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Why licensing authorities need to consider the net value of new drugs in assigning review priorities: Addressing the tension between licensing and reimbursement

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Pharmaceutical regulators and healthcare reimbursement authorities operate in different intellectual paradigms and adopt very different decision rules. As a result, drugs that have been licensed are often not available to all patients who could benefit because reimbursement authorities judge that the cost of therapies is greater than the health produced. This finding creates uncertainty for pharmaceutical companies planning their research and development investment, as licensing is no longer a guarantee of market access. In this study, we propose that it would be consistent with the objectives of pharmaceutical regulators to use the Net Benefit Framework of reimbursement authorities to identify those therapies that should be subject to priority review, that it is feasible to do so and that this would have several positive effects for patients, industry, and healthcare systems.

Keywords: Public health, Licensing, Cost effectiveness analysis, Reimbursement

Healthcare systems are struggling to pay for the newest pharmaceutical therapies; especially those produced through exploitation of the developments in biotechnology and genomics. These costs can be orders of magnitude greater than the conventional small molecule therapies (18).

There has been a variety of responses to this problem. Some have argued that cost of developing new drugs is too high and that this threatens our ability to reap the benefit from recent advances in medical science. Others have argued that the return on investment in the pharmaceutical industry is not sustainable (2), whereas still others have argued that these costs should be met as they are an investment in future innovation (18).

Those responsible for managing healthcare budgets have designed systems that attempt to allocate resources to therapies on the basis of some assessment of the value of the health produced (4;15;17). These processes have been criticized for impeding patient access to therapies that the licensing authorities have already assessed and deemed to be of value (1).

In this study, we briefly review the evidence for the increasing influence of cost-value assessments in determining market access. We then consider the function of the licensing

authorities. The section Licensing, Reimbursement, and the Public Health examines the nature of the tension between licensing and reimbursement. In the section Combining Costs, Effectiveness, and a Public Health Perspective, we outline a proposal for the adoption of value-based assessment in a small but important area of licensing activity—expedited review—arguing that this would improve the ability of licensing authorities to meet their stated objectives. The section Challenges to Implementation of a Net Benefit Approach considers potential benefits and problems with value-based licensing.

LICENSING, VALUE ASSESSMENTS, AND MARKET ACCESS

Until the 1990s, licensing was the sole hurdle to market access for the pharmaceutical industry. However, the past 20 years has seen the gradual development of an additional hurdle to market access. Organizations responsible for managing healthcare budgets increasingly require evidence on value for money. To be good value, drugs have to provide health gain at a price that is deemed affordable. Canada and Australia were early pioneers of this approach, and by 2007, many major markets have established processes that consider the value, or efficiency, of new drugs as part of the reimbursement decision making process. Even the United States, the Medicare Payment Advisory Commission is now required to consider the budgetary implications of its recommendations (13).

As a result of these developments, pharmaceutical companies are concerned about the sustainability of the return on the large investments they make in the research and development; and researchers are increasingly concerned that the public will not be able to reap the benefits of today's rapid expansion in medical knowledge (18).

Pharmaceutical Licensing

The U.S. Food and Drug Administration and the European Medicines Evaluation Agency are responsible for licensing drugs for approximately 80 percent of the world pharmaceutical market. The stated aims of these two organizations are remarkably similar, and both include the promotion of public health (11;12).

Of interest, although the public health is mentioned in both mission statements, neither organization provides a definition of what they mean by "the public health." The Oxford Textbook of Public Health provides the following definition: "Public health is the process of mobilizing and engaging local, state, national, and international *resources* to assure the conditions in which people can be healthy." (italics added) (8).

To effectively pursue the objective of promoting the public health, licensing authorities may legitimately wish to consider whether a specific "mobilization of resources" makes a greater or lesser contribution to people's capacity to be healthy, than an alternative "mobilization of resources." Thus, consideration of what economists call opportunity cost is not inconsistent with the objectives of the licensing authorities.

