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Working Paper 2

A review of health technology assessment methods in the field of pharmaceuticals

HTA and pharmaceutical coverage decisions

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Summary

In the transition of the Polish health care system to a social insurance system similar to that of many Western European countries, many issues have arisen. A number of such issues concern the basic of making decisions in Polish health care.

Under the Soviet model of health care, decisions were made based on socialist ideology and central planning. A new basis is needed. Following the lead of other European countries, Poland wishes to gain information on how decisions can be guided by health technology assessment. Some key problems in Poland include:

1 Attempts to set standards on safety and quality;
2 The basis of coverage, that is, the definition of the benefits package;
3 Payment for highly qualified services.

Health policy makers in European Union countries (and Switzerland) have addressed these and related problems, especially using Health Technology Assessment (HTA) and linking it to regulatory and reimbursement decisions. Using HTA actively would result in standards being based on effectiveness and cost-effectiveness, coverage decisions being based (in part) on systematic evidence of effectiveness, and highly qualified services being regulated and reimbursed based on effectiveness. This working paper deals with the issue of definition of pharmaceutical benefits based on HTA.

Health Technology Assessment

HTA may be defined as "a structured analysis of a health technology, a set of related technologies, or a technology-related issue that is performed for the purpose of providing input to a policy decision" (Banta, EUR-ASSESS glossary).

HTA is a form of policy research that systematically examines short- and long-term consequences of the application of health technologies. The goal of HTA is to provide input to decision making in policy and practice. The essential properties of HTA are this orientation to decision making and its multidisciplinary and comprehensive nature (Banta, Introduction to EUR-ASSESS).

Health technologies are the drugs, devices, procedures, and the organisational and support system within which health care is delivered.

HTA takes a broad view of technology and of technological change and carries out analyses of such issues from a number of perspectives. The field includes studies of ethical and social consequences of technology; factors speeding or impeding development and diffusion of health technology; the effects of public policies on diffusion and use of health technology and suggested changes in those policies; and studies of variation in use of technologies. The most prominent part of HTA is to determine, insofar as possible, the benefits and financial costs of a particular technology or group of technologies. The main goal of such studies is to improve "value for money" in health care.

Given this broad context, HTA is not defined by a set of methods but by its intent. A technical assessment of a pharmaceutical or medical device carried out by a program as

part of a regulatory decision can be considered HTA. Likewise, an ethical analysis concerning gene therapy done to clarify its implications before deciding whether to provide it can be considered an HTA. The most frequent activity in HTA is a synthesis or systematic review of available information, especially on efficacy and cost-effectiveness, to assist different types of policy decisions. A prospective randomised clinical trial or prospective cost-effectiveness study done for policy reasons, as in the Netherlands or the United Kingdom, is also a technology assessment. On the other hand, clinical research or even clinical trials done solely for the purpose of increasing scientific knowledge are not technology assessments.

Technology assessments are useful to a wide range of decision makers in health care, including government policy makers, insurance companies and other payers, industry, planners, administrators, clinicians, and patients. This report concerns the use of HTA in making policy decisions concerning pharmaceuticals (drugs), especially regulatory and payment decisions.

This report includes a "Methodological Appendix" which discusses the basics and methods of HTA in some details. The Methodological Appendix is background for Working Papers 2,3 and 4 and will be provided with each of those reports. Therefore, these Working Papers will only deal with HTA at a general level in their text.

Assessment of Pharmaceuticals

Probably more information is available on the efficacy and safety of pharmaceuticals (drugs) than of any other technology. The main reason that this is true is because of the regulation of pharmaceutical products. At the same time, drugs have been subject to much attention as a contributor to health care costs and as a technology whose risks, benefits, and cost-effectiveness must be considered carefully.

It has been said that the only relatively complete, organised system for HTA is that carried out under the supervision of drug regulatory agencies (Banta and Luce, 1997, p. 177). It continues to be true, despite much progress in HTA, that many technologies have not been carefully assessed, while a great deal of information is available on drugs. This may explain, in part, why coverage decisions concerning pharmaceuticals are generally more explicit than other health technology coverage decisions.

Traditionally, clinical trials of drugs have been randomised controlled trials (RCTs) in which a drug is tested against placebo or, less commonly, an alternative drug. A number of the earliest health technology assessments carried out in the 1930s and 1940s involved drugs such as penicillin, sulfonamides, antimalarial drugs, and anti-tuberculosis drugs (Banta and Luce, p. 1977). Another visible form of pharmaceutical assessment concerns cancer chemotherapy, where clinical trials have been an integral part of drug development since the 1950s.

Adverse consequences (side effects) of drugs have also been prominent in assessment. All drugs have side effects, so balancing risks versus benefits is very important in this field. RCTs are not so useful in assessment of side effects, so other types of studies, such as epidemiological surveillance, are often necessary.

Other types of assessment are less common in the pharmaceutical field. Economic assessment is still relatively uncommon, although some drug regulatory and

reimbursement programs are now demanding economic data. Examples include Australia and the Canadian provinces of Ontario and British Columbia. Cost-effectiveness studies concerning drugs are becoming more common.

Other types of assessments of drugs are less common. Assessments seldom compare equivalent drugs for relative efficacy or cost-effectiveness, for example, but focus instead merely on demonstrating efficacy. Even here, information is often faulty, often relying on "surrogate endpoints" such as lowered blood pressure or improved urine flow without actually dealing directly with patient outcome (Liberati et al, 1997) Relatively little attention is paid to indications of use of the pharmaceuticals, which is a very important issue, since physicians often use drugs for indications that are not demonstrated to be efficacious.

Regulation of Pharmaceuticals

A landmark in pharmaceutical regulation was the passage of the US Food and Drug Amendments of 1962, which required proof of safety and efficacy from well-designed clinical trials before the pharmaceutical product could be marketed in the USA. The trials are actually organised and/or paid for by industry. The US Food and Drug Administration (FDA) supervises this process and approves the drugs for marketing. This model has been generally followed in most countries of the world.

In the European Union (EU), the European Commission has pushed toward a single market for pharmaceuticals. It has created a multistate procedure for marketing approval of drugs. The procedure is administrated by the European Medicines Evaluation Agency (EMEA), located in London. While the system of pharmaceutical regulation in the European Union is still being developed, Member States of the EU have no option but participation in the European system. In short, centrally registered drugs are in effect registered throughout the EU. Drugs registered in a Member State go through a "mutual recognition" procedure in which drug registration is being harmonised throughout the EU.

