Review Article

Reference Pricing for Generics: Unplanned Consequences of Planned Swiss Regulation

Zweifel P*

Department of Economics, Univeristy of Zurich, Switzerland

*Corresponding author: Zweifel Peter, Department of Economics, Univeristy of Zurich, Switzerland

Abstract

Reference pricing of pharmaceuticals became common during the 1980's in Europe as a response to ever-increasing Health Care Expenditure (HCE) and pharmaceutical expenditure in particular (see Lopez-Casasnovas and Puig-Junoy [1] for an early review including also Australia, British Columbia, and New Zealand). The most recent initiative is by the European Commission, who seeks to harmonize reference pricing between the member states of the European Union [2]. Although not a member of the European Union, Switzerland too has a reference pricing scheme, which its Federal Office for Health (FOH) seeks to modify for generics. Rather than using a copayment of 10 percent on low-cost and a 20 percent copayment on high-cost generics, the planned new scheme would set the benchmark at the 25th percentile of the price distribution and make patients pay out of pocket for the full excess of price over this benchmark in addition to a basic 10 percent copayment.

Keywords: Generics; Pricing; Consequences; Reference

Introduction

This paper, based on an expert report commissioned by Intergenerika, the Swiss association of manufacturers and importers of generics and biosimilars, purports to answer the question of whether this modification is apt to improve the performance of the Swiss healthcare system. It therefore adopts a much more comprehensive approach than e.g. Toumi et al. [2] who emphasize effects on HCE. Its starting point is the cost distribution associated with a treatment cycle using a drug that Intergenerika deems realistic for a certain health condition. (Table 1) exhibits the money cost only; the cost of administering the medication borne by patients will be added in (Table 2) below. In view of this generalization, a treatment cycle rather than the DDD (Daily Defined Dose) is used as the unit of reference because the DDD would have entailed time costs amounting to fractions of a minute.

Col. 1 of (Table 3) exhibits the cost of a cycle using the most widely prescribed branded drug, again according to Intergenerika. While originally expressed in Swiss francs (CHF), the figures entered are in $ for convenience because the 2014 exchange rates is close to 1:1. The net cost borne by patients is shown in col. 2, reflecting a copayment of 20 percent on high-cost drugs in Switzerland. For comparison, the financial treatment cost using a realistic number of generics available in the country is entered in col. 3. The status quo reference price is set at the average of the three cheapest medications available (a generic without exception) plus a 20 percent surcharge. For prices above that benchmark, copayment increases from 10 to 20 percent. Since this average value amounts to $ 350 per treatment cycle, the current benchmark equals $ 420. Accordingly, the first half of col. 3 exhibits rather low out-of-pocket costs for patients, whereas the second half, rather high ones (marked bold). Note that only short-term effects are considered at this point. Producers do not adjust their prices yet, and there is no innovation effort that could be undermined in the longer run.

The planned new scheme makes patients bear the full difference between the price of the generic and a modified reference price which probably will be fixed at the 25th percentile of the cost distribution. The right-hand side of (Table 1) reveals some unexpected consequences of this seemingly minor modification. The new reference price would be set according to the 25th percentile of the cost distribution shown in col. (3), amounting to $ 350. Thus, there is no change for the three cheapest generics (upper part of col. 7, in bold). However, from then on the new copayment rule applies, according to which patients would have to come up for the basic 10 percent copayment plus the full excess of the generic over the reference price. This causes their out-of-pocket cost of a treatment cycle to rise sharply.

Evidently, manufacturers of more expensive generics will face a drop in demand forcing them to lower price before long. Quite likely, this is the intention of the FOH as the regulator acting on behalf of policy makers who would like to see a dampening of the increase in HCE. However, as will be argued below, the planned new scheme has additional implications which include the behavior of the generics producers, prescribing physicians, their patients, and even modifications in the structure of the Swiss market for pharmaceuticals.

The price of the original drug and hence its cost for a treatment cycle is not part of the distribution of generic prices. However, the patented drug enters the determination of the three cheapest available drugs and their associated treatment cost and of the 25th percentile of the cost distribution, respectively.

From a social perspective, this raises the question of whether the planned new reference pricing scheme is apt to improve the performance of the Swiss healthcare system. Here, 'performance' is defined as the benefit-cost ratio for the insured, who (rather than health insurers, let alone politicians) bear the cost of healthcare through their taxes, fees, and insurance contributions. From the theory of economic policy, five criteria are common fort the assessment of an economy's

Table 1: Status quo and short-term effects of the planned new reference pricing scheme.

Status quo: staggered copayment					Plannednew scheme	
Cost of treatment cycle, branded drug	Copayment on branded drug	Cost of treatment cycle, generic	Average of three cheapest generics, + 20 %	Copayment on generic 10%, 20%	Reference price at 25th percentile	Copayment on generics, = 10% + excess over reference Price
(1)	(2) = 0.2· 1000	(3)	(4) = (300+350 +400)/3· 1.2	(5) = 0.1·(3) or 0.2·(3), respectively	(6)	(7) =0.1·(3) or = 0.1·350 + ((3)-(6))⎮ >0
1000	200	300	420	30	350	30
1000	200	350	420	35	350	35
1000	200	400	420	40	350	85
1000	200	420	420	42	350	105
1000	200	450	420	90	350	135
1000	200	490	420	98	350	175
1000	200	530	420	106	350	215
1000	200	---	1000*	---	---	---

Table 2: Marginal WTP for product attributes, financing through copayment[a].

Attribute	MWTP	Standard error Delta[4]	Standard error Bootstrap[5]	z value (Delta)
Constant	261.50	8.54	9.11	30.62
Hypopglycemia[1]	1.19	0.09	0.10	13.48
Weight[2]	25.15	1.90	2.19	13.23
Swing[3]	53.69	6.34	6.31	8.47
Flexibility[3]	31.04	6.29	6.37	4.94

[a]All values are in Euro per year; 1 Euro = 1.35 Swiss francs (CHF) at 2011 exhange rates; = 1.23 CHF at 2014 exchange rates
[1]Decrease of the risk of hypopglycemia by one percentage point
[2]Avoiding weight gain
[3]Dummy variable, status quo = 0, alternative = 1
[4]Standard errors calculated using the Delta method
[5]Standard errors using bootstrapping with 1,000 replications

performance [3]. In the following, these criteria are applied to the healthcare system. Such an application may be unusual for healthcare providers but can be justified by noting that HCE claims 12 percent (in the case of Switzerland) and close to 17 percent (in the case of the United States, respectively) of GDP, making the healthcare sector one of the most important of the economy.

