

Why licensing authorities need to consider the net value of new drugs – addressing the tension between licensing and reimbursement.

Christopher McCabe,¹ Karl Claxton,² and Anthony O'Hagan³

1. Professor of Health Economics, Warwick Medical School, University of Warwick, United Kingdom

2. Professor of Economics, Centre for Health Economics, University of York, York, United Kingdom

3. Professor of Probability and Statistics, Department of Probability and Statistics, University of Sheffield, Sheffield, UK

Address for correspondence:

Medical School Building
Warwick Medical School
University of Warwick
Gibbet Hill
Coventry
CV4 7AL

Tel: 02476 150189

Fax: 02476 528375

Email: Christopher.McCabe@warwick.ac.uk

Word Count:

Abstract 171

Text 5541

Acknowledgements

This manuscript benefited greatly from constructive comments Dr. Penny Mohr and two anonymous referees. All errors remain the responsibility of the authors.

Abstract

Pharmaceutical regulators and health care reimbursement authorities operate in different intellectual paradigms and adopt very different decision rules. This leads to situations where drugs that have been approved for use by licensing authorities are not made available to patients because the judgement of the reimbursement authorities is that the cost of therapies is greater than the health gain they produce. This in turn creates great uncertainty for pharmaceutical companies attempting to plan their investment in research and development, as licensing is no longer a guarantee of market access. In this paper we propose that it would be consistent with the objectives of pharmaceutical regulators to utilise 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 a number of positive effects including reducing the tension between regulatory and reimbursement authorities, produce downward pressures on the cost of drug development and inject greater certainty in to the pharmaceutical industry's investment planning environment.

Introduction

It is increasingly clear that health care systems are struggling to bear the cost of the newest pharmaceutical therapies; especially those produced through exploitation of the developments in biotechnology and genomics. The cost of newer biotechnology therapies can be orders of magnitude greater than the conventional small molecule therapies.¹

The realisation that within current budgets we cannot afford all these new drugs has produced a variety of responses. 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.¹ Others have argued that the return on investment in the pharmaceutical industry is not sustainable², whilst still others have argued that the cost of these new drugs should be paid as they are, at least partially, an investment in future innovation.³

Governments and other authorities responsible for managing health care budgets have designed systems which attempt to allocate resources to therapies on the basis of some assessment of the value of what those therapies produce.^{4 5 6 7} These processes have, to a greater or lesser degree, all met with criticism for impeding patient access to therapies which the licensing authorities have already assessed and deemed to be of value.⁸

Kommentar [CJM1]: Add reference to recent ViH paper railing against reimbursement decision making processes.

In this paper we briefly review the evidence for the increasing influence of cost-value assessments in determining market access. We then consider the function of the major pharmaceutical licensing authorities – the Federal Drug Agency (FDA) and the European Medicines Evaluation Agency (EMA). The third section of our paper considers whether the objectives of the licensing

¹ The cost 1 year's anti-tnf therapy shortly after launch was reported to be £8000, compared to a range of £480 to £1200 for leflunamide, a conventional DMARD launched around the same time. – NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. New Drugs for Rheumatoid Arthritis. Wolfson Unit, Newcastle upon Tyne 2000

and reimbursement authorities are necessarily in conflict. In section four we outline a proposal for the adoption of value-based assessment in a small but important area of licensing activity – accelerated licensing – arguing that this would improve the ability of licensing authorities to meet their stated objectives. Section Five highlights and attempts to respond to the criticisms of our proposals drawing in part upon the literature that criticised the use of value assessments in reimbursement decision making processes. ^{4 5}

Licensing, value assessments and market access.

For most of the last 50 years successful navigation of the safety and efficacy licensing processes has been the sole hurdle to market access for the pharmaceutical industry. However, the last 20 years has seen the gradual development of an additional hurdle to market access. Organisations responsible for managing health care budgets have increasingly required evidence that drugs are good value before agreeing to pay for them. To be good value drugs had to provide health gain at a price that was deemed affordable in the context of the available budget. Canada and Australia were early pioneers of this approach; and by 2006 many major markets have established processes that consider the value, or efficiency, of new drugs as part of the reimbursement decision making process. (See Box 1). Even the United States of America, through the recent Medicare Drug Improvement and Modernization Act, has created a framework within which it is legitimate for reimbursement decisions to take account of cost effectiveness issues. (ref).