Although consideration of opportunity cost may not be inconsistent with the licensing authorities' objectives, to date they have not done so. Licensing has operated in a consumer protection framework. Their role has been to ensure the product is safe and efficacious. The consumer decides whether the cost to them is justified by the expected health gain. However, the cost of drugs means that such individual decisions are increasingly rare. The opportunity cost implications of paying for a specific treatment are rarely confined to an individual. In systems where the healthcare budget is fixed, paying for new interventions displaces other treatments. Under insurance, the inclusion of a more expensive treatment increases insurance premiums and, at the margin, some individuals are squeezed out of the healthcare insurance market. As the cost of new drugs increases, the link between licensing in a consumer protection framework and the promotion of public health becomes increasingly tenuous.

LICENSING, REIMBURSEMENT, AND THE PUBLIC HEALTH

Licensing focuses upon quality, efficacy, and safety. It considers whether the benefits the therapy provides to the many outweigh the harm that it will do to a few; benefits and harms are considered in terms biochemical markers and clinical events. Such measures, with the exception of mortality, are disease specific. Thus, licensing only considers the population of people with the condition for which the therapy will be licensed. It is unable to consider the benefits and harms to the total population. This is a significant constraint on its capacity to promote public health, as it cannot compare the population health implications of prioritizing the licensing of one therapy or another.

There is a perception that reimbursement processes are fundamentally different to licensing processes. However, both share the central principle of balancing the benefits and the harms in deciding whether it should be made available. The difference between them is in the scope of benefits and harm, and the population they consider. Reimbursement authorities increasingly recognize that, when resources are limited, one of the harms associated with providing a therapy for one person is the opportunities for health gain forgone for others. The resources consumed are not available to provide other treatments. Reimbursement authorities consider these *opportunity costs* of reimbursement as well as the *therapeutic benefit*.

Balancing Public Health with Individual Rights

Licensing authorities have a responsibility for protecting and promoting individual rights as well as promoting public health. An individual's right to access a safe and efficacious

drug should not be curtailed on the grounds that the drug is not an efficient use of society's resources. The individual has the right to decide whether it is a valuable use of their private resources, and all individuals have that right, equally, including the extremely wealthy who pay for their health care from private resources.

Processes that prioritize some treatments by definition do not treat all individuals equally. When licensing authorities do not treat all individuals equally, it would seem sensible that such unequal treatment should be consistent with the authorities' stated objectives.

Fast Tracking and Public Health

The Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) operate schemes to reduce the time to licensing for some drugs. These fast-track processes gives special treatment to the individuals with the target diseases for the selected therapies. All things being equal, they will receive new treatments more quickly than individuals whose treatments are approved through the standard process. However, the criteria by which therapies are selected for the fast-track licensing process are not obviously focused on promoting public health; focused as they are on innovative modes of action and biochemical measures of magnitude of effect.

The advantages of being subject to the fast-track processes can be significant. For example, the EMEA fast-track procedure halves the target time to a decision, compared with the normal licensing process; the FDA fast-track procedure reduces the target time from 10 months to 6 months. Given the revenue streams of block buster drugs, even 4 months additional revenue can represent a substantial benefit.

The FDA-accelerated approval process will accept surrogate end points. This finding can have a major impact on the time to licensing as it reduces the duration of trial follow-up. This finding in turn drives down the cost of Phase 3 trials, one of the major costs in pharmaceutical research and development.

As the licensing authorities adopt a disease specific approach to assessing benefit, unless the benefit is confined to mortality, they cannot assess whether fast-tracked therapies contribute more or less to the public health than therapies in the standard processes. This problem has long been recognized in the health economics literature with the result that many reimbursement processes accept quality-adjusted life-years (QALYs) as a measure of health outcome (3;14).

