

# Automatic Generic Substitution – Clinical implications for patients

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**Foreword:** Recently, it has become clear that the Department of Health (DH) is considering the introduction of Automatic Generic Substitution of medicines by pharmacists in 2010. Since this change could proceed without a formal consultation,<sup>1, 2</sup> we believe that it is necessary to set out the possible clinical implications and encourage a public consultation to take place.

Generic substitution has the potential to be disruptive to patients' medication regimens, and impact upon adherence. There is also potential for under treatment or adverse events in some individuals. Therefore, we believe that it would be unwise to implement Automatic Generic Substitution by pharmacists, which would take place without the knowledge or consent of the prescriber.

When faced with the considerable challenge of balancing NHS healthcare

budgets, it is all too easy to make oversimplified calculations. Indeed, the General Practitioners Committee has suggested that saving more than 0.4% of primary care medicines costs through Automatic Generic Substitution is unlikely, and inappropriate switching by pharmacists could put patients at risk. Implementing the scheme could also prove costly.<sup>3</sup>

There are many cases where generic prescribing is fully appropriate and vital to containing costs. Indeed, generic prescribing already accounts for 83% of all prescriptions in the UK. However, by considering Automatic Generic Substitution, we not only run the risk of losing sight of the people who matter, the patients, but also increasing healthcare costs through poorer outcomes. This document aims to highlight these important issues.

## Executive summary

- Generic prescribing is already high (83%) in the UK
- Under Automatic Generic Substitution, medicine substitutions could occur at the pharmacy without the knowledge or consent of the prescribing clinician
- A tick-box to prevent substitutions might not be adequate to safeguard patients
- Any list of medications exempted from Automatic Generic Substitution is unlikely to cover all situations where substitution could be detrimental to the patient
- Automatic Generic Substitution could result in many switches between different generic medicines. A patient could receive a different medication, with a different appearance and dosage instructions on each visit to the pharmacy
- Switches in medications could cause confusion for the patient, resulting in reduced adherence to medication. Pharmacists would therefore need to explain the substitution to each patient. However, this might not be sufficient to overcome this confusion, particularly for elderly patients and others receiving multiple medications
- Generic substitution can lead to under treatment or increases in adverse events, so substitutions should not be made without the consent and awareness of the prescribing doctor or nurse
- Generic substitution as proposed for the UK is not the same as exists in most other European countries. In half of EU countries, the pharmacist is not obliged to dispense generic medicines.<sup>4</sup> Therefore, if the patient wishes to continue to have the brand medicine, they are free to request it. Such arrangements have not been proposed in the UK, so the patient would have no choice but to be dispensed the generic medicine. In a further quarter of EU countries, generic substitution is not allowed at all.<sup>4</sup>

## Introduction

When medicines are developed, they are initially manufactured by a single company, under protection from a patent. The medicine is given a brand name which is different to the name of the active ingredient. Once the patent expires, other manufacturers are permitted to produce versions of the medicine. These versions contain the same active ingredient, and are known as 'generic'. National Health Service (NHS) prescribers are encouraged to prescribe generics because they are often cheaper than branded medicines.

Currently, pharmacists dispense brand-name medicines when they are specified on a prescription by the doctor or nurse.<sup>5</sup> Prescribers have been targeted by a range of educational and financial initiatives that have encouraged them to prescribe generic alternatives where they are appropriate for their patients. Consequently, the proportion of prescriptions that use generic medicine names has risen from 51% in 1994 to 83% in 2006.<sup>5</sup> Indeed, UK generic prescribing levels are among the highest in Europe.<sup>4</sup>

The Department of Health (DH) is now considering the introduction of 'Automatic Generic Substitution'.<sup>1, 2, 6</sup> This would mean that pharmacists who receive a prescription specifying a brand-name medicine would be obliged to dispense a generic version of the medicine. It is likely that the prescribing clinician would not be notified when a substitution has occurred, and the patient would not be able to choose to receive their original medication.

The DH recognises that generic substitution is not always appropriate, since it has suggested that certain categories of medicines could be exempt from automatic substitution.<sup>1, 2</sup> They have also indicated

that prescribers could opt out of substitution on each prescription to ensure a branded medicine is given, possibly by use of a tick-box.

These provisions indicate that the DH is aware that there are clinical and safety reasons that some medicines should not be prescribed generically. The requirement for exemptions suggests that prescribers might not always consider the safety and efficacy issues associated with generic substitution. In addition, a tick-box could easily be overlooked. Therefore, the tick-box might not provide a viable safety net for conditions, medications or patient groups outside of any official exemption list.