As a result of these developments, pharmaceutical companies are increasingly 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.¹ (refs)

Pharmaceutical Licensing

The United States Food and Drug Administration and the European Medicines Evaluation Agency are responsible for licensing drugs for approximately 80% of the world pharmaceutical market. The stated aims of these two organisations are remarkably similar.

The EMEA's mission statement reads as follows:

"...in the context of a continuing globalisation, to protect and promote public and animal health by

- developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorisation,
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals,
- facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry, and
- mobilising and coordinating scientific resources from throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programmes, to perform inspections for ensuring fundamental GXP* provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals."⁹

The FDA's mission statement is:

"... is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by

helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health. “¹⁰

Both organisations have responsibility for promoting the public health through speeding innovative therapies to market, whilst ensuring that the potential harm of these therapies to the few are outweighed by the expected health gain to the many.

What is the public health?

Interestingly, although the public health is mentioned in both mission statements – neither organisation provides a definition of what they mean by ‘the public health’ on their website. For the purposes of this paper we consider the definition provided by Oxford Textbook of Public Health (ref):

“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).

The definition includes consideration of the use of resources. In order to most effectively pursue their objective of promoting the public health, licensing authorities may legitimately wish to consider whether a specific ‘mobilisation of resources’ makes a greater or lesser contribution to people’s capacity to be healthy, than an alternative ‘mobilisation of resources’. Thus, consideration of what economists call opportunity cost is not inconsistent with the objectives of the licensing authorities, and, as we explain below, it may facilitate the pursuit of their objectives.

Licensing, reimbursement and the public health

Current licensing arrangements consider quality, efficacy and safety only. Indeed, to a large degree the central question in the licensing process is whether the benefits the therapy provides to the many outweigh the harm that it will do to a few. Licensing processes consider benefits and harms of a therapy primarily in terms of impact upon biochemical markers and/or clinical events. However, the measures of benefit and harm are, with the exception of mortality, disease specific. As a result licensing authorities can only consider the population of people with the condition for which the therapy will be licensed. They are unable to consider the benefits and harms to the wider community they serve. This significantly constrains their capacity to promote the public health as they cannot compare health gain and resource implications of prioritising the licensing of one therapy or another. ..

It is frequently argued that reimbursement processes are fundamentally different to licensing processes, acting as a barrier between patients and therapies which are beneficial. However, reimbursement processes share the central principle of balancing the benefits and the harms of a therapy in deciding whether it should be made available. The difference between reimbursement and licensing authorities is in the scope of benefits and harm, and population they consider. Reimbursement authorities recognise 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. That is the resources consumed as a result of that decision are not available to provide treatment to another person; or indeed different health care for the same person. Formally, reimbursement authorities consider these *opportunity costs* of reimbursement as well as the *therapeutic benefit*.

At its most simple, the difference is one of perspective. Licensing authorities adopt a disease based population perspective, whilst reimbursement authorities adopt a covered population perspective. Neither of these perspectives is appropriate for the objective of promoting public health; unless the covered population is the same as the population served by the licensing authority.

Balancing public health with individual rights

Licensing authorities should not utilise a pure efficiency criterion for determining licensing. They have responsibility for protecting and promoting individual rights as well as promoting public health. Individuals' rights to access safe and efficacious drugs should not be curtailed simply because the cost of those drugs means that they are not an efficient use of society's resources. The individual has the right to access them if they consider them to be a valuable use of their private resources.

All individuals have the right to equal treatment by the licensing authorities. However, in circumstances where the licensing authorities do not treat all individuals equally, it would seem sensible that such unequal treatment should be consistent with the authorities' objectives of promoting the public health. There is one specific form of unequal treatment that we wish to focus on – processes that prioritise the licensing of some treatments.

Fast tracking.

