

Paper presented at the John Deutsch Institute Conference, “Health Services Restructuring: New Evidence and New Directions”, November 17-18, 2005 at Queen’s University. The final version is published in a book entitled *Health Services Restructuring: New Evidence and New Directions*, edited by C.M. Beach, R.C. Chaykowski, S. Shortt, F. St-Hilaire, and A. Sweetman, 2006 (Kingston: John Deutsch Institute, Queen’s University). Published in cooperation with McGill-Queen’s University Press and available at: <http://mqup.mcgill.ca> .

Effectiveness of Reference Drug Programs and Policy Implications

Sebastian Schneeweiss, MD, ScD

Nov. 21, 2005

Sebastian Schneeweiss MD, ScD, Associate Professor of Medicine and Epidemiology, Harvard Medical School, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120. Phone: (617) 278-0937, Fax: (617) 232-8602, E-mail: schneeweiss@post.harvard.edu

Abstract

In the current economic environment, health care systems are constantly struggling to contain rapidly rising costs. Drug costs are targeted by a wide variety of measures. Many jurisdictions have implemented reference drug programs (RDPs) and others are considering them. This paper summarizes the mechanism and rationale of RDPs and presents evidence of their economic effectiveness and clinical safety. RDPs for pharmaceutical reimbursement are based on the assumption that drugs within specific medication groups are therapeutically equivalent and clinically interchangeable and that a common reimbursement level can thus be established. If the evidence documents that a higher price for a given drug does not buy greater effectiveness or reduced toxicity, then the RDP does not cover the extra cost. RDPs or therapeutic substitutions based on therapeutic equivalence are seen as logical extensions of generic substitution based on bioequivalence of drugs. If the goal is to achieve full drug coverage for as many patients as possible in the most efficient manner, then RDPs in combination with prior authorization programs are safer and more effective than simplistic fiscal drug policies, including fixed co-payments, co-insurances, or deductibles. RDPs will reduce spending in the less innovative but largest market, while fully covering all patients. Prior authorization will ensure that patients with a specified indication will benefit from the most innovative therapies with full coverage. In practice, however, not all patients and drugs will fit exactly into one of the two categories. Therefore, a process of medically indicated exemptions that will consider full coverage should accompany an RDP.

A. CLINICAL AND ECONOMIC RATIONALE FOR REFERENCE DRUG PROGRAMS

A.1 Mechanism of RDPs

Drug-plan perspective

Patient perspective

A.2 Clinical rationale for RDPs: Therapeutic substitution

Therapeutic equivalence

Breadth of reference groups

A.3 Economic rationale for RDPs: Balanced incentives

Incentives and disincentives of RDPs

The economics of RDPs

RDPs in context of market-driven health care systems

Limits of RDPs and synergies with other drug cost-containment measures

B. SOME EMPIRICAL EVIDENCE OF THE EFFECTIVENESS OF RDPs

B.1 A metric of success

B.2 Evidence from British Columbia's RDP implementation

Drug utilization

Economic effectiveness

Unintended outcomes

B.3 Selected alternative strategies in other jurisdictions

Drug co-insurance in Quebec

Prescription drug limit in New Hampshire

Drug budgets in Germany

Three-tiered co-pay systems in the US

B.4 Evidence in light of Maclure's criteria

C. PRACTICAL IMPLICATIONS WHEN INTRODUCING AN RDP

C.1 Generation of evidence of therapeutic equivalence

C.2 Information technology

C.3 Information to physicians, pharmacists, and patients

C.4 Exemptions

C.5 Negative campaigns and how to respond

D. CONCLUSION

In the current economic environment, health care systems are constantly struggling to contain rapidly rising costs. Drug costs are targeted by a wide variety of measures. Many jurisdictions have implemented reference drug programs (RDPs), and others are considering them. This paper summarizes the mechanism and rationale of RDPs, presents evidence of their economic effectiveness and clinical safety, and concludes with the practical implications of an RDP policy that I implemented.

A. CLINICAL AND ECONOMIC RATIONALE FOR REFERENCE DRUG PROGRAMS

A.1 Mechanism of RDPs

Drug plan perspective: RDPs for pharmaceutical reimbursement are based on the assumption that certain medications within a drug group are clinically interchangeable and that a common reimbursement level can thus be established. If the evidence documents that a higher price for a given drug does not buy greater effectiveness or reduced toxicity, then the cost-conscious drug plan should not cover the extra cost. Thus, drug plans implementing RDPs will fully cover only the cost of the least expensive drugs in a therapeutically equivalent group of drugs by defining a maximum reimbursable amount called the reference price. Ideally, this approach can provide complete coverage for prescription drugs, while reducing expenditures and providing an incentive for pharmaceutical manufacturers to lower prices and further broadening patients' choices among fully covered drugs.¹

The term *reference price* has led to the widely used but confusing term *reference pricing*, which falsely suggests that RDPs are a pricing policy, whereas they are a reimbursement policy.

German sickness funds were the first large insurer groups implementing RDPs in the early 1990s; RDPs now cover about 60% of their prescription drug market. The German Federal Association of Sickness Funds determines reference prices on an annual basis using several low-cost representatives of therapeutically equivalent drugs and reference values to compare different active ingredients in a regression model.²

Drug plans tend to appreciate the financial predictability and scalability of RDPs:

- Savings within RDPs can easily be predicted because a fixed reimbursement limit is set for a group of drugs,³ and
- by lowering the reimbursement limit or expanding an RDP, drug plans can increase their savings.

