EXPERT REVIEWS

Societal value of generic medicines beyond cost-saving through reduced prices

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Objective: This paper aims to provide an overview of the added societal value of generic medicines beyond their cost-saving potential through reduced prices. In addition, an observational case study will document the impact of generic entry on access to pharmacotherapy in The Netherlands and an illustrative exercise was carried out to highlight the budget impact of generic entry. Methods: A narrative literature review was carried out to explore the impact of generic medicines on access to pharmacotherapy, innovation and medication adherence. Data from the Medicines and Medical Devices Information Project database in The Netherlands were used for the case study in which the impact of generic medicine entrance on the budget and the number of users was calculated as an illustrative exercise. Results: Generic medicines have an additional societal value beyond their cost-saving potential through reduced prices. Generic medicines increase access to pharmacotherapy, provide a stimulus for innovation by both originator companies and generic companies and, under the right circumstances, have a positive impact on medication adherence. Conclusion: Generic medicines offer more to society than just their cost-saving potential through reduced prices. As such, governments must not focus only on the prices of generic medicines as this will threaten their long-term sustainability. Governments must therefore act appropriately and implement a coherent set of policies to increase the use of generic medicines.

KEYWORDS: access • adherence • generic medicines • innovation • value

In current times of financial and economic hardship, many European governments have accommodated generic medicines as a means to contain increasing pharmaceutical expenditures [1]. Generic medicines are substitutes for originator medicines with the same quality, safety, and efficacy and whose bioequivalence has been demonstrated by appropriate bioavailability studies [2]. Generic medicines offer equally high-quality treatment at lower costs, as prices of generic medicines in Europe tend to be 20–80% lower than those of their originator equivalent counterparts [3–5], although these can be as low as 2–4% of the prices before patent expiry in some countries [6–9]. Many European governments have therefore adopted policies to increase the use of generic medicines, which can be situated at both the supply side (i.e., policies related to market access, pricing and reimbursement of generic medicines) and the demand side (i.e., incentives for physicians, pharmacists and patients to prescribe, dispense or ask for generic medicines) [1,10,11]. Several countries have achieved substantial savings on their pharmaceutical expenditures through generic medicines, as extensively documented in the literature [6–9,12–17]. However, a viable and sustainable generic medicines industry contributes more to society than only an opportunity to contain pharmaceutical expenditures through reduced prices. From a health perspective, generic medicines might also have an important impact on access to pharmacotherapy, innovation and potentially also to medication adherence.

This paper aims to provide an overview of the added societal value of generic medicines, other than their potential for cost-savings through reduced prices. To this effect, a narrative literature review has been carried out to explore the impact of generic medicines on access to pharmacotherapy, innovation and medication adherence. In addition, an

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Table 1. Additional budget impact in the case of no generic entry.

Active substance	Year of generic entry	Cumulative additional budget impact from year of generic entry until 2013			
		Scenario 1: cost/DDD of originator 1 year before generic entry	*Scenario 2: cost/DDD −25%*	*Scenario 3: cost/DDD −50%*	*Scenario 4: cost/DDD originator 2013*
Omeprazole	2002	€3.723.211.200	€2.485.790.959	€1.248.370.718	€278.914.203
Simvastatin	2003	€3.113.110.854	€2.169,515.868	€1.225.920.882	€92.847.327
Amlodipine	2004	€512.592.561	€323.948.636	€135.304.712	€-24.349.674
Lisinopril	2002	€203.481.074	€114.016.890	€24.552.707	€-26.982.167
Perindopril	2006	€248.644.918	€146.424.076	€44.203.234	€38.472.526
Clopidogrel	2009	€171.295.644	€105.403.600	€39.511.556	€-55.096.848
Ramipril	2004	€83.560.214	€50.247.347	€16.934.480	€-34.800.651
Temozolomide	2010	€22.118.058	€11.812.928	€1.507.798	€12.980.117
Alendronic acid	2005	€260.027.874	€154.482.802	€48.937.731	€23.532.389
Esomeprazole	2010	€117.128.314	€37.499.26	€-42.129.778	€31.724.186
Pantoprazole	2009	€628.212.327	€417.912.301	€207.612.275	€43.677.412
Fluvastatin	2008	€13.06.634	€5.172.827	€-2.718.980	€-2.097.061
Felodipine	2003	€10.784.844	€2.979.650	€-4.825.454	€14.032.246
Quinapril	2004	€42.530.801	€21.471.360	€411.919	€-8.657.306

Four different scenarios are calculated in which the cost/DDD of the originator medicine remained at the level of 1 year before generic entry, decreased by 25%, decreased by 50% or decreased to the level of the cost/DDD of the originator medicine in 2013. The data shown in the table are the cumulative additional budget impact for the Dutch government from the year of generic entry until 2013 for the respective scenario.
DDD: Defined daily doses.

observational case study was used to describe the impact of generic entry on access to pharmacotherapy in The Netherlands and an illustrative exercise was carried out to depict the impact of generic entry on both the budget and the number of users in The Netherlands.

