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Viewpoint

# Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe[1]

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Given the current financial climate there is an ever-increasing need to substitute drug treatments to optimize expenditure. A closer examination of the beliefs surrounding when substitution is appropriate led a group of European healthcare experts to argue that in some cases these beliefs may be unfounded and that guidelines are needed for clinical practice.

## Can patients' needs be balanced against the drive for cost containment?

The need to manage and minimize costs is increasingly important for healthcare systems across the world. Generic substitution is already used widely throughout Europe and payers are increasingly looking towards therapeutic substitution to make additional savings (see Table 1 for definitions). These are valid methods for containing costs, particularly for conditions such as cardiovascular disease, where large numbers of people need to be treated in the best possible way to minimize disease burden. However, when switches of medication are driven purely on economic grounds, there may be potential conflicts between the needs of the healthcare provider and those of individual patients, and this may impact on patients' safety and treatment outcomes.

The Therapeutic Substitution Consensus Group comprises a number of European experts in clinical pharmacology, clinical cardiology, medico-legal practice, bio-ethics, payer/policy practices and health economics. A consensus was drawn on a robust approach to the development of best practice that would meet the needs of all interested parties. It is accepted that certain types of products are not considered for therapeutic substitution and biosimilars are outside the scope of this viewpoint.

## A number of factors need to be considered prior to implementing a substitution

Current policies on substitution are shaped by payers and budget holders, who by necessity have had to focus more on population, rather than individual, cost/benefit, although policies advocating increased patient choice make such policies more difficult to draft. There is increasing emphasis on the identification of opportunities for therapeutic substitution of branded medicines, though there are few measures in place to help payers ensure that they do actually save money above and beyond the initial cost of the drug.

Ethical considerations reflect the dichotomy between the needs of cost-driven policies of generic/therapeutic substitution and the concurrent requirement to champion the needs and interests of the patient. The following broad considerations were identified: Who makes, and who should make, decisions about generic and therapeutic substitution? What unpalatable truths may need to be faced in order to have an honest discussion (e.g. there has

**Table 1**
Definitions of generic and therapeutic substitution

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| • Generic substitution occurs when a different formulation of the same drug is substituted. All generic versions of a drug are considered by the licensing authority to be equivalent to each other and to the originator drug. |
| • Therapeutic substitution is the replacement of the originally-prescribed drug with an alternative molecule with assumed equivalent therapeutic effect. The alternative drug may be within the same class or from another class with assumed therapeutic equivalence. |

to be a realistic acceptance of the limited resources of any healthcare system)? How should we act when we have new evidence?

The premise on which generic substitution rests is that the substituted drug is equivalent to the original drug. However, there are documented examples where pharmacological variations exist, even between originator and generic formulations and between different generic formulations of the 'same' drug [1, 2]. Although two formulations may be considered bioequivalent at a population level, individuals may fall outside of this range with some receiving higher or lower doses than expected [3, 4], irrespective of the manufacturer – branded or generic. These differences may be compounded by other factors, such as age, co-morbid conditions, concomitant medication and disease status, none of which are normally considered in bioequivalence studies [5]. There are some examples where differences in excipients and formulation quality (including changes in a brand's manufacturing line) can affect clinical efficacy and the occurrence of adverse events in patients [6–8]. These factors are more obvious in the case of therapeutic substitution where a different drug is assumed to have the same effect.

Whereas payers monitor the effects of generic/therapeutic substitution through economic analyses, clinicians may be more aware of negative effects, such as reduced efficacy and/or compliance or increased side-effects. Hypertension was selected as an example for consideration by the group due to the large number of antihypertensive drugs in several different classes, in both branded and generic forms. Clinically, assumptions of an overall class effect may lead to unsuitable therapeutic substitutions in patients with a co-morbidity or previous intolerance. As most patients do not reach their blood pressure target, it is critical that substitution policies do not increase the effect of any of the contributing factors, including: non-adherence to drug therapy, the use of less effective drug combinations or an increase in unwanted side effects due to the switch [9–11]. In chronic diseases, patients may be confused by repeated formulation changes following generic substitution; this highlights the need for good patient counselling from pharmacists.

The prescriber is required to obtain the patient's informed consent to any medication. In order for informed consent to be valid, the patient must have mental capacity (competency) to make the decision in question, and the said decision must be voluntary and free from coercion. In addition, the patient must be properly informed; they must be told about the benefits of the treatment, any alternatives and must be made aware of the material risks. A risk can be said to be material if a reasonable person in the patient's circumstances, if warned of the risk, would be likely to attach significance to it.