In keeping with this approach, Section 2 is devoted to a description of the five performance criteria and their application to health care. In Section 3, the planned new pricing scheme is examined in the light of these five criteria. It may be worth pointing out already at this juncture that an exclusive focus on HCE would be too narrow. Nevertheless, the effects on HCE are discussed in depth because policy makers tend to argue with them almost to the exclusion of anything else. Section 4 contains a conclusion and final assessment.

Criteria for Assessing the Performance of an Economy (and its Healthcare Sector)

In the theory of economic policy, five criteria are commonly used for measuring the performance of an economy Fritsch et al. [3]. Some authors add an 'acceptable' income distribution as a sixth criterion; however, opinions are divided as to what constitutes 'acceptable'. Is it sufficient for the poorest members of society to have food, clothing, and housing, or must their share in total income be prevented from falling short of some lower bound? One could also argue that criterion No. 5, an income distribution ac-cording to merit, is acceptable at least for those able to work; for the remaining poor, welfare payments and subsidies are designed to guarantee them a sufficient income.

Criterion No. 1: Provision with goods and services according to preferences

An economy that fails to produce those goods and services that are desired by consumers cannot achieve good performance. Applied to the healthcare sector, the services provided need to match citizens' preferences. Evidently, these cannot be preferences expressed at 'last minute', e.g. right before a surgical intervention. Rather, consumers should be able to choose a health insurance policy that covers a set of medical services to a certain degree and at a certain premium; they make this choice almost always when healthy.

Criterion No. 2: Static efficiency

This criterion states that the goods and services demanded according to criterion No.1 should be available at the least possible cost. In the current health policy debate, this is almost always interpreted as meaning that available medical services need to be provided at less HCE. However, the set of available healthcare services is expanding fast. In this situation, the criterion should be reversed to state that for a given amount of HCE, the set of goods and services delivered should be as comprehensive as possible. Therefore, static efficiency calls for a favorable performance-cost ratio which may be attained at rather high HCE. Indeed, recent research [4] suggests that even in the United States, willingness to pay for reducing just the variance rather than the expected value of health status (to which medical care contributes) exceeds the marginal cost measured as an extra 10 percent of HCE by a factor of eight.

Criterion No. 3: Adaptability of production

An economy is continuously subject to changes in demand and supply (mainly as a consequence of technological change). Applied

to the healthcare sector, service providers and health insurers should respond speedily to new developments in demand (notable due to aging but also new health conditions) and supply (new medical technology, lower-cost alternatives of treatment).

Criterion No. 4: Dynamic efficiency

This is the requirement that criteria No. 1 through No. 33 need to be attained not only at a given point in time but over time as well. This is only possible without the 'right' mix of types of innovation, viz. product and process innovations. Product innovation creates new (combinations of) characteristics that meet with increased willingness to pay (WTP by consumers [5]. This transpires into a higher sales price, which in turn creates scope for higher wages, shortened hours of work, and fringe benefits. By way of contrast, process innovation (which often goes along with organizational restructuring) means 'the same product but at lower cost'. While resisted by the workforce, it is forced on producers in particular by international competition. In the healthcare sector, resistance by professionals is particularly marked whereas pressure from international competition is largely absent.

Criterion No. 5: Income distribution according to merit

This criterion (also known as the 'no rents' condition) is of crucial importance. In health care, physicians, pharmacists, hospitals, pharmaceutical companies, and insurers should not be able to reap incomes and profits beyond what is necessary to keep them in their activity. As long as they can achieve cartel and monopoly rents, they need not strive to satisfy criteria No. 1 through No. 4. For an (admittedly extreme) example, consider a physician who (1) does not care about the preferences of his or her patients, (2) makes no attempt to provide services at least cost, (3) adjusts neither to changed preferences of patients nor new therapeutic possibilities, and (4) pursues only product innovation while neglecting process innovation. As long as he or she continues to earn a 'decent' income, there is no pressure to satisfy the other four criteria of performance.

Contribution of the Planned New Reference Pricing Scheme to the Healthcare Sector Performance

In this section, the planned new reference price scheme for generics is held against the five criteria of performance just defined.

The planned new scheme and provision with goods and services according to consumer preferences

The new reference pricing scheme envisaged by the FOH is unlikely to contribute to an improved matching of healthcare services provided with preferences of the insured. While not restricting patient choice directly, it does subject patients to the full excess of the pharmacy price over the new, lower reference price. This will cause patients but also physicians, as found by Rischatsch et al. [6] to turn away from the hitherto preferred drug therapy (the beneficial effect on moral hazard will be discussed in Section 3.2.1 below). This would not entail a great welfare loss were it not for the fact that attributes that are typically judged unimportant by medical authorities have considerable utility value, as found by Sennhauser und Zweifel [7] in their study of WTP values associated with attributes of a new diabetes therapy (Table 2).

Their Discrete Choice Experiment (DCE) involved 1,100 members of German social health insurance in 2007. Participants had to repeatedly choose between the status quo therapy (human insulin NPH) and a (hypothetical) alternative. 602 of them were non-diabetics, 202, type 1 diabetics, and 306, type 2 diabetics. Within this latter group, 152 were insulin-naïve (i.e. did not have to use insulin), while 154 were insulin-dependent. Diabetics were over-represented because the DCE was designed to also measure preference heterogeneity. Both the status quo and the alternatives were represented by four attributes.

1. *Risk of hypoglycemia (Hypoglycemia in (Table 2))*: The frequency of this life-threatening condition is estimated at one to two times per week; given a time horizon of six months (see *Weight* attribute), the risk of at least one episode attains 100 percent. The new therapy examined (using an insulin analog) reduces this risk by 30 percent.

2. *Weight gain (Weight in (Table 2))*: This very much affects type 2 diabetics, 80 percent of whom suffer from excess weight. The status quo therapy typically adds another 2.5 kg within six months, whereas the insulin analog avoids a weight gain.

3. *Swinging*: This means that contrary to the status quo, the new preparation does not need to be swung (not shaken!) prior to injection in order to guarantee uniform dissolution and hence injection of the right amount of insulin.

4. *Flexibility* concerning the time of injection constitutes another benefit of the new therapy. In the status quo, NPH insulin reaches its maximum effect quickly, calling for a last daily injection around 10 PM. The insulin analog deploys its effect more slowly, permitting patients to inject it between dinner and bedtime (however, the timing should be regular).

In addition, the DCE contained two price attributes describing the mode of financing,

5. *Copayment* was zero for diabetes patients in the status quo since German social insurance fully covers the cost of human insulin NPH. The alternative calls for an out-of-pocket payment of Euro 226 ($ 283 at 2014 exchange rates) per year.

