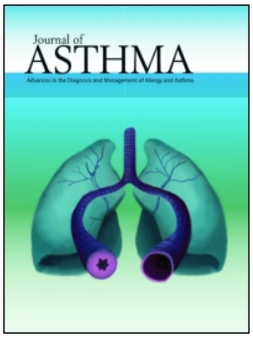

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# Brand and generic use of inhalation medication and frequency of switching in children and adults: A population-based cohort study

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**ABSTRACT**

*Background*: The expiration of patents of brand inhalation medications and the ongoing pressure on healthcare budgets resulted in a growing market for generics. *Aim*: To study the use of brand and generic inhalation medication and the frequency of switching between brand and generic and between devices. In addition, we investigated whether switching affected adherence. *Methods*: From dispensing data from the Dutch PHARMO Database Network a cohort aged ≥ 5 years, using ≥ 1 year of inhalation medication between 2003 and 2012 was selected. Switching was defined as changing from brand to generic or vice versa. In addition, we studied change in aerosol delivery device type (e.g., DPI, pMDI, and nebulizers). Adherence was calculated using the medication possession ratio (MPR). *Results*: The total cohort comprised 70,053 patients with 1,604,488 dispensations. Per calendar year, 5% switched between brand and generic inhalation medication and 5% switched between devices. Median MPRs over the first 12 months ranged between 33 and 55%. Median MPR over the total period was lower after switch from brand to generic and vice versa for formoterol (44.5 vs. 42.1 and 63.5 vs. 53.8) and beclomethasone (93.8 vs. 59.8 and 81.3 vs. 55.9). *Conclusion*: Per year, switching between brand and generic inhalation medication was limited to 5% of the patients, switching between device types was observed in 5% as well. Adherence to both generic and brand inhalation medication was low. Effect of switching on adherence was contradictory; depending on time period, medication and type, and direction of switching. Further research on reasons for switching and potential impact on clinical outcomes is warranted.

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## Introduction

To control healthcare costs, the Dutch health authorities adopted a preference policy, which enabled pharmacists to favor the dispensations of generic drugs irrespective of the physician's prescription [1–3]. Switching of inhalation therapy may coincide with a change of aerosol delivery device type as substitution is permitted if generic names are used on the prescription [4]. In principle, the choice of aerosol delivery device type is based on patient characteristics, like age, inspiratory force, device characteristics, and patient's preference [5] and each aerosol delivery device type requires careful and repeated instruction. Unexpected change in aerosol delivery device type may lead to confusion and incorrect use.

In order to get generic medications licensed, proof of clinical bioequivalence is needed. As the drug delivery and intended action of inhaled drug products for local action, such as dry powder aerosol delivery device types (DPIs) do not rely on the systemic circulation, the bioequivalence cannot be demonstrated based on drug concentration in blood/plasma [6]. The European Medicines Agency (EMA)'s "*guideline on requirements for clinical documentation of orally inhaled products for asthma and COPD*" states that for aerosol delivery device types with the same substance and required flow rate, similar in vitro performance is sufficient to show equivalence [7]. In vitro performance includes particle-size distribution, fine particle fraction of emitted dose, and flow-rate dependency tested under validated circumstances.

Healthcare professionals are concerned about switching between asthma drugs because it may negatively affect disease control through low adherence, and incorrect use

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of aerosol delivery device types [3,8]. In literature, there is evidence that switching has a negative impact on adherence and disease control through changes in color, size, and packaging [9–12]. Data from a questionnaire study showed that patients who switched asthma medication, more often experienced difficulties using the device (23% vs. 13%), were less likely to be adherent (55% vs. 68%) and were less likely to report being asthma controlled (69% vs. 83%) compared to patients who did not switch [13]. pMDIs, DPIs, and nebulizers have different flow-dependent pulmonary deposition patterns that could account for differences in therapeutic effect, independent of pharmacokinetics. DPIs, in particular, can vary markedly in design and method of operation [14]. This could lead to different handling errors in a real-life context [15]. When long-term users of branded inhaled drugs are dispensed generics delivered by a different aerosol delivery device type, they are likely to be unfamiliar with the new device and could become aware of a change in taste/sensation [16]. This may reduce their confidence in the efficacy of the generic drug, increasing the risk of poor compliance and possibly loss of asthma control.

To assess whether the raised concerns are valid, we investigated the frequency of use and switching between brand and generic inhalation medication, the frequency of switching between aerosol delivery device types and calculated the adherence before and after switching in real life in the Netherlands. We hypothesized that switching does occur frequently and that it might influence adherence.

## Methods

### Database

We conducted a cohort study in a large population-based patient centric network of healthcare databases (the Dutch PHARMO Database Network, www.pharmo.nl). This database combines data from different healthcare settings, including general practice (GP), in- and out-patient pharmacy and hospitals. It includes high-quality complete information linked on a patient level, including patient demographics, drug-dispensing records from community pharmacies, hospital-discharge records, and GP diagnoses of more than two million individuals throughout the Netherlands [17]. The Out-patient Pharmacy Database comprises detailed information on the dispensed package, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification system as well as coded by sales registry number [18]. This study was approved by the independent compliance committee of the PHARMO Institute.