Patient perspective: If a physician prescribes a drug that costs more than the allowed reference price for that group of drugs, the patient is required to pay the cost difference out-of-pocket or through secondary insurance. Ideally, this should lead to a discussion between patients and physicians about alternative drugs that are fully covered under an RDP, assuming that physicians are fully informed about RDPs and understand the evidence on therapeutic equivalence. In reality, patients often learn from their pharmacist that their co-payment has increased because of an RDP. Their pharmacists may advise patients about their options, and patients will ask their physicians to change their prescription to avoid a co-payment. As a plan shifts to an RDP, physician services will be temporarily increased due to switching patients' medications but ideally discontinuations will not increase.

RDPs are further perceived as fair to low-income patients because patients do not need to give a co-payment if they choose a therapeutically equivalent drug below the reference price.

A.2 Clinical rationale for RDPs: Therapeutic substitution

Reference Drug Programs (RDPs) for pharmaceutical reimbursement are based on the assumption that drugs within specific medication groups are therapeutically equivalent and clinically interchangeable and that a common reimbursement level can thus be established. If the evidence documents that a higher price for a given drug does not buy greater effectiveness or reduced toxicity, then the RDP does not cover the extra cost. RDPs or therapeutic substitutions based on therapeutic equivalence are seen as the logical extension of generic substitution based on the bioequivalence of drugs.

What is appealing about RDPs? If we assume an ideal world and that the above definition of an RDP can be fully implemented, then every beneficiary of that plan can receive the best available treatment with full coverage. While the assumptions of the system are complex, they are based on a clear logic and are therefore easy to explain to patients and implicitly guide prescribing according to medical evidence and price: Expensive medications can be substituted by fully covered drugs without any harm or loss of effectiveness. On the contrary, many less sophisticated measures of drug-cost containment such as fixed co-payments or proportional co-insurances do not guide patients and their physicians to less costly but equally effective drugs but leave them to define the “evidence” for the best alternative on their own over and over again. This may have serious unanticipated effects (see section B). Of course, the RDP world is not this simple.

Therapeutic equivalence: The effectiveness and safety of RDPs depend entirely on the ability to establish therapeutically equivalent reference groups. Therapeutic equivalence commonly refers to drug products that, when administered to the same person in the equivalent dosage regimen, provide essentially the same therapeutic effect or toxicity.⁴ The RDP in the Netherlands specified therapeutic equivalence as having the same therapeutic action, being used for the same range of indications, being equivalent in their undesirable effects, and being administered by the same route.

Therapeutic equivalence is best demonstrated in head-to-head randomized clinical trials (RCTs) that compare two or more active drugs regarding clinical outcomes in the population that most frequently uses the drugs. Unfortunately, manufacturers have no incentive to sponsor head-to-head trials as long as licensing agencies require placebo-controlled trials; thus most recent large-scale head-to-head comparisons have been government sponsored.^{5,6} Even rarer are studies that include populations that will be the greatest users of the drugs, i.e., elderly patients with multiple co-morbidities.

Secondary strategies to establish therapeutic efficacy are frequently used, including the indirect comparison of several active drugs through combining several placebo-controlled trials and adjusting for measured differences in the baseline characteristics of the trials.^{7,8} This pragmatic approach is susceptible to bias by unmeasured confounders when two RCTs based on different populations are compared.

Alternatively, evidence can be generated for specific target populations using large, linked administrative databases.⁹ AHRQ’s DEcIDE Network is using such pharmacoepidemiologic studies to produce comparative effectiveness research results.¹⁰ While such studies can make valid inferences regarding safety outcomes,¹¹ sophisticated techniques are necessary to adjust for confounding by indication when comparing the effectiveness of drugs.¹²

Simon et al.¹³ described specific principles for applying research evidence to formulary decisions. Similar criteria can be formulated to establish reference drug groups: (1) experimental data should take precedence over epidemiologic data and models; (2) morbidity or mortality

outcomes should take precedence over surrogate or intermediate outcomes; And (3) claims for advantages of new treatments should consider the full range of alternatives rather than those selected by industry.

A complicating factor is that decisions about therapeutic equivalence in RDPs have to be made soon after drugs are approved for marketing, whereas it can take many years for head-to-head trials to be conducted or for other, more indirect, evidence to be generated. Therefore, grouping of recently marketed drugs into reference groups must be temporary and should be revisited as more evidence becomes available. Such regular review of reference groups regarding new drugs, new evidence on older drugs, and new prices should be seen as required maintenance of RDP systems.

Breadth of reference groups: Decisions need to be made from the outset on how broadly or narrowly a group is to be defined, which can have substantial implications. A group can be as narrow as including only dihydropyridine calcium channel blockers and theoretically as broad as including all antihypertensives. A broad categorization has the economic advantage of including antihypertensives such as thiazides in a reference group with angiotensin-converting enzyme (ACE) inhibitors, adrenergic receptor binders, and calcium channel blockers, and the wide variation in their prices would result in larger drug-plan savings. The obvious limitation is that therapeutic equivalence among antihypertensives will be very difficult to establish, and, in fact, it is quite clear that many antihypertensives are not therapeutically equivalent. Therefore, an RDP policy would have to develop a set of exemption rules that could rapidly become as complex as hypertension treatment guidelines themselves, e.g., JNC7. This would reduce the simplicity of the RDP logic that is considered one of its major strengths.

On the contrary, reference groups that are very narrow will generate little medical controversy but, at the same time, will result in more limited economic advantages.