Methodology

Literature review

A narrative literature review was carried out to explore the impact of generic medicines on access to pharmacotherapy, innovation and medication adherence. The following databases were searched: Pubmed and Embase. The search strategy was developed using combinations of different terms relevant to the subject. The following search terms were used: generic medicines; generic drugs; generics; adherence; patient adherence; compliance; generic substitution; innovation; innovativeness; patient access; access; pharmacotherapy; and therapy.

Studies could be published in English, French or Dutch. Additional articles were identified by a review of the reference lists of articles and articles known to the authors.

Case study

Data source

Data were derived from the Medicines and Medical Devices Information Project (GIP) database in The Netherlands. The National Health Care Institute systematically collects data on the developments of the use of medicines and medical devices in outpatient care in their GIP database. Data are collected from 23 health insurance companies, who had a nationwide coverage of around 97% in 2012. The data from the health insurance companies are subsequently incremented by the GIP to obtain a nationwide picture, thereby taking into account the differences in age structure and gender between the different health insurance companies and their market share.

The variables delivered in the extracted dataset were the name of the active substance, the Anatomical Therapeutic Chemical-code, the counting defined daily doses (DDD, index 2013 [18]), the total costs and the total number of users, each time split up between the originator medicine and the generic versions. The concept of DDD is used because it enhances the comparability between different drugs and drug classes, especially where there are differences in pack sizes and available tablet strengths [19,20].

Selection of medicines

A total of 14 active substances were selected for the analysis (Table 1). The active substances were selected so that different therapeutic areas were covered and that the generic versions of the active substances entered the market between 2002 and 2012 in order to have data of at least 2 years before and after the generic entry. The selected medicines were omeprazole (A02BC01), pantoprazole (A02BC02), esomeprazole

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(A02BC05), clopidogrel (B01AC04), amlodipine (C08CA01), felodipine (C08CA02), lisinopril (C09AA03), perindopril (C09AA05), ramipril (C09AA05), quinapril (C09AA06), simvastatin (C10AA01), fluvastatin (C10AA04), temozolomide (L01AX03) and alendronic acid (M05BA04).

Calculation of budget impact

An illustrative exercise was carried out to calculate the budget impact if no generic versions of the 14 selected active substances would have entered the market. For this exercise, it was assumed that the number of counting DDD would have evolved in the same way as it has actually evolved with the entry of generic medicines. Four different scenarios of potential budget impact were calculated: one in which the cost/DDD of the originator medicine would remain at the level of the year prior to generic entry; one in which the cost/DDD of the originator medicine would be 25% lower; one in which the cost/DDD of the originator medicine would be 50% lower; and one where the cost/DDD of the originator medicine at the year of generic entry would be at the level of the cost/DDD of the originator medicine in 2013.

For each selected active substance, the cost/DDD of the originator medicine was calculated by dividing total costs by the number of counting DDDs in the year before generic entry. This cost/DDD of the originator medicine was then multiplied by the number of counting DDD for each year. The cumulative budget impact was then estimated by calculating the difference between the calculated total costs and the actual costs and this for the entire period between generic entry and 2013.

Calculation of impact on the number of users

An illustrative exercise was carried out to calculate the impact on the number of users if no generic versions of the 14 selected active substances would have entered the market. For this exercise, it was assumed that the total costs (i.e., budget) would have evolved in the same way as they have actually evolved with the entry of generic medicines. The average cost per user for the originator medicine was calculated in the year prior to generic (i.e., dividing total costs by total users). Assuming that the average cost per user would have remained constant, the number of users that could have been accommodated with the budget of 2013 was subsequently calculated (i.e., dividing total costs in 2013 by average cost/user of year prior to generic entry).

Results

Impact on access to pharmacotherapy

Generic medicines play an essential role in treating diseases. They not only increase the affordability of modern day pharmaceuticals, their reduced prices also increase access to pharmacotherapy [21]. For instance, a recent study, which analyzed the availability of essential medicines around the globe, highlighted the important contribution of generic medicines to an increased availability of essential medicines. Worldwide, the availability of essential medicines was found to be more than non-essential medicines. The median availability of essential medicines was 61.5%, of which a substantial contribution was made by generic medicines (53.3%) [22]. Since 2001, the average price of treatment for seven therapeutic areas in Europe where generic medicines are available has declined >60%, whereas the number of treatment days where a generic medicine is used has increased >200%. In the end, the total cost of treatment for governments remained even but substantially more patients were treated. In 2013, for instance, of the 82 million patients receiving treatment for hypertension in the EU, 48 million were treated by a generic medicine (i.e., 59%) [23].

