Essential Medicines in the United States

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BMJ Publishing Group
April 25, 2003
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Executive summary

Introduction

This report has been produced at the request of UnitedHealth Foundation. UHF has been interested for some time in the concept of an essential medicines list that could improve access to health care for the uninsured population. This report focuses on the potential for developing an essential medicines list for seniors in the United States.

Methods

- An in-depth policy review was carried out on essential medicines and related concepts, such as drug formularies.
- We consulted with experts in the fields of pharmacoconomics, pharmacology, evidence-based medicine, health care policy, geriatrics and biostatistics.
- To see if there is an international consensus on a basic drug benefits package, we did a comparative analysis of drug lists from English-speaking developed countries and the World Health Organization (WHO).

Defining essential medicines

An essential medicines list should:

- Satisfy the priority health needs of the population
- List medicines for which subsidies are available to all who need them
- Involve explicit evaluations of medications based on comparisons of safety, clinical effectiveness, relative cost and cost-effectiveness
- Be created with clear and open references to the best clinical evidence
- Be updated regularly

There are three general types of drug lists:

- Highly selective essential drug lists include only one or a few drugs within each therapeutic class and are intended as models for the development of formularies and national drug lists.
- Formularies list medicines that have been evaluated for safety, efficacy and cost, whose purchase a particular organization will subsidize.
- National drug lists are similar to formularies, but are often open to continuous updating as new agents that pass national regulatory standards are evaluated.

Unlike formularies, which are often seen as cost-containment measures, the essential medicines approach focuses on getting the best value for money spent on pharmaceuticals while guaranteeing access for the entire population to a reasonable, sustainable, evidence-based standard of care.

Failing to provide adequate access to essential outpatient medicines may lead to undesirable outcomes, such as:
• Increasing the number of adverse health events in vulnerable populations
• Increasing the rate of emergency room visits and hospitalizations among vulnerable populations

The private health care market has failed to provide adequate access to essential medicines. A particular challenge, which the private market may not meet adequately, is to provide patients and physicians with accurate, objective, unbiased information about pharmaceuticals.

Developing a list of essential medicines

It would be extremely problematic to develop a rational essential medicines list from scratch by identifying common conditions and evaluating the drugs that treat them. We believe that a better approach is to start with an existing evidence-based list, such as the one developed by the Department of Veterans Affairs (VA) or one of certain state Medicaid formularies. Explicit methods need to be devised for updating the list as new drugs are developed and approved. Drugs should be added only if their marginal added benefit justifies their cost.

We think the main challenges to developing a list are:

• Using a statistical measure to identify common conditions whose treatments would qualify for an essential medicines list: The difficulties start with the need to establish fair and meaningful criteria for determining which conditions can be defined as common. Inevitably, issues of equity would arise around any conditions that were left out. We do not recommend this approach.

• Accounting for gaps in clinical evidence, particularly for the aging population covered under Medicare: Research studies often do not include the elderly. In the short term, an explicit process of expert consensus can be used to fill such gaps. In the long term, identified gaps should help guide design and funding of clinical research.

• Deciding to what degree therapeutics are interchangeable: Generic and therapeutic substitution may be used, but with caution. A few agents within each therapeutic class should be identified as reference drugs against which others may be compared.

• Accounting for potential bias in analyses of cost-effectiveness: Only analyses whose designs meet strict criteria should be accepted for list development. The benefits of requiring pharmaceutical companies to produce such analyses as part of new drug submissions, as happens in Australia, must be weighed against the costs. In lieu of rigorous analyses, decisions between agents with comparable clinical benefit should be made based on negotiations on price.

Implementing a list of essential medicines

Once a list of essential medicines is compiled, challenges and opportunities associated with implementing it will arise and will include the following.

• Medication exchanges must be made in a safe and clinically effective fashion.

• In administering the benefit, it may be best to use a system that offers full reimbursement only for lower cost alternatives, but does not prevent patients from buying the nonpreferred products.
• There is likely to be indication “slippage.” That is, medications are likely to be prescribed to treat other indications than those for which they were included on the list. This can be addressed by adjusting reimbursement prices so that risk is shared between buyers and sellers, and potentially, by interventions that will influence prescribing practice.

• Market leverage can be used to negotiate lower prices, and innovations in information and technology can reduce transaction costs.

• Public, physician and pharmacist education is critical to the success of an essential drugs program, as is a strategy for informing the press of the potential advantages of the program. To present the list in its most positive light, it might be best to refer to drugs as “preferred” rather than “essential.”

**Accounting for important stakeholders**

The political challenges to implementing a list of essential medicines may far outweigh the methodological challenges. An effort to establish a national drug program using a limited list of medicines is likely to encounter substantial opposition from powerful vested interests. At all stages of list development and implementation, attention must be paid to the interests of large stakeholders, particularly patients, pharmacists, physicians, third-party payers and the pharmaceutical industry.

• Patients and physicians may see an essential list as an attempt to limit their choices and to ration care. For this reason, an extensive education campaign must accompany the development and implementation of the list.

• Involvement of physicians, pharmacists and the public in developing policies for the list and its implementation should be maximized. It may be particularly useful to involve large public advocacy groups that represent broad patient interests, such as the American Association of Retired Persons (AARP).

• The process could place the pharmaceutical industry in an adversarial position relative to the selection committee and purchasers. Perhaps the most notable concern is that such a list would adversely affect the incentives for the industry to invest in research and development and, more generally, in the U.S. economy.

**Access to essential medicines for seniors in developed countries**

Developed nations have taken various approaches to provide seniors and other vulnerable people with essential medicines. In particular:

• Countries tend to use formularies or national drug lists to define the range of benefits.
• Underlying these lists is an ideological commitment to covering all seniors.

**Access to essential medicines for seniors in the United States**

Both the public and private sectors in the United States have extensive experience developing and managing lists of medicines based on safety, efficacy and cost. Their approaches to the maintenance and implementation of such lists overlap to a considerable degree.
Recent private innovations include:

- Disease management programs for people with chronic diseases
- The use of information and technology to disseminate information and minimize transaction costs

**Comparative analysis of national drug lists**

Our comparative analysis of national drug lists shows the following:

- An international consensus on a core drug benefits package, that is evidence-based, does exist.
- Differences between the contents of various lists are likely explained by varying degrees of selectivity in list development and by specific negotiations between manufacturers and purchasing committees.

**Recommendations**

In light of these findings, we offer the following recommendations:

- That an initiative should be launched to design a national essential medicines list for the United States and a system to guide its use.
- That the drug benefit program based on list contents is a reference-based or similar system that provides full reimbursement only for essential drugs, but allows exceptions when they are deemed clinically necessary. Also, if the patient is willing to pay more or the manufacturer is willing to lower the price of the drug to match the price of the essential agent, the program should allow free access to comparable agents that are not on the list.
- That, given the structure of the American health system and the recent innovations to drug benefits management made in the private sector, the initiative should involve a mix of private as well as public entities.
- That, given the potential for controversy and conflict of interest, the process must be as explicit and open as possible.
- That list development should start with an existing evidence-based formulary rather than with an effort to identify common conditions.
- That, if the list is intended for the Medicare population, careful consideration be given to the clinical issues involved in providing care for the aging population.
- That it may be better to call the list a “preferred” drug list rather than an “essential” drug list.
- That careful attention should be paid to the numerous potential barriers to the effective development and implementation of an essential medicines list that were identified in this report, including the interests of important stakeholders.
- That, in particular, extensive education programs tailored for the public and for physicians should accompany the process. A major aim of these programs should be to counter the likely perception
that this is a new effort to ration care. The private market will ration care if left do so, with the result being the gaps in coverage and escalating costs that are currently manifest.
Introduction

This report has been produced at the request of UnitedHealth Foundation. UnitedHealth Foundation is interested in the concept of an essential medicines list that could be used to improve access to health care for the uninsured population. This report focuses on the potential for developing an essential medicines list for seniors in the United States.

The report aims to answer two main questions:

1. Taking into account the experience in other countries and organizations, how can an essential medicines list meaningfully address the needs of uninsured and underinsured Americans?

2. How would an essential medicines list apply to the Medicare prescription drug debate?

After analyzing international and domestic experience with essential drugs, some fundamental concepts became apparent:

- The development of an essential medicines list cannot be separated from the potential uses of the list.
- The political challenges to creating and implementing a list may far outweigh the methodological challenges.
- There are powerful stakeholders whose interests must be taken into account at all stages in list development and implementation.
- Extensive work has already been done toward providing access to essential drugs within the United States. Examples of practices adopted in both the public and private sector include the widespread use of medical formularies and the related practice of generic substitution.

Therefore, in outlining the issues and challenges related to creating a list, we will also address the policy issues that must be considered. This report ends with recommendations for using the concept of essential drugs to improve access for uninsured American seniors.
Methods

Policy review

A comprehensive, in-depth policy review was conducted by searching the peer-reviewed literature and Internet for relevant information on essential medicines, basic drug benefits packages, drug formularies, rational prescribing, measures for controlling drug expenditures, opinions of the pharmaceutical industry and physician groups, private sector formulary management, and Medicare reform.