A.3 Economic rationale for RDPs: Balanced incentives

Incentives and disincentives of RDPs: RDPs have been called incentive pricing¹⁴ because they provide several incentives to direct prescribing and pricing in favor of the drug plan:

- 1) Patients have an incentive to request prescribed drugs that are fully covered under RDP,
- 2) Manufacturers have an incentive to lower the price of their products to the reference price, and
- 3) Manufacturers have an incentive to bring true innovations on the market because they can set a higher price for the new drug that will be fully covered until competitor drugs become available.

In addition to these incentives, there is a clear disincentive for manufacturers to lower prices below the reference price, diminishing the chances for a market place that is below the reference price. This is particularly an issue after RDPs have been in place for a long time and all drugs have lined up at the reference price. Germany had reached that point in the early 2000s. To solve the lack of market place, it further lowered the reference price so that some co-payment by the patient was required for all drugs unless the manufacturer soon reduced prices further.

Sometimes, policymakers weaken incentives in the process of negotiating with interest groups. In Germany, RDPs excluded all patented drugs from reference groups so that the full manufacturer's price was reimbursed even if it was above the reference price. This is contrary to the philosophy of RDPs and, of course, provided a strong incentive to produce, patent, and

market more drugs with no incremental effectiveness. The pressure increased to control rising expenditures, and this loophole was recently closed.

The economics of RDPs: When drug plans decide to implement RDPs for a specific drug class, the direct savings can easily be calculated as a function of the price variation within the reference group and the utilization of the respective drug in the group. Savings are largest if the highest priced drug within a group is also the most utilized drug, since the plan will pay only up to the (lower) reference price.

From the perspective of the drug market, the reduction in sales is a function of shifts in utilization and the manufacturer's price. If the incentive for patients to switch to a lower priced drug within a reference group is weak because the difference in price is small, many patients may decide not to switch but to pay the price difference out-of-pocket, and thus nothing will have changed from the manufacturers' perspective. It was suggested that, in such situations, manufacturers will cut their losses in the RDP market and lower their price to the reference price but increase the prices of products outside the RDP market. Such a response would eliminate or reduce cost savings for the drug plan, depending on the volume of the non-RDP market and the extent to which patients may substitute RDP drugs with those outside RDP.

From the perspective of a comprehensive health insurance system, the effects of RDPs on health care expenditures other than for drugs need to be considered. It can be argued that most implementations of RDP programs come with some upfront investment in the form of policy development costs and health services expenditures for switching patients. Maintenance costs for adapting evidence and reference prices of RDP programs must also be considered.

RDPs in context of market-driven health care systems: RDP programs are most prevalent in publicly funded health care systems that have no or minimal price negotiations, e.g., Germany, Canada, and the Netherlands.¹⁵ In market-driven health economies, bilateral price negotiations between the drug insurer and the manufacturer, often granted in the form of rebates, have a more important role in controlling the plan's spending.¹⁶ The magnitude of a rebate usually depends on the market power of the plan and the availability of alternative drugs and generics. In such health care markets, multi-tiered formularies are similar to RDPs.¹⁷ Typical three-tiered co-pay systems stagger the patient co-pay and require the lowest co-pay for generic drugs (tier 1), higher co-pays for preferred brand-name drugs, i.e., those with well-negotiated prices (tier 2), and the highest co-pays for non-preferred brand-name drugs (tier 3). This allows individual price negotiations and places drugs into lower co-pay categories depending on how much the manufacturer has lowered prices, which in turn will direct the utilization toward their lower-priced products. Like RDPs, multi-tier systems are based on the assumption of therapeutic equivalence within each drug group.

It is also important to distinguish between systems in which a publicly funded system is insuring drugs and health services together versus more segmented systems in which pharmaceutical benefit plans operate to maximize their own profits and would not consider substitution effects into health services, e.g. more physician visits.

Limits of RDPs and synergies with other drug cost-containment measures: In a system with the goal of achieving full drug coverage for as many patients as possible in the most efficient manner, the combination of RDPs with prior authorization programs is the most logical approach. RDPs will reduce spending in the less innovative but largest drug market while fully covering all patients; however, RDPs can penetrate only those markets with several therapeutically equivalent alternatives.

How can fully covered access to single-drug markets and true innovations be assured without overburdening plans with patients who do not require these drugs but would do just as well with a more-established (often safer) drug therapy? Prior authorization programs apply clinical treatment guidelines to ensure that patients with the correct indication will benefit from the most innovative therapies with full coverage while others will be referred to older drugs without compromising safety.^{18,19}

In practice, it must be acknowledged that not all patients and drugs fit into exactly one of the two categories. Therefore, an additional process of medically indicated exemptions from RDPs that considers full coverage should be implemented.

B. SOME EMPIRICAL EVIDENCE OF THE EFFECTIVENESS OF RDPs

Several overviews on current implementations of RDPs have been published and may add details to this summary.^{20,21,22}

B.1 A metric of success

To assess the effectiveness of RDPs, we need to define measures of success. An ideal drug policy from the perspective of insurers and patients will reduce net expenditures without reducing full access to appropriate drug therapy. It can be assumed that the interests of beneficiaries overlap with those of the plan since increased plan expenditures will lead to increased premiums or taxes, depending on the financing structure, which are not desirable to beneficiaries.