The availability of generic medicines is also likely to increase access to pharmacotherapy for certain medicines of which the reduced prices of generic medicines are expected to improve the cost–effectiveness of existing pharmacotherapy, thereby introducing these medicines earlier in the treatment algorithm. This was the case for atorvastatin, for instance, of which generic equivalents entered the market in European member states in 2012. A literature review, which examined the cost–effectiveness of atorvastatin in cardiovascular diseases, demonstrated that generic atorvastatin is cost-effective compared to simvastatin for a number of indications (i.e., in primary and secondary prevention of cardiovascular disease, secondary prevention of coronary heart disease, patients at low cardiovascular risk, and patients with acute coronary syndrome). The cost–effectiveness of generic atorvastatin is influenced by the price difference between branded and generic atorvastatin, on whether the comparator is a generic or branded statin, and on the size of the required reduction in the low-density lipoprotein cholesterol level [24].

In addition to improving the cost–effectiveness of existing pharmacotherapy, the entry of generic medicines may also make it cost-effective to manage previously untreated patients. The entry of lower-priced generic medicines, for instance, would make statin therapy cost-effective for a wider range of individuals with annual risks of major vascular events well below those previously recognized in the clinical treatment guidelines [25,26].

The entry of generic medicines at lower prices might also lead to a more optimal treatment of some diseases. For instance, there is evidence in the literature that ductal closure of preterm infants benefits from a higher dose of the orphan medicine ibuprofen administrated earlier in life. At present, physicians are hesitant to prescribe this higher dose because of the high price of the non-generic orphan medication [27].

Impact on innovation

Innovation is essential for the generic medicines industry, as today's innovative medicines give rise to tomorrow's generic medicines and all generic medicines can trace their origins back to originator medicines [28]. A robust generic medicines market is generally understood to have a positive impact on innovation in the pharmaceutical sector [28]. Entry of generic medicines generates competition, which is essential for inducing

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innovation by originator companies [21,29]. This competition is usually accompanied by a reduction of prices of medicines and a reduction of the market shares of originator medicine. As such, originator companies' turn-over on the respective originator medicines decreases substantially, providing a stimulus for originator companies to bring new, (innovative) medicines to the market in order to sustain their business model [30]. In turn, savings on the pharmaceutical budget generated by generic medicines can be used to accommodate the introduction of innovative, more expensive medicines while containing costs [21,28].

Generic medicines not only provide a stimulus for originator companies to innovate, they also encourage generic companies to innovate in order to differentiate themselves in this highly competitive market, for instance, by addressing the needs of patients and pharmacists [21,31]. These companies try to create a market advantage through the creation of another type of 'added value'. This type of innovativeness by generic companies becomes evident in, for instance, packaging specifically designed to help patients and minimize pharmacy dispensing errors, packaging to reduce wasting, smart packaging to support medication adherence, production of combinations of routinely co-prescribed off-patent medicines to aid patient compliance, development of novel drug delivery systems, development of devices to facilitate administration of medicines, etc. This topic is, however, poorly documented in the literature but confirmed by practicing hospital pharmacists.

Impact on medication adherence

By concentrating on the needs of patients and pharmacists, the different types of innovativeness of generic medicines might have a positive impact on medication adherence. However, the reduced prices of generic medicines might also have their impact on medication adherence. High out-of-pocket costs for medicines are one of the best documented barriers to medication adherence [32]. Previous research has shown that increased co-payments are associated with a decrease of both first-fill adherence [33] and re-fill adherence of medicines [34–44]. As such, a reduction of co-payments has a positive effect on medication adherence.

Generic medicines, which generally benefit from lower prices and co-payments than their originator equivalents, might subsequently have a positive impact on medication adherence [44–53]. In the USA, where 3-tiered plans are instituted, generic medicines generally have the lowest co-payment, followed by preferred branded medicines and non-preferred branded medicines which have the highest co-payment. Both Shrank *et al.* and Briesacher *et al.* showed that initiation of therapy with generic medicines versus preferred medicines or non-preferred medicines increased medication adherence [45,46]. Two case studies by Simoens *et al.* in a Belgian hospital setting demonstrated an improved patient medication adherence to statin therapy following a switch to generic statins [44]. Also in Italy, where a reference pricing system applies to off-patent medicines, an increased medication adherence for patients treated with generic medicines versus off-patent originator medicines was observed after 34 months of observation [47]. In The Netherlands, generic substitution of antihypertensive drugs did not lead to lower medication adherence between 1999 and 2002. Instead, medication adherence increased from 81.3% for patients who stayed on the originator medicine to 86.4% for patients who switched to generic medicines [48]. Nevertheless, The Netherlands might be a special case as there is no co-payment on medicines.

