to the high cost of innovation. This therefore seems, at first blush, like a useful factor to include when considering how much to pay the manufacturer. However, trying to determine the cost of innovation for a specific drug is more or less impossible. The reason for this is the difficulty of knowing the probability of failure at the time the project was started.

When accounting for the cost of an innovation, it is necessary to consider not only the cost of innovation of the product under consideration, but the (unknown) probability that the project was going to fail at the time it was started. It is necessary to take this probability into consideration, since investigating new drugs is a risky business and many drugs are investigated which turn out to have no commercial value at all. If firms earn enough only to pay for the innovation costs of their successes, they will not stay in business for long. While it is possible to use evidence on failed drugs to estimate the average cost of successful drugs (including the cost of investigating failed drugs) it is not possible to do this for a single drug for a rare disease; the reason is that firms are rationally willing to investigate even long-shot chemicals which would treat a commercially important disease like hypertension, but no firm would investigate a long-shot drug for a rare disease with 5000 patients globally. The expected probability of success for a compound for a rare disease must be relatively high in order to justify spending money on the project. Thus it is not clear what is the *ex ante* cost of innovation, taking into account the probability of failure, since the probability of failure in specific cases is unknown.

Another way of seeing why it not appropriate to use realized costs of an innovation is that some very valuable innovations turn out not to cost much: the key to obtaining the patent, after all, is that someone sees something that was not obvious before. This spark of invention may not cost much, but without the appropriate rewards in place, inventors will not engage their minds to think about these things and innovations will not occur.

Therefore it is simply not possible to use or impute innovation costs for a specific drug, although the average cost of innovation should be rewarded appropriately. What, however, are the average costs of innovation for orphan drugs? This is unknown and deserves further investigation. I explore in the next two paragraphs the costs of innovation and the share of these costs which should be borne by Canadians.

DiMasi, Grabowski and Hansen (2003) argue that the average cost of innovation for drugs generally is approximately US\$800m. This estimate appropriately includes the cost of capital and the cost of failed drugs. While others have argued that this widely cited paper far overstates the true cost of innovation, it remains the most credible estimate available. There has also been a claimed slide in research productivity in recent years, which may result in higher average innovation costs for new drugs.

The DiMasi, Grabowski and Hansen analysis does not consider how the cost of innovation varies either with the probability of success of a given compound or with the market opportunities for different types of therapies. This is an important point. A firm may be willing to invest an average of US\$800m to develop a drug which it hopes will yield, say, US\$2bn in annual sales, but it will certainly not do so to develop a drug with a maximum potential of US\$200m in annual sales. One would therefore expect that the cost of innovation for drugs varies proportionally with the expected market size and profitability of the drug. That is to say, firms will take bigger risks and invest more when there is a bigger potential prize available. When the prize is small, the investment must be small too. As DiMasi, Caglarcan and Wood-Armay (2001) observe, the increasing use of pharmaco-economic evaluations early in the drug development process guides research decisions. Thus firms will naturally invest much smaller amounts in drugs which are expected to have low cost-effectiveness.

One important reason why innovation costs for orphan drugs must be low is that the costs of clinical trials for these drugs tends to be low. On average, the cost of clinical trials comprises over half the research and development cost (DiMasi, Grabowski and Hansen, 2003). Potential blockbuster drugs commonly have thousands of patients in clinical trials. Orphan drugs are likely to be different (Office of Technology Assessment, 1993, p. 71). Balasubramaniam (2000) found that the seven orphan drug marketing approvals in 1999 had a mean of 588 subjects in clinical trials with a range between 152 and 1281 total patients. This compares with an average of more than 5,000 subjects for the typical new drug introduction in the late 1990s. (Grabowski, 2003) Thus, even considering only the cost of clinical trials, without considering pre-clinical expenses or the ex ante probability of success, orphan drug development would on average cost considerably less than other drugs.