6. *Contribution*: Inclusion of the new preparation at the cost of Euro 226 per diabetic and year would cause an increase in the employee's annual contribution to social health insurance amounting to an estimated Euro 8.54 ($ 10.7), or 0.5 percent. Since employers pay part of the contribution, respondents were asked to look up their own share prior to the interview.

Probit estimation (=1: respondent prefers the alternative) with two-way random effects (taking into account that the same respondent chose several times, which induces autocorrelation in the residuals) resulted in estimates of contributions to utility and hence, WTP values. (Table 2) displays WTP values given that the mode of financing is *Copayment*; they differ little from those if financing is through *Contribution* except for the constant. Its value is an estimated Euro 261.50 ($ 270) for *Copayment* compared to Euro 161.75 ($ 202) for *Contribution* (not shown). Both estimates thus indicate a basic preference for the alternative, contrary to most DCEs which show so-called status quo bias. Not surprisingly however, when the mode of financing is through *Contribution*, making non-diabetics pay as well, this basic WTP is lower.

Table 3: Longer-run consequences of the planned new scheme, taking account of generic innovation.

Status quo					Planned new scheme		
Treatment cost per cycle, branded drug / Money only	Total net cost, 20% Co pay, branded drug	Treatment cost per cycle, generic, money only	Time cost, generic at $ 40/hr	Total net cost per cycle, generic, co pay 10%, 20%	Copayment on generics')	Total net cost, generic, reference price = $ 350	For comparison: Total short-run net cost
(1) = (1) from (Table 1)	(2) = 0.2· (1) + 480	(3) = (5) from (Table 1)	(4) = 400 - 0.25· 40 by type	(5) = (3) + (4)	(6) = 0.1· 350	(7) = 35 + (4)	(8) = (7) from Table 1 + (4)
1,000	680	30	480	510	35	515	510
1,000	680	35	470	505	35	505	505
1,000	680	40	460	500	35	495	545
1,000	680	42	450	492	35	485	555
1,000	680	90	440	530	35	475	575
1,000	680	98	430	528	35	465	605
1,000	680	106	420	526	35	455	635

In view of their *z* values, all attributes are highly significant. Starting with *Hypoglycemia*, the 30 percent reduction promised by the insulin analog is worth Euro 33.57 (= 30·1.19, $ 42) to respondents. However, avoidance of weight gain is almost as valuable, its WTP value amounting to Euro 25.15 ($ 31). Even more amazingly, no need to swing the preparation (*Swinging*) is also associated with a WTP of Euro 31.04 ($ 39), and the rather small gain in *Flexibility*, Euro 36.11 ($ 46).

These findings are of importance because generics often contain small, 'medically irrelevant' innovations. The generic Sumatriptan-Mepha may serve as an example. In Switzerland, it is sold in four formulations and two package sizes. In addition, it features six attributes that would be typically judged 'medically irrelevant' by an institution such as NICE (National Institute for Cost Effectiveness) in the United Kingdom. They are (1) a patient guide, (2) a leaflet providing diagnostic advice, (3) a 'headache pass', (4) an alcohol tampon, (5) instructions for use of the pen for injection, and (6) a sticker with a calendar facilitating regular injection. In contrast, only one package size, one formulation (50 mg blister tablets), and none of the six extra attributes are on offer in Denmark, which introduced a reference pricing system in 2001.

Since lowered reference prices evidently reduce the scope for financing minor innovations of this type, one is led to conclude that the planned new scheme runs the risk of suppressing them although they may meet with considerable WTP on the part of the insured and patients. It causes the provision with goods and services in Swiss health care to reflect consumer preferences to a lesser degree, thus infringing performance criterion No. 1.

The planned new scheme and static efficiency

Recall that static efficiency means a favorable ratio between goods and services provided and cost to consumers. Since healthcare services are largely financed through health insurance, this becomes the ratio between goods and services covered and contribution paid (or copayment at the time of utilization, respectively; the fact that the two are related is neglected here for simplicity; see e.g. Zweifel et al. [8], chs. 6.4 and 6.5).

The planned new scheme and drug expenditure: In the political debate, the effects of reference pricing on drug expenditure are of paramount interest. Indeed, reference prices amount to a variant of so-called indemnity insurance which is known to suppress moral hazard [8]. This can be illustrated by a simple example [9]. Let an insured be willing to pay a maximum of 50 $ out of pocket for treatment with a drug. Given the 20 percent rate of copayment applicable in Switzerland for a higher-priced preparation, it may cost as much as the equivalent of $ 250 at the pharmacy, and yet the insured will buy it. However, this scope for increasing price is rarely used in full even by producers of pa-tented drugs. A possible explanation is that they are aware that doing this would render an insurance-based healthcare system unsustainable [10]. For this reason, let the cost of the generic considered be $ 200 only for a treatment cycle. This amount would be out of reach for many consumers; however, thanks to insurance cover-age, the net out-of-pocket cost is a mere $ 20. Clearly, insurance coverage causes an expansion of demand known as moral hazard in insurance economics [11].

The importance of moral hazard depends on the own-price elasticity of demand. Estimates referring to an individual drug are rare; however, Tellis [12] comes up with a value of -1.6 for Europe. This needs to be distinguished from the aggregate own-price elasticity that relates the average price on the market to the overall demand for drugs. Santerre and Vernon [13] divide U.S. pharmaceutical expenditure by a price index to calculate a quantity indicator. The estimates of the aggregate own-price elasticity lie between -0.33 and -0.49 for patented drugs. Contoyannis et al. [14] regress nominal drug expenditure in Quebec on a price index to obtain values between -0.12 and -0.16. These can be transformed into own-price elasticity's by applying the formula, $(dA/A)(dp/p) = (1+e_{x,p})$, where $A := p.x(p)$ symbolizes drug expenditure, $x(p)$ quantity demand dependent on price, and $e_{x,p} := (dx/x)/dp/$ the own-price elasticity. Therefore, the implied values for Quebec lie between -1.12 and -1.16. They are comparatively high (in absolute value) because Canadian national health insurance acts as a purchaser who is strongly responsive to price.

Since the two short-term scenarios discussed below refer to a particular generic, the own-price elasticity of -1.6 estimated by Tellis [12] is applied below (there are no pertinent estimates for Switzerland).

However, Santerre und Vernon [13] also present estimates of cross-price elasticities. In the case of physician services and drugs, they arrive at values between 0.45 and 0.56, indicating substitutability (patients respond to higher physician fees by using more drugs). Since patented drugs and generics are even closer substitutes, one is led to conclude that a decrease of generics prices brought about by the planned new scheme will boost the demand for the more expensive branded drugs (within a substance category).

Should the FOH as the regulator introduce the new reference pricing scheme for generics as planned, there are two possible scenarios in terms of drug expenditure (effects on cost per case treated will be examined in Sections 3.22 and 3.2.3 below).