Within such a framework, it can be assumed from a medical perspective that plans want to offer therapeutically equivalent drugs that are fully covered. Plans would also be interested in expanding the use of drugs, e.g., statin therapy, if this would improve the health and/or quality of life of their beneficiaries and possibly reduce net health care spending in the future. There are realistic scenarios in which over-utilization of drugs or their utilization for less than optimal indications, e.g., untargeted over-utilization of antipsychotic medications in nursing homes,²³ will lead to plan spending that could be reduced without harming patients or that will even improve their health, e.g., the linkage of antipsychotics to excess mortality in elderly patients.²⁴ However, drug plans should generally be advised to not get involved in the very controversial business of deciding which drug therapy is inappropriate for specific patients.

Accepting that there will always be some inappropriate overuse of drugs and to instead focusing on avoiding underuse of important medications, a simple metric of success is money spent per daily dose. A successful implementation of an RDP would clearly reduce spending per daily dose and at the same time assure access to therapeutically equivalent drugs.

A comprehensive metric of economic success are net savings that include spending components outside the RDP or even the drug plan, i.e. substitution with drugs outside the RDP, use of other health services, and administrative costs.

B.2 Evidence from British Columbia's RDP implementation

The introduction of RDPs for five reference groups in British Columbia (BC) in 1995 and 1997 was expected to produce large savings and help contain the growing drug expenditures borne by the province's publicly funded program of drug benefits, Pharmacare. Over the last 10

years, drug expenditures per Pharmacare beneficiary have increased by 150%,²⁵ similar to international trends.^{26,27} Only in the two to three years during the active expansion of RDPs, 1995-1997, was the growth in Pharmacare's expenditures slowed. Extension of the policy was delayed by lobbying from drug manufacturers, competition from other policies for decisionmakers' attention, turnover of ministry decisionmakers, and electoral politics. Starting in 1998, the growth of Pharmacare's costs resumed its pre-policy rate of about 15% per year. The BC government initiated a public review of its RDP policy that concluded in a decision to keep and possibly expand RDPs,²⁸ similar to a report by the Canadian Auditor General in 2005 that suggested RDPs for Canada's national Pharmacare program.²⁹

There is greater evidence in support of the economic and clinical impact of BC's RDP policy than exists for any other drug insurance policy. Many different drug cost containment strategies have been tried and are currently implemented around the world.^{30,27} However, few have undergone rigorous evaluations of their consequences for health and net savings. The few policies outside of BC's that have been well evaluated, including a co-insurance policy in Quebec,³¹ prescription drug limits in New Hampshire,^{32,33} or delisting of un-scientific drug therapy,³⁴ have shown unanticipated effects that are summarized below.

The results of studies analyzing the BC experience can be summarized the following way:

Drug utilization: RDPs lead to substantial switching of 10% to 50% of current drug users to less costly, fully covered alternatives that resulted in a slight reduction in overall utilization in terms of dispensed daily doses.^{35,36,37,38} However, there appeared to be no increase in the rate of discontinuation of drug therapy or in a substantial substitution with more costly medications outside the RDP drugs.³⁵ An exemption process, which allows physicians to request exemptions from the policy for individual patients in frail health or who have special clinical needs, was used by 10% to 40% of patients³⁵ and appears to have lessened the resistance to implementing RDPs.³⁹

Economic effectiveness: RDPs resulted in moderate to large savings in drug expenditures depending on the reference group.^{35,36,37,38} For ACE inhibitors alone, the net health care savings in the first year were equivalent to 6% of all expenditures for cardiovascular drugs by Pharmacare.⁴⁰ Savings were largest in drug classes for which a frequently used drug was priced substantially above the average price of competitor drugs, e.g., enalapril or nitrate patches.³⁶ There was a modest transient implementation cost, as physicians monitored patients more closely after switching them from a high-priced to a reference drug.^{41,42} Considering multiple spending components, RDP produced sizable net savings mostly due to existing drug users switching drugs and increasingly to new users starting drugs priced below the reference price.⁴³

In contrast to the German experience with RDPs, drug prices RDP groups in BC did not decrease.⁴³ This may be a special case, since drug reimbursement in other, more populous, Canadian provinces is linked to the lowest price charged in any of the provinces. Manufacturers may have decided to lose market shares in the smaller province of BC rather than to lose revenues in the larger provinces.

Unintended outcomes: No severe negative effects that would have led to emergency hospital admissions, long-term care admissions, or death could be attributed to RDPs in BC.^{41,44}

An uncontrolled pre-post study in New Zealand investigated an RDP policy for statins that set the reference standard as fluvastatin, which left it the only fully reimbursable statin. Patient co-payments for an alternative statin were about NZ\$ 50 (US\$ 26) per month. In a group

of patients who switched therapy when the policy started, an increase was seen in serum lipid levels⁴⁵ and a borderline significant increase in risk of vascular complications was noted in the following six months.⁴⁶ However, besides the economic and psychosocial motivations of patients to pay the co-payment, many factors could have influenced their decision to switch or not switch to fluvastatin, including comorbidity, co-medications, and other co-payments, which were not considered in the analysis. Further, patients were likely to have been healthier on average in the preceding six months to have survived to the second six-month interval.⁴⁷

More research is needed to assess the effects of implementing RDPs on minor health outcomes and quality of life.

Although the thorough evaluation of the BC experience by three independent academic groups supports the economic benefits and clinical safety of RDPs, other analyses suggested that RDP savings were not sustained but were largest in the phase of active expansion.^{48,49} More intensive cost-containment will be needed as drug expenditures continue to escalate. One possible strategy would be to continuously expand RDP to other drug groups and further reduce reference prices.