### Study population

The dynamic study population comprised all patients aged 5 years or older, using inhalation medication for at least 1 year during the study period. All patients were followed from study entry (1st of January 2003 or fifth birthday, whichever came last) until the end of the study period (31st of December 2012 or leaving the pharmacy, whichever occurred first).

### Brand-generic cohort

From the study population, we identified all patients, who got dispensations for inhalation medication for which generic substitutes were available at any time between 2003 and 2012. Because of the dynamic character, the calculations were done per calendar year, thus we selected only patients with the complete calendar year of follow-up and at least one dispensation in that specific calendar year. The information on availability of generic substitutes during the study period was retrieved from the medicines information bank from the Dutch Medicines Evaluation Board [19]. The inhalation medications for which generic substitutes were available included short acting beta2 agonists, short acting muscarinic antagonists, inhaled corticosteroids (ICS), and long acting beta2 agonists (online Table 1). If for a specific ATC code, less than 0.5% of the received medications were generic, this ATC was not included in the analyses.

Switch was defined as a change from brand to generic or vice versa compared to the prior dispensing of a medication with the same ATC code in the previous 365 days, but not necessarily in the same calendar year (online Figure 1).

Per calendar year, we categorized patients into three groups: patients exclusively using brand; patients exclusively using generics; and patients using both generic and brand medication in a specific calendar year (mixed users).

**Table 1.** Baseline characteristics.

| Variable | | | |
|---|---|---|---|
| Participants (*n*) | 70,052 | | |
| Age, year (median) | 44.5 (25.5–59.7) | | |
| Gender, % men | 47% | | |
| | Medication users | | |
| year | Total (*n*) | Adults | Children |
| 2003 | 20,290 | 17,363 | 3,009 |
| 2004 | 24,039 | 20,725 | 3,397 |
| 2005 | 31,952 | 27,509 | 4,551 |
| 2006 | 34,744 | 30,155 | 4,712 |
| 2007 | 37,960 | 33,085 | 5,023 |
| 2008 | 38,817 | 34,239 | 4,712 |
| 2009 | 41,421 | 36,639 | 4,931 |
| 2010 | 41,443 | 37,019 | 4,555 |
| 2011 | 41,070 | 37,042 | 4,162 |
| 2012 | 37,876 | 34,462 | 3,503 |

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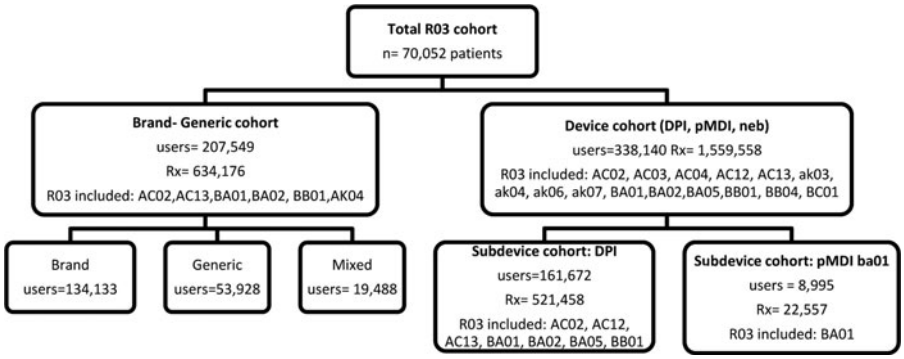


**Figure 1.** Overview of the different cohorts.

### *Device cohort*

From the study population, we identified all patients who used inhalation medication for which different devices, per ATC code, were available between 2003 and 2012. We classified the type of device as follows: pressurized metered dose aerosol delivery device types (pMDIs), DPI, or wet nebulizers. To gain more insight into switching within device category, we subclassified the DPI into Breezhaler®, Clickhaler®, Cyclohaler®, Diskus®, Easyhaler®, Handihaler®, Inhalette®, Novolizer®, Rotadisk®, and Turbuhaler®. For the pMDIs, only beclomethasone (ATC code R03BA02) was classified into subclasses; Becotide®, Becloforte®, Extrafine®, and Autohaler® (online Table 2). Unfortunately, we did not have information in our data, which holding chamber was used with the pMDI.

### *Adherence*

Adherence was calculated by using the medication possession ratio (MPR), which is defined as the sum of the days for which inhalation medication was dispensed divided by the total number of days between the first and the last prescription plus the duration of the last prescription, multiplied by 100 and expressed as a percentage. Adherence was calculated, stratified per generic, brand, and switch. We calculated the MPR for five different switches, namely: (1) switch from generic to brand and vice versa; (2) switching from generic to brand without switch in aerosol delivery device type (DPI/pMDI/NEB) and vice versa; (3) switching from generic to brand with concurrent switch in delivery system and vice versa; (4) switching between delivery systems; and (5) switching between delivery systems without concurrent switch in generic/brand switching.

