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Issues for countries considering introducing the “fourth hurdle”: The case of Hungary

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Objectives: This study outlines the needs and current development of the “fourth hurdle” (i.e., requirement of effectiveness and cost-effectiveness data for drug coverage policy decisions) in Hungary, describes the legal background and seeks to address some of the most important questions in this field.

Methods: The study draws on international experiences and discusses five issues that a given jurisdiction needs to consider before introducing the “fourth hurdle” for pharmaceuticals.

Results: The “fourth hurdle” is very relevant in Hungary because many existing drugs are unevaluated and many new, expensive drugs are becoming available. On the other hand, the existing resources for health technology assessment, including economic evaluation, are quite limited. All the five issues are relevant in the Hungarian setting and were helpful in determining exactly how the “fourth hurdle” should be applied.

Conclusions: The most important issue seems to be that the implementation of the “fourth hurdle” needs to be achieved in a way consistent with the limited resources for HTA in Hungary. Specifically this means that, in setting priorities for drugs to evaluate, additional criteria need to be applied. In particular, priority should be given to assessing drugs that have been evaluated in other countries, because this affords the opportunity to adapt existing studies or models to the Hungarian situation.

Keywords: Drug, Fourth hurdle, Effectiveness, Cost-effectiveness, Hungary

Several countries have already introduced the “fourth hurdle,” namely a requirement for cost-effectiveness evidence before reimbursement of new drugs. The first three hurdles, which already exist in most countries, require the demonstration of efficacy, safety, and quality of the manufacturing process. Countries considering introducing the “fourth hurdle” can learn from the experiences of others. This is particularly important for smaller countries, such as Hungary, where resources for the evaluation of health technologies may be in short supply. Hungary has moved toward introducing the “fourth hurdle” for pharmaceuticals since the pub-

lication of the Hungarian guidelines for economic evaluation in 2002 (11). This development is well supported by the Act No. CLIV of 1997 on Health, which clearly states among the basic principles (Title 2. paragraph 2 point 5) that health care services have to be evidence based and cost-effective.

This study outlines the needs and current development of this new requirement in Hungary, describes the legal background and seeks to address some of the most important questions in this field. The study draws on international experiences and discusses five issues that a given jurisdiction

needs to consider before introducing the “fourth hurdle” for pharmaceuticals.

These five issues are (i) Should evidence be requested for all new drugs, or just some? (ii) How should drugs be prioritized for assessment? (iii) Should data from other countries be accepted? If so which? (iv) Should an independent assessment be made of the evidence, including company submissions? (v) Should a two-stage appraisal process be considered?

Answers are suggested for these questions, consistent with what can realistically be achieved within current resources, in a country where only eighteen economic evaluations have been conducted and published during the past 10 years. We believe that the issues, challenges, and possible solutions related to the “fourth hurdle” in Hungary are relevant and generalizable to the other new member states of the European Union.

THE HUNGARIAN CONTEXT

The first three hurdles (quality, safety, and efficacy) are applied in Hungary in a manner similar to other European Union member states, through the registration procedure. A pharmaceutical product can be marketed only if it is registered and a permit for marketing has been obtained. Registration is the responsibility of the National Institute of Pharmacy (Országos Gyógyszerészeti Intézet, OGYI). The National Institute of Pharmacy (NIP) is a state owned agency, which both registers products and issues permits for marketing. The NIP accepts the drug approvals of the U.S. Food and Drug Administration (for normal procedure) and the European Agency for the Evaluation of Medicinal Products (for centralised European procedure). The duration of the registration procedure varies widely, taking 2 years (for normal procedure), 1 year (for decentralised procedure), and 3 months (for centralised European procedure). The NIP does not conduct pharmaco-economic studies, as these are not part of the registration procedure. Subsequent price negotiations, with the National Health Insurance Fund Administration (NHIFA) precede market introduction. Permits for distribution are approved by the Chief Medical Officer (6).

Some authors categorize effectiveness under the third hurdle (efficacy). However, clinical trials for drug registration provide efficacy and safety data, but are usually inadequate to address real-world decision making about treatments in a particular country, or in a particular setting. Health technology, for instance drug therapy, with demonstrated efficacy based on clinical trials, may not be effective outside of the controlled conditions of the trial (10;13). Therefore, it is likely that the effectiveness data required for the fourth hurdle will extend beyond those presented for drug registration.

RESULTS

Based on this understanding of the Hungarian context, the five issues are now explored in turn.