Considering Opportunity Cost in Licensing to Promote the Public Health

Considering the potential harms to the wider community (opportunity costs) necessarily entails an assessment of the likely cost of the therapy. To date, licensing authorities have explicitly and consciously avoided considering the expected cost of the therapies (18). Rawlins, arguing for more efficient safety testing in pharmaceutical research and development, explicitly discounted a role for price consideration in licensing, arguing that considering price in licensing would ignore citizen's equal right to access safe and effective therapies. Rawlins was also concerned that decision makers would confuse the decision about the safety and efficacy and its cost-effectiveness.

We agree with Rawlins that licensing authorities cannot ignore the rights of individuals to access safe and effective treatments that they can afford, just because others cannot afford them. Furthermore, our proposal would not carry the risk of highly effective but expensive treatments would not be licensed. However, it is not inappropriate to consider the expected cost of drugs when choosing whether a particular drug should receive preferential treatment in the licensing process. For these therapies, other people's rights to equal treatment within the licensing process has already been abrogated and, therefore, it is legitimate to consider whether the total benefit to the community is greater than the total harm to the community.

At the beginning of the 21st century, the vast majority of health care is funded through the organizations that have very real resource constraints. The aging population and the causal relationship between age and demand for health care means that these resource constraints are likely to become more not less severe, even if we assume that the cost of healthcare stabilizes. In this environment, licensing authorities' contribution to the public health may be substantially improved by an explicit consideration of the expected cost of the drugs they review.

Some have expressed a concern that a high regulatory hurdle will discourage investment in healthcare research and development and, thus, interfere with the innovation cascade that has been observed over the past 50 years. It is undoubtedly true that the utilization of cost-effectiveness in prioritization would be likely to have some impact upon healthcare research and development. However, given the success rate of pharmaceutical research and development, where the failure rate at Phase 3 is generally accepted to be in the region of 2 out of 3; it does not necessarily follow that more caution in investment would lead to fewer effective therapies arriving at market. This would only be the case if there was no capacity for improving the targeting of investment decisions. If this were the case, lower investment would lead to fewer treatments being developed with the same relative success rate and, thus, a lower number of effective therapies making it to market. However, there are reasons to believe that the current pricing environments may not promote efficient investment decisions. Typically, industry is allowed to amortize the cost of the failed therapies in research and development through the price of the successful treatments. For companies that have a portfolio of treatments in development, a major proportion of the risk of the investment is effectively underwritten by the healthcare payers' commitment to paying high prices for future successful drugs. If this

Box 1. Net Benefit

Incremental cost-effectiveness ratio (ICER) $= \Delta C/\Delta E$
Net monetary benefit (NMB) $= R_T \Delta E - \Delta C$
Net health benefit (NHB) $= \Delta E - (\Delta C/R_T)$

R_T = Threshold ratio; ΔC = Difference in mean cost between comparators; ΔC = Difference in mean effect between comparators

commitment is tempered, then companies will be more risk averse, and we should, therefore, observe fewer failures in late stage development. It is only if the Phase 3 successes systematically tend to have a lower than average probability of success on the basis of Phase 2 data, that encouraging more risk averse investments at Phase 3 would be expected to lead to fewer successful treatments reaching market.

COMBINING COSTS, EFFECTIVENESS, AND A PUBLIC HEALTH PERSPECTIVE

If we knew which health-generating activities would be displaced by the additional resources required by a new technology, then we could directly address the question of whether the overall public health would be improved by asking whether the gains in health generated by the new technology exceed the health gains displaced elsewhere in the wider community. In other words, the true cost of the technology is the total net health forgone by the community to make the therapy available.

Based on some assessment of what is likely to be displaced within the healthcare system (a cost-effectiveness threshold) (7), we can translate resource costs into health and directly compare health gain to health cost or equivalently convert heath gains into resources and compare the equivalent monetary benefits to monetary costs (see Box 1) (10). These net health or net monetary benefits combine health benefits and costs that fall across the wider community and enable assessment of whether a technology is likely to improve the public health.