Adherence before and after switching from brand and generic and vice versa was calculated for the three maintenance medications for which a generic substitute was available namely beclomethasone, budesonide, and formoterol. MPR was calculated for the total study period; following the first dispensation. For patients exclusively using generic or brand, a period MPR was calculated in a 6 and 12 months period following the first brand or generic dispense, to exclude occasional use.

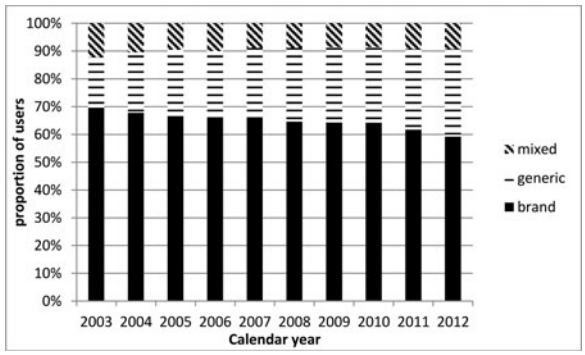


**Figure 2.** Proportion of users with generic only, brand only, or mixed use of all ATC codes within the brand-generic cohort, stratified by calendar year.

For patients with switching, MPR calculations were restricted to patients with at least two dispensations before and after switching and to the same patients before and after switch to control for patient characteristics. The MPR was calculated for the total study period before and after switching, and in the 6 and 12 months before and after the switch date. We excluded the switch dispensation from this analysis as this would introduce differential overestimation of adherence in patients who switched. In case of multiple switching the follow-up time was censored at the next switch (online Figure 2).

### *Statistical methods*

Descriptive statistics were used where numbers are provided by counts and percentages. For continuous variables, we provided medians and interquartile ranges (IQRs). To describe the use of generic and brand medication, we divided the number of users with only generic, or only brand, or mixed dispensations by the total number of users per calendar year. The prevalence of dispensing was calculated as percentage of users per calendar year,

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**Table 2.** MPR (*100%) of maintenance medications, budesonide, beclomethasone, formoterol, per ATC code, stratified by generic and brand, for the total study period or for the 12 months following the first generic or brand dispensation, and before and after all types of switching.

| | Budesonide | | | | Beclometason | | | | Formoterol | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No switch | *n* | Median (IQR) | | | *n* | Median (IQR) | | | *n* | Median (IQR) | *n* | Median (IQR) |
| Total study period | | | | | | | | | | | | |
| Generic only | 593 | 64.9 (35.6–103.8) | | | 2215 | 33.0(11.5–72.3) | | | 211 | 47.6 (28.9–82.8) | | |
| Brand only | 7077 | 51.6 (29.5–83.5) | | | 1811 | 58.6 (34.9–89.3) | | | 4939 | 39.6 (24.5–63.8) | | |
| Only 12 months after first dispensation | | | | | | | | | | | | |
| Generic only | 507 | 54.8 (41.1–82.2) | | | 1697 | 32.9 (16.44–57.0) | | | 187 | 32.9 (21.9–49.3) | | |
| Brand only | 5151 | 54.8 (41.1–82.2) | | | 1675 | 48.0 (27.4–64.5) | | | 4447 | 32.9 (23.6–49.3) | | |
| Switch# | | Before switch | | After switch | | Before switch | | After switch | | Before switch | | After switch |
| Only 12 months after first dispensation | | | | | | | | | | | | |
| Switch brand-gen | 77 (3) | 50.68 (38.9–79.2) | 77 | 59.45 (41.1–97.4)* | 102 (63) | 40.82 (27.4–60.5) | 102 | 54.79 (27.6–82.2)* | 68 (2) | 41.1 (25.1–54.5) | 68 | 32.88 (24.7–48.8) |
| Switch gen-brand | 28 (0) | 46.44 (25.7–71.9) | 28 | 47.95 (27.4–54.8) | 57 (4) | 38.36 (25.6–55.3) | 57 | 53.7 (29.2–70.1) | 19 (0) | 32.88 (28.8–41.1) | | 24.66 (16.4–49.3) |
| Total study period | | | | | | | | | | | | |
| Switch brand-gen | 242 | 66.0 (41.3–102.7) | 242 | 71.3 (47.7–106.4)* | 117 | 93.8 (58.0–119.5) | 117 | 59.8 (32.3–98.0)* | 203 | 44.5 (32.3–66.0) | 203 | 42.1(31.3–58.8) |
| Switch gen-brand | 33 | 87.2 (56.8–140.7) | 33 | 63.7 (41.6–80.0)* | 107 | 81.3 (48.1–121.7) | 107 | 55.9 (33.7–87.3)* | 39 | 63.5 (50.9–96.7) | 39 | 53.8 (25.5–69.6)* |
| Switch brand-gen without device switch | 240 | 62.5 (39.0–98.4) | 240 | 69.6 (47.4–102.3)* | 114 | 93.7 (57.8–119) | 114 | 60.4 (32.5–98.2)* | 197 | 44.5 (32.4–66.2) | 197 | 41.3 (30.9–58.8)* |
| Switch gen-brand without device switch | 29 | 83.8 (49.2–140.3) | 29 | 64.8 (41.6–83.0) * | 71 | 87.5 (58.5–121.6) | 71 | 63.4 (35.4–88.2)* | 20 | 64.8 (42.4–98.0) | 20 | 59.8 (48.1–69.0) |
| Switch device | 255 | 73.3 (45.1–104.2) | 255 | 74.0 (46.5–106.4) | 36 | 54.2 (35.2–93.7) | 36 | 66.8 (22.3–85.0) | 257 | 53.9 (33.8–80.4) | 257 | 45.7 (28.5–75.0) |
| Switch device without gen/brand switch | 224 | 76.8 (47.4–104.9) | 224 | 74.0 (46.7–105.3) | 21 | 50.1 (27.3–77.1) | 21 | 70.2 (23.4–87.7) | 207 | 54.8 (34.5–80.4) | 207 | 47.4 (30.3–75.5) |

