NOFSA statement on generic bisphosphonates

To the Editor: Dr Nic de Jongh,[1] Medical Director of Cipla Medpro, expressing the wish to '… set the record straight in terms of inaccurate and irrelevant comments [by] the National Osteoporosis Foundation of South Africa',[1] addresses two separate but interrelated topics: the pharmacology of alendronate, and the fundamental issue of who is ultimately responsible for patient care and maintaining health delivery standards in this country.

The debate on generic bisphosphonates has become rhetorical, and I therefore limit my comments to the specific points raised by Dr De Jongh.

1. Our reference to the 'Notice of rejection' did not involve an old application of 1998/9, but was published in the *Government Gazette* in 2004.[2]

2. We remain concerned about the paucity of scientific literature on the pharmacology of generic bisphosphonates. The three articles quoted by Dr De Jongh, all originating directly from the pharmaceutical industry and published in the journal *Arzneimittelforschung*, often involved small subject numbers (only 23 in one study) and with other limitations are unlikely to contribute significantly to the scientific depth of our understanding of the subject. Moreover, none of these articles involved the local generic alendronate Osteobon, so if Dr De Jongh is consistent they should probably be regarded as irrelevant.

3. The suggestion that NOFSA is questioning the integrity and credibility of the Medicines Control Council is absurd. Given the lack of data on generic bisphosphonates and the rather unique pharmacokinetic profile of alendronate (e.g. extremely poor intestinal absorption of < 1%; high inter- and intra-individual variability), it is surely understandable that responsible care providers would have concerns about safety and efficacy – it is also not surprising that the drug was placed on the MCC's Non-Substitutable List. The precedent of the MCC approving a generic drug, yet placing the ethical drug on their Non-Substitutable list, is well established, not unique to alendronate, and no reason whatsoever to accuse NOFSA of questioning the integrity of the MCC.

4. The mechanism of bisphosphonate-induced oesophageal irritation may include inhibition of the cholesterol biosynthetic pathway, since this appears to be the primary molecular mechanism of action of these drugs. However, those of us who daily treat osteoporosis with bisphosphonates know that the dominant, if not the only, effect is a direct, presystemic toxic one on the gut – hence the ability to limit oesophageal irritation by not lying down after oral ingestion of the drug, and prevention of this side-effect by giving the drug intravenously.

Who is responsible for patient care and maintaining health delivery standards as these pertain to osteoporosis in general, and the pharmacotherapy of the disease in particular? According to De Jongh and Cipla Medpro, neither local clinicians nor international world experts on osteoporosis are '… appropriate experts on regulatory science'. Even clinical pharmacologists are not suitably equipped! Whereas I acknowledge the fact that there is no room for an arrogant, medical profession that unilaterally dictates what the treatment of osteoporosis should comprise, it would clearly not be in our patients' best interests if this role were to be taken over by the pharmaceutical industry or by anyone else.

It is NOFSA's right and a core responsibility to remain abreast of every aspect of osteoporosis management. Therefore to suggest that '… NOFSA should rather focus on the goals of its own organisation and acknowledge the benefits of generic alendronate …' is undeserving of further comment. NOFSA will continue to assess all new developments, including new pharmaceutical agents in the field of metabolic bone disease, in a critical, scientific and fair fashion, always insist on sound evidence-based data, promote true cost-efficacy, and above all else always act in the best interests of the patient.

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1. De Jongh JN. NOFSA statement on generic bisphosphonates. *S Afr Med J* 2006; **96:** 1138.
2. Notice of rejection of the application for registration of Osteobon 10 tablets (Application No. 330114). *Government Gazette* Notice 261 of 2004.

Phyto-oestrogens in soy-based products – concerns regarding the adverse effects on puberty

To the Editor: A large body of evidence documents the role of phyto-oestrogens in influencing hormone-dependent states. Infants fed soy formula receive high levels of phyto-oestrogens, in the form of soy isoflavones, during a stage of development at which permanent effects are theoretically possible. Delayed effects of soy-based infant formula on subsequent child or adult health have thereby been postulated, generating substantial controversy in the lay and medical press.[1] Furthermore, concerns about possible adverse effects of exposure of infants to phyto-oestrogens in soy-based formulas are founded on hypothetical possibilities and are related to knowledge of the role of oestrogens at critical stages of development and in mediating reproductive or neuro-endocrine disruption in various animal species.[2]

The effects on human pubertal and reproductive development of phyto-oestrogen exposure in infancy have not been systematically investigated. Therefore, given the lack of data on the long-term effects of soy formulas, Strom *et al*.[1] undertook a retrospective study among adults who as infants were fed

on either soy formula or cow's milk formula. The researchers concluded that exposure to soy formula does not appear to lead to different health or reproductive outcomes.