When considering provision of the technology for an individual patient, if the net benefit is positive, then there will be a net increase in the public health. Of course the overall contribution of the technology to the public health requires some assessment of the size of the current and future population that could benefit from this technology. The greater the population net benefit, the greater the contribution to the public health. Assuming that the measure of health gain captures all important effects of therapies submitted to the licensing authority, net benefit provides a basis on which the licensing authority can assess the case for fast-track review. The licensing authority can then allocate the priority review resources to those therapies that are expected to make the greatest contribution to the public health.

An important characteristic of this system is that the assessment of contribution to the public health would have to be undertaken at the healthcare system level. This is because it is the interaction between the healthcare system budget and current activities that determines the cost-effectiveness threshold (7). As the major licensing authorities serve multiple healthcare systems, each with different budgets and portfolios of activity, separate net benefit calculations would have to be done for each system, and the results summed.

For the purposes of ranking therapies for fast-track licensing, the expected net benefit for healthcare systems in which the intervention was expected to be negative would be set to zero, on the basis that these systems would not in fact pay for the therapy and, therefore, the expected health loss would not be incurred. Thus, the correct calculation would be to sum the expected net benefit across all healthcare systems in which expected net benefit was positive.

CHALLENGES TO IMPLEMENTATION OF A NET BENEFIT APPROACH

The use of net benefit in licensing would face the same criticisms as its use in reimbursement. However, there are some additional potential challenges with using the net benefit approach in licensing. First, if the criterion for fast tracking is the population net benefit, then the probability that a therapy will be fast tracked will be directly related to the prevalence of the disease. If society does not wish to see this type of inequality, the individual expected net benefit can be used to select therapies for fast track. This would maintain a link between fast-tracking selection and promotion of the public health, although it would no longer maximize the contribution to public health of the fast-track system.

Second, the difference in the value of a unit of a health gain would vary between systems. Systems with large budgets would attribute greater net benefits for any given therapy. This would mean that therapies for diseases prevalent in wealthier healthcare systems would be more likely to be fast tracked, which would in turn create an incentive to develop therapies for diseases prevalent in these healthcare systems. However, the operation of the free market already ensures that there is an incentive to develop therapies for diseases prevalent in countries with the greatest ability to pay. It is not obvious that the use of the net benefit framework would make things worse. Indeed, individual nations that wished to promote the development of treatments for disease that were most prevalent in poorer countries could specify an

alternative cost-effectiveness threshold for evaluating the net benefit of such treatments.

Perhaps more importantly, the variation in the value of a unit of health gain might create incentives for companies to propose lower prices in countries with lower budgets to maximize the expected net benefit across all the healthcare systems. In such circumstances, it would be important that these prices were then implemented in practice.

In principle, there is also an issue of the value of the innovations foregone as a result of reduced incentives to invest in healthcare research and development (16). However, as discussed above, this assumes that the current investment behaviors are efficient from a population health perspective. Given the failure rate in Phase 2 and 3 of the clinical developments programs, there is a prima facie case that the level of investment could be reduced without adversely affecting the productivity of the research and development pipeline.

Associated with the argument for considering the option value of the innovation foregone is the observation that incremental advances may act as stepping stones to break through developments. There is a concern that displacing even marginal developments in treatment will disrupt the process of incremental advances and, thus, threaten subsequent breakthroughs. In principle, this is true. However, in the context of promoting public health, the question is whether the net value of the expected future health gain foregone from the incremental benefits and subsequent breakthrough is greater than the expected health benefits from providing incentives for faster access to more cost-effective treatments, and potentially for more people.

Benefits of Adopting the Net Benefit Framework for Priority Review

The most obvious benefit of adopting a net benefit framework approach to selecting therapies for priority review is to strengthen the link between the licensing processes and promoting the public health. However, there are other potential benefits; the net benefit framework could promote more efficient production process in manufacturing, and perhaps more importantly, would be particularly valuable in formalizing the standards for considering a claim substantiated.