Regulator neglects own-price elasticity of demand: The FOH is dominated by medical professionals who tend to think of medical care as a need. Neglect of moral hazard effects would lead it to set reference prices as low as possible, e.g. by setting the benchmark even lower than at the 25th percentile of the cost distribution. Let this price be so low as to result in a cost of $ 150 per treatment cycle when using a generic, much less than the $ 350 shown in (Table 1) above. This price is assumed to still cover the cost of production and marketing for the time being (this assumption will be relaxed in Section 3.5 below). Therefore, at least one variety of the drug is available at the cost of $ 150, whereas the insured were using the cheapest generic (say) at a treatment cost of $ 300 (see col. 3 of (Table 1) again). For them, the out-of-pocket cost therefore drops by 50 percent. Due to, $e_{x,p} = $ -1.6 this particular generic manufacturer sees its quantity sold increase by 80 percent and its sales revenue, by 20 percent, applying the formula $(dA/A)(dp/p) = (1+e_{x,p})$, above.

The generic firm charging a price leading to $ 400 per treatment cycle (say) may try to maintain its price, which was below the previous benchmark of $ 420, thus making patients pay $ 40 out of pocket (see cols. 3, 4, and 5 of (Table 1)). At the new reference price of $ 150, however, the out-of –pocket cost increases to $ 265 (10 percent of 150 + excess of 400 over 150). This is a 563 percent hike which drives sales to zero given that the own-price elasticity is -1.6.

This example suggests that a price resulting in treatment cost of $ 150 cannot be maintained. While the example is overly simple, Zweifel and Crivelli [10] used a Cournot duopoly model to derive the reference price as the dominant solution even for producers of patented drugs. They studied the impact of the German reference pricing scheme introduced in 1989 (which differs from the Swiss one only by the fact that there was a zero rather than 10 percent copayment up to the reference price). The authors' predictions were confirmed by several case studies. A more recent study by Appelt [15] revolves specifically about the market for generics in Germany. For the period 2002 to 2007, after a 2000 reform that encouraged health insurers to negotiate pharmaceutical prices, its author exhibits a significantly negative relationship between the relative deviation from the reference price and the value of the initial price. In addition, this relationship is particularly marked in the lowest price category while

fading in the top categories, suggesting that low-price manufacturers raised their prices toward the reference benchmark.

However, if prices converge to the reference price in the longer run, the boost to sales calculated above is only transitory since the ceteris paribus clause is no longer valid. When the average price in the market falls, the insured have little reason to change their medication, resulting in lowered price elasticity. In this case, an estimate may apply (see Santerre and Vernon [13] cited above). In the example of (Table 1), the (unweighted) average cost per treatment cycle is $ 420; therefore, a price reduction to $ 350 or 17 percent, respectively (reflecting the reference price) causes quantity sold in-crease by some 7 percent. Expenditure on generics does decrease somewhat, by 11 percent since. Small effects of this type may explain why Norway discontinued its reference pricing systems after eight years only; the savings turned out to be insufficient in comparison with the administrative expense for running the scheme [16]. This indicates a failure to reach the policy objective of significantly reducing or at least stabilizing pharmaceutical expenditure and through this, contributions to social health insurance.

Regulator takes own-price elasticity into account: Conceivably, the FOH is aware of moral hazard effects, causing it to avoid too low a reference price. For illustration, let the new reference price be $ 350 (Table 1) - to the disappointment of all those who hoped for a marked drop in prices of generics. Also, let all producers accept this price, in keeping with Zweifel and Crivelli [10] and Appelt [15]. In this event, the price reduction of 17 percent is associated with a quantity increase of 7 percent and in an expenditure decrease of 11 percent, as in scenario A. Effects of this magnitude correspond to past experience. In their survey of 22 European countries, Dylst et al. [16] found that the introduction of reference pricing, while forcing producers to lower their prices to the benchmark value, was associated with an increase of consumption. In Belgium for instance, the utilization of the generic Esomeprazol soared from 0.1 mn. to 1.27 mn. DDD within two years. As to drug expenditure, it did drop in Germany and the Netherlands for a short period only to resume its growth again.

The planned new scheme and its effects on the cost of ambulatory care: The fact that a more stringent reference pricing scheme may reduce pharmaceutical expenditure does not imply that expenditure on ambulatory care is reduced as well (see Section 3.2.3 on the effects on the cost of hospital care). The reason is the behavior of pre-scribing physicians who (at least in Switzerland) seem to respond to financial incentives. This is a finding by Rischatsch et al. [6], who selected the three widely prescribed generics, Omeprazole, Amlodipine, and Ciprofloxacine for their study. Econometric estimates suggest that during the period 2005 to 2007, physicians were up to three times more likely to prescribe Omeprazole und Amlodipine than the original patented drug, *ceteris paribus*. The likely reason is that their margins (including price concessions) on generics are higher than on patented drugs (in most cantons of Switzerland, physicians may sell drugs on their own account). While the probability differential cited above does not apply to all physicians sampled in the case of Ciprofloxacine, it does apply to the important subgroup of general practitioners.

The planned new scheme is certain to put pressure on the margins that generics manufacturers can offer physicians prescribing on their

own account, who will tend to avoid the effort involved in convincing patents of the bio-equivalence of the generic and the original preparation. This effort is especially important when (as shown in Section 3.2.1) attributes beyond the purely medical are relevant for patients. In sum, prescribing physicians are predicted to revert to patented (and more expensive drugs) on the long run.

One might argue that Rischatsch et al. [6] only show that financial incentives matter to physicians dispensing drugs on their own account,. Yet even physicians working in U.S. Health Maintenance Organizations (HMOs), where financial incentives of this type are absent, frequently abstain from generic substitution when treating older (and hence likely sicker) patients [17]. More generally, a study by Reich et al. [18] finds that the risk of counter-indicated treatment increases when physicians are under pressure to keep within a budget. Their examination of the records some 50,000 German patients aged 65 and older leads the authors to conclude that 22 percent fail to receive the appropriate drug therapy when the criteria of Beers [19] and Holt et al. [20] are applied. All of these patients had a Managed Care-type insurance policy; the authors deem a similar share of inappropriate treatment as unlikely in a conventional fee-for-service setting. This finding is of relevance in the present context be-cause according to Rischatsch et al. [6], Swiss physicians prescribe the three generics selected with a 40 to 100 percent higher probability if their patient has a HMO-type policy, compared to the conventional fee-for-service policy. Therefore, at least in the Managed Care segment (which by now accounts for a market share in excess of 50 percent in Switzerland), the planned new scheme runs the risk of not only hurting the health of older patients but also result in higher cost of ambulatory care.