In addition to drug programs in the United States, particular attention was paid to drug programs in other English-speaking developed countries and at the World Health Organization (WHO). Details of the searching techniques used are available on request.

Expert consultations

In the effort to identify key issues in developing an essential medicines list, we held semi-structured interviews with experts in the fields of geriatrics, pharmacology, pharmacoconomics, evidence-based medicine, health care policy and biostatistics.

We are grateful to the following international experts for the time they generously gave to help us with this project:

- Dr. Jerome Avorn, Associate Professor of Medicine; Chair, Department of Pharmacoconomics, Harvard University
- Professor Nick Freemantle, Professor of Clinical Epidemiology and Biostatistics, University of Birmingham, England
- Professor David Henry, Professor of Clinical Pharmacology; Deputy Head, Medical Practice & Population Health, University of Newcastle, Australia
- Dr. Hans Hogerzeil, Coordinator for Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, World Health Organization
- Dr. Rosanne Leipzig, Associate Professor of Medicine, Geriatrics & Adult Development and Health Policy; Vice-Chair for Education, Mount Sinai School of Medicine
- Dr. Mitchell Levine, Professor of Clinical Epidemiology & Biostatistics and Medicine; Director, Center for the Evaluation of Medicines, McMaster University, Canada
- Dr. David Matchar, Professor of Medicine; Director, Center for Clinical Health Policy Research at Duke University Medical Center; Director of Evidence-based Practice Center, Duke University
- Dr. Thomas Rector, Senior Researcher, Center for Health Care Policy and Evaluation, UnitedHealth Group
- Dr. Marcus Reidenberg, Professor of Pharmacology, Medicine and Public Health; Head, Division of Clinical Pharmacology, Cornell University
- Dr. Franco Sassi, Lecturer in Health Policy, Department of Social Policy, London School of Economics, England

Comparative analysis of national drug lists

To get a realistic idea of whether an international consensus exists on a core basic drug benefits package, we carried out a comparative analysis of drug lists from English-speaking developed countries that have national drug programs. We included lists from the following countries:
Essential Medicines in the United States

- Australia
- Province of Ontario, Canada
- New Zealand
- United Kingdom

Two other key lists that we considered were:

- World Health Organization core and complementary lists of essential medicines
- United States Department of Veterans Affairs (VA) National Formulary

Efforts were made to facilitate lateral comparison between lists. An example of the comparison, focusing on cardiovascular drugs, is included as Appendix A to this report. Appendix B contains details of the methodology used in the comparison.
Defining essential drugs

Which drugs are essential?

The concept of essential drugs assumes that there is a subset of all medicines that are indispensable and should be available to all. Access to these medications should be a public priority. The World Health Organization, which has been a pioneer in this field, defines essential drugs in the following way:

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available in the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. [WHO, 2002]

The four main criteria, then, for identifying an essential drug are:

- Relevance for public health
- Clinical effectiveness
- Safety (minimal toxicity)
- Comparative cost-effectiveness

The ideal list of essential medicines would be created with explicit criteria that provide for clear and regular updates. The WHO has also initiated a program to establish standard treatment guidelines for the drugs on the list. The goal for both the list and the guidelines is that they should be based on the best available clinical evidence. [WHO, 2002]

What types of drug lists exist?

Lists of essential drugs exist in various forms, including essential medicines lists, formularies and national drug lists.

- The WHO model list of essential drugs is intended to inform the development of formularies and national drug lists. It is a highly selective list that, in many cases, gives examples of one or a few drugs in a therapeutic class, assuming that countries will determine which and how many drugs within that class to include, based on cost and availability. As of the most recent committee meeting, the WHO is moving toward listing a few acceptable alternative drugs with comparable clinical performance within a pharmacological class, rather than one single agent in each class. [Hogerzeil H, personal communication, 2003]

- Formularies are lists of medicines that have been evaluated for clinical effectiveness, safety, and usually for cost, if not for cost-effectiveness. Medicines listed are often designated for full or partial subsidy by the institution that manages the formulary. Critics of formularies and formulary systems suggest that, in practice, they have adverse effects on patients’ health. The cause of these adverse effects is not clear, but critics argue that the overall effect is to shift costs to other segments of the health service budget, resulting in a net increase in expenditure. [Horn S et al., 2002; Horn S, 1996] The studies underlying such objections have been questioned, however, on the grounds of methodological problems and potential conflicts of interests. Specifically, authors note that such
studies were supported by the pharmaceutical industry. [Ross-Degnan D and Soumerai S, 1996] Formularies are nearly ubiquitous in international health systems and in the U.S. public and private sectors. The Institute of Medicine describes formularies as “an essential part of modern health care systems.” [Blumenthal D and Herdman R, 2000]

- National drug lists may not be directly analogous to formularies, as they are often open to the continuous inclusion of new drugs that meet their selection criteria, but they are created by taking into account a similar range of clinical and economic issues.

We suggest two ways of thinking about an essential medicines list as it compares to formularies and national drug lists. The first approach is to think of a spectrum of comprehensive drug lists (see Figure 1). At one extreme is a list of all medicines considered acceptable for clinical use (all drugs approved by the Food and Drug Administration, for example). At the other extreme is a model essential medicines list. Formularies and national drug lists fall somewhere in between these two extremes, depending on the degree of selectivity that went into setting them up.

![Figure 1. Comparing different types of drug lists.](image)

The second way of distinguishing an essential medicines list from a formulary is more ideological. Formularies, whether they are seen in a positive [Blumenthal D and Herdman R, 2000] or negative [Horn S et al., 2002] light, are often seen as cost-containment measures. [American College of Physicians (ACP), 2001] By contrast, the main reason to have an essential medicines list is to guarantee access for the entire population to a reasonable, sustainable, evidence-based standard of care. As the WHO puts it, such drugs must be available “at a price the individual and community can afford.” [WHO, 2002]

An essential medicines list presumes that there is an opportunity cost to providing a more expensive or less effective medicine. It recognizes that getting the best value for national expenditure on pharmaceuticals is a primary goal. [Hogerzeil H, private communication, 2003] But continued equitable access to medicines is its first and guiding priority, not cost containment.

**Why consider an essential medicines list?**

Whether an essential medicines list could save money for a health system in the long-term is a complex issue and would be difficult to demonstrate. The true virtue of a list rests more in promoting equity in a
society by ensuring that all citizens can access drugs that they need. Researchers have identified a subset of medicines as essential and looked at the impact of limiting reimbursement in vulnerable populations. These studies show that patients who cannot afford medicines end up using less of both essential and non-essential prescriptions. [Tamblyn R et al., 2001; Soumerai SB et al., 1994; Soumerai SB et al., 1991] The consequences of this include more adverse health events and more visits to the emergency room and hospital. [Tamblyn R et al., 2001; Soumerai SB et al., 1994] Patients with multiple chronic illnesses (those who most need medicines) are most likely to have reduced access to essential medicines. [Fortess et al., 2001]

One study of the impact of increased co-payments on people who had had myocardial infarctions found there was no difference in either medication use or adverse health events. [Pilote L et al., 2002] This study was conducted among elderly patients in Canada, where all patients were still covered, in some capacity, by a comprehensive drug benefits plan, even after the change in reimbursement. As access to essential medicines in this study did not change, it is not surprising that there was no increase in adverse events.

Can we rely on the private health care market to ensure access to essential drugs?

Based on both economic theory and historical experience, we cannot rely on the private health care market to ensure access to essential drugs. Despite spending more than twice as much per capita as some nations in the Organization for Economic Community and Development (OECD) [Garber A, 2002], nearly 75 million (or one in four) Americans were uninsured at some point during 2001 and 2002 [Families USA, 2003], and up to 40 percent of the elderly population in the United States have no prescription drug coverage. [Gross D, 2002] Those without insurance, particularly the elderly and those with multiple chronic diseases, are likely to go without medications because of the cost. In a recent survey of eight U.S. states, nearly one in four seniors did not fill prescriptions or skipped doses for financial reasons. [Kitchman M et al., 2002]

Much of the information that reaches patients and providers of health care comes from pharmaceutical companies. This information may not be unbiased. The development of an essential medicines list using transparent criteria, based on the best clinical research, and with clear links between supporting evidence and agents on the list, could redress imbalance of drug information and potentially help to contain overall health expenditure in the process.
Developing an essential medicines list

As part of this report, we were asked to consider creating an example of an evidence-based essential medicines list. After consulting with experts and reviewing the literature, however, we believe it is neither feasible nor especially valuable to do so at this point. While the essential medicines concept is extremely relevant to the United States, we do not believe that the best approach is to create a list from scratch, particularly from outside the United States. As we will discuss below, the essential medicines concept may be more effectively applied to evaluating medicines for inclusion on a list or formulary that has already been established within the United States.