Both the FDA and the EMEA operate schemes to reduce the time to licensing for drugs that are deemed to be innovative. The EMEA has two schemes, conditional marketing authorisation and marketing authorisation under exceptional circumstances. The FDA has two schemes, Accelerated Approval and Priority Review. For the purposes of this paper, we refer to these as fast track licensing. Although these schemes account for quite a small proportion of all reviewed by the licensing authorities they frequently carry a large price premium and represent a significant challenge to the reimbursement authorities. (need to get examples from last two years, how about the new MS drug?).

Fast track licensing by definition 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 with conditions that are

treated by drugs approved through the standard licensing procedure. However, the criteria by which therapies are selected for the fast track licensing process do not appear to be consistent with promoting the public health. The criteria for the EMEA and FDA are shown in Boxes 2 and 3 respectively.

The advantages of being subject to the fast-track processes are 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. In addition, under Priority Review the FDA is willing to accept surrogate endpoint data as evidence of efficacy. This can have a major impact on the time to licensing as it reduces the duration of trial follow-up required to collect evidence of efficacy. It also impacts upon the research and development costs of getting the therapy to market. This in turn should influence price and thereby access to therapy when it is licensed.

On first inspection these criteria seem perfectly appropriate. As ever, the devil is in the detail. Both organisations consider therapeutic benefit, beyond mortality, in disease specific and primarily biochemical terms. In adopting this disease specific approach, when the therapeutic benefit is not confined to mortality it is not possible to assess whether those therapies which are entered into the fast track contribute more or less to the public health than therapies which are not. This is because such a comparative assessment requires a single measure of outcome which can capture the health gain from any therapy. This problem has long been recognised in the health economics literature with the result that many reimbursement processes accept QALYs as a measure of health outcome.¹¹ (need to get references – there is a ISPOR review paper I think)

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.¹

“They take no account of the actual or potential price of the product to consumers. This absence of a fourth hurdle is appropriate for two reasons. First, in a democracy, it would be wrong for any state to deny its individual citizens the right to purchase goods merely because the price was deemed to be too great. Second, there is a very real danger that drug regulators, either consciously or unconsciously, would confuse the decisions, and when confronted with a difficult cost-effectiveness problem would retreat behind arguments about efficacy, safety or the balance between the two.”

The first objection we have addressed above, recognising that licensing authorities must protect the rights of individuals to access safe and efficacious therapies that they consider good value for their private resources. The second objection suggests a misunderstanding of the role of cost effectiveness analysis. It suggests that there may be multiple decisions; the decision as to whether something is effective; whether it is safe and whether it is cost effective. Of course, there is only one decision; whether the therapy should be made available for the treatment of patients. This depends upon balancing the harms (safety plus opportunity cost) and, benefits (effectiveness). It also assumes that the decision process is and will remain opaque. Where stakeholders in a decision process have access to the information on effectiveness, safety and cost effectiveness, it will be eminently clear whether a decision has been made on grounds of effectiveness, safety or cost effectiveness.

Cost effectiveness analysis is an explicit framework for describing, quantifying and synthesising information on the three streams of evidence required for the decision; benefit, harm and opportunity cost. The explicit nature of the cost

effectiveness analysis framework would make it harder, not easier to fudge the rationale for specific decisions.

One suspects that the objection to the consideration of cost by licensing authorities is the fear that very expensive but highly effective therapies would not be licensed. As described above, this would not be appropriate. However, it would not be 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 organisations 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 health care stabilises. (need a reference for impact of age on demand for health care) 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.

Below we describe how cost information could be used to inform decisions as to which therapies should be entered into fast-track licensing procedures and discuss the potential public health benefits that might result.

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 in order to make the therapy available.

Based on some assessment of what is likely to be displaced within the health care system (a cost-effectiveness threshold)¹² we can translate resource costs into health and directly compare health gain to health cost or equivalently convert health gains into resources and compare the equivalent monetary benefits to monetary costs (see Box 3). These net health or net monetary benefits combine health benefits and costs which 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 priority review. The licensing authority can then allocate the priority review resources to those therapies which 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 health care system level. This is because it is the interaction between the health care system budget and current activities that determines the cost effectiveness threshold.¹²

As the major licensing authorities serve multiple health care 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 health care 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 in fact be incurred. Thus the correct calculation would be to sum the expected net benefit across all health care systems in which expected net benefit was positive.