*Notes*. $n$ = number of users. IQR = interquartile range. *$p$ value $< 0.05$ for Wilcoxon signed ranks test. #Switching only users with minimum two prescriptions before and after switch.

per ATC code and per device. We stratified by gender, frequency of use (one to three vs. more than four dispensations per year) and age (5–18 vs. ≥18 year). To compare adherence before and after switch, we tested MPR differences by paired measurements with the Wilcoxon signed rank test. We considered a $p$ value $< 0.05$ as statistically significant. All analyses were performed in SPSS version 21, SPSS Inc. Chicago.

## Results

The total study population included 70,052 patients with a total of 1,604,488 dispensations of inhalation medication. Median age at cohort entry was 44.5 years (IQR 25.5–59.7), and 47% were men. At cohort entry 13,365 (19%) were children <18 years old (Table 1). An overview of the cohorts is shown in Figure 1.

Patients were included only once, users were counted each time when they used medication per calendar year.

### *Brand-generic switching*

The brand-generic cohort, defined to estimate the prevalence of switching from brand to generic drugs and vice versa, included 634,176 dispensations of inhalation medication for which a generic substitute was available. Of these, 188,845 (35.1%) were generic. The proportion of generic users increased from 18% in 2003 to 31% in 2012. The generic dispensing rate was the highest for beclomethasone, 59% of the total beclomethasone dispensations from 2003 to 2012 were generic (online Figure 3). On average 10% of the patients in the study cohort used both generic and brand drugs in 1 calendar year (Figure 2).

Switching between brand and generic (or vice versa) within the same ATC code was observed in 5% of the brand generic cohort per year, and remained stable over time (Figure 3).

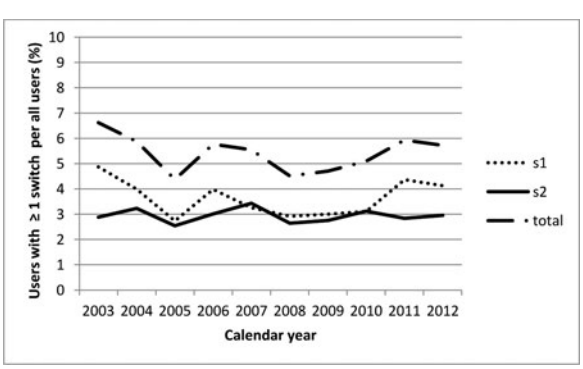


**Figure 3.** Patients with ≥ 1 switch (within the same ATC code) per calendar year. s1 = switch from brand to generic; s2 = switch from generic to brand; and total = s1 + s2.

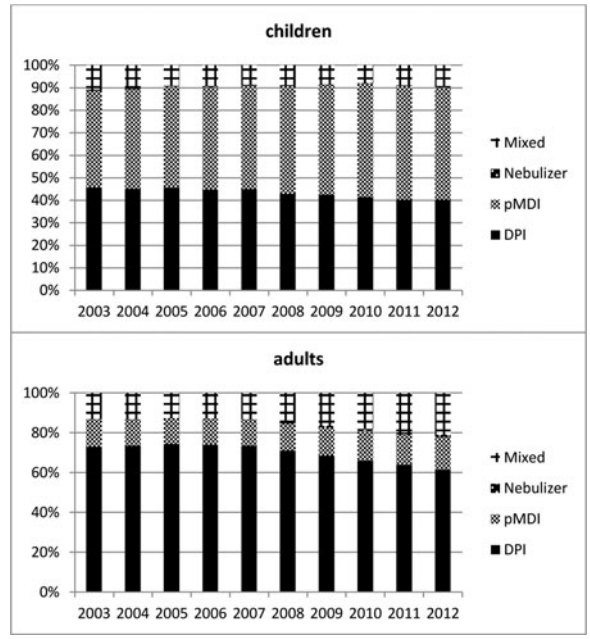


**Figure 4.** Proportion of users per device per calendar, (a) children and (b) adults.

The proportion of switching per ATC code was highest in salbutamol; 6% of the salbutamol users switched in the study period (online Figure 4). The proportion of generic salbutamol increased from 29 to 39%. All results were similar when stratified by frequency of use or by age (data not shown).