However, based on the WHO’s work on essential medicines, there is a rational approach to creating an essential medicines list from scratch. [Hogerzeil H, private communication, 2003] This would involve:

- Identifying a subset of “common conditions” among the target population
- Evaluating the safety and relative clinical effectiveness of drugs used to treat those conditions
- Evaluating drugs with comparable clinical benefit for relative cost and cost-effectiveness
- Concurrently identifying or developing standard evidence-based treatment guidelines that inform both the development of the list and the use of listed medicines

There are a number of challenges associated with developing an essential medicines list using this approach.

What are “common conditions”?  

There is no generally accepted methodology that we can use to identify “common” medical conditions. To do so in an explicit way would mean using a single statistical measure to compile a list of common conditions. To our knowledge, this was not the approach taken by the WHO when it developed its original list in 1977. Nor have other developed countries explicitly taken this approach in developing their national formularies. [Henry D, private communication, 2003] There are practical, ethical and political reasons why this approach may not be feasible.

Practically speaking, this approach requires that the term “common” be statistically delineated in a way that is relevant to the outpatient setting. It is not clear what statistical measure might be appropriate or, indeed, if any single measure could be adequate. Following are descriptions of several problems associated with potential statistical measures.

- Data on mortality is perhaps the most straightforward and most easily available. But, in evaluating outpatient interventions with the goal of helping patients to live with conditions, mortality is clearly not the best criterion to consider (very few people die from depression, for example). [Leipzig R, private communication, 2003]

- Similarly, while prevalence data is easily available, it will likely identify common conditions for which there is no effective outpatient treatment (such as lung cancer). [Freemantle N, private communication, 2003] It also does not distinguish between diseases that may vary widely in their severity and in their effect on quality of life and productivity.

- Measures of burden of disease that combine morbidity and quality of life with mortality data may be more useful. These include disability-adjusted life years (DALYs), quality-adjusted life years, and healthy life years. But DALYs have been criticized for the value judgments they imply about human
life. [Arneson T and Nord E, 1999]. They are also not yet widely available for specific developed countries or for subsets of populations.

- A more relevant way to think about the burden of disease in this context may be to consider summary measures of the utilization of services. A utilization measure potentially identifies what might be considered “remediable burden” – that is, medicines that are most commonly needed and conditions treated in the ambulatory setting that represent the highest burden to the health system. [Freemantle N, private communication, 2003]. A listing of the medicines and medication classes most commonly prescribed in the United States would be an example of the former. [Kaufman DW et al., 2002; Rathore SS et al., 1998]. An example of the latter would be a listing of the most common causes for outpatient visits (which could be compiled from the National Ambulatory Survey).

- The “avoidable” burden of disease is another category that has been estimated using DALYs. [Hollinghurst S, Bevan G et al., 2000]

- A direct survey of physicians and the public offers yet another method of defining common conditions. The advantage of this last approach is that it would involve important interest groups at a formative stage in list development.

- An additional practical consideration is that there is an appreciable degree of variation in disease burden by age, race and gender. This would somehow need to be adjusted for in the analysis, if the goal is to produce a single list of common conditions.

A more fundamental ethical problem with focusing on common conditions is that it ignores or discriminates against patients with rare diseases for which there are effective and cost-effective treatments. [Reidenberg M et al., 1996]. Patients with rarer diseases may actually stand to benefit more on an individual basis from certain medicines. [Sassi F, private communication, 2002]

If, despite these issues, you wished to develop a list from scratch, we would recommend:

1. That a large number of conditions be included.
2. That once the list is established, additional effective and cost-effective medicines not be excluded solely on the basis that they treat diseases not on the original list of common conditions. Effective treatments for patients with rare diseases should be available on a name-to-patient basis. [Hogerzeil H, personal communication, 2003]
3. That both patients and physicians be involved in the process.

What if there are gaps in the available research evidence?

In many cases, there is no research evidence to support the inclusion of a drug on the list. Those who have evaluated the acceptable clinical evidence for drugs that treat even common clinical conditions have found considerable gaps in the evidence base. [Leipzig R and Levine M, private communications, 2003]
This may be a particular problem if the list is created specifically for a Medicare prescription drug benefit and therefore is most appropriately based on evidence of efficacy and safety in the over-65 population. Key issues of concern include the following.

- Little is understood about the unique effects and side effects of medical interventions in the over-65s. [Avorn J, 1990; Avorn J and Leipzig R, private communications, 2003]

- While those over the age of 65 are included in some clinical trials, the average age in most trials is less than 65. The conclusions about efficacy of medications for the senior population must often be derived from subgroup analyses. [Stuart B and Briesacher B, 2000; Leipzig R, private communication, 2003]

- This is particularly true for the most rapidly growing segment of the population: those over 85 years of age. [Garber A, 2002] In this population, adverse events may be different or more severe. There is greater potential for drug interactions because the elderly are often taking multiple drugs, and there may be different priorities for benefits (such as quality versus length of life). [Leipzig R, Reidenberg M, private communications, 2003]

The process of creating and maintaining an essential medicines list may provide researchers with an opportunity to identify and fill the gaps in evidence.

**We recommend:**

1. That there be explicit guidelines specifying what kinds of clinical evidence will be considered acceptable and what criteria can be used for grading the evidence that is available. [Levine M, Hogerzeil H, private communications, 2003]

2. That there be clear mechanisms for making decisions in the absence of good evidence. This may involve convening expert committees and using the RAND appropriateness approach for achieving expert consensus. [Matchar D, private communication, 2003] When experts are involved, potential conflicts of interest should be declared and accounted for.

3. That if the list is intended principally for Medicare beneficiaries, careful attention should be paid to the specific clinical issues found in the aging population.

4. That the process of creating a list should guide future research funding and design.

**How acceptable is it to substitute one drug for another?**

The concept of substituting drugs is applied widely in the creation of formularies and formulary systems in both the public and private sectors. It involves two assumptions about the interchangeability of medications:

- Bioequivalent generic preparations can be exchanged for brand name drugs (generic substitution).

- Chemically different drugs (usually in the same drug class) can be exchanged for drugs with comparable therapeutic effects (therapeutic substitution or therapeutic interchange).
Despite its wide acceptance, there have been concerns about the practice of generic substitution. It is possible that variations in the packaging of generics and in the inert ingredients used in their formulation may cause different physiologic reactions in some patients. [ACP, 2001] These differences may also impact on patient adherence. The FDA has been testing generic drugs since 1990 to ensure that they reach standards of bioequivalence and that they are labeled and manufactured appropriately. [ACP, 2001] Pharmaceutical and Therapeutics committees do, in certain circumstances, conclude that the generic version of a given compound is not acceptable. In general, however, in a report evaluating the Department of Veterans Affairs (VA) National Formulary, the Institute of Medicine concluded that “generic substitution should no longer be controversial.” [Blumenthal D and Herdman R, 2000]

The question of whether therapeutic substitution is acceptable and safe is more contentious. Key discussion points follow.

- Even drugs within the same class have different dosage schedules and side effects.
- Not many randomized controlled trials have been published that directly compare different medications in the same drug class [Anis A, 2002] (though in Australia, there have been a surprising number of head-to-head trials submitted to the Pharmaceutical Benefits Advisory Committee, even though they are often unpublished and of questionable quality). [Henry D, private communication, 2003]
- Not surprisingly, the pharmaceutical industry in Canada has questioned the validity of therapeutic substitution. [Reference Drug Consultation Panel (RDPCP), 2002] The industry has legally challenged formulary practices that restrict access to brand name medications in the states that have instituted formularies as part of their pharmaceutical assistance programs (including Florida and Michigan). [Pharmaceutical Research and Manufacturers Association (PhRMA) 2001; Rubin A and Rubin H, 2003]

Despite these concerns, we feel that both types of substitution are a crucial component of the essential medicines approach. In the next section of this report, we consider ways of implementing the list that address some of the risks of substituting medications.

The WHO identifies, but does not recommend, a third type of substitution – that is substitution between drugs not necessarily in the same class that are therapeutically similar. An example would be all drugs used to treat hypertension. Apparently there have been some preliminary attempts to adopt this approach in Australia. [Hogerzeil H, private communication, 2003] We do not believe that this type of substitution should be incorporated into a drugs benefit program in the United States.

**We recommend:**

1. That the generic equivalent for each pharmacological compound always be listed.

2. That a clinically minimal number of reference drugs should be chosen within a given medication class. (Reference drugs are those found to have an acceptable standard of clinical benefit and side effect profile within a drug class.) [Rector T, private communication, 2003]

3. That, in some circumstances, it may be appropriate to identify multiple reference drugs to account for the range of efficacies, side effect profiles, and usage requirements within a given therapeutic class. [Avorn J, Reidenberg M, Hogerzeil H, private communications, 2003]
4. That the process of list development should be used to guide the design of more relevant, head-to-head clinical trials.

