"Much of a physician’s assessment of a patient ends in a prescription; when, in actual fact this is only the beginning..." Professor Laloo pointed out at the outset of his review of the ethical responsibility of ‘doing good, without harm’ as the guiding principle in medicine.

**KEY MESSAGES**

- Prescribing medication demands ongoing review of possible adverse effects, as the clinician’s care of a patient continues over ensuing months and years
- Side effects of chronic medication can have a slow onset and the clinician should be alert to this potential harm
- Affordability of generics is greatly enhanced by a competitive environment in which there are at least 10 generic products for a particular drug entity
- Adverse events associated with prescribed medication are extremely poorly reported in South Africa. This needs greater attention from practising clinicians
- There is no ‘MCC-approved list of non-substitutable medicines’: while there is concern about medicines with a narrow therapeutic range, practical steps can be taken to achieve expected clinical efficacy.

This principle should be uppermost in a clinician’s mind as he prepares to write a prescription for the patient in front of him. The prescription must reflect an effort to prevent or remove harm, while weighing and balancing potential benefits of therapy against risks. The patient’s wishes need to be considered, and overriding them as unimportant is paternalistic and against the concept of informed consent (Table 1).

“In our application of evidence from clinical trials, when we select a patient for treatment, we are expecting a particular response. If the patient does not respond as expected or the clinical problem is difficult, we need to go back to the drawing board using the maxim: ‘When the clinical problem gets tough, the tough get a history’.”

Three case studies are illustrative of the importance of considering risk and benefit when prescribing for an individual patient.

**Table 1. Non-maleficence - do no harm**

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<tbody>
<tr>
<td>1.</td>
<td>Refrain from providing ineffective treatments</td>
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<td>2.</td>
<td>Do not act with malice towards patients</td>
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<td>3.</td>
<td>Beneficial treatments may have serious side effects</td>
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<td>4.</td>
<td>‘Do no harm’ works best when balanced with ‘beneficence’</td>
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**Case 1**

An insulin-dependent diabetic female presents with recurrent urinary tract infection (UTI). She has chronic persistent asthma which is being treated with budesonide 160μg and formoterol fumarate dehydrate 4.5μg (Symbicord) twice daily. In recent months her asthma worsened, requiring increasing treatment, but she continued to experience poor control and severe recurrent exacerbations. She is referred to a pulmonologist who identifies the presence of bibasal crackles. On high-resolution computed tomography, the diagnosis of fibrosing alveolitis is made. She is prescribed what was then seen to be appropriate treatment of prednisone and azathioprine; over time she develops right heart failure and is eventually sent home on oxygen support.

However, the clinical question remains unanswered: “Why did this patient with asthma get idiopathic pulmonary fibrosis?”

The search for an answer began with her illness and medication history:

It was noted that she had been given nitrofurantoin for recurrent UTI, which she had been taking for five years. The product insert and research of published literature revealed that nitrofurantoin can be toxic to the pulmonary system after long exposure (six months). If the general practitioner had reviewed this aspect of the patient’s history earlier and checked for adverse drug reactions, this lung damage could have been largely avoided.

**Case 2**

A 60-year-old woman with pelvic-ureteric reflux is treated for her recurrent UTIs with macrodantin prophylaxis for >5 years; she has a history of smoking and is experiencing progressive nausea. On suspicion that she has chronic obstructive pulmonary disease (COPD), she is referred to a pulmonologist who identifies nitrofurantoin-induced pulmonary toxicity. On CT scan, there is evidence of hepatomegaly.

Again, stopping the nitrofurantoin improved liver function and reduced the nausea and the lung function improved. The clinical lesson from this case is that if a patient is on long-term therapy, read about the side effects and monitor the patient, even though, as in this case, the onset of side effects may be slow.

**Case 3**

A 53-year-old electrical engineer, who had never smoked, was diagnosed in 2013 with asthma (cough, tight chest, dyspnoea on effort). He has a history of ischaemic heart disease and a myocardial infarct and a coronary artery stent *in situ*. He was placed on aspirin therapy; given rosuvastatin for his dyslipidaemia and perindopril plus bisoprolol 10mg for hypertension. He was prescribed salmeterol 25μg and fluticasone (250μg) – (Sereflo) 2 puffs per day. His symptoms increased progressively and eventually he was using salbutamol up to 15 times per day. He was unable to do normal daily activities without getting short of breath and he felt ‘at death’s door’. He was given esomeprazole 40mg for his gastro-oesophageal reflux. He also underwent sinus surgery.

The latter medication was ‘the clinical thorn’. When the bisoprolol (β-blocker) was stopped, his FEV1 improved within two weeks and he improved steadily. After nine months he was back in the gym!