Notably, the switching percentage in beclomethasone (R03BA01) was highest in 2003 and 2004, both from brand to generic as from generic to brand, but dropped from 2005 onward (online Figure 5).

### *Device switching*

For patients within the device cohort ($n$ = 338,140), the use of pMDI, DPI, and wet nebulizers is shown in Figure 4. In children, most dispensations were pMDIs (49%), while in adults, DPIs were dispensed most frequently (73%).

On average 16% of the adult users in the device cohort used more than one kind of aerosol delivery device type per calendar year, in children this was 9%. On average 2% of users in the device cohort switched from device (within the same ATC) within 1 calendar year between 2003 and 2012. In adults, switching increased over time, with most switches from DPI to pMDI, while children switched mostly from pMDI to DPI.

Amongst the 161,672 users of DPI ($n$ = 47,532 patients), on average 3% switched between devices of the same ATC code per year. Eight percent of the users in the beclomethasone pMDI device subcohort (users = 8,895) switched between different beclomethasone pMDIs. In 2003 and 2004, switching

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from becotide and becloforte to generic beclomethasone was most frequent. In September 2002, generic beclomethasone was licensed into the Dutch market, soon thereafter Becotide® and Becloforte® were off license.

### Medication possession ratio

The mean MPR was low for budesonide, beclomethasone, and formoterol, the three maintenance inhalation medications for which generic substitute was available (Table 2). The median MPR (IQR) for the first 12 months following the first dispensation since study start for patients exclusively on brand was 55% (41–82) for budesonide, 48% (27–69) for beclomethasone, and 33% (23–49) for formoterol. The median MPR (IQR) for the first 12 months following the first dispensation for patients exclusively on generic was 55% (41.1–82.2) for budesonide, 33% (16.4–57.0) for beclomethasone, and 33% (21.9–49.32) for formoterol. Patients ($n = 102$) who switched from brand to generic beclomethasone were more adherent in the first 12 months after switching compared to 12 months before switching (median MPR 55% (IQR 27–82) versus 41% (IQR 27–61) (Wilcoxon signed rank test $p = 0.015$). Also, patients who switched from brand to generic budesonide ($n = 77$) were more adherent to budesonide in the first 12 months after switching compared to 12 months before switching (median MPR 59% (IQR 41–97) vs. 51% IQR (38–79), $p = 0.015$).

In contrast, adherence for switching from brand to generic without concurrent switch of device type was lower after switch for beclomethasone and formoterol users.

Sensitivity analyses of the above calculations for 6 months showed comparable results. Incident users (= defined as <365 days use of the specific ATC-code since study start) and stratification per age group or per gender, and concurrent switching between generic and brand with device switch, were too low for analysis.

## Discussion

In this study, we provide population level data on the use of generic and brand inhalation medication and the frequency of switching between brand and generic, and between inhalation devices during a 10-year period from 2003 to 2012. In addition, we investigated whether switching was associated with changes in adherence. Five percent of patients had one or more switches between brand and generic per year and 16% used more than one device. Adherence was low, and hardly affected by switching.

Our results provide evidence that in the study period many patients continued to use brand medication, but use of generics tended to increase overtime.

This increase is in line with the trend in recent years shown by data from the Dutch Foundation of Pharmaceutical statistics where the proportion of generic medicines among the total number of prescription medicines dispensed by pharmacies increased to 70% in 2013. Yet generic medicines accounted for just 16% of the costs of all medicines [20]. However, when evaluating the potential cost benefits of switching aerosol delivery device types, all relevant costs should be considered, including those arising from additional consultations, the time required for training and the management of any subsequent acute events [21]. This would be the scope for a next study.

For some drugs, e.g., beclomethasone, there was a marked switch from generic to brand. This was already observed by Fraser et al. [22]. In our study, the use of brand beclomethasone increased when beclomethasone pMDI with ultrafine particles (Qvar®) was introduced to the market [23]. Extra caution is needed when Qvar is switched to generic beclomethasone pMDI, as generic beclomethasone particles are much larger than those of Qvar (3.5 vs. 1.1 um), which requires adjustment of dose and may affect efficacy [24–26].

In line with previous research [27], adherence to both generic and brand inhalation medication within the first 12 months following the first dispensation was low for beclomethasone, formoterol, and budesonide with MPR ranging between 40 and 55%. In principle, adherence is considered good in case the MPR ≥ 80%. From adherence studies on chronic medication, it is known that adherence is the highest upon treatment initiation, but decreases rapidly in the first 3–6 months [28–30]. MPR calculations and fixed time periods are not ideal to calculate adherence; however, it is a common method used in database studies to estimate drug use [31]. Differences in adherence before and after switch were observed in users of budesonide and beclomethasone, where the median MPR was different after switch, direction depending on the time period, type of medication, and type of switch. The numbers were, however, low.

The low use of ICS was also observed in a study in the United States by Fung et al. They studied the effect of generic only drug benefits on patients use of ICS in an elderly population, Patients reduced their already low ICS use in response to losing drug coverage. The clinical effect of these drug use changes was not analyzed in this study [32].