Therefore, Member States of the European Union have less and less influence over pharmaceuticals available in their market. Pressures from the European Commission, the EMEA, and the industry will inevitably lead to greater and greater harmonisation of this "internal market".

Poland has a pharmaceutical registration process analogous to that of other European countries. In theory, that process is carried out on the basis of evidence of efficacy and safety. However, Polish experts have been quite critical of decisions in this process, which seems to need improvements. In any case, when Poland becomes a member of the EU, it will be required to follow the decisions of the EMEA.

Coverage of Pharmaceuticals

There are no European regulations or directives dealing with health care issues related to coverage for health care provision in general or pharmaceuticals specifically. A number of issues have encouraged European countries to make more explicit decisions concerning pharmaceutical coverage. These issues include:

1 the visibility and costs of pharmaceuticals, which make up about 15% of health care expenditures in EU countries;
2 issues of efficacy and safety with many drugs, which arise continually;
3 extensive evidence of overuse and misuse of pharmaceuticals;
4 the relative ease of identifying and assessing pharmaceuticals, compared with many other areas of health technology.

Therefore, coverage decisions concerning pharmaceuticals are already explicit in essentially all members of the European Union (and in Poland, for that matter). This area is considered by the European Commission to fall within the "competence" of each Member State. Pharmaceuticals can be placed on a "positive list", a "negative list", or both. The European court has explicitly held that negative lists, pharmaceuticals that will not be reimbursed in a particular Member State, are legal, since Member States have a legitimate interest in controlling the health budget. However, evolving European law requires that the basis for such decisions must be transparent, objective and verifiable. Therefore, HTA plays an increasingly important role in such decisions.

Coverage decisions go far beyond just listing products that will be paid for or not paid for, however. Member States also retain substantial autonomy in the area of pricing reimbursement, and user charges. All Member States wish to control pharmaceutical expenditure. A variety of mechanisms have been adopted with this aim in view, operating on patients, doctors, and the industry. Such mechanisms have stimulated the development of cost and cost-effectiveness studies in HTA, in the field that is generally now referred to as "pharmaco-economics".

Contents

1 Introduction

Other reports have described the background of Poland and the Polish health care system, so this report will not repeat that material.

What is very clear is that the Polish health care system has changed dramatically in recent years. The main change has been to move away from the centralised model of the Soviet system and the development of decentralised administration. With this change, the role of the Ministry of Health has also changed dramatically, so that it is becoming an instrument for policy development and leadership rather than the head of a centralised health care bureaucracy. A great deal of decision-making is now delegated to other parts of the health care system.

To develop its new role, the Ministry of Health needs sources of information that will guide future developments. Health technology assessment (HTA) is such a source of information. It is because of this that the Polish Ministry of Health has asked TNO to advise it on how to link HTA with different policy areas, focusing on health benefits coverage. This report focuses on a related area, those decisions that are still made in the Ministry of Health, or those decisions that may be made in the future.

2 Assessment of Pharmaceuticals

A great deal of information is available concerning the efficacy and safety of drugs. The main reason that this is true is because of the regulation of pharmaceutical products, which requires manufacturers to test drugs rigorously before they can be marketed. At the same time, other organisations, such as research organisations, focus on the assessments of drugs. HTA agencies pay an increasing amount of attention to drugs.

As indicated, the traditional focus of pharmaceutical assessment is efficacy and safety. Traditionally, clinical trials of drugs have been randomised controlled trials (RCTs), in which a drug is tested against a placebo or an alternative drug. Pharmaceutical assessment is a well-established part of research and of HTA.

While efficacy and safety information is more available in the field of drugs than in other areas of health technology, the system is far from perfect. A number of problems can be identified:

1 Clinical trials do not often involve the comparison of similar drugs. Therefore, the clinician lacks fundamentally important information in making choices of drugs for patients.
2 The focus of clinical trials is demonstrating efficacy. There is less attention paid to the question of efficacy under what circumstances. One critical aspect under-emphasised in trials is indications for use. A drug is often only efficacious for certain indications, but most drugs are used for indications that have never been the subject of trials.
3 The end-point of efficacy trials is often "surrogate endpoints" that is, endpoints that may not be directly related to an improvement in patient health outcome (Liberati et al, 1997). Those arguing for surrogate endpoints say correctly that a trial to demonstrate effects of health outcome is more difficult to organise and usually will take longer than a drug based on surrogate endpoints. However, many surrogate endpoints have not been shown to be associated with better health of patients.
4 Other types of information, such as costs and cost-effectiveness, are less often assessed. Nonetheless, such assessment information is growing rapidly, stimulated by concerns about the costs of drugs. Likewise, assessments of quality-of-life are still not very common.

The widespread availability of information on efficacy and safety has simplified the task of regulators and payers for care enormously. In many cases, prospective studies are not necessary to determine whether or not a drug is useful.

Pharmacoepidemiology. The field of pharmacoepidemiology is a field dedicated to the study of the use and effects of drugs in large numbers of people (Strom, 1989). It incorporates what was previously called "post-marketing surveillance". As the name implies, the field is a blend of clinical pharmacology and epidemiology. The field is particularly concerned with the study of drug effects and adverse reactions (side effects).

The need for post-marketing studies is due to several reasons. First, pre-marketing studies are very limited and cannot answer many questions. They tend to be rather small and of limited duration. They are conducted in artificial environments ("ideal circumstances") where patients tend to be homogenous in age and sex and are less

likely to have complicating medical conditions that might confound the results of the trial. And, as already noted, they tend to compare a new drug to a placebo instead of to another active drug. The strength of prospective trials is their high internal validity, but they can be difficult to apply in the "real world".

Post-marketing studies tend to be observational rather than experimental, and are therefore aimed at examining effectiveness (as compared with efficacy) and, especially, safety, in the real world of medical practice. They are useful in learning about drug-drug interactions; about effects in previously untested population such as the elderly, children, and patients with multiple diseases; effects of overdoses; and many other aspects of everyday practice, including prescribing patterns.

Post-marketing studies are generally more useful for studying safety than clinical trials for one simple reason: side effects are generally not common. A side effect that appears in 1 in 100 patients may not be noticed in a clinical trial, but such a side effect may be extremely important when the drug is used in millions of people. Therefore, post-marketing studies play a very important part in the assessment of drugs.