Should cost-effectiveness analyses be used?

In theory, cost-effectiveness analyses (CEAs) provide a powerful tool for making rational decisions about which medications to cover in a cost-constrained environment. Fundamentally, the goal of CEAs is to help determine the best allocation of limited resources, with the goal of optimizing population health: “The pursuit of effectiveness alone, regardless of cost, can deprive other patients of care from which they would benefit more.” [Freemantle N et al., 1995]

Since 1993, Australia has required all new drug submissions to its pharmaceutical benefits scheme to have formal CEAs that satisfy extensive guidelines. [Hill SR et al., 2000] They use such analyses to evaluate whether the increased cost of a new agent is justified by a marginal improvement in efficacy or reduced toxicity. Canada is also planning to include CEAs as part of its new central evaluation of pharmaceuticals.

In practice, the use of pharmacoeconomic studies is tricky. Here are some of the main sticking points.

- The analyses, which are frequently funded by the pharmaceutical companies, involve complex models with parameters selected by the researchers.
- There is potential for bias based both on selective choices from the literature and assumptions made in constructing the model. [Kassirer JP and Angell M, 1994]
- There have been reports from researchers in the United States that pharmaceutical companies “considered such analyses to be marketing tools to promote sales” and were aggressive and manipulative in their treatment of those conducting the studies. [Rennie D and Luft HS, 2000]

Australia’s response to these issues has been to demand strict, explicit and transparent requirements for CEAs supporting new drug applications. These include a strong preference for analyses based on clinical trials, with head-to-head comparisons between the new agent and an established treatment with comparable clinical effects. [Productivity Commission, 1996] Unfortunately, there has been an extremely high rate of methodological flaws in CEAs submitted to the scheme. [Hill SR et al., 2000] At the same time, the requirements for the analyses have placed the Australian government in an adversarial relationship with the pharmaceutical industry. [Productivity Commission, 1996]

The overall conclusion in Australia is that the use of CEAs has been worthwhile, if controversial. It should also be noted that pharmaceutical companies have continued to make a substantial profit under this system. [Henry D, private communication, 2003] However, given the relative influence of the pharmaceutical industry in the United States, it is less clear whether the benefits of instituting similar requirements would justify their costs in the U.S. setting.

We recommend:

1. That pharmacoeconomic analyses should not be considered unless they conform to strict and explicit guidelines, such as those used in Australia, or unless the process by which they are conducted is made strictly rigorous and transparent. [Rennie D and Luft HS, 2000]
2. That the costs of requiring such analyses (both directly and in terms of a strained relationship with the pharmaceutical industry) should be carefully weighed against the potential benefits.

3. That, in lieu of pharmacoeconomic guidance, drugs of comparable benefit should be selected based on price negotiations with pharmaceutical manufacturers.

How should an existing list be updated?

For the reasons already outlined, and in particular because of the challenges associated with identifying common conditions, we believe it is more feasible to establish the essential medicines approach by adapting a list of medicines that already exists, rather than by creating a new list from scratch. Existing lists, such as formularies established for state Medicaid programs or the VA National Formulary, are based on formal evaluations of clinical evidence and have a track record of meeting the needs of vulnerable populations. [Reidenberg M, Matchar D, private communications, 2003]

Whether the decision is to use an existing list or to build one from scratch, the process of updating is a crucial aspect of the essential medicines concept. Updating can include new drug applications as well as re-evaluation of the medicines on an existing list. In Australia, drugs are placed in one of three categories: [Productivity Commission, 1996]

- Has significant clinical advantages over the established therapy for a given condition (either it is more effective with similar toxicity or as effective with less toxicity)
- Is similar to the established therapy in effectiveness and toxicity
- Is less effective that the established therapy but also less toxic

The basic principle is that a new drug must offer some added benefit over the established therapy. When there is no clear added benefit, the drug must be available at the same or lower price. Finally, when the new drug does add benefit, the Australian government uses economic analyses to determine whether the added cost is justified by the marginal additional benefit.

We recommend:

1. That an evidence-based formulary, such as that of the VA or certain state Medicaid programs, be used as the starting point for a national essential medicines list.

2. That the contents of that list be evaluated for relative efficacy, cost and cost-effectiveness.

3. That a clear updating process be established for adding new drugs when the added cost is justified by the expected benefit.

4. That, in the early stages of list development (the first few years), there should be frequent updates to allow for flexibility. Updating can become less frequent once the contents of the list have stabilized. [Hogerzeil H, private communication, 2003]
Implementing an essential medicines list

As we understand it, the proposed use of an essential medicines list is to inform the government of a decent minimum benefits package of medicines to which it will subsequently guarantee universal access. In this capacity, the list itself serves essentially as a formulary, and the policies around its use amount to what the Institute of Medicine describes as a formulary system – that is, “the elements that a system might employ in managing a formulary to achieve policy objectives.” [Blumenthal D and Herdman R, 2000]

We believe there are several challenges in implementing the list. A discussion of these challenges is followed by recommendations of best practices that we have derived from the literature, expert opinion and international experience. In particular, we feel that a program of reference-based pricing may be the best way of administering a benefit based on the contents of an essential list.

How will therapeutic exchanges affect patients and physicians?

At the time when a list of essential medicines is implemented, many patients will be taking drugs that are not on the list. Further, as the list is updated, its contents are likely to change. Both sets of circumstances will necessitate switching between medications, which may discomfit patients. The list, however, is likely to stabilize over time.

Physicians, too, may be uncomfortable with switching drugs. They may be more comfortable prescribing medicines not on the list, or they may judge that in specific clinical situations, an unlisted medicine is better.

These are familiar problems with the formulary systems that have already been implemented in the public and private sectors. Often formulary systems will include policies whereby substitutions of generic or therapeutic equivalents are automatically made at the point when a patient fills a prescription. The Institute of Medicine report on the VA formulary concluded that therapeutic substitution is an acceptable practice, but that the following conditions must be met: [Blumenthal D and Herdman R, 2000]

- Prescriber approval must precede the interchange, either through agreement to general policies or to specific interchanges.
- In systems where the formulary is closed (that is, where reimbursement is provided only for the drugs listed on the formulary), there must be an exception process for nonformulary drugs.
- Attention must be paid to the effects of interchange on patient compliance.
- Physicians and patients must be adequately educated (an aspect that is addressed at greater length below).
- There must be follow-up to identify problems and adverse events, with a particular focus on individuals who were stable on an original drug, are taking multiple drugs, or who have a compromised physiologic status.
- Substitution may be most effective when limited to classes with similar pharmacological entities but substantial diversity in price.

It is worth noting that the approach we are advocating may be distinguished conceptually from a formulary process in that it adds a new benefit where, in many cases, none existed previously. It must, then, be construed as augmenting rather than restricting access to medications.
In addition to meeting the conditions of the Institute of Medicine report, we recommend:

1. That patients be encouraged to view an essential medicines list as adding an important benefit rather than restricting access, and that new patients should be encouraged to take advantage of the opportunities the list provides.

2. That there needs to be a reasonable transition period so that patients already taking medications can consider switching to others that are better reimbursed. [Hogerzeil H, private communication, 2003]

How will the drug benefit be administered?

Formulary systems

The key components in implementing the list are:

- How and at what rate will designated medicines be reimbursed?
- To what degree will drugs that are not listed be financially supported anyway?

There are several basic types of formulary system. [ACP, 2001] Most systems are managed by private pharmaceutical benefits management firms.

- **Open formularies** reimburse for medications whether or not they are listed or recommended by the formulary.
- **Closed formularies** reimburse only for select drugs or therapeutic classes.
- **Selective or partially closed formularies** reimburse more for formulary drugs than nonformulary drugs, which may require prior approval.
- Other plans may set limits on payments of prescription costs.

In addition to the basic format, there are policies relating to how formulary and nonformulary drugs are paid for. There is often a degree of patient cost sharing that may depend on whether the drug is generic and/or included in the formulary.

Cost sharing

The practice of patient cost sharing for health services is widespread, despite evidence that it may not be an effective policy. Investigators from the RAND health insurance experiment concluded that cost sharing generally reduces demand for services without a significant adverse effect on the health of the “average” person. [Newhouse J et al., 1993] An important exception, however, was the “sick poor – approximately the most disadvantaged 6 percent of the population,” among whom cost sharing did have a significant adverse effect on health outcomes. A further RAND finding was that the method of cost sharing studied in the experiment – flat co-insurance rates of 25 percent, 50 percent or 95 percent – was just as likely to reduce demand for services deemed “highly effective” as those deemed “rarely effective.” [Newhouse J et al., 1993]
Reviews of cost sharing for pharmaceuticals tend to focus on these negative aspects: that it reduces demand for essential as well as non-essential care, and that it can have significant adverse effects on the health of vulnerable populations, with a potential resultant increase in overall health expenditure. [Freemantle N and Bloor K, 1996]

We do not believe that traditional approaches to patient cost sharing (such as flat co-insurance rates) should be used in administering benefits with an essential list. If cost sharing is incorporated in the approach, however, we urge policy makers to keep in mind the potential adverse health effects among the most disadvantaged.