The clinical lesson: if a patient’s condition worsens, take a history and check medications. Non-essential medication can even be stopped as part of this checking process to exclude iatrogenic effects. It is clear that β-blockers should not be used in asthmatic patients; although highly selective β-blockers may be safe in some asthmatics, these should only be prescribed in consultation with an expert. Even eye-drops containing β-blockers are best avoided in asthmatic patients.

The elderly are particularly prone to adverse effects of drugs; the overall incidence of adverse effects is estimated to be at least twice that of the younger population.

In summation, Professor Lalloo stressed that the physician should review his and other healthcare specialists’ prescriptions when a patient either does not respond to therapy or symptoms worsen. The ethics of prescribing require ongoing review and monitoring.
Generic substitution - confidence of quality?

The purpose of Act 90, the Medicines and Related Substances Control Amendment Act of 1997, was to provide for sustainable delivery of competitively priced innovative and generic medicine.

Recent legislation in the USA, the Affordable Care Act (2013) and the FDA Safety and Innovation Act, has acted as an incentive for the development of antibiotics and encouraging biosimilars. Even in this resource-rich environment, competitive pricing of medicines has become FDA policy in order to provide affordable healthcare to all Americans. In South Africa, the Medicines Control Council’s (MCC’s) role, like that of the FDA, is to ensure that innovator and generic medicines meet the same international standard. “This is done by two main mechanisms; ensuring that international good manufacturing practices are in place and that registered generics are bioequivalent to the innovator medicine,” Professor Blockman pointed out.

All factories that produce medicines for the South African market are inspected and subjected to random audits, which help to ensure quality medicines are sold in South Africa. The review process for innovator (brand name) drugs differs from that for generic drugs (Figure 1).

Bioequivalence of a generic medicine is based on bioavailability studies in healthy volunteers that show that the same level of the active substance reaches the bloodstream when either the innovator or the generic is given as a single dose in a two-period crossover study. The area under the curve (AUC), maximum concentration reached (Cmax) and time to maximum concentration (Tmax)) must be within the 90% CI (80-125% of the innovator product’s AUC and Cmax as measured on a logarithmic scale) (Figure 2). This does not mean that the generic product is 80% less effective or 25% more effective than the innovator. “The generic product can never be better or worse than the innovator,” Professor Blockman stressed.

![Figure 1. Review process](https://example.com/figure1.png)

**Figure 1. Review process**

<table>
<thead>
<tr>
<th>Brand Name Drug</th>
<th>Generic Drug</th>
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<tbody>
<tr>
<td>1. Chemistry</td>
<td>1. Chemistry</td>
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<tr>
<td>3. Controls</td>
<td>3. Controls</td>
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<tr>
<td>4. Labelling</td>
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<td>5. Testing</td>
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<td>7. Clinical Studies</td>
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<td>8. Bioavailability</td>
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Center for Drug Evaluation & Research, US Food & Drug Administration

![Figure 2. Established bioequivalence limits are 80% to 125%](https://example.com/figure2.png)

**Figure 2. Established bioequivalence limits are 80% to 125%**

Generic A is bioequivalent to the innovator drug

**PASS**

Generic B is NOT bioequivalent to the innovator drug

**FAIL**

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May 2017
“The element of a generic that is not the same as that of the innovator is the carrier/vehicle or other inactive ingredients present in the medication. These may cause a problem in some patients,” Professor Blockman pointed out. The MCC approves the generic based on bioequivalence and the absence of any significant difference between the innovator and the generic, which allows for interchangeable and substitutable practices at pharmacy level. The in vitro studies on which older generics were approved are no longer sufficient for registration today. “Complementary medicines in South Africa are still largely unregulated and can cause far more problems than any recently registered generic in South Africa,” he noted.

Bioequivalence studies are not required for generic products that are provided in directly delivered formats (parenteral aqueous solutions, oral solutions, powders that are reconstituted to a solution and topical aqueous solutions, inhaler products and nasal sprays). “It is accepted that if the formulation contains the same amount of the active ingredient, this will reach the bloodstream in the same way as the innovator molecule does,” he said.

There is still some concern around the use of generic formulations of agents that have narrow therapeutic ranges, e.g. warfarin and anti-epileptic agents. “A practical approach to deal with this problem is to switch from innovator to generic, but not from generic to generic, as in the latter instance unquantified differences may exist as one generic is not tested against another generic,” Professor Blockman said.

With regard to the use of individual bioequivalence, i.e. the measurement of inter- and intra-individual differences, FDA evaluation has shown that this process does not add significant value to the evaluation process and is not necessary to determine bioequivalence.

In conclusion, Professor Blockman pointed out that the principles described are well-accepted but that a myriad of details concerning analytics, statistical evaluation, subsequent auditing and monitoring of side effects require expert and ongoing review.

References

Additional reading