Should Evidence be Requested for All New Drugs, or Just Some?

Australia requires economic submissions from manufacturers relating to all new drugs to be used outside public hospitals, as does Ontario (3;7;8,16). In contrast, The Netherlands only requires submissions for drugs outside the reference price system. Both Portugal and the United Kingdom are also quite selective regarding which drugs they subject to detailed appraisal.

One important factor is the availability of financial and human resources to undertake economic evaluations and to assess their quality. Also, the use of economic evaluation for some or all drugs needs to be viewed in the context of other pharmaceutical policies operating in the country concerned, for example, promotion of generic substitution, reference pricing, prescribing audits and so on.

From a Hungarian perspective it is important to define the term “new drug” from a practical point of view. Drugs fall into the “new drug” category when they first require coverage from the National Health Insurance Fund, or when requests are made to change the indications, the population covered, or the percentage of the subsidy. This is irrespective of how old or new the particular drug is. In Hungary, the number of available drugs at least partly covered by the health insurance increased greatly over the past 10 to 15 years. A sufficient evaluation capacity is needed for economic evaluation, so it is important to determine (realistically) what capacity would be considered as “sufficient” in Hungary for undertaking drug evaluations.

Taking the example of the National Institute of Clinical Excellence (NICE) in the United Kingdom, fifty appraisals were published in the first 3 years, in which seventy-four different drugs, ninety-four medical devices, fifteen clinical procedures, and forty different clinical conditions were evaluated. According to Buxton (2), “this is an impressive start but merely a scratch on the surface.” Buxton also stated that “NICE estimates its guidance to have the potential to increase costs to the NHS (in England and Wales) by approximately 575 million English Pounds.” Questions to be answered and lessons to be learned from the example of NICE are as follows: what capacity for appraisal seems to be realistic in the coming years in Hungary and what should be done about implementation of the results of health economic studies?

Capacity Issues. As was discussed above, a large number of drugs (and medical devices, clinical procedures, and clinical conditions) could potentially be evaluated. Although the number of drugs is numerous, the truly innovative compounds seeking insurance coverage do not exceed more than 5 to 10 drugs per year in Hungary. On one hand, this seems to be a manageable number for economic evaluation, but on the other hand, the available evidence relating to these drugs is sometimes limited and thus their evaluation is sometimes the most challenging. In assessing the capacity to undertake economic evaluations, we need to address

the total budget available, the human resources in terms of trained evaluators, the availability of data, and the capacity of the health care system to use the results. Taking all these factors into account, it is anticipated that it will be possible to undertake around ten appraisals per year.

Affordability Issues. It was mentioned above that there is a potential to increase costs to the NHS (in England and Wales) by approximately £575 million as a result of the NICE guidelines. The Hungarian HTA agency (HunHTA) has a more limited mandate, than NICE. Guidance is not mandatory, nor is a positive budgetary impact expected or planned for. This suggests that those agencies issuing guidance on the reimbursement or use of drugs in Hungary need to be mindful of the budgetary impact. In part this might be handled by the selection of drugs for assessment, as discussed below.

How Should Drugs be Prioritized for Assessment?

In cases where only certain drugs are appraised from an economic perspective, decisions are required on which to appraise (12;15). The most obvious criteria are: (i) drugs that tackle important health problems; and (ii) drugs that are likely to have a large budgetary impact. NICE considers appraising technologies that are likely to have a “major impact on the NHS.”

In Hungary, the intention is to use criteria similar to those applied by NICE. However, these criteria are very difficult to quantify and use in practice, due to the fact that no valid information source is available in Hungary relating to the morbidity and mortality pattern of the population. More evaluations and better databases (disease registers have just been created) need to be in place to identify a particular health problem, and the extent of the burden it creates. The “National Public Health Programme 2001–2010” does not help too much; nineteen priority categories are listed, but the public health items and the expected benefit are not specified in detail (17). The additional factor in the Hungarian situation is the very limited capacity for conducting health economics analyses. Therefore, drugs should be assessed which satisfy the following criteria:

The Availability of Published Reports of Economic Analyses. Economic evaluation in Hungary is likely to be much more feasible if a published HTA report or economic analysis is available on the particular drugs from guaranteed high quality sources; for instance reports from INAHTA agencies or the Cochrane Collaboration. If a report already exists, it can be adapted using available local data. If no published HTA reports are available, the particular drug should not be assessed, unless there is a clear policy, political requirement, or other important circumstances. The lack of existence of a report probably means that the topic (drug) is not recognized as high priority in the countries where INAHTA agencies exist, or on the contrary, an important topic