Studies from New Zealand on switching between Ventolin and salbutamol use in patients with asthma, contradictory results on the effectiveness of generic versus brand name drugs [33–35].

In line with our study, a retrospective study by Thomas et al. in the United Kingdom observed that most switches were from DPIs to pMDIs [36].

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In the Netherlands, the provision of generic medicines and pharmacy services in the Dutch healthcare system has undergone substantial changes in 2008. A number of insurance companies initiated a policy of selective contracting of generic medicines; as of the 1st of July 2008, these insurers reimburse only the cheapest generic product within a number of big-selling therapeutic classes [37]. However, generic substitution coincides with increased responsibilities of Dutch pharmacists on educating patients about the reasons for generic substitution, the benefits of adherent drug use and correct use of inhalation device [38]. Patient education increases the acceptance of use of generic drugs [12]. This is underlined by a recent review that showed nonadherence to therapy and incorrect aerosol delivery device type usage are recognized as major factors in poorly or uncontrolled asthma and Chronic Obstructive Pulmonary Disease (COPD) and switching patients to a different aerosol delivery device type device may exacerbate these problems, particularly in patients who disagree to switch. The authors conclude that where switching is permitted or mandatory, adequate patient instruction and follow-up monitoring should be provided routinely [4].

This is an observational study using a pharmacy database as primary data source. This brings some limitations. Dispensing of a medicine does not equate actual use, nor guarantees a good inhalation technique. Our database could not be used to investigate the reasons for switching as there was no link to clinical data nor to type of holding chamber. Also health insurance data were lacking, while a recent review in the United States concluded that higher out-of-pocket costs for patients, depending on their health insurance, have consistently been associated with lower rates of long-term medication adherence [39]. We observed a relatively low percentage of switching from brand to generic during our study period 2003–2012. Since 2012, new generic asthma drugs came on the market and switching might be higher in datasets with more recent data [13]. Unfortunately, at the time of the study we did not have access to data after 2012.

Note that better or worse adherence for inhalation medication does not automatically imply better disease control. MPR does not tell whether inhalation medication was taken correctly. Inhalation technique is important for efficient aerosol delivery into the lungs, and therefore for efficacy of the drug.

## Conclusion

Generic dispensing in the Netherlands is increasing. Patients on inhalation medication, both generics and brands, have low adherence rates. We did not observe a clear impact of switching on adherence rates, which is reassuring. Effect of switching on adherence was contradictory, depending on the time period, the medication and the type, and direction of switching. However, with more generic drugs coming on the market, the chance of switching may become higher. Further research on reasons for switching and the potential impact on clinical outcomes is warranted.

## Competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work other than detailed above. No other relationships or activities that could appear to have influenced the submitted work. ME is supported by a ZonMw grant (project no: 113201006); HJ reports grants from Chiesi and ZonMw, and personal consultancy fees from Vertex and Gilead, outside the submitted work; MS reports grants from ZonMw, grants from Novartis, grants from GSK, grants from Boehringer, grants from Pfizer, grants from Servier, outside the submitted work; KV reports grants from GSK, grants from ZonMw, grants from Novartis, grants from Boehringer, grants from Yamanouchi, grants from Pfizer, outside the submitted work. RH, JO, and JK report to be an employee of the PHARMO Institute for Drug Outcomes Research. This independent research Institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

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## Contributors

ME, JB, KV, HJ, MS, and JJ designed the study and wrote the manuscript. JK, JO, and RH edited the manuscript and helped to interpret the data. ME, JB, JK, JO, RH, KV, HJ, MS, and JJ were involved in data processing, statistical analyses, and interpretation. HJ is the guarantor. ME had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the final manuscript.

## Ethical approval

This study has been approved by the compliance committee of the PHARMO Institute.