Reference-based pricing

There is a method of cost sharing that is better suited to the essential medicines approach. Reference-based pricing (RBP), which doubles as a price regulatory policy, has received increasing attention. This is based on the principle that “society should pay for an evidence-based standard of drug therapy.” [Reference Drug Program Consultation Panel (RDPCP), 2002] There are several versions of reference-based systems, but the following list sums up the basic concepts:

- Public programs reimburse pharmaceuticals only at the level of a “reference” drug within a therapeutic class.
- Without evidence that another drug is appreciably more effective or less toxic, public programs will not pay the added cost. [Schneeweiss S et al., 2002a]
- There is no limitation on the prescription of a more expensive alternative.
- In the absence of a special authorization for specific indications, the patient must pay the difference in price.
- A related, but not identical program is a three-tiered reimbursement system in which a patient pays one low price for a generic drug, slightly more for a brand name equivalent listed on the formulary, and more still for a brand name nonformulary medicine.

Regions that have adopted a version of reference-based pricing include Australia, New Zealand, British Columbia in Canada, the Netherlands, the Michigan state Medicaid program and some private payers in the United States.

Germany tried this approach during the 1990s, but discontinued the program. [Stuart B, Brandt N, et al., 2000]

Unlike other programs of patient cost sharing, there is a growing body of evidence that reference-based pricing helps to contain costs without leading to appreciable increases in adverse patient outcomes or utilization of other health services. [Schneeweiss S et al., 2002b,c,d] The specific advantages that reference-based pricing offers are that it can: [Hogerzeil H, private communication, 2003]

- Give the best value for money spent on pharmaceuticals.
- Allow unlisted products continued access to the market.
- Influence the pharmaceutical industry to lower prices of alternative products in order to remain competitive.
- Preserve the choice of medications for patients and doctors.

This system’s potential for containing costs is limited in that it does not influence other drivers of expenditure, such as prescription volume and new, effective drug interventions. [Ioannides-Demos L et
al., 2002] The savings related to reference-based pricing may be short-term, in part because prices and prescribing patterns eventually conform to greater use of the reference product. [Stuart B, Brandt N et al., 2000] Assuming the new volume of prescriptions is appropriate, however, this means that more people are able to access drugs they need under such a program.

Following are several criticisms that have been leveled at reference-based pricing. [Ioannides-Demos L et al., 2002; Schneeweiss S et al., 2002a; RDPCP, 2002]

- It creates a disincentive to pharmaceutical innovation, which tends to proceed through small incremental advances in efficacy and tolerability.
- It interjects a financial component into the doctor-patient relationship.
- It potentially creates a “two-tiered health system,” in that patients with low incomes are less likely to pay the co-payment to receive nonreference drugs.
- It places considerably more demands on doctors’ and pharmacists’ time.

There are counter arguments, however, to all of these criticisms. [Hogerzeil H, private communication, 2003] Any truly innovative medications should be adequately reimbursed under this system. In addition, a reference-based pricing program, implemented as an extension of drug benefits guaranteeing access to medications, potentially reduces the financial component of the doctor-patient relationship rather than exacerbating it. Similarly, when certain segments of the population go without medications because of cost, the system is arguably already more “two-tiered” than one that guarantees access to all. Finally, it remains to be substantiated that the reference-based program places more demands on doctors’ time.

Recently, a multidisciplinary panel was convened in British Columbia to evaluate their five-year experience with a reference-based pricing (RBP) program. The plan had been adopted for the coverage of a few different therapeutic classes of medications. The panel consulted with all major stakeholders in the program. Their conclusion was that the program had produced substantial net savings for the health system without compromising the quality of care or increasing inpatient utilization. Their recommendation was that the province should continue the RBP and consider expanding it, with some alterations. [RDPCP, 2002] One observer in the United States has suggested that reference-based pricing is an approach that should be incorporated into plans for Medicare reform. [Haase LW, 2002]

Indication “leakage” or “slippage”

Experts caution that in practice it is difficult to limit the uses of medications to the indications for which they were placed on the list. [Freemantle N, Henry D, private communications, 2003] Medicines listed with special restrictions on their use may be prescribed more broadly than intended. The result is that they may be used to treat conditions for which they have not been shown to be cost effective at the price of reimbursement. An example is proton-pump inhibitors, which are extremely cost-effective for treating severe gastrointestinal injury, but not for managing gastric symptoms. [Freemantle N, private communication, 2003] In practice, it would be difficult to limit their use only to severe injury.

One approach to countering indication leakage is to develop a lower reimbursement price for the wider use of agents like proton-pump inhibitors. Technical methods have been developed to determine such price adjustments. These have been set up to enable the financial risk to be shared between buyers and sellers. [Henry D, private communication, 2003] Additional approaches would involve interventions to influence prescription practice. But the financial cost of such interventions must be weighed against their potential benefits. [Freemantle N, private communication, 2003]
**Opportunities in administering the benefit**

Whether reference-based pricing or another type of reimbursement program is deemed appropriate, at least two potential opportunities for added benefits arise, based on how an essential list is administered. The first such opportunity is that the purchasers of drugs on the list can take advantage of market leverage to negotiate a low price for listed medicines. Assuming that the government will guarantee universal access to these medicines, the price paid for medicines for patients who were previously not receiving drug benefits – and hence are currently paying the retail price – will be considerably lower.

The second opportunity is to take advantage of innovations in information and technology to minimize administrative and transaction costs. This has been one of the major improvements introduced by the pharmacy benefit management firms (PBMs), and it is one that should be integrated into any new system for delivering drug benefits. [Eber B et al., 2001]

**We recommend:**

1. That the drugs on the list be reimbursed using reference-based pricing or a similar system, which does not restrict choice, but provides incentives for choosing lower-cost alternatives with a comparable clinical profile.

2. That drugs in each class should be fully subsidized at the price of reference drugs, but that patients should pay the additional cost for higher-priced agents within that class that do not offer significant additional clinical benefit.

3. That the likelihood of “indication slippage” should be recognized and adequately planned for.

4. That the list be explicitly for reimbursement, not for regulatory purposes. Any drug approved by the FDA should be allowed free access to the market.

5. That the purchaser of drugs on the list should use market leverage to negotiate for substantial reductions in price.

6. That innovations in information and technology should be used to minimize administrative and transaction costs.

**How should patients and physicians be educated about the list?**

Drug companies provide a huge amount of information on their products to both consumers and doctors. Direct-to-consumer advertising in the broadcast media has brought pharmaceutical information to a wide patient audience. But the companies still devote the greater portion of their marketing budget to physicians. [Rosenthal MB et al., 2002]

Pharmaceutical marketing information is unlikely to support an essential medicines list. The implementation of such a list would therefore need to be accompanied by a substantial public education campaign. This campaign would have to be two-pronged: It would need to counter any accusations that the drugs on the list are inferior and it would have to provide good information for patients about correct use and potential side effects of listed drugs. One important way to counter notions that essential drugs
are inferior is to consider naming the list a “preferred” or “core” drug list, rather than an “essential” medicines list. [Henry D, Hogerzeil H, private communications, 2003]

In addition, an information campaign for the public might emphasize these four points: [Hogerzeil H, private communication, 2003]

- Listed medications are the best, safest, and most cost-effective treatments available.
- An essential medicines program offers new benefits where in many cases none existed.
- Under a reference-based pricing system, patients have full freedom to access nonlisted medications if they are willing to pay the difference.
- There is an exception process for nonlisted medications that are considered clinically necessary.

Physicians may need to receive a similar message, perhaps through educational interventions, to influence the prescribing of less costly, therapeutically equivalent formulary products. [ACP, 2001; Avorn J, private communication, 2003] Important additional messages for physicians should emphasize that an essential drugs process will: [Hogerzeil H, private communication, 2003]

- Provide them with good advice and evidence on the most cost-effective treatments.
- Allow them to maintain full clinical freedom.
- Regularly update the contents of the list to account for new interventions and evidence.

In designing education interventions for physicians, attention should be paid to reviews that show that traditional educational interventions, such as lectures and grand rounds, do not change physician practice. [Davis D, Thomson O’Brien MA, et al., 1999] Further, it must be recognized that the cost of interventions to change physician behavior may make ostensibly cost-effective therapies considerably less so. [Mason J, Freemantle N, et al., 2001]

In addition to patients and physicians, it will be crucial to involve and educate pharmacists, as they play a critical role in the administration of drug benefits and related processes of drug substitution.