Table 1. The market share of Top 25 agents (rank order) with the highest health insurance subsidies (2002)

Top agents with the highest health insurance subsidies	Health insurance subsidies (Billion HUF)	Percentage of the total budget for drug subsidies
Top-05	24,2 Ft	12,63%
Top-10	39,9 Ft	20,78%
Top-15	52,4 Ft	27,34%
Top-20	63,8 Ft	33,24%
Top-25	73,9 Ft	38,52%

where not enough evidence available. Given the shortage of professionals and HTA budget in the current stage of the HTA development in Hungary, attempting to produce the first analysis worldwide is not recommended.

Known Clinical Relevance (Endpoint as Real Outcome). As mentioned earlier, Drummond (4) argued that the key component for economic studies is the underlying evidence of clinical effectiveness, which means that endpoints from the study relate to real clinical improvements. If this is not the case, and surrogate outcomes are used as the endpoint of the clinical study, economic analysis should have low priority.

Budget Impact Threshold for Economic Evaluation. If the estimated budgetary impact of the particular drug is greater than the 1 percent or 2 percent of the total drug budget in the coming 2 to 5 years, economic analysis might be initiated. (Similarly, in Australia if the estimated budgetary impact is bigger than Aus \$2 million, a special committee decision is needed in addition to the standard procedure).

As Table 1 shows, a relatively small number of drugs with health insurance subsidies represent a significant percentage of the total budget for drug subsidies. Economic analysis might be particularly beneficial in this group of agents.

Analyzing the agents with the highest health insurance subsidies shows that even the agent in 25th place has a market share of 1 percent. The Top-10 agents have a total market share of 20.78 percent, while the Top-25 agents have 38.52 percent. These data suggest that evaluation of 25 agents would cover a substantial proportion of the total health insurance subsidies for drugs.

Should Data From Other Countries be Accepted? If so Which?

It is generally considered that clinical data for health technologies are transferable from location to location, although in all countries we encounter the problem that data from Phase III clinical trials may not reflect the effectiveness of the drug in regular clinical practice. Setting this problem aside, clinical data from another country are usually acceptable, unless the patients enrolled in the trial, or the regimens compared, are different from those that would apply in the country of interest. Data on practice patterns, and hence resource use, are

likely to be less transferable and some additional data collection in the country of interest is likely to be required, if only to check that data from another country are relevant. It is almost certain that unit cost or price data from another country will not apply and these should be collected for the country of interest (14). The case for new data collection of health state preference values (or utilities) is less clear. NICE requires that the preferences should be relevant for the population of England and Wales, but this does not necessarily mean that preference values from elsewhere are not relevant. The issue of transferability of economic data is crucial for small middle income countries where the capacity for undertaking health economic analysis is limited. This has been discussed by Rutten and Gulácsi (14), who highlighted the most important items that need to be taken into consideration.

Clinical and Epidemiological Data. Clinical data can usually be considered to be transferable, especially within Europe, because no significant genetic or other differences exist among European nations. However, incidence and age-standardized incidence of various lifestyle-related diseases might differ. These might include lung cancer and cancers of mouth (smoking), some cardiovascular diseases (eating too much fat and not having enough exercise), and the incidence of those diseases which are dependent on GDP per capita (environmental exposures, working and housing conditions, health care services). Incidence of a given disease might be the same in different countries, but prevalence (especially the detected and documented prevalence) might be different due to various reasons. To know the size of the target population is crucial to estimate the potential impact of the drug on the health of the population and to calculate the budget impact.

Resource Utilization, Costs, and Cost-Effectiveness. Because practice patterns, resource availability, and prices vary from country to country, these data are generally not transferable. There might also be considerable differences in willingness to pay and ability to pay for health benefits among countries. The same may be true of the health utility values as well. Therefore, in principle, it may be necessary to repeat economic evaluations in different countries. However, one should be aware of the fact that pharmaceutical companies might not repeat cost and cost-effectiveness studies in all countries, especially not in small countries when the potential market is less than 10 or even 5 million population. Therefore, a requirement to produce country-specific studies would not be very realistic.

One practical way forward would be to use an economic model created in one country, populated with local data in another country. However, economic models are often submitted by companies to the appraisal committees under conditions of “commercial-in-confidence,” and, therefore, important details are removed from the published version of the appraisal report. Also, models are often “home made,” by researchers and not created for public use. In particular, they usually do not have good documentation. Often models are

considered to be the “intellectual property” of the researchers and the developers usually wish to publish academic papers before making details publicly available (see below).