B.3 Selected alternative strategies in other jurisdictions

Drug co-insurance in Quebec: Co-insurance policies require patients to share a proportional burden of the medication price, independent of medical necessity or means. This has been criticized for being unfair to many of the sicker patients who require more expensive medications. Therefore, most co-insurance policies now have annual deductibles for patient out-of-pocket payments, and patients are fully covered after such a deductible is reached.

A population-based time series study among seniors in Quebec by Tamblyn et al. found a 9% reduction in the use of essential prescription drugs after the introduction of a 25% co-insurance but also reported that adverse health outcomes more than doubled in elderly patients.⁵⁰ Such strong utilization effects were observed despite annual deductibles of \$200, \$500, or \$700 for prescription drugs, depending on the income bracket applied at the same time.

Some investigators have found that net savings due to greater cost sharing by patients are often less than anticipated because of unexpected increases in utilization of other medical services.⁵¹ One study of limiting reimbursement for psychotropic medications found that such policies led to a significant increase in outpatient visits, the use of other mental health services, and total health care costs. This study estimated that, among patients with schizophrenia, the increased health care expenditures due to limiting psychotropic medication reimbursement exceeded savings in costs of psychotropic drugs by a factor of 17.⁵²

Prescription drug limit in New Hampshire: Soumerai et al. investigated the effect of a program in the New Hampshire Medicaid program imposing a limit of three paid prescriptions per month and its replacement a year later by a \$1 co-payment.^{53,54} The limit of three-prescription cap caused a sudden, sustained drop of 30% in the number of prescriptions filled; no change was observed in the comparison state (New Jersey). Elderly recipients of multiple drugs were most severely affected, dropping their monthly drug use by 46%. When a \$1 co-payment replaced the three-prescription cap, prescriptions for most of the effective medications studied increased to just below the pre-cap levels. During the time the prescription drug limit was in place, the patients in New Hampshire were significantly more likely than those in New Jersey to be admitted to a nursing home or hospital.

Drug budgets in Germany: The cost-saving effects of RDP tapered off in 1993 as expenditures began to rise above pre-program rates.⁵⁵ Consequently, Germany added a plan of “physician drug budgets.” Drug expenditures for each of the 16 states were initially capped at the 1992 levels, with increases renegotiated between insurance funds and physician organizations every year. If drug expenditures increased beyond the budget caps, physicians would be required to repay the difference from the budget allotted for their incomes. The threat of such repayments, although never actually enforced, reduced drug expenditures in 1993 by about 11% and afterwards reduced the rate of increase of expenditures to the rate before RDP.^{27,56} The limits came with no educational support concerning cost-effective prescribing; many physicians exceeded their limits before the end of the quarterly budget periods and began to write “private prescriptions” not covered by insurance funds. Consequently, patients had to pay out-of-pocket for prescriptions until the following budget period started or were admitted to hospitals, which were not affected by the budget caps.⁵⁷ This approach was eventually terminated in October 2001 in response to physicians’ resistance and drug expenditures immediately surged by 13% to 14%.⁵⁸ While the German experience has not been evaluated rigorously, it seems to indicate that physician-based drug budgets can certainly control drug expenditures but, unlike RDPs, do not explicitly guide physicians to more cost-effective prescribing. This approach can possibly lead to under-utilization of needed drugs and unnecessary morbidity and related costs, although this has not yet been formally studied.

Three-tiered co-pay systems in the US: The evidence is mixed for common three-tiered co-pay systems. Motheral and Fairman found that, as compared with single- or two-tier plans, three-tiered co-pay systems had lower prescription utilization and expenditures and reduced net costs. Medication continuation rates were lower, at 6 and 11 months, in one of four classes of chronic therapy examined; however, discontinuation could not be clearly linked to the three-tier medication use. No significant differences in physician office visits, inpatient, or emergency room use rates were found.⁵⁹ Huskamp et al., in contrast, suggested that therapy discontinuation increases among chronic users of ACE inhibitors and lipid-lowering statins.⁶⁰ Although results of the latter study varied depending on the choice of reference group, the limited evidence suggests that the implementation of three-tier systems was not optimal, which may depend on any of the factors listed above, including lack of achievement of full therapeutic equivalence within a group, the implementations were not accompanied by sufficient information campaigns.

B.4 Evidence in light of Maclure’s criteria

Maclure described in his remarkable paper in *Milbanks Quarterly*⁶¹ how existing drug policy options can be displayed in few drug policy dimensions, including health and economic need, cost-effectiveness of drug, and details of administrative data. He concluded his paper with a prediction that “the best policies will be those that combine four types of information: (1) evidence of drug effectiveness, (2) relative prices for similar drugs, (3) individual patients’ health status, and (4) families’ financial need.” Given the current evidence, a carefully implemented RDP policy fulfills Maclure’s criteria 1 and 2 and indirectly, criteria 3 and 4. Criteria 3 and 4 are achieved through health-related exemptions to an RDP and because full coverage in an RDP is achieved independent of health status and financial need.

C. PRACTICAL IMPLICATIONS WHEN INTRODUCING RDPs

C.1 Generating evidence of therapeutic equivalence

As explained in detail above, the availability of robust evidence of therapeutic equivalence in reference groups is essential for RDPs. Consequently, generating and assembling this evidence must be done very carefully and, at the same time, needs to be done in a timely fashion to include new drugs and update evidence for existing ones. It is a common criticism that this process is not clearly described, and it is therefore suspected that no accepted guidelines are applied in establishing therapeutic equivalence. A well-defined and transparent process would benefit all parties involved, including patients who have the highest stakes in relying on the validity of therapeutic equivalence, but also manufacturers and physicians. Ideally, this evidence is created on a national or international level to avoid unnecessary replications and to make the pooling of the most qualified researchers more practical.