However, generic medicines might also have a negative effect on medication adherence, especially in relation to generic substitution. Generic substitution allows pharmacists to dispense a generic medicine containing the same active ingredient, dosage, form and strength as the original medicine prescribed by the physicians. As generic medicines may differ with respect to name, shape, size, color, taste and inert excipients, the act of substitution may therefore lead to confusion and misperception among patients, especially in elder patients. This may result in unintentionally decreased medication adherence, which translates in either not taking a medicine at all or taking double or triple doses of the same medicine. Generic substitution might also lead to concerns about the reliability of the medicine and insecurity about the intervention. This may have an unintentionally negative effect on medication adherence, as the patient may decide to not taking the substituted medicine [53–57]. Van Wijk *et al.*, however, did not observe a relation between decreased medication adherence and generic substitution [48]. This difference might be explained by the fact that patients in The Netherlands are usually registered and serviced at a single pharmacy, which facilitates the communication between the pharmacist and the patient. This emphasizes the importance of the role of physicians and pharmacists in informing patients about generic medicines and providing guidance in appropriate drug use [54,55,58]. Confusion due to different physical appearances of generic medicines might also be avoided if generic medicine manufacturers would be obliged to produce generic medicines with a similar appearance as originator medicines. This, however, may prove to be difficult as a product's packaging and/or physical appearance that serves a branding function is protected by trade dress [59]. This is where pharmacists have to step up and play their role by informing and educating patients, as already described above.

Case study

An observational case study was carried out with data from The Netherlands to document the impact of generic entry on access to pharmacotherapy. Over the last years, the Dutch government and health insurers have implemented several policies to foster the use of generic medicines, which has resulted in widespread use of generic medicines. In addition, the introduction of the preference policy, which is a tendering system whereby health insurers only reimburse the lowest priced medicines, has resulted in very low prices. Looking at the evolution of total costs and total number of users, the selected active substances could be classified in three different groups. For some active substances, the total number of users increased after

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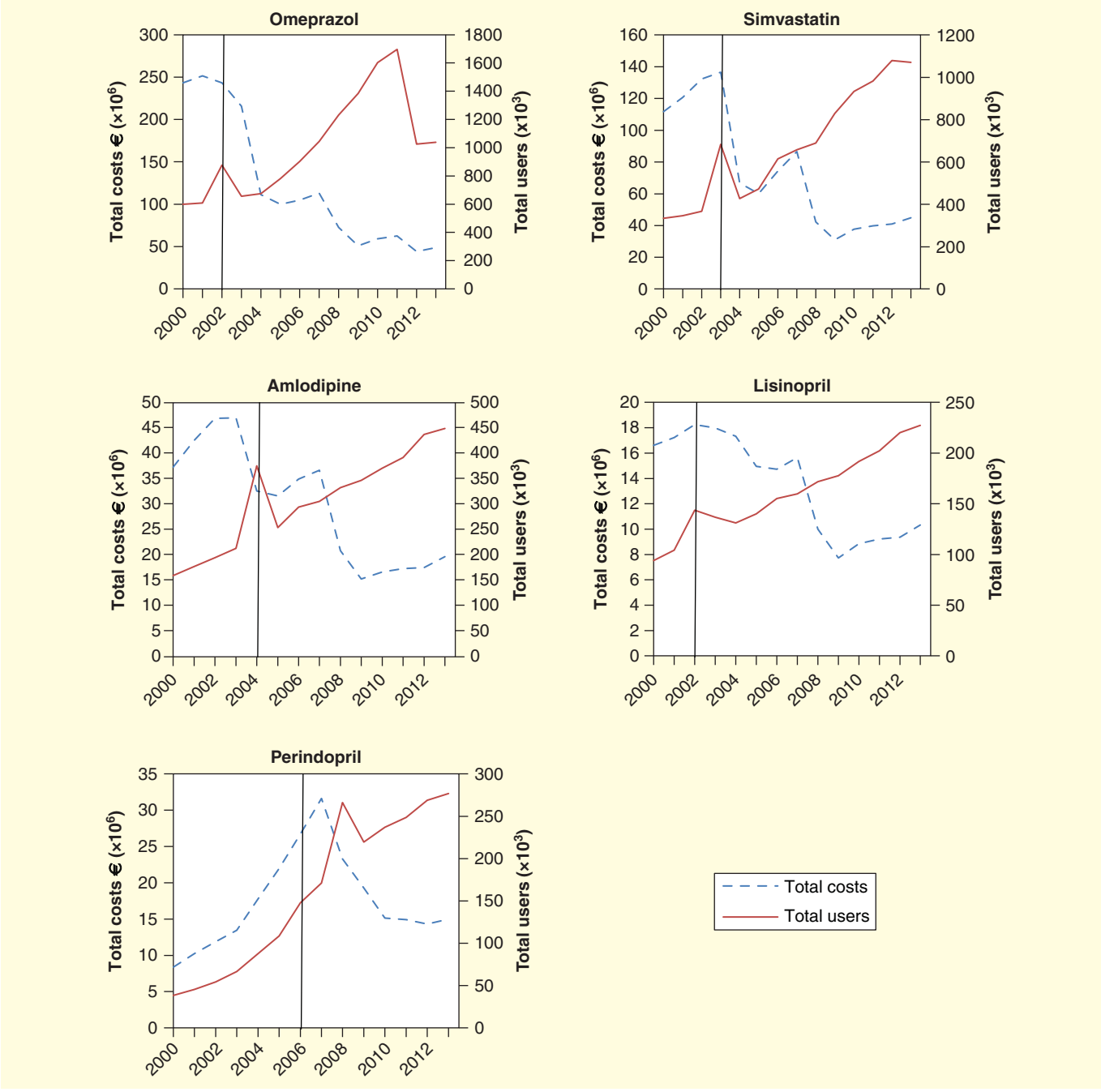