Therefore US\$800m is very likely far above the true average cost of innovation for orphan drugs. A more realistic figure might be a fraction of that, perhaps US\$200m, or C\$250m.⁷

Of course, Canadians need not pay for the entire cost of innovation by themselves, given that the market for drugs is global. Canada's share of the OECD drug market, and its share of OECD income, is approximately 3%. The share of innovation costs which should be borne by Canada is thus approximately 3%. Therefore, as a rough guess, a reasonable amount for Canada to pay for its share of orphan drug innovation costs is approximately \$7.5m per drug (or, with a 6% discount rate, around \$1m per year for ten years). This amount only pays for innovation and development, not marketing and manufacturing costs. Given that historically only about ten orphan drugs have been approved each year in the US, Canada's contribution to orphan drug development should be in the range of \$75m annually. (In the context of the approximately \$18bn that Canadians spend annually on prescription drugs, this is not a large sum.) This amount is the excess of revenues that the sellers of orphan drugs should obtain above and beyond their costs of manufacturing and marketing and administration, and would be

⁷ I am pulling this estimate out of thin air; but I think it is safe to say that the expected cost of innovation into orphan drugs is certain to be much less than US\$800m. Evidently it is necessary to do more analysis on this point.

approximately enough to compensate innovators for their development of orphan drugs.⁸ The level of analysis here is so rough that it is intended only to provide a sense of the magnitude of Canada's required contribution to pay a reasonable share for orphan drug innovation.

(c) Other supplier costs

At a minimum, the average cost of manufacturing, marketing and administration needs to be covered, in addition to providing a return on the (unknown) investment in innovation. The costs of manufacturing, marketing and administration for most drugs is relatively small on a per unit basis, but for some orphan drugs, with their small patient base, average manufacturing costs per unit may be relatively high.⁹ (Typically we would expect considerable economies of scale in drug manufacturing, marketing and administration.) Information on manufacturing costs can be provided by the firm under a confidentiality agreement. However, even when such information is available, it is not necessarily relevant to the insurer: it is not appropriate for the insurer to reward the creation of an expensive manufacturing process – what should presumably be rewarded is value created by the medicine. If production costs are higher than the value created, it is better if the product is not made at all.

What is required is to ensure that the average level of prices is sufficiently high to ensure that firms are paid enough to cover innovation, manufacturing, marketing and administration costs for small-volume orphan drugs. Since the average manufacturing, marketing and administration cost per unit will be inversely related to the volume of sales, the price will typically have to be adjusted upwards in order to make production profitable.¹⁰

Another important point to consider is the definition of a rare disease. Different countries have quite different rules for what qualifies as an orphan drug. It is, however, not clear that it is important to define exactly the limits of what is an orphan and what is not: it may be possible for the rule to vary with the number of patients, rather than having to impose a strict, and ultimately arbitrary, cut off level.

(d) The number of patients who could benefit from the drug globally and in Canada

In this section, I discuss the problem of identifying rarity. In section 5, I introduce a methodology for determining how much extra to pay. The obvious way to account for the rareness of a disease is to examine incidence in the population. This is the approach used in the US Orphan Drug Act, under which drugs treating diseases with incidence below a

⁸ A few caveats are in order here: these numbers are pretty rough; if Canada wants to encourage more development of orphan drugs, it should be prepared to pay higher prices. In any case, the figures are only intended to be a guide for getting a sense of scale of how much of a contribution Canada should be making towards paying for innovation in orphan drugs.

⁹ Even for Aldurazyme, with its relatively small sales, cost of sales is only a small fraction of sales revenues. For the first nine months of 2005 for the Aldurazyme joint venture operated by Biomarin and Genzyme, cost of sales was about 18% of sales, and operating expense was about 50% of Aldurazyme sales (Biomarin Pharmaceutical Inc 10-Q SEC Filing, 11/03/2005).

¹⁰ I simply do not know what would be a reasonable adjustment here. I guess that fixed production and marketing costs are normally not larger than innovation costs, so that perhaps an adjustment in the range of \$7.5m per drug might [!] be reasonable.

given threshold are given favourable tax treatment and special exclusivity. However, this approach is problematic, since firms then have an incentive to game the system by identifying subgroups of diseases as new diseases, thus enabling them to qualify for orphan drug status. Yin (2005) labels this behavior “balkanization” since common diseases are split up into many rarer diseases. This behavior is also sometimes called “stratification.”