Challenges to implementation of a net benefit approach

The calculation of net benefit requires the specification of the joint distribution of costs and health effects for the investigational therapy and existing treatments; the specification of a maximum willingness to pay for health effects and the expected size of the population to be treated over the decision time horizon.

Considering the criticisms of the use of the net benefit approach in reimbursement decision making processes, we can anticipate a number of objections to its use for priority review: i) the evidential and analytic requirements may be difficult to meet, particularly at such an early stage of product life cycle; ii) there is likely to be substantial uncertainty in any estimates of net benefit; iii) a single measure of health outcome is unlikely to capture all the benefits and harms (side effect profiles and forgone health outcome elsewhere) iv); what may be displaced by the new technology is unknown to licensing and reimbursement authorities and thus they cannot provide a legitimate estimate of the cost effectiveness threshold required to calculate the net benefit; v) licensing authorities typically service multiple reimbursement jurisdictions which will vary in many of the factors relevant to net benefit.

i) Many reimbursement authorities around the world review and issue guidance on new therapies at or close to product launch. These authorities frequently consider cost effectiveness information in their decision making processes.⁷ The information required by these authorities is substantially the same as that required to estimate the expected net benefit. Thus it is possible in practice to produce robust estimates of the expected net benefit for a new product at the time of submission for licensing. The immaturity of the evidence base is appropriately captured in the expression of uncertainty around the value of the parameters in the decision model and subsequently in the uncertainty around the expected net benefit.⁵

ii) The explicit quantification of the uncertainty in the estimation of the net benefit is one of the most valuable contributions of adopting the net benefit framework in licensing. It allows the decision maker to explicitly consider the risk of making the wrong decision; i.e not observing the predicted population health gain from the use of the product; to place a value on this risk, and then consider the efficiency of delaying approval until more research is available to reduce the risk of making the wrong decision vs, conditional approval vs. unconditional approval.¹³

iii) The limitations of the existing measures of health outcome used in economic evaluation are well known.¹⁴ This said, measures such as the Quality Adjusted Life Year (QALY) are increasingly accepted as a useful tool by national and international health care organisations.⁷ Research to improve the scope and sensitivity of these measures is on-going. In the interim, organisations that use these measures tend to have decision criteria that explicitly allow the consideration of outcomes that may be inadequately captured by QALY type measures.⁵

It is worth noting that all regulatory and reimbursement decisions implicitly compare multiple outcomes; e.g. side effect profile and effectiveness, within and across diseases, in arriving at a decision. The advantage of the QALY, and similar measures, is that the weight given to a proportion of the multiple

outcomes is made explicit and is thus open to debate and challenge. This, we would argue, compares favourably with the traditional process of implicit weighting of side effects and effectiveness, undertaken by licensing authorities.

iv) It is undoubtedly the case that licensing authorities will not know what is replaced or displaced by the introduction of the new technology. However, the expected value of what is replaced/displaced is incorporated into the analysis via the cost effectiveness threshold used in the calculation of net benefit.¹⁵ The choice of threshold is clearly an important determinant of the net benefit calculation and it is therefore important that it is specified in a legitimate manner. Given the complexity of modern health care systems it is not feasible that for a reimbursement authority to know the value of the displaced activities with certainty. However, if we accept that the national reimbursement authorities have a legitimate right to make reimbursement decisions on behalf of the population they serve, they logically are the legitimate body to specify the threshold value to the licensing authority.

v) Licensing authorities typically service multiple reimbursement jurisdictions and many of these factors will vary across jurisdictions. Whilst calculating the expected net benefit within jurisdiction may be straightforward, the estimation of the supra-jurisdictional net benefit will need to take full account of these variations. Estimating the net benefit for the whole licensing jurisdiction using a single analysis would require inter alia that all health systems used a single price and that all health systems used a single currency. As described above, the solution to these challenges is to produce a series of jurisdiction specific analyses and then sum the estimated net benefits to get the expected net benefit for the licensing authority's jurisdiction. Given the increasing requirement for such analyses post licensing, this would involve producing these analyses earlier in a product development process, rather than necessitating large amounts of new work.