Where a clinician cannot confirm equivalence there are inherent problems for informing patients about the precise risks, benefits and quality of the medicinal products. It should be remembered that the prescriber may be accountable if a drug has an additional unexpected or unwanted effect even if the adverse event is due to a switch performed post-prescription and without the clinician's specific knowledge.

There are few prospective studies assessing potential additional risks associated with substitution and there are no established protocols by which switching is monitored or assessed. This may make it difficult to know whether the money saved on the initial drug will still be saved as treatment outcomes on the substituted drug become apparent.

## Recommendations for defining best practice in generic and therapeutic substitution that meet the needs of all stakeholders

The solution to this issue requires a definition of 'best practice' for both generic and therapeutic substitution. Any such guidelines should reflect the very real need to manage and minimize costs at the same time as being transparent and supported by sufficient evidence. This section outlines the key points that any best practise guidelines should address.

**1** Defining generic and therapeutic substitution
- Generic and therapeutic substitution may be regarded as two separate processes and so there should be best practice guidelines for both.

**2** Equivalence
- The assumption that 'bioequivalent' generic drugs are therapeutically equivalent may not always be correct in limited cases.
- Evidence regarding equivalence should be publicly available from all manufacturers and made transparent.
- All regulatory bodies should apply the highest quality standards equally across all generic and branded drugs.

**3** Governance
- There should be a clear policy for the processes of generic and therapeutic substitution.

- It is good practice for representatives from all interested parties to be involved in the development of policies.
- Pharmacy-led initiatives should be implemented with the awareness of the prescriber.

**4** Best practice

Best practice guidelines are required for both generic and therapeutic substitution policies. These should cover the need for:

- Transparent decision-making criteria that are accessible.
- Clinician awareness and agreement.
- Patient awareness and informed consent.
- Sufficient rationale or economic evidence to support the proposed substitutions (whether at initiation of, or during existing, treatment) must be made readily available to the public, especially when cost is the major driver.
- Due consideration to be given to all factors in healthcare systems and society, and not simply the headline drug cost.
- Improved analysis of generic products as recommended in the recently upgraded bioequivalence guidance from the European Medicines Agency [12].

**5** Education

- Patients should be given better information than they currently receive, including the incidence of any side effects.
- Patients should be given details of any treatment alternatives.
- The role of the pharmacist and other healthcare professionals in delivering patient information should be expanded.

## What needs to happen next?

This viewpoint was written to raise awareness about some of the potential challenges that face payers, clinicians and pharmacists in the delivery of best quality healthcare which maintains the patient's interests. The panel provided key inputs concerning the main issues and formally recognized the need to develop best practice guidelines. The process of substitution is based upon accepted beliefs and the challenge for group members will be in persuading people to audit their current practices.

## Competing Interests

AJ has been, and is, a consultant for, and owns stocks in, several pharmaceutical and biotech companies. RA has 'expert consultant' activities for several pharmaceutical and devices Industries. He is also acting as speaker in symposia organized or sponsored by Industries and received funds for specific research from Industries. BD has served as consultant and had speaking engagements to pharma companies marketing cardiovascular drugs and has been compensated for travel and time spent on research and lectures. KH provides training and education services to the healthcare sector. She regularly speaks at conferences and industry events around the world. Some of these events are sponsored by pharmaceutical companies, others by the NHS, regulatory bodies, professional organisations and private healthcare providers. She is a practising healthcare lawyer at RadcliffesLeBrasseur solicitors in London. She is also Managing Director and Senior Trainer of InPractice Training (GCS Training Limited) in which she also has shares. As an academic researcher in bioethics DAJ has sometimes attended conferences which have been supported by pharmaceutical or biotech companies and occasionally been paid for speaking at such conferences. DAJ has only accepted such invitations when they have not placed any restriction on what was to be said or what was subsequently to be published. JJ serves as a speaker/participant in advisory boards and received research funding from Novartis, Sanofi–Aventis and Abbott. GAM has received consulting and lecturing fees from Daiichi–Sankyo, Takeda, MSD, Novartis. MS provides a consultancy service to various pharmaceutical companies and others who do business with the NHS. This is confined to strategic and planning advice on relationship management and product focussed business strategies. MS is also engaged on activities through the NHS Alliance and privately that develop NHS Strategies and works directly with the Department of Health and other NHS bodies. PS has received honorarra and reimbursements from pharmaceutical companies including Boehringer and Novartis. EAR has received fees for speaking from Sankyo, Novartis, Menarini, Bayer, Recordati and Boehringer. EAR has also received funds for research from Recordati, Novartis and Ministry of Health. EAR has received fees for consulting from Sankyo and Novartis.

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