Another approach is therefore to classify the rareness of a condition by the number of consumers of a drug, or even the number of units consumed. The reason for such an approach is that when a drug is consumed by few people, there is a justification for thinking that its potential market is also likely to be small. The problem here is that many drugs not consumed by many people have small markets mainly because they are more expensive or less effective than other similar drugs. These drugs may not be so much for rare diseases as for common diseases with many treatment options.

Thus the issue is how to avoid the kind of balkanization of disease categories that has occurred in the US. One way to minimize such balkanization is to use a rule in which incentives for rare disease drugs become greater *incrementally* as the disease gets rarer. This avoids firms restricting the applications of their product to make it fit within some artificial threshold. Another approach – if the incentive for innovation is high prices following approval – is to account for frequency of use after approval. Thus if, for example, the usage of a drug was much higher after approval because of off-label prescribing, the drug's maximum allowable price might be revised downward. (This would lead to some disincentive to finding new valuable uses for approved orphan drugs, but there is no way to avoid all the problems here.)

5. A proposed policy for drugs for rare diseases

The discussion above suggests the following. First, it is important to have a rule for whether, and how much, to pay for orphan drugs. Second, the rule should explicitly consider the cost-effectiveness of the drug, just as is currently the case for other drugs. Third, since innovation is important in enabling new therapies, orphan drugs could be eligible for special consideration, but such special consideration should not lead to excessive rewards, given the average costs of innovation, manufacturing, marketing and administration.

My proposed rule is therefore to continue to use standard cost-effectiveness evaluation in which only the drugs with the highest cost-effectiveness are included, with no coverage for drugs which do not meet the standard. Drugs for rare diseases should obtain a special credit in the evaluation, as described below.

In determining the amount to be paid, if the insurer takes the rareness of a disease into account, it must do so in a way that the reward to the firm is increasing with the incidence of the disease and the therapeutic effect of the medicine. That is to say, it should always be more profitable to develop a better drug which cures more people. However, for the sake of developing orphan drugs, it is also important to provide incentives to develop drugs for rare diseases. How can this be done?

Under the standard formulary methodology, drugs are evaluated for cost-effectiveness, with drugs having the highest benefit per dollar of cost included in the formulary. However, this will automatically lead to the exclusion of most orphan drugs,

which tend to have high prices because their per unit costs are inevitably high. Therefore, it is necessary to have a methodology for incorporating rareness of a disease or condition.

When evaluating the cost effectiveness of a given drug, drugs which affect fewer than say 20,000 Canadians should be given a "credit" in the evaluation which is inversely related to the incidence of the disease or condition. Note, for clarity, that the credit is not paid to the manufacturer; it only affects the coverage decision. Recall, from section 4(c) above, that the Canadian share of costs for innovation of a typical orphan drug is approximately \$7.5m. Accounting for high production, administration and marketing costs per unit of the drug, one might double the Canadian share of innovation and excess administrative costs to perhaps \$15m. With an expected effective patent life of say 10 years, and discounting future revenue streams, this is approximately \$2m per year for ten years for each new drug. This amount could be deducted from the expected cost of medicine for the purposes of the cost effectiveness evaluation, divided by the number of units of the drug expected to be consumed.

For example, suppose that 200 Canadians are expected to take drug X as a maintenance therapy, and the price to be paid by the insurer is \$30,000 per person per year. Then when evaluating the cost-effectiveness of the medicine the insurer should deduct from the cost a credit for the rareness of the disease equal to the \$2m divided by the 200 consumers; this implies a "credit" of \$10000 per person per year for the first ten years the drug is used. Thus in the cost-effectiveness evaluation the insurer should impute a cost of only \$20000 per year instead of \$30000. This has the desirable characteristic of automatically adjusting for the rareness of the disease: the diseases and conditions which are the rarest would benefit from the largest credits.