Quality of Life Assessments. There has been a clear trend toward including health-related quality-of-life within clinical trials, especially those sponsored by the pharmaceutical industry. The first such studies were carried out in the mid- to late-1980s, but are becoming more and more frequent. The pharmaceutical industry, in particular, shows strong interest in including quality-of-life as part of the outcomes in drug clinical trials. One important reason that such studies are important is that improved quality of life is in fact an important goal of medical care.

A number of scales, both specific and general, are available for measuring quality-of-life in pharmaceutical trials. One comprehensive discussion of quality-of-life measurement in clinical trials is presented in Revicki (1997).

Economic Assessments of Pharmaceuticals. Experience with assessing the economic consequences of drugs is relatively recent. However, since about 1975, when the costs of health care began to become an important policy issue, costs and cost-effectiveness studies have become increasingly common. Since the mid-1980s, the number of cost-effectiveness studies of drugs has out-stripped studies of other types of technologies. The main reason that this is true is industry support for such studies, and for the "new" field of pharmacoeconomics. Governments that require economic information in drug regulatory process and coverage bodies that seek economic information give further impetus to this process. There seems little doubt that clear evidence of cost-effectiveness of drugs is actively sought by such public programs in Europe.

Industry often argues that a drug, especially a new drug, is cost-effective, by which it frequently means "cost-saving". This argument is inherently appealing, because drugs can often prevent more expensive interventions, such as hospitalisation. However, as in all forms and uses of HTA, such claims must be carefully examined on a case-by-case basis.

3 Regulation of Pharmaceuticals in Europe

The system of regulation of pharmaceuticals can claim to be the only relatively complete, organised system for health technology assessment. In the optimal situation, a series of studies is required to be carried out under the supervision of the drug regulatory/registration agencies and programs. When a company has a drug that it wishes to put on the market, it must support clinical trials. However, before tests in humans, the company must submit laboratory and animal data to the regulatory to obtain a license for human testing. At the end of the process, the regulatory program synthesises the laboratory, animal and human data to decide whether the drug can be approved for marketing or not.

All countries regulate pharmaceuticals in an analogous manner. However, in many situations, the decisions are based on information that is not based on clinical trials carried out in that particular country. Decisions can be based on published articles, information in databases, decisions in other countries, and so forth. Ordinarily, the regulatory agency responds to requests from the industry, which is then required to present the information sought by the agency. This is the case in Poland, by and large.

Such processes should be transparent and based on clear-cut criteria. Otherwise, consumers and physicians cannot have confidence in their results. However, in many cases, the processes are not transparent. Therefore, even if the criteria are clear-cut, it cannot be clear to others how rigorously these criteria are applied in practice. In such a case, the only way of evaluating the outcome is to examine the results; that is, what pharmaceuticals have been admitted to the market, compared to other countries. The Polish system looks adequate on paper, but many informants in Poland have criticised it for its outcomes (as is also the case in reimbursement, see below).

While all countries have developed such regulatory programs, the case of Europe is special. The European Commission, supported by the pharmaceutical industry, has sought to develop one internal market for pharmaceuticals in Europe. The European Council Regulation of 1990 established the European Community procedures for the authorisation of drugs for the European market and for the supervision of medicinal products and established the European Medicines Evaluation Agency (EMEA), located in London.

The present program does not regulate all aspects of pharmaceutical marketing. Further barriers such as lack of standards for package sizes, dosages, and names of products marketed under different names in different countries would need to be addressed before a single market becomes a reality. The greatest problem with further developments in this area is the jealousy of Member States concerning their own sovereignty. This again points out the differing motivations of the European Commission and the Member States in pharmaceutical regulation.

Furthermore, a truly single market would require standardising the systems of regulation of prices/profits. In terms of insurance (see below), there would have to be alignment of how much patients pay for medicine and what drugs are covered by health insurance. It is doubtful if industry would welcome moves to align drug costs, and it is certain that Member States of the EU are not prepared to harmonise the lists of drugs covered.

It is worth noting again that the main impetus in this "Europeanisation" of pharmaceutical regulation was not public health or public protection, but economic development and efficiency (and in addition, pharmaceutical innovation). The regulation of pharmaceuticals is the result of the interplay of decisions taken at the level of the European Union (EU) and the decisions of each state. The relationship between these two different levels is subtle and complex. States are concerned with public protection and public health, but are also deeply concerned about containing the costs of pharmaceutical consumption (Cranovsky et al, 1997). The central aim of the European Union is to remove barriers to the free movement of goods while at the same time encouraging research and development to promote new products, develop industry, and gain exports. At the European level, and in many of the Member States, the pharmaceutical industry is viewed as one of Europe's best performing high-technology sectors. This is highlighted by the fact that, generally, biotechnology products are regulated at the central level.

Nonetheless, the European program of regulation remains highly decentralised. There are three registration procedures for pharmaceutical products:

1 A centralised procedures, reserved for innovative products and leading to a single community-wide authorisation valid for all 15 Member States;
2 A decentralised procedure, which will eventually apply to the majority of products, based on the principle of mutual recognition (accepting the decisions of other Member States concerning registration); and
3 A national procedure limited in principle to applications of local interest concerning a single Member State.

The model of EMEA then has relatively little resemblance to country pharmaceutical regulation, depending as it does on a complex structure of committees, mechanisms of seeking advice, and decisions taken first at the national level. The actual functioning of this program is not of great concern for this project. The important point is that when Poland joins the European Union, it becomes a member of this program. The decisions by EMEA are binding on all Member States. Drugs admitted to the market based on either the centralised procedure or the decentralised procedure will be admitted to the market of all Member States, without choice. Poland has already developed proposed legislation to reform its pharmaceutical regulatory process to conform to that of the EU. This legislation will go into effect on Poland's accession to the European Union.

4 Coverage of Pharmaceuticals in Europe

Coverage of pharmaceuticals is determined by every country in the world by its own independent processes. While countries certainly learn from each other in this area, there is no international program for pharmaceutical coverage. In Europe, in contrast to pharmaceutical regulation, coverage of pharmaceuticals remains almost entirely an issue for each Member State of the European Union.