There are some additional potential challenges with using the net benefit approach in licensing. Firstly, 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 societies does not wish to see this type of inequity, the individual expected net benefit can be used 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 maximise the contribution to public health of the fast track system.

Secondly, 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 health care systems would be more likely to be fast tracked, which would in turn create an incentive to develop therapies for diseases prevalent in these health care 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 use of the net benefit framework would make things worse.

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 in order to maximise the expected net benefit across all the health care systems. In such circumstances it would be important that these prices were then implemented in practice.

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. It will also provide consistency in the treatment of applications for priority review.

However, there are other potential benefits. A favourable 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 produced using higher cost production technologies. Thus the use of the net benefit framework might introduce a mild downwards 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.

Sufficient evidence

Regulatory processes have to decide whether the evidence submitted to them 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 (costs). Historically there has been very little written on the level of evidence required for a claim to be considered 'substantiated'. However, the most recent FDA Modernisation Act ¹⁶ notes that whether a claim is considered substantiated "depends upon a number of 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.'¹⁶

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 prior to approval or give conditional approval whilst more evidence is collected.¹⁷ 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 IV) research and pharmacovigilance programmes. The value of alternative research programmes can be expressed in terms of the expected contribution to the public health.

By incorporating consideration of uncertainty and total health gain into licensing processes, the net benefit framework can influence decision making with the pharmaceutical research and development process prior to licensing. The incentive system will promote the development of therapies that have a high probability of producing substantial health gain and by implication reduce or remove the incentive to develop therapies of marginal value compared to therapies already on the market. This should lead to a higher threshold for positive decisions on the transition to phase 3 trials. All things being equal this should lead to fewer failures in Phase 3. As the need to amortise the cost of failures in phase 3 is one of the major contributory factors to the high cost of developing new therapies, this should in turn lead to a reduction in the average cost of developing new therapies.

Summary

In this paper we have argued that in a world of limited resources, where the price of therapies 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 stated objective of the major licensing authorities is to promote the public health; i.e. the health of the population. The impact of a particular technology on population health is a function of both its effectiveness and its cost. The

greater the cost of a new therapy the greater the proportion of current interventions that will have to cease in order to fund the new therapy; and thus the greater the risk that the therapy, even though licensed, will not be made available to patients because its cost, in terms of other health foregone, is greater than its expected benefit. The framework of cost effectiveness analysis, through the net benefit framework allows the regulator to assess the likelihood of this outcome as part of the expedited review selection process.

It is important to note that we do not consider it legitimate for licensing *per se* to depend upon efficiency concerns. Licensing processes must recognise both individual rights and the public health.

The use of regulatory processes to promote the public health, through fast-tracking innovations that meet a specific policy objective is not a new principle. The US Food Quality Protection Act provided for expedited registration for pesticides that met specific safety criteria.¹⁸ There is some evidence that developers of pesticides, often the same firms involved in the development of pharmaceutical therapies have responded by focussing their Research and Development efforts on pesticides that meet these criteria.¹⁹

The changing nature of the health care market , notably the proliferation of fourth hurdle organisations across the developed world, including the USA; does have implications for the suitability of the current pharmaceutical licensing frameworks. Now may be the time for the regulatory authorities to engage with the value based regulation paradigm.

Box 1: Fourth Hurdle Organisation

Canadian Agency for Drugs and Technologies in Health -	Canada
Pharmaceutical Benefits Advisory Committee -	Australia
National Institute for Health and Clinical Excellence (NICE) -	United Kingdom
Institute for Quality and Efficiency in Health Care -	Germany
Haute Autorite Sante (HAS)	France
Pharmacy Advisory Committee	New Zealand

....

Box 2: EMEA Accelerated Review Criteria

Gelöscht: 17

An accelerated procedure might be initiated... when a medicinal product is intended to provide a major public health need; defined by three cumulative criteria:

- a) the seriousness of the disease to be treated;
- b) the absence of an alternative appropriate therapeutic approach; and
- c) the anticipation of exceptional high therapeutic benefit.