Before Automatic Generic Substitution should be considered, two key issues need to be addressed that could be applicable to a wide range of medications:

1. The practical impact of generic substitution upon patients' medication taking and outcomes
2. The potential impact of varying bioavailability upon outcomes and adverse events

## Practical implications of Automatic Generic Substitution

Automatic Generic Substitution could affect patients' ability to take their medication correctly. This is particularly pertinent for patients with chronic conditions that require long-term medication. Many prescriptions for long-term conditions are completed on a repeat basis, without the patient in attendance, which could increase the likelihood that doctors would overlook any opt-out of substitution.

It is important to remember that generic substitution can lead to many switches between different generic medicines. Generic medicines often have a different size, shape, colour and packaging from each other, and to branded medicine (*Figure 1*).<sup>7</sup> Therefore, a patient could receive a different medication, with a different appearance and dosing schedule, on each visit to the pharmacy. In a European study, one in three patients who had experienced a generic substitution had to become accustomed to a different colour or shape medication.<sup>8</sup>



Figure 1. Medications are produced in a range of shapes, sizes and colours

Patients with chronic conditions often take multiple medications. Indeed, in a US study of patients prescribed antidepressants, nearly a quarter of patients younger than 60 years of age were receiving eight or more medications. For patients aged 60 years-plus, this proportion increased to over one-third, and the most complex regimens included over 20 medications.<sup>9</sup> Given this complexity, it is unsurprising that many patients develop routines based on the appearance of medications, and any change can be confusing.

It is well established that adherence to therapy is affected by the complexity of medication regimens.<sup>10</sup> Switching between medications has been shown to significantly reduce adherence to treatment.<sup>11</sup> Poor adherence is known to be associated with worse outcomes and increased costs for a variety of conditions.<sup>10, 12</sup> These problems would particularly impact upon elderly patients, who are more likely to be taking multiple medications.<sup>9</sup> An elderly patient whose medication is switched might be further affected by confusion, poor eye sight and decreased dexterity. Additionally, elderly patients could experience difficulties when medications are substituted for less easily ingested formulations.<sup>13</sup> The number of patients affected by these issues is set to increase as the population ages.<sup>14</sup>

Patients with certain conditions requiring carefully balanced combinations of medications would also be disproportionately affected by medicine substitutions. For example, people with Parkinson's disease often take a combination of medications, which must be taken at the correct time for them to avoid worsening of their symptoms.<sup>15</sup> Patients with Parkinson's disease could be understandably concerned about apparent changes in their medication. In addition, changes in formulation type could affect symptom control.<sup>15</sup>

Patients' understanding and acceptance of generic substitution should not be overestimated. Many patients' knowledge about their medication has been found to be very limited.<sup>16, 17</sup> In one study, over one-third of patients did not know the purpose of their medication, and knowledge was not better among better educated patients.<sup>16</sup> Indeed, the more complex the medication regimen, the less patients know about the

medicines they are newly prescribed.<sup>18</sup> Moreover, it cannot be assumed that patients will question their doctor if they are confused by a substituted medicine, particularly among patients of lower literacy levels.<sup>19</sup> Frail elderly could also find additional visits to their GP difficult. To reduce this confusion, pharmacists would need to explain the substitution to each patient. However, if the substitution is obligatory, they would not be able to dispense the branded medicine if the patient remained unhappy.

The confusion caused by switching medications could be compounded by changes in dosage schedules when substitution occurs. For example, a patient with osteoporosis switched from Adcal D3 to Natecal D3 would have to change from taking their medication twice daily, preferably in the morning and evening,<sup>20</sup> to taking it two hours before or after meals.<sup>21</sup> They would also need to be concerned about interactions with common food types, including tea and cocoa,<sup>21</sup> which were not applicable to their original medication.<sup>20</sup>

Lack of adherence to medication can be caused by patients not understanding medicine instructions.<sup>22</sup> Patients with lower literacy levels and older people would again be disproportionately affected, since they would be less able to identify changes in pharmacy instructions. This could also impact upon patients for whom English is not their first language. Although data are not available for the UK, a US study identified that nearly half of pharmacy instructions were above recommended reading levels, and key information was missing in many cases.<sup>23</sup> To avoid such problems, pharmacists would be required to explain the substitution and its implications in every case, which would involve a

significant time investment. In one UK study of generic substitution by GPs, nearly half the affected patients were dissatisfied when their medication was to be substituted, with a fifth being 'very unhappy'.<sup>8</sup> The authors concluded that "great care must be taken to inform patients appropriately" when substitutions are made.