Recall that physicians who lack the right to dispense drugs on their own account have a reduced incentive to prescribe generics to begin with. But according to Rischatsch et al. [6], his incentive is further weakened when patients are exposed to the higher copayments that would be caused (at least in the short term, see Section 3.2.1) by the planned new scheme. Their findings suggest that Swiss physicians also care about the financial burden their treatment decisions place on patients. Indeed, patients with an insurance policy subjecting them to a higher deductible were twice as likely to receive a generic ceteris paribus as those subject to the mandatory minimum deductible. This leads to the prediction that prescribing physicians who do not dispense on their own account will also revert to the more expensive branded preparations if the new scheme should be enacted.

The estimates of own-price elasticity and research cited give rise to the expectation that the new planned scheme will increase the volume of drug prescriptions, which according to Zweifel [21] was associated with a reduced cost of ambulatory care per case treated, at least when controlling for income-generating ambulatory care technology at the disposal of physicians represented by the presence of a laboratory, and an x-ray facility, and the right to dispense drugs on their own account. However, an increased volume of prescriptions goes along with a higher cost of pharmaceutical treatment. In particular, 1 CHF of extra drugs dispensed on own account was associated with an increase in 1.30 CHF in total cost per ambulatory case because more lab, x-ray, and counseling services were billed as well (the impact on the propensity of hospitalization is discussed in Section 3.2.3 below).

All these findings are based on physician billings submitted to a health insurer during 1976-1978; unfortunately, to the best knowledge of the author, no more Swiss research of a comparable degree of detail has come forth since. For the time being, one is therefore led to suspect that the new planned scheme for generics has the potential of causing an increase in the cost per patient receiving ambulatory care.

At this juncture, it is appropriate to focus on the long-run consequences of the planned new scheme. In (Table 2), a complete convergence of generics prices leading to the benchmark amount of $ 350 per treatment cycle is assumed. The increase of the lowest-priced generics to this benchmark [15] in the case of Germany) can be explained by the fact that a reference price serves as a coordinating signal. Each producer can count on his competitors approaching this benchmark, thus lowering the risk of being exposed to strong price competition. In addition, when focusing on long-run effects, it is appropriate to also examine the role of them in or innovations characterizing generics. For simplicity, these 'medically irrelevant' attributes are summarized in a reduction in the time needed for administering the drug. Let treatment using the patented drug call for 12 hours of patient time per cycle, valued at $ 40 per hour (this roughly corresponds to the average Swiss wage as an indicator of opportunity cost). The cheapest generic is assumed not to contain any innovation, whereas the next expensive saves patients a quarter of an hour per treatment cycle. Thus, the most expensive generic engenders time cost amounting to $ 420 ($= 12 \cdot 40 - 6 \cdot 0.25 \cdot 40$) (see col. 5 of (Table 3)).

According to col. 1 of (Table 3), patients who use the original drug bear net cost (including their cost of time) amounting to $ 680 ($= 0.2 \cdot 1000 + 480$) per treatment cycle. Evidently, the cost advantage of generics over branded rugs shrinks when time costs enter the picture. While the cost ratio of the cheapest generic is 0.15 ($=30/200$) in (Table 1) (see cols. 1 and 5), it is 0.75 ($=510/680$ in (Table 3) (see cols. 2 and 5). However, in the status quo lower-priced generics at least benefit from their continuously increasing advantage in terms of time saved; for the last one still subject to 10 percent copayment only, the cost ratio drops to 0.72 ($= 492/680$). From then on, the 20 percent copayment currently applies, causing the most expensive generic to exhibit a cost ratio of 0.77 ($= 526/680$) relative to the branded alternative.

When the reference price is set at the 25th percentile of the generics cost distribution, the out-of-pocket cost of a treatment cycle becomes $ 35 ($= 0.1 \cdot 350$, see col. 6 of (Table 3)) for all generics since their manufacturers accept the new reference price resulting in gross cost of $ 350. The cheapest generic now engenders net total cost amounting to $ 515 ($=35 + 480$), see col. 7; from this maximum, it decreases to attain $ 445, associated with the most expensive generic. This is not the case under the status quo (see col. 8). Favoring the manufacturer of the most expensive generic presumably is not the intention of the FOH.

Admittedly, these statements are valid only to the extent that patients on the longer run are able to impose the pharmaceutical treatment with the minimum net cost. Yet this is rather likely in the light of the finding by Rischatsch et al. [6] that Swiss prescribing physicians consider the financial consequences of therapies for their patients.

The planned new scheme and the cost of hospital treatment: While much utilization of drugs occurs in ambulatory care, focusing narrowly on the cost impact in ambulatory practice would be justified only if hospitalization were a decision governed by medical concerns only. But a study by Hefner [22] already suggested otherwise. In its quest to lower pharmaceutical expenditure in Medicaid, the government of Louisiana had issued a rather restrictive formulary. However, rather than checking whether a preparation was reimbursable, treating physicians simply referred borderline cases to the hospital. Apparently they deemed the opportunity cost of verification excessive, causing them to devote their time to the diagnosis and treatment of other (possibly more lucrative) patients. Since hospital stays were costly relative to ambulatory care al-ready at that time, the state of Louisiana ended up spending more rather than less on Medicaid.

Due to cultural similarities, experiences made in Germany are of particular relevance to Switzerland. Effective 2003, German social health insurers and pharmaceutical firms negotiate reductions on the list prices of drugs. While this is not the same as reference prices mandated by a regulator, the consequences for prescribing physicians are similar. They must make effort to convince their patients to change in favor of a drug with a reduced price. Kostev et al. [23] studied 3,600 female patients who were treated for mammal carcinoma initially using Tamoxifen. Between January 2008 and December 2011, 47 percent of them were made to accept treatment with a bioequivalent preparation (possibly another branded drug rather than a generic) whose manufacturer offered a price reduction. One year after the change, 44 percent of patients had discontinued treatment with the new therapy, compared to 34 percent without a change; after three years, the values were 52 and 46 percent, respectively (both differences significant at the 1 percent level). These findings are *ceteris paribus* to the extent that initial diagnosis, adverse drug reactions, and demographic characteristics were controlled. Although the authors did not examine the risk of hospitalization, it is likely to increase due to discontinuation of drug therapy. This consideration is important because the new scheme envisaged by the Swiss FOH is likely to induce changes in drug therapy, as argued in Section 3.5.2 above.

Hospitalization can also be the result of counter-indicated drug therapy, which is estimated to have increased by up to 88 percent in Germany over the years 2008-2012 by Reich et al. [18]. This estimate is *ceteris paribus* to the extent that age, gender, and cost of treatment in the preceding year are controlled for. The maximum value of 88 percent refers to patients with particularly high cost during the preceding year; in addition how-ever, the risk of hospitalization increases markedly with the number of prescribed drugs (including changes of therapy). Therefore, the new scheme planned by the FOH may also cause an increase in the cost of hospital treatment.