Figure 1. Evolution of total costs and total number of users for five active substances of which the total number of users increased after generic entry whereas the total costs decreased. The vertical line indicates the time of generic entry.

generic entry, whereas total costs decreased at the same time (Figure 1); for some active substances, the total number of users remained almost constant after generic entry, whereas total costs decreased (Figure 2); and for other active substances, the total number of users decreased after generic entry, whereas total costs decreased (Figure 3).

In addition, an illustrative exercise was carried out to calculate the budget impact if no generic versions of the 14 active substances would have entered the market in The Netherlands. Assuming the number of counting DDD would have evolved in the same way as with generic entry, Table 1 shows the impact on the pharmaceutical budget if no generic versions of the 14 selected active substances would have entered the market. The numbers shown are the cumulative additional budget impacts for the respective active substance for all the years between generic entry and 2013 for the respective scenarios. For instance, if the cost/DDD of omeprazole would have remained at the level of 1 year before generic entry, this would

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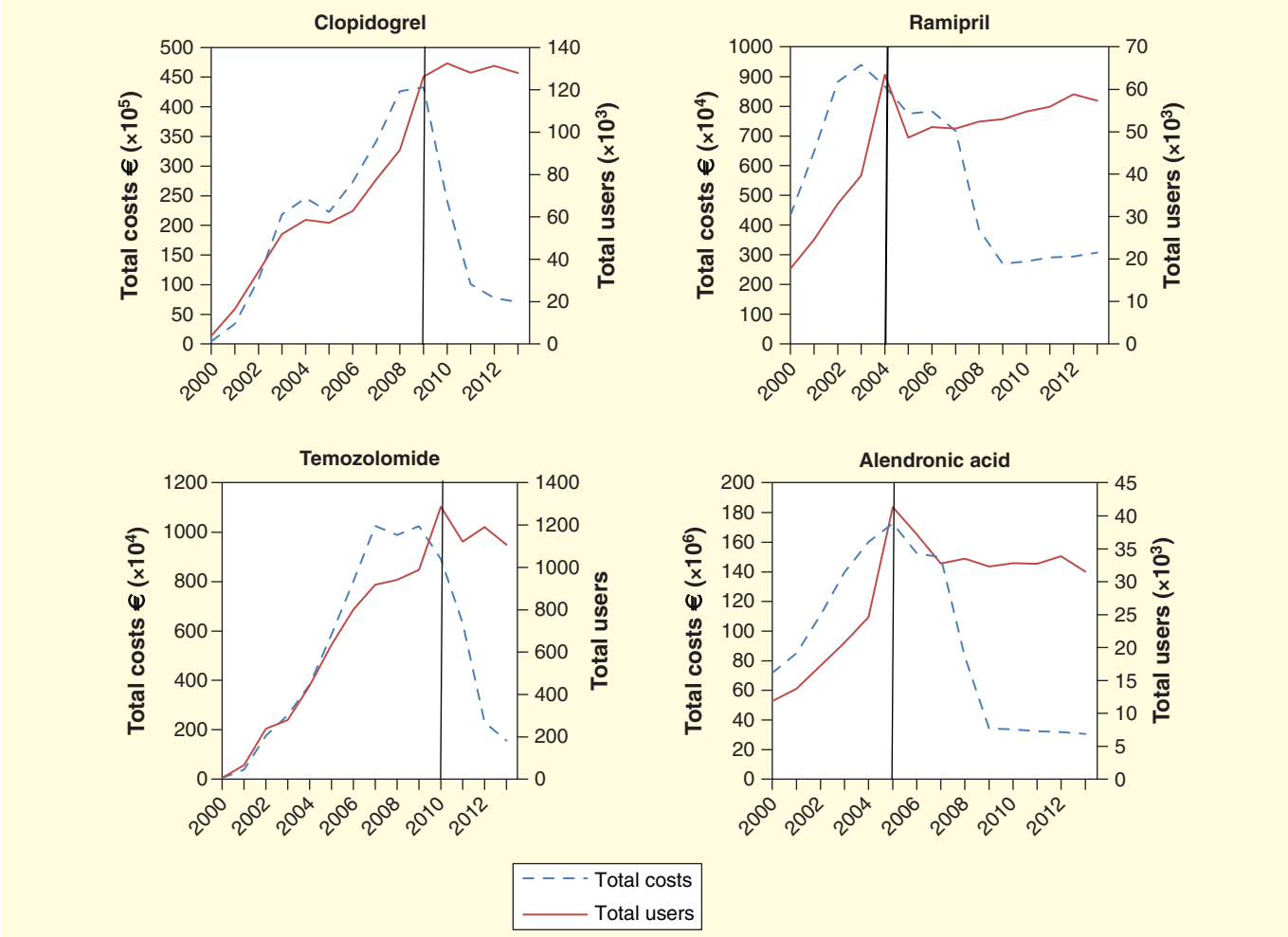

Figure 2. Evolution of total costs and total number of users for five active substances of which the total number of users remained constant after generic entry, whereas the total costs decreased. The vertical line indicates the time of generic entry.

have cost the Dutch government an additional €3723 billion between 2002 and 2014. This illustrative exercise illustrates the importance of generic medicines to contain pharmaceutical expenditures, whereas increasing access to pharmacotherapy at the same time.