## Transparency statement

The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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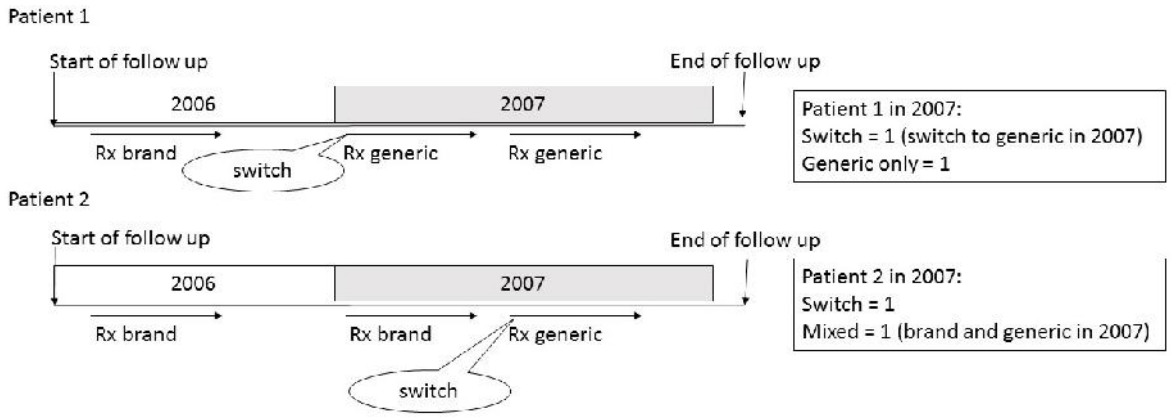
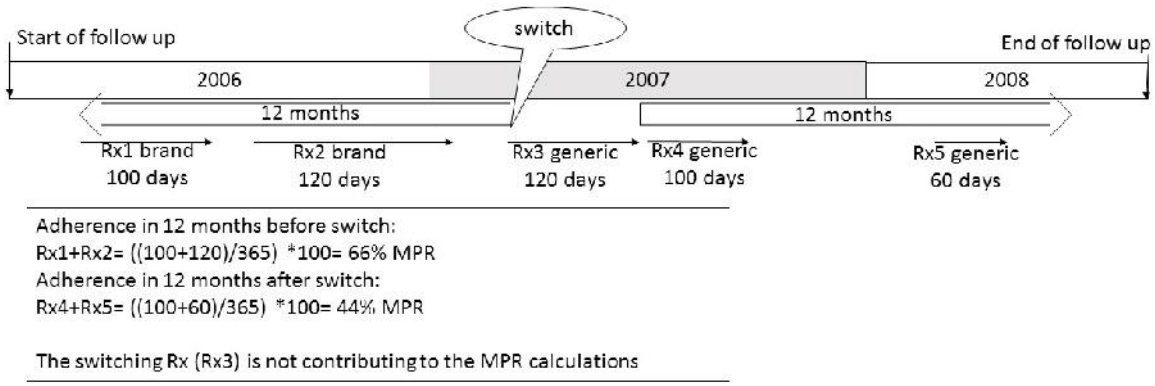
**Online SUPPLEMENTS:**