Should an Independent Assessment be Made of Evidence, Including Company Submissions?

In all countries operating a fourth hurdle, assessments are made of the relevant evidence on cost-effectiveness as part of the decision-making process. An important component of the evidence is contained in submissions from manufacturers and sponsors of the health technologies concerned. Whilst these often contain high quality analyses from consultants or academic researchers funded by the company, submissions should be viewed as advocacy for the product (i.e., attempts to show the product in the best possible light). The lengths to which various jurisdictions go to assess the evidence in company submissions varies greatly. In some places, especially the smaller countries, the assessments are undertaken in-house, within the Ministry or drug reimbursement agency. In other jurisdictions the in-house staff are supported by a committee of academic economists and health service researchers who also assess the submissions (e.g., in Australia).

At the other end of the spectrum, organizations like NICE in the United Kingdom commission their own independent assessment of the evidence from academic research centres. These technology assessment reviews include not only an assessment of the company submissions, but also meta-analyses of the clinical literature and additional economic models.

Should a Two-Stage Appraisal Process be Considered?

The main argument in favor of a two-stage process is that, at the time of launch of a new drug, very little is known about its long-term benefits when used in regular clinical practice. Therefore, the initial economic assessment has to be based on efficacy data from Phase III clinical studies, perhaps augmented by modelling. In some countries the existing arrangements already provide for the possibility of gathering additional data and/or a review of guidance at a later date (e.g., 3 years). On an intellectual level this makes a lot of sense. The main difficulties are practical ones. For example, if the new drug is approved for reimbursement, will the sponsoring company be willing to consider further randomized controlled trials? Who will pay for the studies, including the study drug, post-reimbursement? How feasible would it be to remove a drug from the reimbursement list, or at least restrict its use, should the longer-term data be unimpressive? On the other hand, the longer-term cost-effectiveness results may be more impressive if clinicians learn to target the drug effectively, or obtain satisfactory therapeutic results by using a lower dose than was used in the clinical trials. In principle, a risk-sharing deal is one way around some of the difficulties

outlined above. An example of one such deal is the agreement in the UK between the government and the manufacturers of beta interferon for multiple sclerosis. In this case NICE was skeptical about some of the long-term outcomes, in particular the clinical outcomes for patients who have to discontinue therapy. After much argument, the government decided to allow treatment for certain categories of patients, at the drug price requested by the manufacturers. However, it intends to monitor the long-term progress of patients and may ask the companies to return some of the income they receive from sales of the drugs if the results are less impressive than claimed (1). This is a very promising drug coverage option in Hungary, in cases where the patient population is small, the clinical outcome is well defined and the treatment process itself is well controlled. These criteria apply for those drugs that are covered by a special budget, in accredited hospitals, administered by named and accredited provider organizations and doctors, using defined clinical protocols on named patients.

DISCUSSION AND CONCLUSIONS

Consideration of the five issues has proven a useful exercise in the Hungarian context. The most important issue seems to be that the implementation of the fourth hurdle needs to be achieved in a way consistent with the limited resources for HTA in Hungary. Specifically this means that, in setting priorities for drugs to evaluate, additional criteria need to be applied. In particular, priority should be given to assessing drugs that have been evaluated in other countries, because this affords the opportunity to adapt existing studies or models to the Hungarian situation. Therefore, the methodological priority is to develop, and further refine, the approaches for adapting economic data from one location to another. Adaptation will also be greatly assisted if commercial-in-confidence restrictions are relaxed.

The obvious need for countries like Hungary to collaborate with other countries in the European Union begs the question of whether there will ever be a centralized procedure for drug reimbursement within the EU, to mirror that for drug licensing. This is clearly a possibility in the future, but several commentators (5;9) have pointed out that there are several hurdles to be overcome.

Perhaps the experience of countries like Hungary, in adapting studies from elsewhere, and collaborating with researchers and ministry officials in overseas countries may help identify the main methodological and practical issues that need to be resolved before EU harmonization can take place.

POLICY IMPLICATIONS

New policies concerning the reimbursement diffusion and use of health technologies are often developed in isolation.

By using the example of introducing the “fourth hurdle” for pharmaceuticals, this study illustrates that it is possible to learn from other countries’ experiences, yet still apply new policies in ways that best suit the local circumstances. The process of learning from others is particularly important in countries with limited resources for health technology assessment.

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