Finally, it will be essential to adequately inform journalists about the program and its potential advantages. Drug benefits programs are easily undermined by print articles emphasizing the negative opinions of health professionals or relating stories of “victims” of the restrictions imposed by the program. [Henry D, private communication, 2003]

**We recommend:**

1. That a large-scale public education campaign emphasizing the above-listed messages should be initiated to counter the notion that essential drugs are inferior and to educate patients about drugs on the list.

2. That the list be called a “preferred” drug list rather than an “essential” medicines list.

3. That innovative interventions should be designed to educate physicians with adequate objective information about essential drugs. [Avorn J, private communication, 2003]

4. That journalists need to be well informed about the program and its potential advantages.
Accounting for the interests of important stakeholders

An essential drugs process that does not account for the interests of important stakeholders is unlikely to go very far. Here we discuss the issues that we believe will be raised by the major stakeholders – the pharmaceutical industry, third-party payers, pharmacists, physicians and patients. This is followed by recommendations for how to take these interests into account in developing the list.

Pharmaceutical industry

Without a well-functioning, innovative pharmaceutical industry, it would not be possible to have a discussion of essential medicines. In the past, efforts to use lists of medications to restrict the availability of drugs have put the pharmaceutical industry on an adversarial footing. In Florida and Michigan, the Pharmaceutical Research and Manufacturers of America (PhRMA) filed federal lawsuits challenging state Medicaid formularies [PhRMA, 2001; Rubin A and Rubin H, 2003]. The industry has indicated that governments taking an active role in limiting the medicines available in their jurisdiction make it a more hostile environment for pharmaceutical investment and marketing. [RDPCP, 2002; Productivity Commission, 1996]

The American pharmaceutical industry has clearly stated that it supports the extension of a universal Medicare prescription drug benefit. Depending on how it is designed, such a program would benefit the industry. The industry supports coverage of all prescription drugs, however, and not those limited to a specific list. [PhRMA, 2003]

The industry’s main objection to lists that limit availability is that they curb incentives for innovation. [RDPCP, 2002; Ioannides-Demos L et al., 2002] To bring a new drug to market requires a vast expenditure in research and development. [PhRMA, 2003] However, pharmaceutical companies do not disclose their budgets, and it is not clear how they differentiate between spending on research and marketing, nor is it clear how much a list would really reduce their profits. [Henry D, private communication, 2003] Finally, an essential medicines program should be designed to reward true innovation. It is conceivable that medications with particularly favorable risk/benefit ratios will command a higher price than they otherwise would have done. [Hogerzeil H, private communication, 2003]

Third-party payers

Third-party payers are groups that serve as intermediaries between patients and physicians, paying the proportion of health care costs designated by benefits programs. In the United States, the most prominent of those groups are private health plans, large employers, and the federal and state governments. They all face similar pressures – the need to control rapid increases in health care costs while attempting to maintain or improve the quality of care for patients. Their ability to do so has crucial ramifications for the proportion of the population that has access to health care and for the degree of that access. [Blumenthal D, 1999]

Presumably, a well-designed essential medicines program would be an attractive solution to the challenges faced by this group. The reference-based pricing program in British Columbia has been well received by the principal third-party payer there, the provincial government. [RDPCP, 2002]
**Pharmacists**

Pharmacists are on the front line of any drug benefits program, and their participation is crucial. This is particularly so for programs of medication substitution that are currently common in private sector formularies, and in the reference-based pricing approach advocated in this report. In the Canadian province of British Columbia, where reference-based pricing was instituted, pharmacists raised concerns that the need to explain the government’s policy to patients would place increased and uncompensated demands on them. They indicated that the need to deal with concerns and issues around drug substitution and the exceptions process was particularly time consuming. [RDPCP, 2002] As pharmacists in the United States are already engaged in many such activities in the private sector, this will not be a new burden for many of them. Further, this may be seen as an opportunity for pharmacists to become involved at the stage of policy development, so that their interests will be better represented and a more efficient system can be designed.

**Physicians**

Many doctors would favor a list for two main reasons: It would remove barriers to necessary medications for their patients and it would encourage doctors to think more about their prescribing choices. [Lavizzo-Mourey RJ and Eisenberg JM, 1990; RDPCP, 2002]

Physicians and physicians’ groups have concerns about public and private efforts to enact limited lists of medications. [ACP, 2001; Lavizzo-Mourey RJ and Eisenberg JM, 1990; RDPCP, 2002] They are concerned that lists:

- Limit professional independence
- Are sometimes created and/or implemented by groups lacking physician representation
- Create more work for physicians that is not compensated
- Limit their patients’ access to new, innovative drugs
- Increase the perception of doctors as “rationers of care” or “barriers to therapy” rather than healers [Lavizzo-Mourey RJ and Eisenberg JM, 1990]
- Encourage the questionable substitution of one drug for another [Ioannides-Demos LL et al., 2002] or of drugs for other types of therapy [Lavizzo-Mourey RJ and Eisenberg JM, 1990]

Similar to pharmacists, however, physicians are already increasingly exposed to formulary systems implemented in the private and public sectors. Rather than limiting their autonomy, the essential medicines process can be seen as an opportunity for physicians to become more involved in policies that determine their range of clinical options and that potentially extend access to more of their patients.

**Patient groups**

Support for an essential medicines list may depend on the nature of the patient or patient group.

- Groups such as the American Association of Retired Persons (AARP), which take a broad advocacy approach, recognize the need for Medicare reform that improves access to prescription drugs. [Gross D and Bangan N, 1999]
• In the past, however, advocates for particular patient or population groups have criticized attempts to limit medication coverage to specified drugs. This is because such efforts have often appeared to limit patients’ access to the “newest” or “best” drugs. [RDPCP, 2002] For example, the Mental Health Association of Michigan joined the Pharmaceutical Research and Manufacturers of America (PhRMA) in filing a lawsuit against Michigan’s prescription drug plan on the grounds that it “deprived mentally ill patients from access to certain interventions.” [Rubin A and Rubin H, 2003] Such objections should not be viewed uncritically, however, as patient groups are often given substantial funding by the pharmaceutical industry. [Lenzer J, 2003]

• Other consumer and patient groups have raised concerns that formularies may not adequately account for racial variations in patients’ responses to medicines. Among those with more serious chronic conditions (such as lupus) there is also a fear that forced substitutions of medications will result in serious side effects. [Freundlich N, 2003] For these reasons, it is crucial to have a well-delineated process in place for effecting exceptions, along with clear mechanisms for making necessary medications available on a name-to-patient basis.

• Various interested groups have also suggested that processes of selecting drugs for coverage must be more transparent. [RDPCP, 2002]

• In addition, as discussed previously, an essential medicines list created by identifying the most common conditions is likely to draw criticism from patient advocacy groups if specific diseases are not included on the list.

We recommend:

1. Given that the interests of various groups will be directly opposed, it is critical that the process be as explicit and transparent as possible in both design and execution.

2. Processes such as the one proposed here, not unlike many negotiations in the private sector, will inevitably place the selection committee and/or purchaser in an adversarial position with regard to the pharmaceutical industry. [Freemantle N, Henry D, private communications, 2002]

3. It is important to remember, however, that the pharmaceutical industry is a linchpin of the economies of both the United States and the world at large. Pharmaceutical products play an absolutely pivotal role in maintaining and improving the health of the public, and, potentially, in containing the overall health budget in the process.

4. The industry must be assured incentives to continue research and development and investment in the economy.

5. The increased level of transparency that this process will demand may also necessitate a shift in industry focus toward innovation and away from marketing (which has tended to obscure objectivity and transparency in the conduct and dissemination of research and cost-effectiveness studies).

6. The establishment of a well-designed essential medicines program may be in the interests of large third-party payers, and their support and involvement should be sought.
7. The involvement of physicians, pharmacists and the public should be maximized at all stages of policy development and implementation. This is particularly important when decisions are first made about fundamental values and priorities that will guide the choosing of drugs for the list.

8. It may be particularly useful to involve large public advocacy groups, such as the AARP, that represent broad patient interests.

9. It is essential to convey the idea that this is a proposal to extend access rather than a program to limit or ration care, and that it includes a process that will address exceptional individual needs.
Access to essential medicines for seniors in other developed countries

Other developed countries may not have directly followed the World Health Organization's concept of essential medicines, but they have taken steps to ensure that their elderly and vulnerable outpatient populations have access to necessary medicines. As the following analysis will make clear, the greatest degree of commonality between their approaches is in the fundamental ideological commitment to providing for the vulnerable.

Canada

Coverage

All seniors in Canada are covered by a drug benefit plan, but the level of coverage varies between provinces.

Review and pricing process

- Not unlike the situation in the United States, the Canadian review of medications begins with a central examination of each medication’s safety and efficacy by a governmental regulatory body.

- Once a new drug has been approved, the Patented Medicines Prices Review Board sets a maximum entry price based on a comparison to other similar medicines or, in the case of breakthrough drugs, based on prices in other countries. [Stuart B et al, 2000]

- Approved drugs are then re-evaluated at several levels of government – federal, provincial and territorial – for inclusion on drug formularies.