However, it is only one scenario to assume that the same rise in use would have taken place if the cost had remained high. As such, an additional illustrative exercise was carried out to calculate the impact of generic entry on the number of users. Assuming the costs would have evolved in the same way as with generic entry, Table 2 shows the impact on the number of users if no generic versions of the 14 selected active substances would have entered the market in The Netherlands. For instance, if the cost/user of omeprazole would have remained at the level of 1 year before generic entry, the total costs in 2013 would have only allowed accommodating approximately 118,000 users instead of the 1,040,000 at present. These calculations show the increase in the number of users that has been made possible by entrance of generic medicines at lower prices.

Discussion

Generic medicines have been a popular means for governments to contain pharmaceutical expenditures, as extensively demonstrated in the literature [6–9,12–17]. This paper has shown that generic medicines have more benefits than only in terms of generating cost-savings through reduced prices. First, generic medicines improve access to pharmacotherapy. The reduced price of generic medicines improves the cost–effectiveness of existing pharmacotherapy, makes it cost-effective to manage previously untreated patients or leads to a more optimal treatment of some diseases [24–27]. For instance, our illustrative exercises for the case study showed that without entrance of generic medicines, the Dutch health care system would have spent substantially more on medicines to accommodate the same number of users or would only have been able to accommodate substantially less patients with the same budget. However, it can be assumed that the evolution of total costs would have differed if generic medicines would not have entered the market. The case study also demonstrated that the total number of users substantially increased after generic entry for certain active substances but not