Many medications are delivered using devices, and switching to generic alternatives at the pharmacy will also entail switching these devices. A recent investigation into switching of inhaled corticosteroid device (inhalers) without a doctor's consultation showed that switched patients were nearly twice as likely to experience unsuccessful treatment (which included one or more hospitalisation), compared with matched control patients.<sup>24</sup> This confirms expert recommendations that inhalers should not be prescribed without making sure that the patient can use the device satisfactorily.<sup>25</sup>

These issues make it clear that generic substitution without prior consultation between the patient and prescriber could cause much confusion and disruption for patients. This is likely to be detrimental in terms of treatment adherence and outcomes. Contrary to the Automatic Generic Substitution proposed in the UK, the pharmacist is not obliged to dispense generic medicines in most other European countries where generic substitution by pharmacists has been implemented.<sup>4</sup> Therefore, the pharmacist can dispense the generic or branded medicine, according to the patient's needs and choice. Under the scheme proposed for the UK, the patient is likely to have no choice but to accept the generic medicine.

## Bioavailability and formulation issues

Generic medicines have the same active ingredient as the branded medicine. However, they are not always identical to the branded medicine. The amount of drug that finally reaches the site of action is known as the 'bioavailability'. The bioavailability is very important, because this will determine how effective the medicine will be. Too little drug reaching the target could lead to less effective treatment, but too much could increase side effects. The bioavailability can vary between branded and generic medicines, and between different generic medicines, with the same amount of active ingredient. This is because the formulation and excipients (other ingredients included in the medicine) affect the absorption and metabolism of the drug.

Branded medicines undergo a rigorous process of clinical trials assessing safety and effectiveness before they are approved for human use. However, generic medicines can be approved on the basis of pharmacokinetic studies carried out on a minimal number of healthy volunteers, where they are shown to be 'bioequivalent' to the branded medicine. This means that the rate and extent of their bioavailability lies within 'acceptable predefined limits' compared with the original branded medicine. For a generic medicine to be considered bioequivalent, the European Medicines Agency (EMA) requires the measures of bioavailability (area under the curve and  $C_{max}$ ) to be within 0.8 and 1.25 of the original medicine's values.<sup>26, 27</sup> Thus, the relative bioavailability of the generic medicine can lie anywhere between 80% and 125% of the original medicine's values.

Bearing in mind that patients can be switched between different generic

medicines, they could receive a medicine with 125% bioavailability on one occasion, and 80% on the next. This would equate to a 36% loss in bioavailability. If the patient were switched back to the 125% bioavailability medicine, they would experience a 45% increase in bioavailability. For some medicines that are recognised to have a narrow window of effectiveness before harm is caused (Narrow Therapeutic Index [NTI] medicines), the Danish Medicines Agency has already narrowed the limits for bioequivalence to 90–111%<sup>28</sup> to address safety concerns. Different patients will respond in different ways to switches in medicines, and one simulation has suggested that as many as 10% of patients could be in potential danger from overdosing or under treatment when switched between generic medicines.<sup>29</sup> Furthermore, a Swedish study has identified a significant increase in reported adverse events associated with the increase in market share for generic medicines.<sup>30</sup> These findings suggest that bioequivalence tested in healthy volunteers might not be a reliable surrogate for clinical trials in patients. In a situation where patients could experience adverse effects, automatic substitution by the pharmacist without the prescriber's knowledge could put patients at unnecessary risk.

Epilepsy is an example of a condition treated with NTI medications. Switching to and from generic medications can result in breakthrough seizures,<sup>31</sup> and patients might not always be able to recognise the symptoms of over- or under-treatment straight away.<sup>32</sup> Lithium carbonate is a further example, since changing preparations can cause toxicity and requires the same precautions as initiating treatment.<sup>33</sup> The DH has suggested that some categories of medications might be

exempt from Automatic Generic Substitution “in the interests of patient safety”.<sup>2</sup> In addition to NTI medications, the Association of the British Pharmaceutical Industry (ABPI) has suggested that the following classes of medicines be exempted from Automatic Generic Substitution:<sup>6</sup>

- Biologicals and biosimilars, which the EMEA states are not interchangeable
- Controlled medicines
- Different formulations or routes of delivery
  - Some medicines have different formulations for different indications
  - Certain excipients are not tolerated by some patients, including lactose and gluten. Others can cause allergic reactions in some patients. Serious reactions to excipients that can vary between medicines, including dyes<sup>34</sup>, have been reported
  - Religious concerns would affect the use of porcine insulin in some patients
- Modified and sustained release preparations
  - Changing between these preparations could affect tolerability and adherence
  - The clinical effect can also vary between sustained-release preparations. For this reason, the British National Formulary recommend that prescribers should always specify the anti-angina medicine diltiazem by brand<sup>33</sup>

Clearly, these are cases where automatic generic substitution should be avoided. However, is it safe to assume that these are the only cases where generic substitution can be detrimental to the patient’s health? It is known that many medicines have the potential to interact with each other.