- Drugs are classified on the formulary as either a full listing (doctors can prescribe them as necessary) or a restricted listing (doctors must obtain approval from the province before prescribing them).

- Depending on the province, various additional measures are taken to influence the choice of lower-cost alternatives for achieving similar clinical benefit. One example is British Columbia, which has instituted both a low-cost alternative program and a reference-based pricing plan.

- Recently, an effort has been made to centralize the process of formulary development and thereby to limit the duplication of effort between levels of government. Evaluations by a central committee will take into account the results of pharmacoeconomic analyses.

- This committee’s recommendations will then go to decision makers for individual reimbursement plans, who will use them in deciding which drugs their programs will cover.
Australia

Coverage

All seniors in Australia are covered by a drug benefit plan that provides substantial subsidies for pharmaceuticals. Unemployed or retired seniors are given an allowance of $2.90 (Australian dollars) per week for prescription drugs (as part of their pensions or benefit payments), and pay a maximum of $3.70 to fill individual prescriptions. [Biggs A, 2002]. When they have reached a “safety net” threshold (currently 25 prescription items per household), additional prescription medicines are free of charge.

Review and pricing process

- Australia has a national drug regulatory agency called the Therapeutic Goods Administration that evaluates new drugs for safety and efficacy. The agency gets advice from an independent body of experts – the Australian Drug Evaluation Committee.

- A subset of medicines are registered with the agency and listed on the Pharmaceutical Benefits Schedule (PBS) for reimbursement by the federal government.

- There are some unique aspects of Australia’s PBS. To begin with, a central Pharmaceutical Benefits Advisory Committee (PBAC) makes explicit recommendations to the federal health minister regarding which drugs should be listed on the PBS. The PBAC uses both clinical and pharmacoeconomic criteria to make its evaluations. The committee also makes recommendations to a separate pricing authority as to the prices at which new drugs are “cost effective.” The committee and the pricing authority use a reference-based methodology to set prices for drugs in each therapeutic group at the level of the least expensive drug in that group (usually a generic brand). Clinical trial data are used to establish equivalent doses of drugs within a therapeutic group. Companies are allowed to charge a “brand premium” for their products, but the patient must pay this. [Henry D, private communication, 2003]

- Some reports indicate that the PBS has been a success, providing citizens with good access to essential medicines while holding costs down to a level that compares favorably with other nations. [Productivity Commission, 2001] In theory, the PBS also increases overall returns to the pharmaceutical industry by increasing sales volume through subsidies for its products. [Productivity Commission, 1996]

- There have been concerns, however, about the practices and sustainability of the program. In particular, there is worry that the international pharmaceutical industry will find the Australian environment too hostile for significant investment and for the marketing of “new innovative” new pharmaceuticals. [Productivity Commission, 1996] These fears do not seem to be borne out in practice so far, but it is notable that Australia has a relatively small domestic pharmaceutical industry.

- There is some evidence from a recent comparison of international pharmaceutical prices that the PBS is fulfilling its mission. On average, prices in Australia are level with those in several other countries, including New Zealand, France and Spain, and they are significantly lower than in several other countries, particularly the United States.

But, prices for pharmaceuticals classified as “new innovative” are more comparable to what they cost in countries with higher drug prices. Prices for so-called me-too drugs (for which therapeutic
alternatives are available) are relatively low. According to the Australian Productivity Commission report, the United States has particularly high prices for “me-too” products relative to other nations, while Australia and New Zealand have the lowest prices. [Productivity Commission, 2001]

United Kingdom

Coverage

All senior citizens in the United Kingdom (those older than 60) receive medications free of charge. When they fill a prescription, they sign the back of the prescription form to indicate that they are over 60. The benefit entitles them to all pharmaceutical products listed in the British National Formulary.

Review and pricing process

- The British National Formulary is a detailed list that designates agents for inclusion and reimbursement from the National Health Service (NHS), based primarily on clinical efficacy and safety. Though fairly inclusive, it is a selective list that does not include all agents approved for use in the country.

- Prices for medicines are not directly regulated in the United Kingdom, but there is regulation based on the profits of pharmaceutical companies.

- Recently, recognizing the need to promote high-quality and cost-effective practice, the NHS introduced the National Institute for Clinical Excellence (NICE). This is an independent organization, affiliated with the National Health Service. It produces evidence-based best practice guidelines for disease management and also makes formal technology appraisals of new and existing interventions (such as COX-2 inhibitors). NICE’s decisions are the products of “independent groups that include healthcare professionals, patients and people who are familiar with the issues affecting patients and carers.” [NICE, 2003]

- In theory, “once NICE guidance is published, health professionals are expected to take the Institute’s guidance into account when exercising their clinical judgement.” [NICE, 2003] In practice, however, there is not yet widespread uptake of the NICE recommendations. [Freemantle N, private communication, 2003]
**Access to essential medicines for seniors in the United States**

There have already been widespread efforts within the United States to improve access to essential medicines for senior citizens, while controlling costs and quality. To minimize the duplication of future efforts, it is important to look at the work that has already been done. Coverage for seniors as well as the evaluation and pricing of drugs is currently spread between the public and private sectors.

**Coverage**

Seniors receive drug benefits either through employer-sponsored private health plans, Medicare managed-care plans or Medigap policies. Those who qualify for Medicaid by income criteria are eligible for coverage under state programs. Some states have also been able to extend drug coverage to seniors at certain income levels above the poverty line. [American Association of Retail Pharmacists, 2002]

Unfortunately, a large proportion of seniors who qualify for this coverage may not be aware of their eligibility. [Kitchman M et al., 2002] There is also evidence that many patients in California, where seniors without drug benefits are supposed to receive the same discounts at pharmacies as Medicaid beneficiaries, may not be getting the appropriate discounts. This may be particularly true in low-income neighborhoods. [Lewis JH et al., 2002] In a survey of eight U.S. states, the percentage of seniors without any prescription drug coverage varied between 18 percent and 31 percent, depending on the state. Those with lower incomes who do not qualify for Medicaid coverage (the “near-poor”) are disproportionately likely to lack drug coverage. [Kitchman M et al., 2002]

**Review and pricing process**

**The roles of the FDA and Medicaid**

- The FDA’s process for approving new medicines involves a thorough assessment of their safety and efficacy. [Meadows M, 2002] The FDA does not consider issues of cost, cost-effectiveness, or efficacy relative to other medicines in the same class in its appraisals. [Farley D, 2003]

- There is no public effort in the United States to set the price for new medicines. Once a medicine is approved by the FDA, it is up to third-party payers, in either the public or private sector (or the Pharmaceutical Benefits Managers they contract out with), to decide whether it will be covered and to negotiate a price with the manufacturer. There is no public disclosure of prices that have been agreed upon between manufacturers and payers.

- Since the 1980s, it has been a common practice among state Medicaid programs to exclude certain drugs from coverage that are considered "marginal" or "non-essential." These "negative drug lists" are constructed based on evidence of efficacy and safety, but taking into account cost, so that in a group of similar medications, only the least expensive are included. [Soumerai SB and Ross-Degnan D, 1990]
The role of Pharmacy Assistance Programs

Many states have recently tried to extend access to medications while controlling pharmaceutical costs and encouraging rational, cost-effective prescribing. These efforts, usually called Pharmacy Assistance Programs, vary in the populations they cover and in the ways they define benefits. [American Association of Retail Pharmacists, 2002] For example, the Oregon Health Resources Commission subcontracts with the Oregon Health and Sciences Evidence-Based Practice Center for assistance in making transparent, evidence-based evaluations of specific classes of pharmaceuticals for inclusion on the state health plan list. [Office for Oregon Health Policy and Research, 2002] Michigan has instituted a reference-based pricing system similar to that in British Columbia. [Michigan Department of Community Health, 2002]

The role of the Department of Veterans Affairs

The Department of Veterans Affairs is the largest single purchaser of pharmaceuticals in the United States. It has instituted an evidence-based national formulary system in order to standardize its benefits package and contain costs. In addition to establishing a “partially-closed” formulary (with restrictions on some drug classes), the formulary system includes generic and therapeutic drug substitution to minimize costs.

The role of the private sector

In the private sector, most drug benefits plans are now administered by pharmacy benefit management firms (PBMs). PBMs serve as intermediaries between pharmaceutical companies, physicians, pharmacies and third-party payers. [ACP, 2001]

- PBMs develop formularies based on the recommendations of pharmaceutical and therapeutics (P and T) committees and cost considerations. They negotiate discount prices and dispensing fees with retail pharmacies to buy pharmaceuticals at bulk discounts. They also receive rebates from manufacturers, a percentage of which they share with the health plan or employer that contracts with them.