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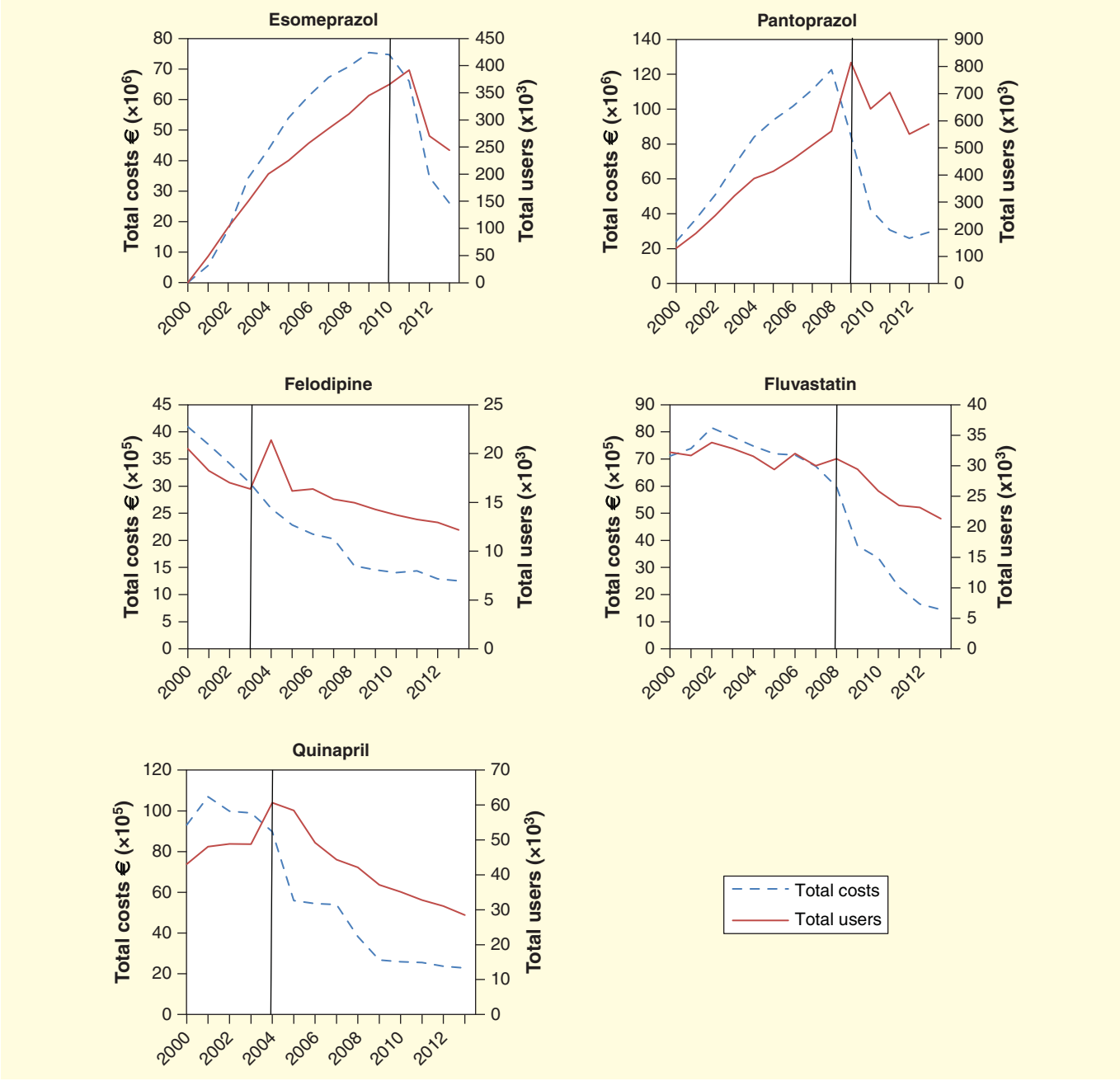

Figure 3. Evolution of total costs and total number of users for five active substances of which the total number of users decreased after generic entry, whereas the total costs decreased. The vertical line indicates the time of generic entry.

for all. There might be several reasons to explain this even or decreased use such as changes in medical guidelines (e.g., simvastatin and pravastatin are the first-line treatment options in The Netherlands since a few years), changes in reimbursement conditions (e.g., tightening of reimbursement conditions for proton pump inhibitors) or the entrance of more effective alternatives. However, a shift in marketing strategies of originator companies, where originator companies try to switch the patient from the cheaper off-patent medicine to newer, more expensive medicines still under patent is a well-documented reason for a decreased use of some active substances after entrance of generic medicines [60]. Some originator companies even used denigration strategies to limit the use of generic medicines, which has already led to fines imposed by the authorities [61–63]. However, one must be careful that the reduced prices of generic medicines do not lead to overuse of certain medicines. Therefore, physicians continue to have an important responsibility to prescribe a medicine only if medically justified, even if they are cheap.

Generic medicines have also an important impact on innovation. The entry of generic medicines and the resulting

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Table 2. Additional impact on the number of users in the case of no generic entry.