There are no European regulations or directives dealing with health care issues related to coverage for health services provision. The only EU policy document dealing with this issue is a 1992 Council recommendation that proposed that Member States should establish positive and negative lists and organise the role of social protection in preventing illness and in treating and rehabilitating the persons concerned so as to meet the following objectives under conditions determined by each State: to ensure that all persons resident within the territory of the State have access to necessary health care as well as to facilities seeking to prevent illness and to maintain and, where necessary, develop a high-quality health care system geared to the evolving needs of the population, and especially those arising from dependence of the elderly, to the development of pathologies and therapies and the need to step up prevention (European Council, 1992). In short, it is the responsibility of the Member States to define and develop specific policies for high-quality health care.

In an important case (Case 238/82 Dephar), the European court considered the legality of a negative list, excluding certain expensive products from reimbursement by health insurance institutions. The court held that such schemes might be legal and compatible with EU policy, recognising that Member States have a legitimate interest in controlling the health budget.

Another development concerning Europe and its influence on pharmaceutical payment is that arguments between governments and providers have increasingly involved citations to European rules. The European Court of Justice has ruled that consumers can legally import cheaper over-the-counter drugs from another country, provided that the drug is approved in their own country (Jacobzana, 2000). The Court has also ruled in favour of parallel imports, in which a cheaper version of the drug may be imported from another country. Recent decisions have concerned the right to receive and be reimbursed for care or health services in another country, but these cases have no direct application to pharmaceuticals (until now).

Pricing and Reimbursement Policies Toward Pharmaceuticals. As has already been made clear, pricing and reimbursement policies remain under the autonomous control of the Member States of the EU. In December 1988, the European Council adopted a directive relating to the transparency of measures regulating the pricing of medicinal products and their inclusion in the scope of national health insurance schemes (Directive, 1989). The "Transparency Directive" acknowledged that the Directive was an initial step toward harmonisation and that further measures should take place progressively. The Directive requires that national authorities adopt transparent, objective, and verifiable criteria when deciding on price or profit regulations or the setting up of limited and positive lists of drugs. If defines a time limit of 90 days for national authorities to agree or set a price on newly introduced products and requires that they state the reasons if they fix a price different from that sought by the company.

5 Use of Pharmaceuticals

Although policies developed to control and channel pharmaceutical development and use sketched above are complex, they are not actually the main determining factor in pharmaceutical use. Naturally, if a drug is not admitted to the market, it generally is not available. If it is not admitted to the reimbursement list, its use will be discouraged. However, the key decisions are generally made by physicians who recommend drugs to patients and write prescriptions for their use. This is the main problem for health care systems; the most important person in the process neither uses nor pays for the product. Furthermore, the patient (or consumer) generally pays only a fraction, often only a small fraction, of the cost. In Europe, most patients have rather complete coverage of important pharmaceuticals. Patients are therefore not very sensitive to the costs of pharmaceuticals, neither to themselves nor in the aggregate. Furthermore, the knowledge of physicians concerning efficacy and safety of drugs is limited and quite subject to pharmaceutical industry promotion; the physicians may have inadequate concern about the safety and efficacy of the products that they prescribe. Patients also lack the ability to transform information on drugs into knowledge concerning appropriate use.

At best, the decisions concerning whether the long-term consequences of new medicines are positive or negative are difficult. No medicine is safe; it may be relatively safe in relation to the benefits gained. The degree of uncertainty can be reduced by HTA and related studies, but the available studies often do not address the questions that physicians might appropriately ask. For example, few studies give guidance to answering the question, under what circumstances can this drug contribute to the health of this particularly patient?

This problem is confounded by the stance of industry, which is fundamentally motivated by profits. The main issue for industry, aside from profits, is innovation, which allows the company to sell its products at a high price (in early years). Therefore, the information furnished to physicians by industry is not reliable. It is biased in favour of a particular product or products of that company. Safety and efficacy are secondary considerations.

Government, physicians, insurance companies, and others have responded to this situation by attempting to develop systems of changing physician behaviour, especially prescribing practice. Almost all countries are involved in developing some sort of guidelines for pharmaceutical use and prescribing (Kanavos, 1991). Particularly active countries, using guidelines to link HTA to prescribing practice, include the Netherlands and the United Kingdom (Kanavos, 1991). Monitoring of prescribing practice is also increasing. Peer reviews are the main method for determining if physicians are conforming to guidelines. Feedback and co-operation with physicians may change their prescribing behaviour (Jacobzana, 2000). A combination of printed materials, one-on-one education, special seminars, and feedback seems to be the method with the best results. In some countries, such as the Netherlands, physicians and pharmacists have taken the initiative to work together to develop pharmaceutical guidelines to improve practice.

Finally, cost-effectiveness of prescribing can only be improved by involving patients (Jacobzana 2000). Patients need to be involved and to approve such moves. Providing

better information to patients and encouraging them to use it for decision-making is a largely future challenge for HTA and for better pharmaceutical use.

6 Paying for New, Expensive Pharmaceutical Products

The issue of paying for new, expensive pharmaceutical products is quite visible in Europe, and has generated a significant controversy. As stated above, the main concern of the European Commission is innovation, and the main concern of industry is innovative linked to profits. Entry to the market is often determined centrally for such drugs. However, the price of new products is very often quite high, and countries with to control such prices or costs. Several countries have developed special pricing, reimbursement, and delivery policies for this class of drugs.

A particularly visible case was that of a new AIDS treatment (Cranovsky et al, 1997). In France, the high potential costs triggered a national debate. The National AIDS Council proposed that the choice of recipient be made by national lottery. The National Advisory Ethics Committee stated that a lottery scheme should be the last resort and held only at the local hospital level when choice could not be made on the basis of medical criteria. The visible outcry by AIDS groups is perceived to have led the Prime Minister to openly oppose the lottery idea. A committee of experts was set up to define eligibility criteria. While AIDS groups are particularly influential, this case illustrates that it is often quite difficult to limit access to drugs primarily on grounds of costs.