Box 3: FDA Accelerated Approval Criteria

Gelöscht: 16

“The Drug Product if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. Improvement can be demonstrated by, for example, (1) evidence of increased effectiveness in treatment, diagnosis or prevention of a disease; (2) elimination or substantial reduction of treatment limiting drug reaction ; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.”

Box 3: Net Benefit

$$\text{Incremental Cost Effectiveness Ratio (ICER)} = \Delta C / \Delta E$$

$$\text{Net Monetary Benefit (NMB)} = R_T \Delta E - \Delta C$$

$$\text{Net Health Benefit (NHB)} = \Delta E - (\Delta C / R_T)$$

R_T = Threshold Ratio; ΔC = Difference in mean cost between comparators;

ΔE = Difference in mean effect between comparators

Formatiert: Deutsch
(Deutschland)

Gelöscht: ¹⁸

Formatiert: Deutsch
(Deutschland)

References

1 Rawlins, M. Cutting the cost of drug development? Nature: Drug Discovery 2004;3:360-362

² Angell, M. Excess in the Pharmaceutical Industry CMAJ 2004;171:12

3 Palmer S. Smith PC. Incorporating option values into the economic evaluation of health care technologies. Journal of Health Economics 2000;19(5):755-766

4 Pharmaceutical Benefits Advisory Committee. Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee (PBAC): including major submissions involving economic evaluations.

<http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-guidelines-index.htm> (accessed 12th April 2006)

5 National Institute for Clinical Excellence Guide to the Methods of Health Technology Appraisal NICE London April 2004

6 Canadian Agency for Drugs and Technologies in Health Guideline for the economic evaluation of health technologies: Canada 3rd Edition 2006

-
- http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf (accessed 12th April 2006)
- 7 PharmacoEconomic Guidelines around the world. International Society for PharmacoEconomics and Outcomes Research (ISPOR)
- <http://www.ispor.org/PEguidelines/index.asp> (accessed 24th November 2005)
- 8 ABPI House of Commons Health Select Committee Inquiry in the National Institute for Clinical Excellence: Submission from the Association of the British Pharmaceutical Industry 10 January 2002
- http://www.abpi.org.uk/information/industry_positions/NICE%20-%20select%20committee%20submission%20ABPI%20final.doc (accessed 18th November 2005)
- 9 <http://www.emea.eu.int/mission.htm> (accessed 1st September 2005)
- 10 <http://www.fda.gov/opacom/morechoices/mission.html> (accessed 1st September 2005)
- 11 Drummond, M.F., Sculpher M.J., Torrance G.W., O'Brien, B.J., Stoddart, G.L., Methods for the Economic evaluation of Health Care Programmes. Third Edition OUP 2005 Oxford
- ¹² Culyer A.J., McCabe C., Briggs, A.H., Claxton K., Buxton, M. Akehurst R., Sculpher M., and Brazier J.E. Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. *J. Health Serv. Res. Policy* (forthcoming).
- 13 Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence. *Lancet* 2002;360:711-715.
- 14 Brazier J.E. Deverill M. Green C. Harper R. Booth A. A review of the use of health status measures in economic evaluation *Health Technology Assessment* 1999;3(9)
- 15 Culyer A.J., McCabe C., Briggs, A.H., Claxton K., Buxton, M. Akehurst R., Sculpher M., and Brazier J.E. Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. *J. Health Serv. Res. Policy* (forthcoming).

-
- 16 Food and Drug Administration. Food and Drug Administration Modernization and Accountability Act of 1997. 1997, Section 114
- 17 Claxton K, Neuman PJ, Araki SS, Weinstein MC. The value of information: an application to a policy model of Alzheimer's disease. *International Journal of Technology Assessment in Health Care* 2001;17:38-55.
- 18 United States Congress. Public Law 104-170 - US Food Quality Protection Act 1996
- 19 Yogendra, S. The US Food Quality Protection Act: A review of the dynamics of pesticide regulation and firm responses. Innogen Working Paper 11 July 2004.