The planned new scheme and indirect costs: Illness causes not only direct costs of treatment but also indirect costs, which comprise the value of (1) life years lost due to premature death, (2) lost workdays lost due to short-term disability, (3) workdays lost due to chronic illness, and (4) time of family members and friends spent on care. Problems of measurement limit the analysis to components (1) to (3) at best [24]. Their report uses 1998 data to estimate these three components of indirect cost and to compare it to the direct cost.

For diseases affecting muscles and skeleton, its Figure 3-1 exhibits a maximum ratio of 5.6: 1 (= Can\$ 8.9 bn. / 1.6 bn.), followed by cancer with 5.1:1 (= Can\$ 7.6 bn. /1.5 bn.). The indirect costs of illness may therefore exceed the direct ones by multiples.

In the case of Coronary Heart Disease (CHD), Health Canada [24] also documents changes from 1993 and 1998. During this period, indirect costs decreased from about Can\$ 13.2 bn. to 11.7 bn. whereas direct costs fell from Can\$ 7.9 bn. to 6.8 bn. Yet costs that can be attributed to CHD are shown for the year 1998 only (Figure 3-1 of the report), amounting to Can\$ 4.5 bn. (direct) und Can\$ 7.5 bn.(indirect), respectively. These values presumably are underestimates; if however the errors are of the same relative importance, their ratio might be approximately correct. Under this assumption, the ratio of indirect to direct cost for CHD was 1.13 (= 13.2/7.9) but in 1998, 1.72 (= 7.5/4.5). This indicates that the saving in direct cost in the treatment of CHD (the drop from Can\$ 7.9 to 4.5 cited above) came at the price of a more than proportional increase in indirect cost. With drug expenditure accounting for 26 percent of treatment cost (a share that is higher than for other diseases), it is likely that savings were sought here as well (the changes between 1993 and 1998 are not documented by expenditure category). This also means that expenditure on generics for the treatment of CHD are not known, precluding an estimate of their contribution to the reduction of its indirect cost.

Smith und Waycaster [25] use more recent data for estimating the direct and indirect costs of bacterial conjunctivitis in the United States. Direct costs amounted to \$ 491 mn. Since mainly children are affected, the authors limit themselves to component (4) of indirect cost. Estimating the time spent by parents accompanying their children to physician visits at two hours and valuing it at \$ 17 per hour, they obtain a (very conservative) value of \$ 97mn. Therefore, the ratio of indirect to direct cost amounts to 1:5 (=97/491), way below the values of 1.13:1 and 1.72 for CHD in Canada found above. In their conclusion, the authors remark that more effective antibiotics such as fourth-generation Fluoroquinolones might increase this ratio, without however quantifying parents' time saved or addressing the question of whether the branded product could be substituted by a generic.

In sum, while a minor change in the choice of therapy induced by the planned new scheme may cause a substantial increase in (or relief from) indirect cost burdening the economy, available information precludes a prediction as to the direction and magnitude of such an effect.

The planned new scheme and adaptability of provision

Applied to the healthcare sector, adaptability requires that the performance criteria No. 1 (provision with healthcare services in accordance with consumer preferences) and No. 2 (favorable cost-benefit ratio of provision) are sustained in the face of changes in the economic environment. These changes are new therapies, but also organizational innovation (e.g. Managed Care). This section is devoted to the question of whether the new reference pricing scheme for generics planned by the FOH is apt to contribute to a better attainment of criterion No. 3 (Adaptability of provision).

The point of departure is the observation that branded drugs often contain a breakthrough innovation, featuring a characteristic

that was not hitherto available. Ideally, they make the treatment of a disease possible for which there was no therapy before. However, break through innovations require several years of research and development, which is not conducive to rapid adjustment in the 'production of health'. Conversely, generics become available shortly after patent expiration. Through their lower price, they generate savings for health insurers (and hence society in general), thus freeing resources that can be used elsewhere (e.g., adding innovative patented drugs to the benefit list). In the United States as in Switzerland, these savings are reflected in lowered premiums for Managed Care-type policies that favor the use of generics. However, as shown in Section 3.1, generics also have innovative properties that are valued by potential as well as current patients, adding to their WTP.

Thus, there is a trade-off between slow adjustment (in return for major therapeutic advances) and rapid adjustment (in return for minor advances). The planned reference pricing scheme causes a shift in this trade-off towards slower adjustment in return for major advances because it puts pressure on the profit margins of especially the manufacturers of higher-priced generics who are constrained to accept the reference price. These manufacturers had incorporated minor innovations in their drugs, enabling them to achieve a higher sales price. Faced with a uniform reference price and reduced profit margins, they will not be able to pursue this strategy in the long run. Therefore, a high degree of adaptability in small steps turns into adaptability with no advances, whereas a lower degree of adaptability with major advances is favored since branded drugs are exempt from the envisaged change in reference pricing.

A DCE performed in 2003 suggests that such a shift would not be in accordance with preferences of Swiss consumers. The 1,000 participants were asked to choose between the status quo (a health insurance contract granting access to fee-for-service care) and a Managed Care-type alternative. One attribute of the alternative was a delay of two years in access to new therapies (which comprised not only breakthrough innovations). The choices indicate that such a Managed Care-type policy would be accepted only in return for a premium reduction amounting to 24 percent of the nationwide average premium at the time [26], indicating that the Swiss are interested in a high degree of adaptability. In addition, the DCE provides an answer to the question of whether they would be willing to subscribe to a policy that reimbursed generics only (or the lowest-priced alternative available on the market, respectively). On average, no compensation was demanded for this restriction, including by respondents who had been in hospital in the course of the past 12 months. Admittedly, these findings are based on hypothetical choices. Yet in view of the fact that observed costs and prices in health care are heavily distorted by a multitude of regulations, they do provide some second-best evidence. It indicates that impeding minor but quickly available pharmaceutical innovation would not be in accordance with the preferences of Swiss citizens.

The planned new scheme and dynamic efficiency

Dynamic efficiency (Performance criterion No. 4) calls for the appropriate mix of product innovation and process innovation. By bestowing new attributes on goods and services, product innovation boosts WTP of consumers, while process innovation serves to lower the cost of production of goods and services with unchanged

attributes. There are at least two reasons why the balance between the two is biased in favor of product innovation in the case of health care. One is health insurance which makes that differences in the price of drugs are hardly reflected in the net cost of drug therapies (Table 3). It may even by lower for the more expensive drug provided its use is sufficiently time-saving, boosting demand for it. The second reason lies in the fact that Swiss social health insurers are bound to the principle of domestic purchasing, which serves to relieve the country's healthcare providers from the pressure of international competition.