- PBMs use various strategies to contain costs and influence prescribing patterns. These include closed or partially restrictive formularies, limitations on the number of prescriptions and refills and limitations on the size of prescriptions. [Academy of Managed Care Pharmacy, 2000] They also use various methods of cost sharing with patients, such as tiered payment systems. [Fox PD et al., 1999] With the permission of physicians, they will substitute generic or formulary drugs in the same class for prescriptions that are made for off-formulary products. [Eber B et al., 2001] To influence prescription practice, they do prospective and retrospective drug utilization reviews of physician prescribing.

- PBMs sometimes set up disease management programs for people with potentially high-cost conditions, such as diabetes and heart disease. These programs encourage medication compliance and help patients take a more active role in managing their condition. [Eber B et al., 2001]

Concerns that have been raised about PBMs include the following:

1. Undisclosed pricing arrangements with manufacturers may compromise the medical appropriateness of their formulary decisions as well as their ability to contain costs.

2. Centralized decision-making by PBMs removes physicians from final drug selection. [Eber B et al., 2001]
3. PBMs have engaged in business mergers with pharmaceutical manufacturers that have attracted attention. Manufacturers are seeking to use PBMs as a way of vertically integrating their products (controlling them from development to distribution). This has led some employers to call for more oversight of PBM practices. The Federal Trade Commission has allowed such mergers only with strict guidelines, but recent negative attention has led to the dissolution of some of these arrangements. [ACP, 2001]
Comparative analysis of drug lists

The matrix in Appendix A shows that there is some international consensus on a basic evidence-based drug benefits package. The comparison shows that the VA National Formulary contains most, if not all, of these same consensus therapeutics.

The WHO list also overlaps well with areas of consensus between the different countries. And though the WHO does not list, for example, labetalol, it does leave open its possible inclusion by designating atenolol as an example from an essential therapeutic group.

In light of the processes of drug selection and purchase for the various lists described above, it seems likely that most variations between lists can be explained by the following factors:

- **Varying degrees of selectivity** employed in list development and maintenance. The Australian scheme, for example, tends to have fewer agents in a given therapeutic group than the British National Formulary. This is likely a reflection of the fact that Australia imposes cost-effectiveness criteria in the process of creating its list, whereas the United Kingdom tries to influence more cost-effective prescribing patterns through recommendations made by NICE regarding drugs already listed on the BNF.

- **Specific deals on the cost of therapeutics** negotiated between manufacturers and purchasing committees making certain agents in a drug class more affordable in some settings than others.
**Recommendations**

In light of these findings, we recommend:

- That an initiative be launched to develop a national essential medicines list for the United States and a system to guide its use.

- That the drug benefit program based on list contents is a reference-based or similar system that provides full reimbursement only for essential drugs, but allows exceptions when they are deemed clinically necessary. Also, if the patient is willing to pay more or the manufacturer is willing to lower the price of the drug to match the price of the essential agent, the program should allow free access to comparable agents that are not on the list.

- That, given the structure of the U.S. health system and the recent innovations to drug benefits management made in the private sector, the initiative should involve private as well as public entities.

- That, given the potential for controversy and conflict of interest, the process should be as explicit and open as possible.

- That list development should start with an existing evidence-based formulary rather than an effort to identify common conditions.

- That, if the list is intended for the Medicare population, careful consideration should be given to the specific clinical issues involved with caring for the aging population.

- That it may be better to call the list a “preferred” drug list rather than an “essential” drug list.

- That careful attention should be paid to the numerous potential barriers to the effective development and implementation of an essential medicines list that are identified in this report, including the interests of important stakeholders.

- That extensive education programs for the public and for physicians should accompany the process to counter the likely perception that this is a new effort to ration care.
Acknowledgements

We would like to thank Professors Nick Freemantle and David Henry, and Drs. Hans Hogerzeil, Thomas Rector, Marcus Reidenberg and Franco Sassi for their peer reviews of this report.
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### Appendix A – Comparative matrix of cardiovascular medicines

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All: + Available in a formulation that includes a diuretic; ^ Available in a formulation that includes a calcium channel blocker
Australia: *Restricted use **Special authorization required***Restrictions on some dosages or formulations****Special benefit
ONTARIO, CA: *RESTRICTED USE
NEW ZEALAND: *NOT FULLY SUBSIDIZED BY GOVERNMENT; **REQUIRES SPECIAL AUTHORITY; (+*) FORMULATION WITH DIURETIC NOT FULLY SUBSIDIZED
VA: *RESTRICTED USE; **RESTRICTIONS ON USE LEFT TO THE DISCRETION OF REGIONAL VA AUTHORITIES

WHO: *WHO COMPLIMENTARY LIST; # INDICATES "AN EXAMPLE OF A THERAPEUTIC GROUP AND THAT VARIOUS DRUGS COULD SERVE AS ALTERNATIVES...CHOICE IS THEN INFLUENCED BY COMPARATIVE COST AND AVAILABILITY OF EQUIVALENT PRODUCTS"; **** "THE WHO EXPERT COMMITTEE...RECOGNIZES THE VALUE OF LIPID-LOWERING DRUGS IN TREATING PATIENTS WITH HYPERLIPIDAEMIA. HMG-COA REDUCTASE INHIBITORS...ARE A FAMILY OF POTENT AND EFFECTIVE LIPID-LOWERING DRUGS...SEVERAL...HAVE BEEN SHOWN TO REDUCE THE INCIDENCE OF [OUTCOMES INCLUDING ALL-CAUSE MORTALITY]...ALL REMAIN VERY COSTLY BUT MAY BE COST-EFFECTIVE FOR SECONDARY PREVENTION...SINCE NO SINGLE DRUG HAS BEEN SHOWN TO BE SIGNIFICANTLY MORE EFFECTIVE OR LESS EXPENSIVE THAN OTHERS IN THE GROUP, NONE IS INCLUDED IN THE MODEL LIST; THE CHOICE OF DRUG FOR USE IN PATIENTS AT HIGHEST RISK SHOULD BE DECIDED AT THE NATIONAL LEVEL [WHO MODEL LIST, 2002]
Appendix B: Methodology used for drug list comparison

For ease and validity of comparison, the drug lists chosen for this analysis were:

- From English-speaking countries
- From developed countries
- Developed by a formal, transparent process that included a standard review of clinical evidence

The WHO core and complementary lists were also included as the pre-eminent example of an evidence-based essential medicines list. Below are descriptions of how the lists were accessed and, where appropriate, explanations for the choice of specific lists.

Australia


Ontario, Canada

Each province in Canada has a separate formulary for defining drug benefits for its citizens. The Ontario formulary was selected because it is explicitly evidence-based and because of recommendations by experts consulted for this project. [Levine M, Henry D, Private communications, 2003]


New Zealand


United Kingdom


Department of Veterans Affairs (VA)

The VA National Formulary was included because:

- The VA is the largest single purchaser of pharmaceuticals in the United States
- The National Formulary is evidence-based
The Formulary has recently been evaluated favorably by the Institute of Medicine. [Blumenthal D and Herdman R, 2000]

It was recommended as an example of an evidence-based formulary list within the United States by experts we consulted (Matchar D, Avorn J, Private communications, 2003).

The population covered by the VA comprises many people who are chronically ill or over the age of 65, and hence it is applicable to the Medicare population.


World Health Organization

We included the complimentary as well as the core essential medicines lists in the analysis. The complimentary list is said to “present essential medicines for priority diseases which are efficacious, safe and cost-effective but not necessarily affordable, or for which specialized health care facilities or services may needed.” [WHO, 2002] Drugs on this list were included as this approach was considered appropriate for a developed country.

The list has been amended to reflect changes made to anti-hypertensives decided upon at a recent committee meeting (April 2003). [Hogerzeil H, private communication, 2003]


Construction of the comparison matrix

A matrix was constructed – an example of which is given in Appendix A – to facilitate the lateral comparison of drugs on different lists. Efforts were made to develop a therapeutic classification that allowed for the listing of all unique agents on all lists. This classification closely resembles that used for several of the individual lists, but reflects a unique effort to account for the idiosyncrasies of the different lists.

In addition, for ease of comparison, the following decisions were made about listing drugs:

• Whenever possible, only the generic name was listed for a given agent.
• Separate preparations, routes of administration, and dosages were not included in the matrix.
• Whenever special restrictions, authorization processes, or differences in level of subsidy applied to specific agents, these were captured in the matrix. A legend at the bottom of the matrix defines these designations for individual lists.

Limitations to this approach

There may be further variation between the lists based on the different preparations and dosages available. The WHO Essential List, in particular, often lists only a single dose (for example, captopril scored tablet, 25 mg), whereas the other lists include multiple dosages and preparations for different agents in the same therapeutic class. It bears pointing out, however, that agents such as captopril are designated by the WHO only as examples of a therapeutic group that may be considered essential. The presumption is then that
countries will choose specific agents and dosages to make available, based on comparative cost and availability.

Despite its limited precision we feel that our approach is an adequate method for approximating the degree of consensus between different lists.