C.2 Information technology

RDPs require periodic updating of reference prices as well as the rebuilding of reference groups. The communication of such information to all pharmacies must be accurate and timely. Pharmacy computer networks, as they are already widely in use, are therefore a valuable infrastructure for implementing RDPs.

C.3 Information to physicians, pharmacists, and patients

Successful implementation of an RDP cannot be achieved without substantial information campaigns to physicians, pharmacists, and patients. Since RDPs are based on a logic that can combine reduced drug spending with full access to therapeutically equivalent drugs, it is critical that all involved groups understand that this is not just another fiscal cut by budget planners who may not understand clinical practice. Most patients who understand the concept of RDPs are favoring RDPs as compared with alternatives such as increased premiums, co-insurance, or deductibles.³⁹ Similar observations were made with general practitioners and family physicians in Canada, although a minority of physicians believed that all drugs should be fully covered independently of any fiscal constraints.⁶² Distributing correct and easy-to-understand information will also combat the anticipated negative campaigns (see below).

C.4 RDP exemptions for individual patients

A perfect RDP system would result in full therapeutic equivalence and not provide any reasons for a patient to be exempt from the policy of receiving full coverage for a higher priced drug. In reality, however, reference groups need to be defined with somewhat limited data and may therefore not be appropriate for every patient. In some cases, there may be special indications for a specific drug that otherwise fits very well into a reference group. Exemptions from an RDP for medical reasons are a flexible tool to react to true and perceived claims that a drug within a reference group may not be therapeutically equivalent for specific patients. Such exemptions seem to be a low price to pay to allow drug-plan decision makers to feel more comfortable in their responsibility and to convince physicians to fully participate in an RDP.

C.5 Negative campaigns and how to respond

The announcement of drug cost-containment policies that affect a large number of patients is often followed by massive criticism from a range of stakeholders. The announcement of BC's RDP program caused outcries by pharmaceutical industry and patient advocacy groups that were followed by advertisements in newspapers and television.³⁹ In addition to such measures, the German expansion of RDPs that lowered reference prices across the board and closed the loophole for patented but not innovative drugs resulted in a major lawsuit at the European Court.

Such activities can be anticipated and counter-measures should be part of an implementation plan. Such measures include a careful and transparent process of establishing reference groups; information campaigns among physicians, pharmacists, patients, and the media; temporary reimbursement for pharmacists and physicians for their time commitment to explain therapeutic substitution; announcement of a proactive evaluation by an independent group using rapid monitoring (weeks);⁶³ and thorough evaluations (years). Such one-time investments surrounding the implementation of an RDP can substantially increase its success. The lack of a comprehensive information campaign was considered partially responsible for the failure of the Norwegian RDP policy.

D. CONCLUSION

Drug markets can be divided into a small group of truly innovative drugs that includes no or only one therapeutically equivalent drug and a much larger group of drugs that includes several therapeutically equivalent competitors. If the goal is to achieve full drug coverage for as many patients as possible in the most efficient manner, then reference drug programs in combination with prior authorization programs are safer and more effective than simplistic fiscal drug policies, including fixed co-payments, co-insurances, and deductibles. RDPs will reduce spending in the less innovative but largest market, while fully covering all patients. Prior authorization will ensure that patients with a specified indication will benefit from the most innovative therapies with full coverage. In practice, it should be acknowledged that not all patients and drugs fit into exactly one of the two categories. Therefore, a process of medically indicated exemptions that will consider full coverage should accompany an RDP.

The primary goal of every drug cost containment policy must be to provide the best patient care given limited resources. Refining existing policies such as RDPs that have withstood rigorous evaluations of clinical and economic consequences rather than trying completely new policies with unknown risks could bring us closer to the goal of delivering such comprehensive and affordable care.

Glossary of selected key terms:

Bioequivalence: refers to chemical equivalents that, when administered to the same person in the same dosage regimen, result in equivalent concentrations of drug in blood and tissues.

Drug class: There is no universally accepted definition of what constitutes a class of drugs, and classification systems vary in their composition. The more similar drugs are in their chemical structure and clinical effects, the more likely they are to be grouped in one class.

Reference drug program (RDP): Under an RDP, drugs are clustered into *reference groups* of equivalent therapeutic effectiveness and reimbursed up to a common limit, the *reference price*.

Reference group: A cluster of drugs that are therapeutically equivalent. These reference groups may or may not be identical to drug classes identified by other classification systems.

Reference price: is the amount reimbursed by the drug plan under an RDP. It usually fully covers one or more drugs within a reference group.

Therapeutic equivalence: refers to drug products that, when administered to the same person in the equivalent dosage regimen, provide essentially the same therapeutic effect or toxicity.

Bioequivalent products are expected to be therapeutically equivalent.

Acknowledgements:

Dr. Schneeweiss was supported by grants from the U.S. Agency for Healthcare Research and Quality (2-RO1-HS10881) and the National Institute on Aging (1-RO1-AG021950), Department of Health and Human Services, Rockville, MD, USA.

I am thankful for the guidance I received from Drs. Maclure and Soumerai during the process of evaluating RDPs in British Columbia.