Active substance	Number of users in 2013	Number of users in 2013 if price remained constant	Additional users through entrance of generic medicines
Omeprazole	1.039.096	117.847	921.249
Simvastatin	1.071.042	124.585	946.457
Amlodipine	447.908	88.164	359.744
Lisinopril	227.301	62.446	164.855
Perindopril	276.703	73.980	202.723
Clopidogrel	127.923	15.171	112.752
Ramipril	57.346	12.999	44.347
Temozolomide	1107	16	1091
Alendronic acid	140.178	20.967	119.211
Esomeprazole	243.995	119.162	124.833
Pantoprazole	587.430	134.671	452.759
Fluvastatin	21.327	6475	14.852
Felodipine	12.183	6241	5942
Quinapril	28.473	11.266	17.207

Assuming that the total costs would have evolved as they actually did and that the average cost/user would have remained at the level of the year prior to generic entry, the number of possible users with the budget in 2013 is calculated.

competition reduces the turn-over of originator companies on the respective product. As such, this is an incentive for originator companies to innovate, being either real or perceived, which can be achieved in a number of ways. The best way (for society) therefore is to channel more resources in research and development for new, clinically meaningful innovative products to keep the companies' product portfolio competitive. Another, less risky strategy that is frequently used by originator companies is to prolong the lifetime of successful products by incremental innovations to extend the patent period (i.e., controlled-release formulations, single isomer drugs, etc.) [30]. However, this might not be of significant added value from a societal perspective, as premium prices have to be paid for products with limited added value compared to the existing products. It is the difficult task of governments and legislators to find a balance between the length of patent protection to enable manufacturers to recoup their investments in R&D and savings by the entrance of generic medicines. Generic medicines also have another impact on innovation, as many generic medicine companies aim to innovate by concentrating on patients' and pharmacists' needs in their quest to get a competitive advantage over other pharmaceutical companies [21,31].

Finally, generic medicines might also have a positive impact on medication adherence. The reduced prices of generic medicines might improve medication adherence, as high out-of-pocket costs for medicines are one of the best documented barriers to medication adherence [32]. However, the entrance of generic medicines and the associated act of generic substitution might also lead to confusion and misperception among patients, which might eventually result in unintentionally decreased medication adherence. In Europe, several governments have implemented measures to encourage the prescribing of generic medicines. However, in most cases physicians remain free in their decision to prescribe a generic versus originator medicines. Nevertheless, generic substitution by the pharmacists is allowed in many European countries, although the physician can prevent generic substitution in most countries [10]. In case of substitution, this is where physicians and pharmacists have to take up their informative and educational role for patients to explain the concept of generic medicines and thereby prevent confusion and misperception. Generic medicines thus might have a potentially positive impact on medication adherence but only under the right circumstances.

Over the last years, the introduction of new, innovative drug has declined and it will be interesting to monitor the impact on the generic medicines industry. In the USA, prices of some generic medicines also increased over the last years, as recently observed, but there are no signs at this time that the same phenomenon is happening in Europe [64]. However, these increased prices of generic medicines are likely caused by the fact that some companies went out of business in the respective markets due to the low profitability as results of the reduced prices. This reduced competition created monopolistic conditions for some molecules, which led to increased prices.

Taking into account the many benefits of generic medicines, as illustrated before, governments must realize that continuously putting pressure on the prices of generic medicines and treating them solely as a cost-saving mechanism will serve only to stifle their capability to deliver continued benefits long-term [21]. The business model of the generic medicines industry is based on the supply of high volume at low prices. As such, concentrating on the prices of generic medicines without appropriate measures to increase their volume jeopardizes the long-term sustainability of this industry [65]. This was also demonstrated in previous research, which showed that the extent to which price competition from generic medicines leads to price reductions is associated with their market share [66]. A viable and sustainable generic medicines market is thus needed to continue profiting from benefits of generic medicines in the long term. Governments must therefore implement a coherent set of policies on both the supply and the demand side to

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sustain the development of a sustainable generic medicines market.

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Key issues

- Generic medicines have contributed considerably to contain escalating health care budgets in the past but contribute more to society than only their cost-savings potential through reduced prices.
- The reduced prices of generic medicines improve the cost–effectiveness of existing pharmacotherapy, make it cost-effective to manage previously untreated patients or lead to a more optimal treatment of some diseases.
- Generic medicines can have a positive impact on medication adherence but only under the right circumstances.
- The entrance of generic medicines provides a stimulus for originator companies to invest in innovation.
- Generic medicines companies are stimulated to innovate in order to differentiate themselves in the highly competitive market.
- To maximize the benefits of generic medicines in the long-term, governments must act judiciously to implement a coherent set of policies to increase the use of generic medicines instead of continuously putting pressure on the prices.

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