Patients treated with NTI medicines might also receive other, non-exempt medicines. Thus, theoretically, a pharmacist could switch a concomitant medication and alter the effects of the NTI medicine. This could be a particular issue for the elderly, who often have multiple conditions and receive multiple medications. A study of patients registered with 201 UK general practices showed that patients aged 65–69 years received repeat prescriptions for an average of 5.9 medications in 2005.<sup>35</sup> This increased to 9.1 medications for patients aged 85 years-plus.<sup>35</sup>

Many medications taken by elderly patients are broken down by the same liver enzyme, increasing the potential for interactions. Additionally, elderly patients are more sensitive to medications, and are less able to eliminate them from their bodies. It is therefore recommended that dosing is carefully assessed for elderly patients to avoid adverse events.<sup>36</sup> Any increased risk for adverse events would be in addition to the potentially numerous practical issues already facing an elderly patient whose medication is switched.

There are several clinical examples of situations where generic substitution has led to unforeseen efficacy and safety concerns. In the case of oral contraceptives, it has been suggested that variation in bioavailability within the accepted limits for generic medicines can lead to ovulation and, therefore, unwanted pregnancy.<sup>37</sup> Indeed, both increases and decreases in bioavailability could lead to a variety of undesirable effects for a range of medication used in obstetrics and gynaecology.<sup>37</sup>

The efficacy of proton pump inhibitors (PPIs) varies significantly between individuals and it has been suggested that bioequivalence studies should not be seen

as sufficient for these medicines. This variation increases further in children, suggesting that generic substitution of PPIs should be approached even more cautiously in this group.<sup>38</sup> Finally, switching between branded and generic or between generic antiarrhythmic agents has been seen to be associated with arrhythmic events.<sup>39</sup>

For local-acting non-absorbed medications, bioequivalence cannot be assessed, and approvals of generic versions are made on the basis of similar active-ingredient levels alone. However, non-active ingredients (excipients) also play an important role in the penetration of topical medications. Moreover, some excipients of topical preparations may themselves be clinically active.<sup>40, 41</sup> There was up to five times difference in the skin penetration of different formulations of topical ibuprofen 5% in one UK study.<sup>42</sup> In the case of inflammatory bowel disease, the Monthly Index of Medical Specialities states that different formulations of aminosalicylates are designed to reach different parts of the colon, and are therefore not interchangeable. They further advise that a brand name should always be specified.<sup>43</sup>

Potential efficacy and safety problems have been noted for some generic preparations applied to the eyes. Generic versions of prednisolone, a treatment for eye inflammation, have been found to form precipitate, potentially reducing the potency of the medicine.<sup>44</sup> Other generic eye medicines have been associated with corneal toxicity.<sup>45</sup> These findings have led to calls for suspension and other properties of generic eye medicines to be considered for 'generic equivalence' to be established.<sup>45</sup>

Bioequivalence studies also cannot assess the effects of varying types and quantities of excipients included in oral generic

medicines. Concerns have been raised that generic alendronate prescribed to treat osteoporosis has caused severe oesophagitis, possibly even contributing to the death of at least one elderly patient.<sup>46</sup> It is well known that alendronate can cause oesophagitis, so patients are instructed to take the medicine first thing in the morning and avoid lying down for at least 30 minutes after dosing.<sup>47</sup> However, some generic versions of alendronate have been shown to adhere to the oesophagus and rupture, leaving pieces of tablet stuck to the oesophagus lining.<sup>48</sup> This problem is thought to be related to inactive ingredients included in the tablets.<sup>48</sup> Studies in animals further confirmed a dramatic increase in oesophageal ulceration in those treated with generic alendronate, compared with the branded medicine.<sup>49</sup> Oesophagitis can have serious consequences for the patient,<sup>46</sup> which makes it important that the prescribing physician should make the decision for generic alendronate to be dispensed.

These examples show that there are indeed conditions where generic substitution should be avoided that are outside of the ABPI's recommended exemptions. It cannot be safe to assume that there are not still further situations where generic substitution could have adverse consequences. Therefore, introducing Automatic Generic Substitution with specified exemptions could create a two-tier health service on the basis of incomplete evidence. Overall, the potential for adverse events and under-treatment makes it unwise for generic substitution to be allowed to take place without the full awareness and involvement of the prescribing doctor or nurse.



## Conclusion

Generic prescribing currently occurs at very high levels in the UK. This situation is vital to preserve healthcare budgets and should therefore continue at current levels. However, switching medications can have a range of practical and clinical consequences for patients. The pharmacist plays a very important role in informing the patient, but the prescriber is aware of the patient's overall health and situation. The prescriber will also be in a position to note and treat adverse events, should they occur. In addition, the prescriber should be fully aware of treatment decisions made on their behalf. We believe that the decision to dispense generic medications should not be

taken out of the hands of the prescribing doctor or nurse.

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