Note that this approach does not allow for very large credits, even for ultra-rare drugs: the reason is that Canada's share of drug development costs is simply not that large. Even if one takes a more generous view of innovation and fixed manufacturing costs, increasing the credit to say \$5m per year for ten years, the additional amount that insurers should be willing to pay does not increase at the same kind of level as we have seen for some rare-disease drugs recently. However, very large credits are inappropriate, since they are in effect allowing compensation of the firm at levels beyond those justified by the real costs of drug development, production, and marketing.

Should the ceiling price or rule be public or secret?

Under this proposal, the insurer reveals only that there is a competition for scarce dollars, and then allows the firms to compete to be covered. An alternative would be for the insurer to reveal openly what it is willing to pay for each drug. If firms have full information about other firms' drugs and about the process of cost-effectiveness evaluation, the two options should yield about the same results given the same budget, since firms both cases will set their price to match the insurer's willingness to pay. However, full information is a strong assumption and it is unlikely that the two options would lead to the same set of drugs being covered.

If the maximum price is not revealed, the insurer may sometimes get a break when the firm offers its medicine in at a lower price than the insurer is willing to pay. If the maximum price is made public, the firm is likely to always choose to set its price at the maximum, so that the insurer is always paying the maximum it is willing to pay. While this would be expensive, it helps to reduce the set of cases where firms which are

uncertain about the true maximum set their price too high, with the result that the medicine is not covered at all. Similarly, from an incentive perspective, an open maximum has the advantage of creating better incentives for firms, since they know that they will be rewarded in proportion to the value of their product.

An open rule would also help to deflect public concern about decisions not to cover, since the public would be able to know what price the insurer had offered and why it had refused to pay more. This would help to put the onus back on the firm in cases where treatment was unavailable.¹¹ Under a policy of hidden willingness to pay, but public declaration of prices by the firm, it is the government which appears quixotic in its decisions to cover or not; but where the government has an established policy of how much it will pay, based on a fixed budget and a focus on paying only for the most effective medicines, it becomes the firm which is unreasonable when it raises its price above the maximum which the government has declared itself willing to pay.

Aligning insurance coverage decisions with other jurisdictions

Coverage decisions are important because of their effect on development of future orphan drugs. However, orphan drug development does not, for the most part, depend heavily on the Canadian market, which represents a small fraction of the global pharmaceutical market. Thus, to the extent that Canada is important, it is because of Canadian influence on coverage decisions in other jurisdictions. It is evident that other jurisdictions are also struggling with pricing of orphan drugs.

However, a good pricing rule should be compatible with what is happening in other OECD countries, and in particular with the major European countries which employ reference pricing. If the European countries use the "pay for anything" rule, then Canada cannot do anything very different; products will not be offered here at prices far below other countries. There is therefore a need for collaborating with other countries, particularly those in Europe which use Canada as a point of reference for their pricing decisions. Biologics tend to have a uniform world price, unlike chemical pharmaceuticals in which there are different prices across most countries. Canada will not be able to obtain lower prices for biologics through its own bargaining power: it needs to cooperate with other countries to establish the framework for reasonable prices.

The difficulty of employing standard cost-effectiveness measures

One problem with trying to employ standard cost-effectiveness analysis for orphan drugs is that often the number of patients is too small to achieve statistical significance in clinical trials. For example, according to Karr (2000) the FDA initially licensed L-carnitine for genetic carnitine deficiency in only 16 patients. In such a case, clinical studies may be inadequate to demonstrate clear outcomes. However, as McCabe, Claxton and Tsuchiya (2005) argue, cost-effectiveness analysis can be performed to at least some level and it is reasonable to use the best information available. They point out that NICE (the British equivalent of the Common Drug Review) has undertaken at least 15 orphan drug reviews using standard cost-effectiveness measures.

¹¹ With the no-rule approach, or where the rule is secret, the firm can simply claim that the insurer has arbitrarily refused to cover a drug. With an open-rule approach, the firm can at best claim that the insurer has set the price schedule too low. In this case, it is the firm which appears arbitrary.