Several countries have set up specific policies for the use of B-interferon 1b, a new drug approved for treatment of multiple sclerosis. Several countries set up specific policies for B-interferon. In some cases, those were based on HTA. In Denmark, for example, the Ministry of Health decided in December 1995 that B-interferon would be restricted to hospital dispensing (Cranovsky et al, 1997). In making this decision, the Ministry considered the views of the Multiple Sclerosis Society, the Danish Society for Research in Multiple Sclerosis, and the Danish Neurological Society. In early 1996 a unit of the Ministry produced an HTA report recommending a number of criteria concerning the use of B-interferon in multiple sclerosis. The report emphasised that there was still limited knowledge of the drug's effectiveness and no knowledge at all of its long-term effectiveness. Subsequently, the Ministry launched a reference program for B-interferon. The program includes the guidelines for eligibility criteria for treatment with B-interferon, practice guidelines for doctors prescribing the drug, and the establishment of a national clinical database. This linkage of HTA and decisions by the Ministry of Health and the development of a reference program for one drug was visible in Europe, and may set important precedents for the future, both in Denmark and in other countries. Simultaneously, the Ministry of Research had established a committee to develop a national strategy for Danish health research. In its report, the committee explicitly mentions HTA and some international experiences. The experience with b-interferon 1b was widely known in Denmark and probably was a contributing factor leading to the formation of a national agency for HTA in 1997 (Jorgensen et al, 2000).

7 The Case of Switzerland

The Swiss system of defining the health benefits package using HTA has been described in working papers 1 and 4. The system for defining pharmaceutical benefits has some additional organisations and principles.

As already described, the federal commission on health insurance benefits (ELK) makes the actual coverage decisions, after presentation of documentation developed under the leadership of the Swiss Federal Office of Social Security (SFOSS). In the area of pharmaceuticals, the Federal Drug Commission advises the SFOSS in the choice of pharmaceuticals to be reimbursed. The FDC is a body that is composed of 28 members representing physicians, pharmacists, sickness funds, compulsory accident insurers, laboratories, and hospitals. The FDC is split into two subcommittees, one of which deals with scientific matters and consists of scientific experts, while the other deals with economic matters, and has representatives of physicians, pharmacists, sickness funds, compulsory accident insurers, and hospitals (Cranovsky, 2000).

Pharmaceutical companies develop applications for coverage of a new pharmaceutical. Each application is examined by the two committees separately and then the entire committee decides whether or not to recommend coverage of the drug. The recommendation is transmitted to the SFOSS. Requests to the SFOSS for price increases are also examined by the FDC, but in this case only by the subcommittee on economic matters.

Drugs, which come to be SFOSS for a coverage decision, have already been examined for efficacy and safety and admitted to the market by the Swiss pharmaceutical regulatory agency (IOCM). IOCM is main concerned with the risk/benefit ratio. The FDC also examines the same scientific material as was submitted to the IOCM, but the FDC is mainly concerned with cost-effectiveness.

The following criteria are used in determining if a pharmaceutical is cost-effective (Cranovsky, 2000):

1 Therapeutic efficacy in relation to other drugs for the same indication or with a similar mode of action;
2 Cost per day or per course of treatment, in comparison with costs for drugs for the same indication or with a similar mode of action;
3 Cost for research work, clinical trials, and introduction on the domestic market, in the case of a new preparation; and
4 Price structuring in Switzerland and abroad.

After the subcommittee has made its determination, the subcommittee for scientific questions meets. It classifies each pharmaceutical into one of four categories, according to the medical need it meets, its therapeutic value, and the guarantees it offers in terms of efficacy and composition:

1 Indispensable;
2 Important;
3 Conditionally necessary; and
4 Unnecessary.

If a drug is classified in category 1 or 2, the price is of little importance, because the first consideration is taken to be access by patients with serious health conditions. Preparations in category 4 are not placed on the reimbursement list. The final decision is made by a plenary assembly of the FDC, which transmits it to the SFOSS.

As in other cases, the Swiss experience shows how principles concerning coverage can be put into operation in a real life situation. At this moment, Poland has analogous tasks and committees, and can profit from the Swiss experience. However, with accession to the European Union, Poland will participate in the European system of drug regulation. Nonetheless, the experience of the Swiss coverage process for pharmaceuticals will still be relevant.

8 The Case of the Netherlands

8.1 Introduction: History and Recent Developments Regarding Reimbursement of Pharmaceuticals

The case of the Netherlands has been described in general terms in Working Paper 1. Coverage of pharmaceuticals is similar, but is further developed, partly because of the field of pharmaceuticals is easier to deal with (all pharmaceuticals are registered, and thereby identified, the number of pharmaceuticals in finite, the evidence is generally more complete). This case will describe the Dutch system for reimbursement of pharmaceuticals.

Regarding new pharmaceuticals, two important procedures exist: market approval of pharmaceuticals and the reimbursement of registered pharmaceuticals. During the last years, an increasing number of pharmaceuticals have been are registered on the European level through the centralised procedure, which means through the European Union program. This means that the pharmaceutical is registered in all member states.

For this purpose, a European drug regulatory office has been set up in London, called the European Medicines Evaluation Agency (EMEA) (Bos, 2000). The Committee for Proprietary Medicinal Products (CPMP) supports this agency. Since 1998, national registration of a drug is possible only when the drug is registered in one specific member state of the European Union (EU).

In addition to the national registration procedure, mutual acknowledgement of registration is possible ('decentralised procedure'). In principle, this means that a national registration of a drug is acknowledged by all other member states. For certain drugs (e.g. vaccines) a European registration is obligatory (Health Care Insurance Board, 2000).

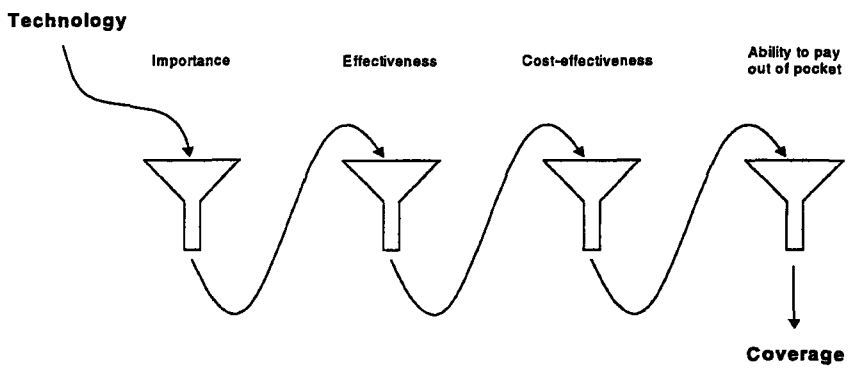
In the Netherlands, the Board for the Evaluation of Drugs (*College ter Beoordeling van Geneesmiddelen - CBG*), which is comparable to the CPMP on a European level, is responsible for registration of all pharmaceutical products. The CBG registers drugs based only on safety and efficacy; cost-effectiveness plays no role in these decisions. Traditionally, approval of pharmaceutical products by the Dutch Board led to an almost automatic reimbursement by health insurance companies and sickness funds. However, listing of pharmaceuticals for reimbursement is more and more based on effectiveness and cost-effectiveness (Bos, 2000).