References

- ¹ Huskamp HA, Rosenthal MB, Frank RG, Newhouse JP: The Medicare prescription drug benefit: How will the game be played? *Health Affairs* 2000;19:8-23.
- ² Stargardt T, Schreyogg J, Busse, R. Pharmaceutical reference pricing in Germany: Definition of therapeutic groups price setting through regression procedure and effects. *Gesundheitswesen* 2005;67:469-78.
- ³ Dormuth C, Burnett S, Schneeweiss S. Predicting drug plan expenditure while planning reimbursement changes using policy simulation. *PharmacoEconomics* 2005;23:1021-30.
- ⁴ Drug Input And Disposition. In: Beers M, and Berkow R, Editors. *The Merck Manual of Diagnosis and Therapy*, Chapter 298. 17th edition. Merck & Co, Whitehouse Station, NJ, 1999.
- ⁵ The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
- ⁶ Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
- ⁷ Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326:1-5.
- ⁸ McAlister F, Laupacis A, Wells G, Sackett D. Users' guides to the medical literature: XIX. Applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class effect. *JAMA* 1999;282:1371-7.
- ⁹ Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-8.
- ¹⁰ Agency for Healthcare Quality and Research. DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network URL: <http://effectivehealthcare.ahrq.gov/decide/index.cfm>
- ¹¹ Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-37
- ¹² Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects in claims databases using physician-specific prescribing preferences as an instrumental variable. *Epidemiology*, 2005 in press.
- ¹³ Simon GE, Psaty BM, Hrachovec JB, Mora M. Principles for evidence-based drug formulary policy. *J Gen Intern Med* 2005;20:964-8.
- ¹⁴ Huskamp HA, Rosenthal MB, Frank RG, Newhouse JP: The Medicare prescription drug benefit: How will the game be played? *Health Affairs* 2000;19:8-23.
- ¹⁵ Ess S, Schneeweiss S, Szucs T. European healthcare policies for controlling drug expenditure. *PharmacoEconomics* 2003;21:89-103.
- ¹⁶ Goodell S, Hoadley J, O'Brien E Williams C. State Pharmacy Assistance Programs vs. Medicare Prescription Drug Plans: How Do They Contain Rising Costs? *Health Care Financing & Organization*, Washington, DC, 2005. URL:http://www.hcfo.net/pdf/issue_1005.pdf
- ¹⁷ Kanavos P, Reinhardt U. Reference pricing for drugs: is it compatible with U.S. health care? *Health Aff* 2003;22(3):16-30.

-
- ¹⁸ MacKinnon NJ, Kumar R. Prior authorization programs: a critical review of the literature. *Journal of Managed Care Pharmacy*. 2001; 7:297-302.
- ¹⁹ Fischer MA, Cheng H, Schneeweiss S, Avorn J, Solomon DH. Prior Authorization Policies for Selective Cyclooxygenase-2 Inhibitors in Medicaid: A Policy Review. *Medical Care* 2005, in press.
- ²⁰ Lo ´pez-Casasnovas G, Puig-Junoy J. Review of the literature on reference pricing. *Health Policy* 2000;54:87–123.
- ²¹ Giuliani G, Selke G, Garattini L. The German experience in reference pricing. *Health Policy* 1998;44:73–85.
- ²² Ioannides-Demos LL, Ibrahim JE, McNeil JJ. Reference-based pricing schemes - Effect on pharmaceutical expenditure, resource utilisation and health outcomes. *PharmacoEconomics* 2002;20:577-91.
- ²³ Gurwitz JH, Soumerai SB, Avorn J. Improving medication prescribing and utilization in the nursing home. *J Am Geriatr Soc* 1990;38:542-52.
- ²⁴ Wang PS, Schneeweiss S, Solomon DH, Brookhart AM. Mortality risk in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005 in press.
- ²⁵ Morgan S: Statistics and drug utilization: Are prescribing rates really that high? *CMAJ* 2001;165:1507-1508.
- ²⁶ Iglehart JK: Health Policy 2001: Medicare and prescription drugs. *N Engl. J Med* 2001;344:1010-1015.
- ²⁷ Ess SM, Schneeweiss S, Szucs TD: European healthcare policies for controlling drug expenditure: Is there anything to be learned? *Pharmacoeconomics* 2002, in press.
- ²⁸ Morfitt GL: Report to the reference drug program consultation panel. April 2002.
- ²⁹ Office of the Auditor General. Report of the Auditor General to the house of commons. Chapter 4, Management of federal drug benefit programs. Ottawa, November 2004.
- ³⁰ Dickson M, Poullier JP: Prescription reimbursement systems in selected European countries. In: Huttin C, Bosanquet N: The prescription drug market. Advanced series in management. North Holland, Amsterdam, 1992.
- ³¹ Tamblyn R, Laprise R, Hanley JA et al.: Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA* 2001;285:421-429.
- ³² Soumerai SB, Avorn J, Gortmaker S, Ross-Degnan D. Payment restrictions for prescription drugs in Medicaid: Effects on therapy, cost, and equity. *New Engl J Med* 1987; 317:550-556.
- ³³ Soumerai SB, Ross-Degnan D, Avorn J, McLaughlin TJ, Choodnovskiy I: Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes. *N Engl. J Med*. 1991;325:1072-1077.
- ³⁴ Soumerai SB, Ross-Degnan D, Gortmaker S, Avorn J: Withdrawing payment for nonscientific drug therapy. Intended and unexpected effects of a large-scale natural experiment. *JAMA* 1990;263:831-839.
- ³⁵ Schneeweiss S, Soumerai SB, Glynn RJ, Maclure M, Dormuth C, Walker AM: Impacts of reference pricing for ACE inhibitors on drug utilization. *J Can Med Assoc* 2002;166:737-748.
- ³⁶ Grootendorst PV, Dolovich LR, O’Brien BJ, Holbrook AM, Levy AR: Impact of reference-based pricing of nitrates on the use and costs of anti-anginal drugs. *Can Med Ass J* 2001;165:1011-1019.
- ³⁷ Marshall JK, Grootendorst PV, O’Brien BJ, Dolovich LR, Holbrook AM, Levy AR: Impact of reference-based pricing for histamine-2 receptor antagonists and restricted access for proton pump inhibitors in British Columbia. *Can Med Ass J* 2002;166:1655-1662.
- ³⁸ Grootendorst PV, Marshall JK, Holbrook AM, Dolovich LR, O'brien BJ, Levy AR. The impact of reference pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. *Health Serv Res* 2005;40:1297-317.