6. Discussion

This paper has argued first that there is an innovation justification for paying extra for rare disease drugs; second that it is essential to have a rule for how much extra to pay; and third that the optimal rule will make the permissible higher price conditional on average orphan drug innovation costs. Orphan drugs can be assessed within the standard cost-effectiveness evaluation framework if they are allocated a credit related to the rarity of the disease. The credit should be based on the number of courses of therapy expected to be used in Canada and the average excess costs of drugs for rare diseases. In effect, this credit is intended to compensate for the high per-unit costs of innovation, production and marketing of rare-disease drugs. Such an approach is justified by the need to stimulate innovation in markets which would otherwise not be large enough to draw commercial interest. Given this justification, the size of the credit is determined by the Canadian share of the average excess costs of orphan drug development and production. This suggests, on a per drug per year basis, a total credit attributable to each orphan drug on the order of two million dollars per year. This credit could enable orphan drugs priced higher than would normally be admitted under standard cost-effectiveness threshold to be eligible for coverage despite its high price. Such a strategy would provide a coherent, justifiable rule for determining when and how much to pay for orphan drugs. It would also allow Canada to contribute to providing incentives for innovation in the global fight against rare diseases, in a way consistent with existing the Canadian approach to cost-effectiveness and without requiring any complicated new tax incentives such as are embodied in the US Orphan Drug Act.

7. References

- Balasubramaniam, T., 2000, "USFDA Orphan Drug Approvals 1999." Available at <http://www.cptech.org/ip/health/orphan/orphan1999.html> last accessed November 3, 2005.
- Davidoff, F, 2001. "The Heartbreak of Drug Pricing." *Annals of Internal Medicine* 134: 1068-1071.
- DiMasi, J., R. W. Hansen, H. G. Grabowski, 2003 "The price of innovation: new estimates of drug development costs," *Journal of Health Economics* 22: 151-185.
- DiMasi, J., E. Caglarcan and M. Wood-Armany, 2001, "Emerging Role of Pharmacoeconomics in the Research and Development Decision-Making Process." *Pharmacoeconomics* 19(7): 753-766.
- Drummond, Michael F., Bernie O'Brien, Greg Stoddart, and George W. Torrance, 2005. *Methods for the Economic Evaluation of Health Care Programmes*. Third Edition. Oxford: Oxford University Press.
- Gericke C, A Riesberg and R Busse, 2005, "Ethical issues in funding orphan drug research and development." *Journal of Medical Ethics* 31: 164-168.

- Grabowski, H. 2003, "Increasing R&D incentives for neglected diseases: lessons from the Orphan Drug Act." Duke University, mimeo.
- Haffner ME, Janet Whitley J and Moses M, 2002, "Two decades of orphan product development" *Nature Reviews Drug Discovery* 1: 821-825.
- Hollis, Aidan, "The Link between Publicly Funded Health Care and Compulsory Licensing," *Canadian Medical Association Journal* 167: 765-767, October 2002
- Hollis, A. and P. Ibbott, 2006, "How Parallel Trade Affects Drug Policies and Prices in Canada and the United States" *American Journal of Law and Medicine*, forthcoming.
- Hughes, D.A., B. Tunnage and S.T. Yeo, 2005, "Drugs for exceptionally rare diseases: do they deserve special status for funding?" *QJM* 98(11): 829-836.
- Karr A, 2000. "Who wants to adopt an orphan?" *Hospital Pharmacist* 7(6): 165-167.
- McCabe C, Claxton K and Tsuchiya A, 2005. "Orphan Drugs and the National Health Service: Should We Value Rarity?" *British Medical Journal* 331: 1016-1019.
- Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards*, Washington, D.C., U.S. Government Printing Office, February 1993.
- Anthony Otley A, Critch J, Butzner J, 2004, "Infliximab for the treatment of paediatric Crohn's disease: Obstacles to accessing a necessary therapy." *Pediatrics and Child Health*, 9(2): 87-90.
- Plan National Maladies Rares, 2005-2008, Ministère de la Santé et de la Protection Sociale (France), 20 novembre 2004.
- Yin W, 2005. "Do Market Incentives Generate Innovation or Balkanization? Evidence from the Market for Rare Disease Drugs." Mimeo, Princeton University Department of Economics.