In the past, generic manufacturers corrected this distortion in the mix of the two types of innovation somewhat in favor of process innovation. Increasingly however, they have at-tempted to enhance WTP of patients by adding minor innovations to their preparations (see Section 3.1 above). One is therefore led to concede that the planned new scheme would force them to revert to their original mission, which is to concentrate on process innovation (the fact that it would reduce the number of generic manufacturers in the long run is addressed in Section 3.5).

The planned new scheme and income distribution according to merit

Falling sales prices cause exits from the industry affected because some firms cannot recover their costs anymore. If the cause is shrinking demand, this signals to producers that they should turn to a different business. In this case, exit constitutes a painful but necessary adjustment to changed market conditions. This needs to be distinguished from exits caused by a new reference pricing scheme designed to put pressure on the prices of generics. They do not reflect changes in demand but are a long-run side effect of public policy.

The comparison between Denmark and Switzerland with respect to the generic Sumatriptan-Mepha cited in Section 3.1 is instructive. On the Danish market there is only one manufacturer left selling one package size and one formulation. While the consequences for the matching of consumer preferences have been expounded in Section 3.1, emphasis here is on the fact that this producer enjoys a monopoly. Indeed, Danzon und Furukawa [27] find a statistically significant reduction in the number of generic firms between 2006 and 2009 in the United Kingdom, Germany, Italy, Spain, and Japan. Surprisingly, these are five out of ten countries examined where market access for generics had been facilitated in or around the year 2000. Only in Canada and Mexico do the authors observe a slight increase (which moreover is statistically significant at the 10 percent level only). Of particular interest is their finding that in six of the ten countries (among them, Germany again), the number of manufacturers of non-branded generics decreased significantly. The fact that Germany belongs to both groups probably is due to its Act of 2003 (which introduced the negotiations for price reductions mentioned in Section 3.2.2) and it's Act of 2006 (which stepped up pressure to engage in these negotiations). The decrease in profit margins apparently caused some firms who had created a brand by investing in minor innovations to exit from the market. Conversely, the two laws favored those generic firms who had been focusing on lowering their cost through product innovation. Since according to Intergenerika branded generics dominate the Swiss market, the study by Danzon und Fukinawa [27] leads to the prediction that the planned new reference pricing scheme will result in a reduced number

of generics manufacturers. However, a small number of competitors facilitate cartelization (and with it, collusion with respect to price).

Hirshleifer J et al. [28] Clearly, monopolies and cartels are not compatible with an income distribution according to merit. They generate rents which permit producers to neglect the other four performance criteria. Pressure to provide generics in accordance with consumers' preferences (criterion No. 1) is reduced, as is pressure to provide them at least cost (criterion No. 2), to adapt without much delay to changes in demand and technology (criterion No. 3), and to undertake not only product but also process innovation (criterion No. 4). Even if the number of producers should not fall, any reference pricing scheme fosters cartelization because competitors now have the same interest, namely economic survival in spite of squeezed profit margins. They tend not only to invest in increased lobbying with the objective of relaxing regulatory constraints but also in exchange of information designed to circumvent them. As a byproduct, they can easily reach an understanding about fixing prices and allocating market shares in an attempt to slow or even avoid convergence to the reference price. In this way, the planned new scheme contributes to further violation of performance criterion No. 5 in the Swiss healthcare.

Admittedly, that there are many other factors contributing to a violation of criterion No. 5. Swiss healthcare providers generally enjoy rents since access to their market is blocked. Admission to the study of medicine is restricted by numerous clauses, foreign physicians are blocked from opening up a private practice, founding a new hospital is near impossible due to public hospital planning, entering the pharmacy market is hampered by a lack of demand in cantons where physicians can dispense drugs on their own account, and health insurers are prohibited from purchasing pharmaceuticals and medical services abroad. One might be tempted to say that an additional, comparatively minor violation of the criterion of income distribution according to merit would not matter much. The opposite is true: When the status quo that is far away from target, one should avoid every move in the wrong direction lest one act like a management granting an increase in wages when the firm is already deep in the red.

Conclusion

The theory of economic policy proposes five criteria for assessing the performance of an economic system, (1) Provision of goods and services in accordance with consumer preferences, (2) Static efficiency, (3) Adaptability, (4) Dynamic efficiency, and (5) Income distribution according to merit. The last criterion (also known as the 'no rents' condition) is of particular importance because its violation undermines the attainment of the other four performance criteria. These five criteria are used to judge whether a new reference pricing scheme planned by the Swiss Federal Office of Health (FOH) is apt to contribute to the performance of the Swiss healthcare sector.

The analysis undertaken shows that preferences of the insured would be served less well because the scheme will push generics with minor but valued innovations out of the market. However, the political debate revolves almost exclusively about static efficiency, i.e. a reduction of healthcare expenditure and hence contributions to social health insurance. Due to the high own-price elasticity of

the demand for a particular drug, the short-run response would be a massive expansion of sales by the first generic manufacturer who accepts a substantially lower new reference price. In order to avoid this effect, the FOH would have to opt for a scheme that results in rather moderate price reductions. In addition, it would have to take the behavior of prescribing physicians into account. Those who have the right to dispense drugs on their own account will respond to the lower mar-gins offered by generic manufacturers by reverting to more expensive branded drugs with comparable therapeutic properties. Physicians lacking this right will react in a similar way; their effort designed to convince patients of the equivalence of the generic does not result in much of a saving for their patients anymore since the planned new scheme diminishes the net cost advantage of generics relative to branded drugs. These predictions follow from research suggesting that in their choice of drug therapy, Swiss prescribing physicians generally take the financial consequences for their patients into account.

Because hospitalization is also governed not only by medical concerns but by incentives impinging on physicians, the planned new scheme is likely to increase the cost of inpatient care. Physicians dispensing drugs on their account will respond to reduced margins on generics by referring more borderline cases to the hospital. The same effect is to be expected due to an increase in changes of drug therapy induced by the scheme, judging from recent German experience. However, hospital expenditure is still a component of direct cost of illness which is often dwarfed by indirect cost (caused by workdays lost in particular). Modifications in medical decision-making induced by the new scheme envisaged by the FOH therefore run the risk of generating a massive burden on the Swiss economy.