A favorable net benefit can be achieved through either greater efficacy or a lower cost. Thus, a me-too therapy that, through innovation in production technology, came to market at a lower price could qualify for priority review, leading to large gains in public health. This is particularly important for biotech therapies, where the production technologies are developed rapidly, and licensed therapies are often manufactured using older higher cost production technologies. The use of the net benefit framework could introduce a downward pressure on the price of new therapies. As the net benefit framework quantifies the expected public health benefit from making a therapy available, it facilitates the estimation of the public health benefit foregone if a therapy is not entered into the priority review process.

Regulators have to decide whether the evidence submitted supports the claim of the sponsor that, at the population level, the expected benefits from the use of the new therapy exceed the expected harms. Historically, little has been written on the evidence required to substantiate a claim. The most recent FDA Modernization Act notes that whether a claim is considered substantiated "depends upon several factors. . . .these include the type of product, the consequence of a false claim, the benefits of a true claim, the costs of developing substantiation for the claim" (13).

The net benefit framework allows the quantification and valuation of both the consequences of a false claim and the benefits of a true claim. It has been shown how, in turn these data can be used to establish whether it is efficient to require more evidence before approval or give conditional approval while more evidence is collected (5;6). The net benefit framework allows the regulator to place a value on the uncertainty attributable to expedited licensing and the expected health gain foregone from declining to fast track. It also allows the identification of the important parameters in the decision problem for which additional research is efficient, when conditional approval is provided. Thus, the net benefit framework can inform both post-launch (Phase 4) research and pharmacovigilance programs.

By incorporating consideration of uncertainty and total health gain into licensing processes, the net benefit framework may influence decision making with the pharmaceutical research and development process before licensing. The use of expedited review as an incentive may promote the development of therapies that have a higher probability of producing substantial health gain and by implication reduce or remove the incentive to develop therapies of marginal value compared with therapies already on the market. This in turn could lead to a higher threshold for positive decisions on the transition to Phase 3 trials. All things being equal, this could lead to fewer failures in Phase 3. As the need to amortize the cost of failures in Phase 3 is one of the major contributory factors to the high cost of developing new therapies, there is the potential for a reduction in the average cost of developing new therapies (9).

The degree to which any of these effects would be observed depends upon the magnitude of the advantage available from the fast-track system. If licensing authorities accepted the appropriateness of using fast-track review systems to promote public health, they could vary the characteristics of the fast-track system as a signaling mechanism.

SUMMARY

Historically, pharmaceutical licensing authorities have acted as consumer protection organizations, ensuring that drugs are safe and manufacturers' claims are reasonable. This model of licensing was consistent with healthcare consumption being

Box 2. Fourth-Hurdle Organizations

Pharmaceutical Benefits Advisory Committee	Australia
Canadian Agency for Drugs and Technologies in Health	Canada
Haute Autorite Sante	France
Institute for Quality and Efficiency in Health Care	Germany
Pharmacy Advisory Committee	New Zealand
Norwegian Medicines Evaluation Centre	Norway
National Institute for Health and Clinical Excellence	United Kingdom

primarily a decision made by individual citizens and funded from the private resources. Increasingly healthcare consumption is determined by system wide guidelines rather than individual preferences, and it is financed from either general taxation or social insurance. Against this background, it may be appropriate for licensing authorities to adopt a broader remit than consumer protection.

In this study, we have argued that, when the price of a therapy has a substantial impact upon the proportion of the population that can access them, it is appropriate, legitimate, and feasible for licensing authorities such as the FDA and the EMEA to use the expected net benefit of a new therapy as the basis on which to identify therapies for expedited review.

The proliferation of fourth-hurdle organizations (see Box 2) across the developed world, including the United States, has implications for the suitability of the current pharmaceutical licensing frameworks. Now may be the time for the licensing authorities to engage with a value-based regulation paradigm.

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