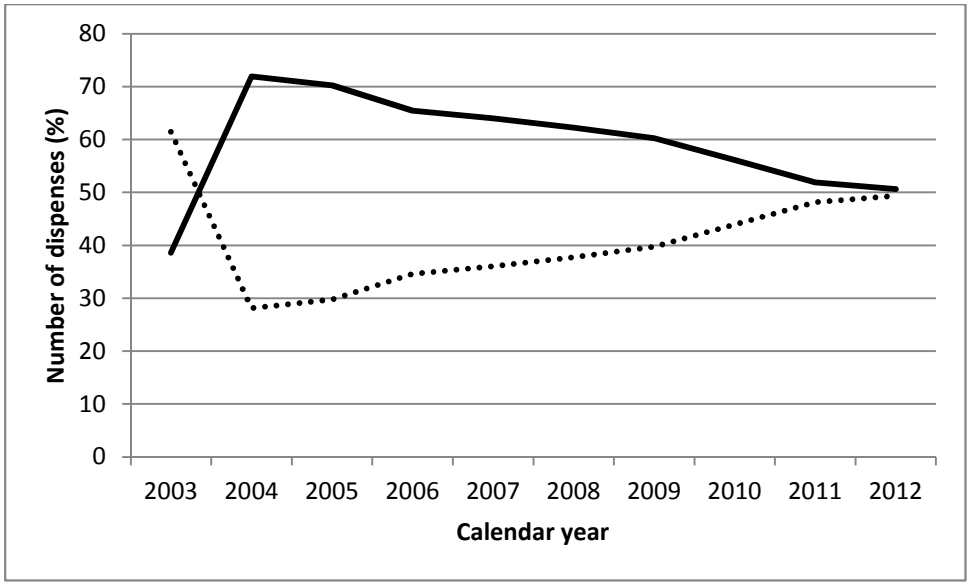
**Online Figures:5, Online Tables: 2**



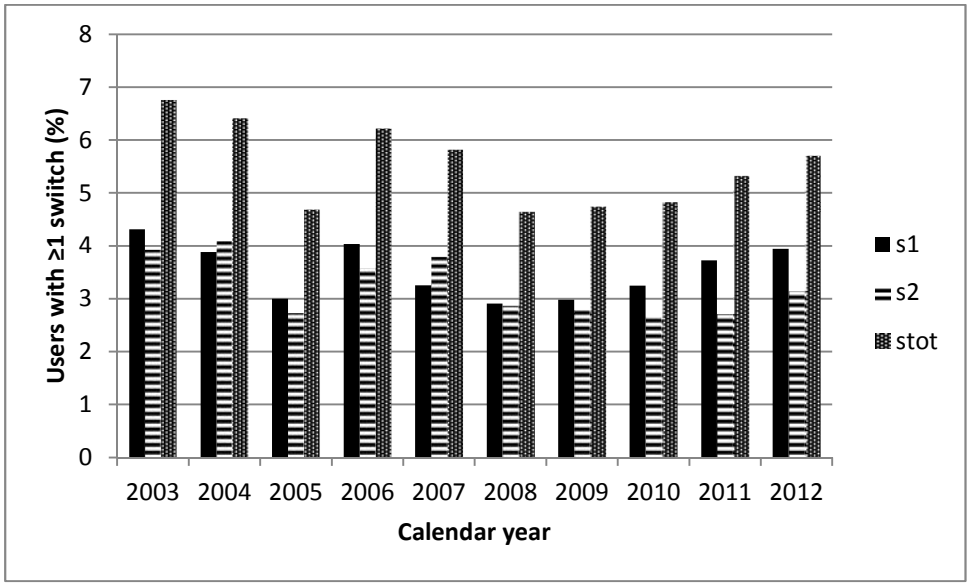

**Online Figure 1**. Graphical illustration of switching



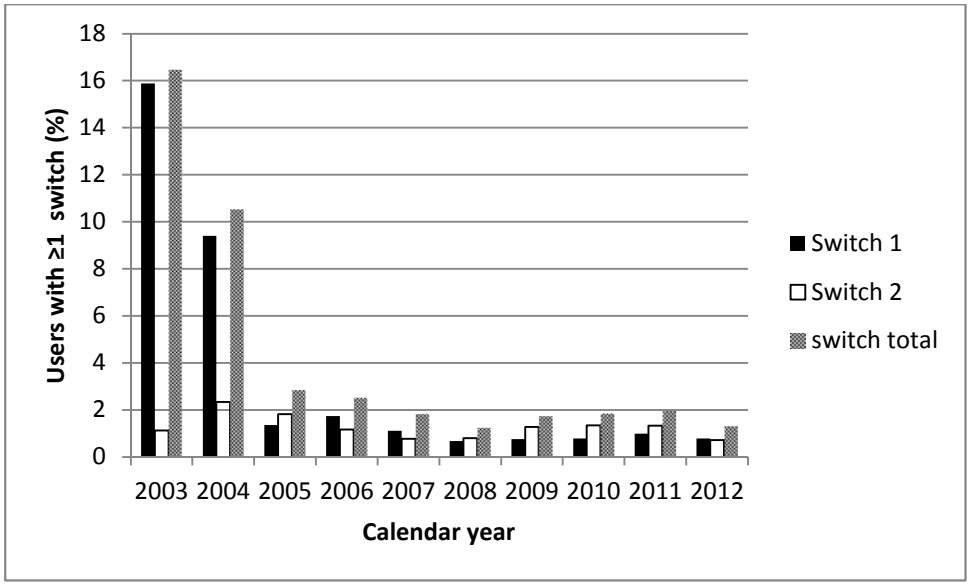

**Online Figure 2**. MPR calculations for patients with a switch, with 2 dispensations in 12 months before switch and 2 dispensations in 12 months after switch. The switching dispensation is excluded from the MPR calculations.




**Online Figure 3**. Number of dispensations per brand and generic for beclomethasone by calendar year. ….= percentage brand. ___=percentage generic.




**Online Figure 4.** Patients with ≥1 switch in salbutamol in the brand/generic cohort stratified by calendar year. s1= switch from brand to generic. S2= switch from generic to brand. Stot= s1 + s2




**Online Figure 5**. Users with ≥1 switch in beclomethasone in the brand-generic cohort stratified by calendar year. switch1= switch from brand to generic. Switch 2= switch from generic to brand. Switch total= s1 and/or s2

**Online Table 1.** Overview of brand inhalation medication with a generic substitute available between 2003 and 2012 per ATC code.

| ATC code | Generic | Brand |
|---|---|---|
| R03BA01 | Beclomethason | Aerobec®, Becotide®, Becloforte®, QVAR® |
| R03BA02 | Budesonide | Pulmicort® |
| R03BB01 | Ipratropium bromide | Atrovent® |
| R03AC13 | Formoterol | Atimos®, Foradil®, Oxis® |
| R03AK04 | Ipratropium/salbutamol | Combivent® |
| R03AC02 | Salbutamol | Aerolin®, Aeromir®, Ventolin® |

.

**Online Table 2.** Overview of subcategories for all dry powder inhales (DPI) and pMDI (only beclomethasone) available between 2003 and 2012.

| **ATC code** | Medication | **DPI device** |
|---|---|---|
| **R03AC02** | Salbutamol, Ventolin® | Cyclohaler, diskus, novolizer, rotadisk |
| **R03AC12** | Salmeterol, Serevent®l | Diskus, rotadisk |
| **R03AC13** | Formoterol, Foradil®, Oxis® | Clickhaler, cyclohaler, diskus, easyhaler, novolizer, turbuhaler |
| **R03BA01** | Beclometason, Becotide® | Cyclohaler, rotadisk |
| **R03BA02** | Budesonide, Pulmicort® | Clickhaler, cyclohaler, easyhaler, novolizer, turbuhaler |
| **R03BA05** | Fluticason, Flixotide®, Flutide® | Diskus, rotadisk |
| **R03BB01** | Ipratropium, Atrovent® | Aerocaps, cyclohaler |
| | | **pMDI device** |
| **R03BA01** | Beclomethason, Becloforte®, Qvar® | Autohaler (breath-actuated), extrafine, becloforte, beclomethasone |