Beyond static efficiency, the impact of the planned new scheme on the adaptability of the healthcare system is of importance. Here, breakthrough innovations thanks to patented drugs which are the fruit of years of research and development compete with minor, readily available innovations featured by generics, which however are also valued by the insured and patients. The scheme is likely to reduce adaptability by suppressing minor but readily available generic innovation, a move that (according to experimental evidence) is in contradiction with consumer preferences. As to dynamic efficiency, the point of departure is that in health care the balance between cost-increasing product and cost-reducing process innovation is distorted in favor of product innovation. It must be con-ceded that the planned new reference pricing scheme would force generic manufacturers to turn away from minor product innovations and to concentrate again on their original mission, i.e. to introduce process innovations. In this way, it would contribute (in a comparatively small part of the Swiss healthcare sector) to an improved balance between the two types of innovation.

Finally, the paper seeks to shed light on the crucial criterion of income distribution ac-cording to merit (the 'no rents' condition). The long-run reduction in the number of generic firms caused by the planned new scheme may end up in a monopoly for a therapeutic category, as the Danish experience demonstrates. At the very least, it facilitates cartelization, moving the Swiss healthcare system still farther away from attainment of performance criterion No. 5. In addition, cartels and monopolies create leeway for rents which permit

producers to heed consumer preferences to a lesser degree (criterion No. 1), reduce their efforts designed to keep cost low (criterion No. 2), delay adjustment to changes in demand and technological possibilities (criterion No. 3, and neglect cost-reducing process innovation (criterion No. 4).

In sum, the new scheme for reference pricing of generics envisaged by the Swiss FOH is very likely to result in a reduced attainment of four out of five performance criteria. It may improve the balance between product and process innovation in a subsector of limited importance. The overall conclusion is the planned new scheme would undermine the performance of the Swiss healthcare sector and with it the competitiveness of the en-tire Swiss economy.

Acknowledgment

References

1. Lopez-Casasnovas G, Puig-Junoy J. Review of the literature on reference pricing. Health Policy. 2000; 54: 187-123.

2. Toumi M, Remuzat C, Vataire A-L, Urbihati D. External Reference Pricing for Medicinal Products: Simulation-based Considerations for Cross-country Coordination. Brussels: European Commission. 2015.

3. Fritsch M, Wein T, Ewers HJ. Marktversagen and Wirtschaftspolitik. Mikrookonomische Grundlagen staatlichen Handelns (Market Failure and Economic Policy. Microeconomic Foundations of Government Activity), 2007.

4. Schoder J, Zweifel P. Flat-of-the-curve medicine: a new perspective on the production of health. Health Econ Rev. 2011; 1: 2.

5. Lancaster KJ. A New Approach to Consumer Theory, in: Journal of Political Economy. 1966; 74: 132-157.

6. Rischatsch M, Trottmann M, Zweifel P. Generic substitution, financial interests, and imperfect agency. Int J Health Care Finance Econ. 2013; 13: 115-138.

7. Sennhauser M, Zweifel P. Ist ein neues Arzneimittel sein Geld wert? Wessen Geld? Bewertung eines neuen Diabetes-Praparats mit Hilfe eines Discrete-Choice-Experiments (Is a New Pharmaceutical Worth the Money? Who's Money? Valuation of a New Diabetes Preparation Using a Discrete Choice Experiment), in: Pharmaco Economics German Research Articles. 2014.

8. Zweifel P, Breyer F, Kifmann M. Health Economics. New York: Springer. 2011.

9. Comanor WS, Schweizer SO. Determinants of Drug Prices and Expenditure, in: Managerial and Decision Economics. 2007; 28: 357-370.

10. Zweifel P, Crivelli L. Price Regulation of Drugs: Lessons from Germany, in: Journal of Regulatory Economics. 1996; 10: 257-274.

11. Zweifel P, Eisen R. Insurance Economics. New York: Springer. 2012.

12. Tellis GJ. The Price Elasticity of Selective Drugs: A Meta-Analysis of Economic Models of Sales, in: Journal of Marketing Research XXV (Nov.). 1988; 331- 341.

13. Santerre RE, Vernon JA. Assessing Consumer Gains from a Drug Price Control Policy in the US, in: Southern Economic Journal. 2006; 73: 233-245.

14. Contoyannis P, Hurley J, Grootendorst P, Jeon S, Tamblin R. Estimating the Price Elasticity of Expenditure for Precription Drugs in the Presence of Non-linear Price Schedules: An Illustration for Quebec, Canada, in: Health Economics. 2005; 14: 903-923.

15. Appelt S. Generic Market Share Dynamics post Patent Expiry: Gauging the Impact of Generic Price Differentials. Munich: Munich University, Graduate School of Economics. 2010.

16. Dylst P, Vulto A, Simoens S. The impact of reference-pricing systems in Europe: a literature review and case studies. Expert Rev Pharmacoecon Outcomes Res. 2011; 11: 729-737.

17. Hellstrom J, Rudholm N. Uncertainty in the Generic versus Brand Name Prescription, in: Empirical Economics. 2010; 38: 503-521.

18. Reich O, Rosemann T, Rapold R, Blozik E, Senn O. Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization. PLoS One. 2014; 9: e105425.

19. Stockl KM, Le L, Zhang S, Harada AS. Clinical and economic outcomes associated with potentially inappropriate prescribing in the elderly. Am J Manag Care. 2010; 16: 1-10.

20. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010; 107: 543-551.

21. Zweifel P. Drugs, physicians, and hospitalization. Adv Health Econ Health Serv Res. 1984; 5: 311-337.

22. Hefner DL. A Study to Determine the Cost-effectiveness of a Restrictive Formulary: The Louisiana Experience. Washington DC: National Pharmaceutical Council. 1979.

23. Kostev K, May U, Hog D, Eisel J, Kremmers T, Kosteic M, et al. Adherence in Tamoxifen Therapy After Conversion to a Rebate Pharmaceutical in Breast Cancer Patients in Germany, in: Journal of Clinical Pharmacology. 2013.

24. Health Canada, Economic Burden of Illness in Canada, 1998 (Catalogue No. H21-136/1998E. Ottawa: Public Works and Government Services Canada. 2002.

25. Smith AF, Waycaster C. Estimate of the direct and indirect annual cost of bacterial conjunctivitis in the United States. BMC Ophthalmol. 2009; 9: 13.

26. Zweifel P, Telser H, Vaterlaus S. Consumer Resistance against Regulation: The Case of Health Care, in: Journal of Regulatory Economics. 2006; 29: 319-332.

27. Danzon PM, Furukawa MF, Danzon PM, Nicholson S. Cross-national Evidence on Generic Pharmaceuticals: Pharmacy *vs.* Physician-driven Markets, The Oxford Handbook of the Economics of the Pharmaceutical Industry. New York: Ox-ford University Press. 2011.

28. Hirshleifer J, Glazer A, Hirshleifer D. Price Theory and Applications. Decisions, Markets, and Information, Cambridge MA: Cambridge University Press. 2005.