In 1991, the Drugs Reimbursement System (*Geneesmiddelen Vergoedingen Systeem* - GVS) was introduced. The aim of this system is to limit costs and encourage a more rational use of drugs. In this system, reimbursement is limited with regard to drugs that have cheaper alternatives (Bos, 2000).

In addition, in 1995 the Health Care Insurance Board introduced a decision-model for pharmaceuticals (*Beslismodel extramurale farmaceutische hulp*), which forms the basis of the current evaluation procedure of pharmaceuticals within the GVS. This model consists of the following criteria: 'necessary care', 'efficacy', 'effectiveness', 'therapeutic value', 'cost-effectiveness' and 'own responsibility'. (This scheme is

similar to that put forward by the Dunning Commission and described in Working Paper 1. See Figure 1). From these criteria, the criterion 'necessary care' is used for groups of pharmaceuticals (e.g. to exclude the group of homeopathic drugs from the benefit package).

Figure 1. Decision criteria.



The remaining criteria are used for the evaluation of specific pharmaceuticals:

Efficacy. The effect is studied under ideal conditions in a homogeneous group of patients, often using intermediate outcomes. This criterion is already evaluated in relation to the pre-market approval.

Effectiveness. The effect is studied in practice, using a heterogeneous group of patients. Therapy (non-) adherence plays a role, and the focus is on final outcomes, such as a reduction in morbidity.

Therapeutic value. The sum of the evaluation of all properties of a pharmaceutical that are relevant to the treatment, which together determine the place of the drug in therapy compared with other available treatment options. To determine therapeutic value the following aspects are evaluated: efficacy, effectiveness, side effects, experience, applicability, user satisfaction and influence on the quality of life. Primarily, therapeutic value is determined by the balance between effectiveness and side effects of the pharmaceutical compared to standard treatment.

Cost-effectiveness. A pharmaceutical is cost-effective if it is efficacious and the relationship between the therapeutic value and the costs is favorable in comparison with other forms of therapy. This criterion is tested by means of a simple evaluation of the consequences for macro costs.

Own responsibility. A pharmaceutical will be paid out of pocket when this is feasible for the patient, the costs are insurable, and exclusion of reimbursement does not lead to undesirable substitution. This criterion is used in one case only: exclusion of pharmaceuticals to stop smoking (nicotine substitution, bupropion (Zyban©) (Toenders, 2001; Health Care Insurance Board, 1999).

In the current procedure, a decision about inclusion of a new pharmaceutical in the benefit package is largely dependent on therapeutic value and efficacy (Health Care Insurance Board, 1999).

In 1997, the Minister of Health asked the Health Care Insurance Board to formulate guidelines for pharmaco-economic evaluation. Pharmaco-economic research should provide a reliable, producible and verifiable insight into the therapeutic value of a drug, the cost of using the drug and possible cost-savings compared with other drugs and/or treatments (Health Care Insurance Board, 1999).

The resulting 19 guidelines are based on Canadian pharmaco-economic guidelines and focus on target groups, the perspective of study, indications, methods of analysis, definition of costs, methods for measuring costs, determination and valuation of quality of life, outcome measures, reliability, validity and results. According to these guidelines, a cost-effectiveness analysis should be performed on those pharmaceuticals for which the manufacturer claims added value compared with existing treatment options. The responsibility of performing pharmaco-economic research lies with the manufacturer. This means that a manufacturer needs to demonstrate information on cost-effectiveness of the new pharmaceutical before claiming additional value of this new pharmaceutical compared to existing interventions.

In 2002, manufacturers are being asked to start using these guidelines, to gain experience. The aim is that pharmaco-economic evaluation will become part of the procedure of evaluating pharmaceuticals in 2005 (Toenders, 2001).

In 2001, the Council of Ministers agreed to the proposal of the Minister of Health to include the results of pharmaco-economic evaluation in the procedure of the GVS. This proposal needs to be approved by the Council of State (*Raad van State*) (website Ministry of Health: http//www.minvws.nl/infotheek.html). In addition to more emphasis on cost-effectiveness data, the health insurance companies and sickness funds will have a prominent role in regulating pharmaceuticals in the coming years.

8.2 Current Process of HTA in Relation to Coverage of New Pharmaceuticals

The Health Care Insurance Board (*College voor zorgverzekeringen - CVZ*) plays an important task in the HTA process related to coverage of pharmaceuticals. This Board aims to stimulate more evidence-based use of social health insurance resources. The Board advises the government which health interventions, including pharmaceuticals, should be reimbursed under the current health insurance system (Ten Velden, 1998).

To process of judging whether a pharmaceutical will be reimbursed under the social health insurance, consist of 3 parts:

Official request of manufacturer for inclusion in the GVS to the Minster of Health. The Minister of Health asks advice of the Committee for Pharmaceutical Aid (*Commissie Farmaceutische Hulp - CFH*), which is part of the Health Care Insurance Board.

Ministerial decision. Final decision by the Minster of Health within 90 days of receiving the application (Health Care Insurance Board, 2001a).

Evaluation. Evaluation of pharmaceuticals by the CFH should be distinguished into two parts:

Generic judgments, which focus on groups of indications or of pharmaceuticals, such as homoeopathic drugs.

Specific judgments of individual pharmaceuticals, which has the following aims.

- To evaluate therapeutic value and effectiveness according to which the Minister of Health can decide to reimburse the pharmaceutical or not. The consequences for the costs on macro level will also be included. This analysis include data on: incidence and prevalence figures, groups of patients for which the pharmaceutical is indicated and the expected effects of substitution, usage of the pharmaceutical (dose and duration of treatment), price of pharmaceutical and total treatment costs.

- To publish the results in the "Pharmacotherapeutical Compass" (*Farmacotherapeutisch Kompas*). The Compass is published by the Health Care Insurance Board and is updated yearly. In the Compass, the CFH gives guidance about treatment of diseases, with an emphasis on available pharmaceuticals. The Compass presents information on the appropriate use of pharmaceuticals in practice and summarizes scientific information on the therapeutic value and/or economic considerations of individual products. The Compass is available free to general practitioners, pharmacists, and medical professionals, who live in the Netherlands and for Dutch universities. This guide, which is available as a book and/or CD, is increasingly linked to coverage and reimbursement decisions and has considerable effect on the prescribing patterns of general practitioners (Health Care Insurance Board, 1999, 2001b, p. 42; Bos, 2000).