- ³⁹ Brunt JH, Chappell N, Maclure M, Cassels A. Assessing the effectiveness of government and industry media campaigns on seniors' perceptions of a Reference Based Pricing policy. *Journal App Gerontol* 1998;17:276-95.
- ⁴⁰ Schneeweiss S, Maclure M, Soumerai S: Reference drug pricing. *Can Med Ass J* 2002;167:126-127.
- ⁴¹ Schneeweiss S, Walker AM, Glynn RJ, Maclure M, Dormuth C, Soumerai SB: Outcomes of reference drug pricing for angiotensin-converting enzyme inhibitors in British Columbia. *N Engl J Med*, 2002;346:822-829.
- ⁴² Schneeweiss S, Maclure M, Soumerai SB: Prescription duration after drug copay changes in the Elderly: Methodological aspects. *J Am Geriatrics Soc* 2002;166:737-748.
- ⁴³ Schneeweiss S, Dormuth C, Grootendorst P, Soumerai S, Maclure M. Net health plan savings from reference drug pricing for angiotensin-converting enzyme inhibitors in elderly British Columbia residents. *Med Care* 2004;42:653-60.
- ⁴⁴ Hazlet TK, Blough DK: Health services utilization with reference drug pricing of histamine2 receptor antagonists in British Columbia elderly. *Medical Care* 2002;40:640-649.
- ⁴⁵ Thomas M, Mann J, Williams S: The impact of reference pricing on clinical lipid control. *NZ Med J* 1998;111:292-294.
- ⁴⁶ Thomas M, Mann J. Increased thrombotic vascular events after change of statin. *Lancet* 1998;352:1830-1.
- ⁴⁷ Weiss N, Heckbert SR: Thrombotic vascular events after change of statin (letter). *Lancet*, 1999;353:844.
- ⁴⁸ Morgan SG. Quantifying components of drug expenditure inflation: the British Columbia seniors' drug benefit plan. *Health Serv Res* 2002;37:1243-66.
- ⁴⁹ Pharmacare of British Columbia. *Pharmacare trends 2000*. BC Ministry of Health Services, Victoria, BC, 2001. URL: <http://www.moh.hnet.bc.ca/pharme/outgoing/PcareTrends2000.pdf>
- ⁵⁰ Tamblyn R, Laprise R, Hanley JA, Abrahamowicz M, Scott S, Mayo N, Hurley J, Grad R, Latimer E, Perreault R, McLeod P, Huang A, Laroche P, Mallet L: Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA* 2001;285:421-429.
- ⁵¹ Johnson RE, Goodman MJ, Hornbrook MC, Eldredge MB. The effect of increased prescription drug cost-sharing on medical care utilization and expenses of elderly health maintenance organization members. *Med Care* 1997;35:1119-1131.
- ⁵² Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P. Effects of limiting Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *N Engl J Med* 1994;331:650-5.
- ⁵³ Soumerai SB, Avorn J, Ross-Degnan D, Gortmaker S: Payment restrictions for prescription drugs in Medicaid: Effects on therapy, cost, and equity. *N Engl. J Med*. 1987;317:550-556.
- ⁵⁴ Soumerai SB, Ross-Degnan D, Avorn J, McLaughlin TJ, Choodnovskiy I: Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes. *N Engl. J Med*. 1991;325:1072-1077.
- ⁵⁵ Schneeweiss S, Schöffski O, Selke GW. What is Germany's experience on reference based drug pricing and the etiology of adverse health outcomes or substitution? *Health Policy* 1998;44(3):253-260.
- ⁵⁶ Schwabe U, Paffrath D: *Arzneimittelverordnungs-Report 2001*. Springer, Berlin, 2001.
- ⁵⁷ Schöffski O: Consequences of implementing a drug budget for office-based physicians in Germany. *Pharmacoconomics* 1996;10 Suppl.2:37-47.
- ⁵⁸ *Arzneien: Kräftiges Plus im Oktober. Ärzte Zeitung*, 07.12.2001.
- ⁵⁹ Motheral B, Fairman KA: Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care* 2001;39:1293-1304.

-
- ⁶⁰ Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Frank RG: The effect of incentive-based formularies on prescription-drug utilization and spending. *N Engl J Med* 2003;349(23):2224-2232.
- ⁶¹ Maclure M. Drug insurance utilization management policies and "reference pricing": an illustrated commentary on the article by Vittorio Maio and colleagues. *Milbank Q.* 2005;83:131-47.
- ⁶² Marshall B, Cassels A, Maclure M, Schneeweiss S: Physician attitudes to drug cost control measures in British Columbia. *Canadian Journal of Clinical Pharmacology* 2003;10:135.
- ⁶³ Dormuth C, Schneeweiss S. Rapid monitoring of adverse outcomes of drug reimbursement restrictions. *Pharmacoepidemiol Drug Safety* 2004;13:S310-S311.