Pharmaceutical aid. Pharmaceutical aid encompasses those registered drugs that have been singled out by the Minister. These drugs can be placed on List 1 (*Bijlage 1*) of the Pharmaceutical Aid Regulation *(Regeling farmaceutische hulp 1996),* which is a positive list and more specifically on:

List 1A with a reimbursement limit. Inclusion on List 1A is applicable for pharmaceuticals that can be substituted by pharmaceuticals with the same therapeutic goal ('*onderling vervangbaar*'). The criteria for substitutability are:

- Similar working mechanism
- Similar field of application (indications)
- Identical route of administration (e.g. oral, intravenous)
- Generally intended for the same age group and absence of clinically relevant differences applying to the whole patient population, such as side effects.

For each cluster of substitutable pharmaceuticals, a reimbursement limit is calculated with prices on a reference year (Autumn 1998). If the price of a drug exceeds the reimbursement limit, the difference has to be paid by the patient (Health Care Insurance Board, 2001a).

List 1 B without a reimbursement limit. There are two options with regard to List 1 B.

- The pharmaceutical is equivalent, but not substitutable: when the pharmaceutical leads to similar or lower costs it can be placed on List 1B. Higher costs means that it will not be reimbursed.

- The pharmaceutical is not equivalent, but has therapeutic added value. Additional requirement may be added before it will be reimbursed only when the pharmaceutical leads to higher costs. If and when the pharmaceutical will be included on List 1B is partly dependent on the budget available.

List 2 when extra conditions apply to the provision of a pharmaceutical. A pharmaceutical will be placed on List 2 if there is a chance that the pharmaceutical will not be appropriate used, when specific knowledge or expertise is necessary, or when the pharmaceutical is extremely costly. Conditions could focus on such issues as a specific patient population, treatment protocol, or approval of the insurance company (e.g. Rivastigmine for treatment of Alzheimer patients and cholesterol lowering pharmaceuticals for patients with familial hypercholesterolaemia or high-risk patients for coronary artery disease).

The pharmaceutical has no added therapeutic value: It will not be reimbursed, unless special circumstances justify reimbursement.

There is insufficient data to judge the therapeutic value and effectiveness of a pharmaceutical: It will not be reimbursed (Health Care Insurance Board, 1999; 2000).

List 1C. In relation to the implementation of pharmaco-economic guidelines, a List 1C is being developed. This List will reimburse new pharmaceuticals that are not substitutable and for which further evaluation is needed (Health Care Insurance Board, 2000, 2001b, p. 56).

The positive list is available (in Dutch only) at the website of the Health Care Insurance Board (**www.cvz.nl** - *'positieve lijst geneesmiddelen'*).

As described in the introduction, the pharmaco-economic evaluations will have a more prominent role in the procedure of the GVS in the coming years. The Minister of Health needs information about efficiency mainly for pharmaceuticals eligible for inclusion on List 1B of the Pharmaceutical Aid Regulation. This means that if a manufacturer claims added value of a pharmaceutical, the results of pharmaco-economic evaluations need to be included in the judgement procedure.

The efficiency of a pharmaceutical will then be judged including the trade-off between therapeutic value and additional costs. If the new pharmaceutical has an equal therapeutic value compared to existing pharmaceutical, it can be included in List 1A. At this moment, the Health Care Insurance Board is implementing the pharmaco-economic

guidelines in their judgement procedure. The goal is to complete the inclusion in the existing procedure in 2005 (Toenders, 2001; Health Care Insurance Board, 1999).

8.3 Examples of Evaluation

In 2001, the following pharmaceuticals were evaluated by the CFH:

Abacavir/ lamivudine/ zidovudine (Trizivir®) - treatment of HIV (indication)
Calcium carbonate / colecalciferol (Calcium-D-Sandoz®) -treatment of insufficient vitamin D3, calcium (elderly)
Desloratadine (Aerius®) - treatment of allergic rhinitis
Dexibuprofen (Seractil®) - treatment of arthritis
Ethinylestradiol/drospirenon (Yasmin®) - hormonal contraceptive
Pioglitazon (Actos®) - treatment of diabetes mellitus II
Risedroninezuur (Actonel®) - treatment and prevention of postmenopausal osteoporosis
Testosteron (Virormone®) - substitution therapy of insufficient testosterone in adult men
Estradiol nasal (Aerodiol®) - treatment of insufficient estrogen in postmenopausal women
Levetiracetam (Keppra®) - treatment of epilepsy
Lopinavir/ritonavir (Kaletra®) - treatment of HIV1 (adults and children > 2 years)
Agalsidase α (Replagal®) - treatment of Fabry disease
Agalsidase β (Fabrazyme®) - treatment of Fabry disease
Alginaat/antacida (Rennie Duo®)- treatment of gastro-esophageal reflux complaints and hyperacidity
Alprostadil urethraal (Muse®) - treatment of erection dysfunction
Tegafur/uracil (UFT®) - treatment of colorectal cancer
Tobramycine (Tobi®) - treatment of lung infections of CF-patients
Almotriptan (Almogran®) - treatment of migraine
Eletriptan (Relpax®) - treatment of migraine
Nateglinide (Starlix®) - treatment of diabetes mellitus II
Olanzapine intramusculair (Zyprexa i.m. ®) - treatment of schizophrenia
Darbepoetine alfa (Aranesp®) - treatment of anemia (chronic kidney disorder)
Pilocarpine oral (Salagen®) - Sjögren patients, treatment of xerostomy after chemotherapy in patients with throat/neck tumors
Venlafaxine (Efexor/Efexor XR®) - treatment of depression
Atovaquon/proguanil (Malarone®) - treatment of malaria
Ethinylestradiol/levonorgestrel (Fem7 Sequi®) - treatment of insufficient estrogen in menopausal women after ovarian removal
Lutropine alfa (Luveris®) - treatment of stimulation of egg cells.
Capecitabine (Xeloda®) - treatment of colorectal cancer
Celecoxib (Celebrex®) - treatment of rheumatic arthritis
Estradiol/dienogest (Climodien®) - treatment of insufficient estrogen in menopausal women after ovarian removal
Imatinib (Glivec®) -treatment of chronic myeloid leukemia
Menotrofine (Menopur®) - treatment of infertility
Ketotifen for the eye (Zaditen®)- treatment of allergic conjunctivitis
Estradiol oral (Estreva®)- treatment of insufficient estrogen in menopausal women after ovarian removal
Temozolomide (Temodal®) - treatment of malign brain tumors

Estradiol/dydrogesteron (Femoston®) - treatment of insufficient estrogen and prevention of postmenopausal osteoporosis
Octreotide (Sandostatine®) - treatment of acromegaly and carcinoid syndrome
Formoterol/budesonide (Symbicort®) - treatment of asthma
Lamotrigine (Lamictal®) - treatment of epilepsy and additional treatment of Lennox-Gastaut syndrome
Fusidin/hydrocortison (Fucidin Hc®) - treatment of eczema
Macrogol/elektrolyten (Klean Prep®) - cleaning of intestines
Temozolomide (Temodal®) - treatment of malignant glioma
Sirolimus (Rapamune®)- kidney transplants (resistance of organ)

For all these pharmaceuticals, a report has been prepared by the CFH, which is available at the website of the Health Care Insurance Board (www.cvz.nl). The report was sent to the Minister of Health, who uses the report to decide whether or not to include the pharmaceutical in the GVS. As an example of the different decisions that the Minister can make according to the positive list of drugs the following pharmaceuticals are selected:

List 1A: Formoterol/budesonide (Symbicort®) - treatment of asthma
Formoterol/budesonide, is known as Symbicort® Turbuhaler and is indicated as a maintenance treatment of asthma. Symbicort® Turbuhaler is a combination of two existing drugs, which are already listed in the GVS. This means that Symbicort ®Turbuhaler can substitute for the two existing drugs (*'onderling vervangbaar'*). At this moment, Symbicort ®Turbuhaler is included in List 1A of the Pharmaceutical Aid Regulation. The reimbursement of Symbicort® Turbuhaler is calculated on the basis of the reimbursement limit of both separate existing drugs that are substitutable.

List 1B: Therapeutic added value and higher costs: Tegafur/uracil (UFT®) - treatment of colorectal cancer
Tegafur/uracil, also known as UFT® , is indicated for treatment of malignant colorectal cancer in combination with foline-acid. UFT® is an oral cytostatic drug, while the standard intravenous treatment (fluorouracil – 5FU, in combination with foline-acid) is given as daycare in a hospital. UFT® has an added value compared to the standard intravenous treatment: the effectiveness is the same, but UFT ® is less toxic. In addition, UFT® is not substitutable by 5FU. Reimbursement under the GVS will lead to higher costs (maximum of about 25 million EURO a year, and a decrease of the hospital budget of 9 million EURO a year).

List 1B: Therapeutic added value and no additional costs: Calcium carbonate/ colecalciferol (Calcium-D-Sandoz®) - treatment of insufficient vitamin D3, calcium (elderly)
Calciumcarbonaat/colecalciferol is indicated for the correction of insufficient calcium and vitamin D3, and also as an additional treatment of osteoporosis in patients with a lack of calcium and vitamin D3. The CFH judged Calcium-D-Sandoz®as having a potential added value for a specific group (elderly with low mobility). Reimbursement under GVS will not influence the costs enormously.

List 2: Agalsidase α (Replagal®) - treatment of Fabry disease
Agalsidase α is indicated for chronic enzyme-substitution treatment of patients with a diagnosis of Fabry disease. Information about clinical efficacy and effectiveness is lacking. This implies that no judgment can be made about the therapeutic value of

agalsidase α (Replagal®). The CFH advised to set additional requirements in relation to the provision of agalsidase α .

No therapeutic added value: Celecoxib (Celebrex®) - treatment of rheumatic arthritis:
Celecoxib is indicated for symptomatic treatment of pain and inflammation of rheumatic arthritis and arthrosis. The manufacturer asked for a new judgement in this case. The CFH concluded that Celebrex® has no therapeutic added value compared to other treatment options of high-risk patients for gastro-intestinal complications such as elderly and patients with gastro-intestinal ulcers. Celebrex® has remained in the current cluster of pharmaceuticals.

9 Discussion

The case of coverage of pharmaceuticals is a good one to point out some of the complexities for linking HTA to coverage decisions. It is also the area of health care that has the longest and most extensive experience3 with basing coverage decisions on HTA.

The first point is that HTA information on pharmaceuticals is more complete than that for other health technologies. The main reason that this is true is that society concerns about pharmaceuticals preceded serious concerns about other health technologies by some years. Pharmaceuticals have been increasingly regulated for efficacy, for example, since the early 1960, while general HTA began in the mid-1970s. Fostered by problems of safety and efficacy of drugs, governmental regulation has developed to assure a favourable benefit/risk ratio in pharmaceutical use.

The special status of drugs as a product certainly fostered this development. The public in general, and government policy makers in particular, have been favourable to the idea that industry products must be regulated in the public interest. It has been far harder to develop analogous approaches to physician practice. Physicians are prestigious professionals, generally trusted by the public and policy makers.

The 40 years experience with pharmaceutical regulation, along with the model of basing decisions on controlled clinical trials (as well as an HTA-type process), has led to a wealth of information on drugs, especially concerning their safety and efficacy. In fact, assessment of drugs has stimulated the development of the general field of HTA. It has shown that research can guide policy decisions.

There is little different in the actual assessment of drugs for regulatory purposes. The methods discussed in the Methodological Appendix are generally quite applicable.

With increasingly visible problems of all health technologies and rising costs of care, other policies have been sought. Reimbursement has been seen as an important tool since 1980 or so. Here, again, pharmaceuticals have led the way. The defined list of pharmaceuticals on the market, and the generally available information on their safety and efficacy, has stimulated use of reimbursement mechanisms, especially coverage. As has been discussed in other reports from this project, most areas of health care practice remain largely undefined and largely unassessed. That is not true in the case of pharmaceuticals.

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A Table 1: Positive and Negative Lists for Pharmaceutical Coverage in Selected European Countries

Positive	Negative
Austria	Germany
Belgium	Luxembourg
Denmark	Spain
Finland	Sweden (OTCs)
France	United Kingdom
Greece	
Germany (proposed)	
Ireland	
Italy	
Portugal	
Netherlands	
Spain	
Switzerland	
Sweden	

Source: Cranovsky et al, 1997; Panavos, 2001.