Timing of exposure is also a critical factor in predicting potential steroid hormone effects. The devastating effects of diethylstilbestrol taken in early pregnancy only became apparent in offspring, who were predisposed to reproductive dysfunction and adenocarcinoma later in life. This genetic imprinting and the effects of phyto-oestrogens on sexual differentiation in many mammalian and avian species relate to prenatal rather than postnatal exposure. Unfortunately, there appears to be no ideal animal model for the human neonate; therefore, it is difficult to extrapolate these animal data to infants. Soy-based formulas are consumed postnatally, not prenatally. Any negative effects from phyto-oestrogens might be expected to be enhanced by exposure of the fetus to isoflavones from soy products consumed during pregnancy.[2]

In the absence of practical examples to support adverse effects of soy-based infant formulas, despite their use for more than 30 years, it could be argued that long-term benefits may ensue from infant exposure to soy-based formulas containing isoflavones because this could confer protection later in life against hormone-dependent diseases. In this regard, it is speculated that the low incidence of hormone-dependent diseases in China and Japan, where soy is a staple, may in part be a consequence of a lifetime exposure to phyto-oestrogens from the traditional diet. The concept of early-life diet influencing later disease outcome is gaining credence. Interestingly, the incidence of such diseases is increasing and this trend appears to be related to a move toward a more westernised diet in these countries.[2]

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1. Strom BL, Schinnar R, Ziegler EE, *et al.* Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001; **286:** 807-814
2. Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE. Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. *Am J Clin Nutr* 1998; **68:** suppl, 1453S-1461S.

Genetic testing for spinal muscular atrophy

To the Editor: We read with interest the description relating to spinal muscular atrophy (SMA) in the black South African population.[1] The authors have described an interesting local group. We are, however, concerned that this may not be representative of the whole of South Africa.

We would be particularly interested to hear more about the clinical phenotype and epidemiology of this cohort of patients. The authors have, for example, included phenotypic patients with facial weakness in their grouping. This is of significance because the international guidelines (ENMC, 1998) regard these as exclusion criteria for SMA.[2] In our cohort of patients, facial weakness in the SMA molecularly genetically confirmed group is not a feature. Our 4 patients who presented with facial weakness, and were found to be negative for the common SMN (survival motor neuron) gene mutation, were subsequently confirmed to have other pathologies (congenital myopathy or congenital dystrophy).

We are concerned that the authors' findings are not representative of the whole of South Africa and that incorrect genetic advice could therefore be given to families and patients of indigenous African descent. As described in our paper,[3] we found no deviation from the international detection rate for the common SMN gene deletion (95 - 100%), regardless of our patients' ancestry. This paper was published in 2002. Our figures have not altered since then and have now increased to a total of 50 patients assessed clinically and genetically confirmed to have SMA, with 22 being of indigenous African origin. We have had no patients of indigenous African origin referred through the services who complied with the international guidelines for SMA and were negative for the common SMN gene deletion on genetic testing.

This discrepancy in SMA findings between two geographically distinct institutions is of diagnostic import, and we look forward to the published evidence from the authors that their discordant black patients have some other defect, either localised to the SMN gene or impacting on SMN gene expression.

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1. Labrum R, Krause A, Rodda J. Genetic testing for spinal muscular atrophy (SMA) in South Africa. *S Afr Med J* 2006; **96:** 200.
2. 59th ENMC International Workshop: Spinal Muscular Atrophies: recent progress and revised diagnostic criteria. 17-19 April 1998, Soestduinen, The Netherlands. *Neuromuscl Disord* 1999; **9:** 272-278.
3. Wilmshurst JM, Reynolds L, Toorn VR, Leisegang F, Henderson HE. Spinal muscular atrophy in black South Africans: Concordance with the universal SMN1 genotype. *Clin Genet* 2002; **62:** 165-168.

Can (or should) doctors be entrepreneurs?

To the Editor: Traditionally, being entrepreneurial is associated with successful business outcomes, and far removed from conservative medical practice.

The concept encourages enterprise, initiative and forward thinking – definitely *not* foreign to medical practice.

Modern business schools use newer terms of risk management, networking and personal challenge to move forward. These principles are critical to surviving changes in the practice of medicine wherever one works, as specialist or generalist, but one must not move too far from core expertise and experience.

One response to change that I have embarked on is the challenge of short-term overseas locum work, which has several significant benefits. Firstly, it is immensely satisfying professionally to function and cope in a foreign environment. Secondly, the financial rewards are definitely worth the effort. Thirdly, the break from routine and the opportunity to explore a new country is therapeutic, and lastly the logistics can be streamlined to minimise disruption to one's practice.

Business people are praised for international travel and promoting foreign trade. South African doctors have been negatively influenced by past medical emigration and are naturally concerned that an overseas venture will be perceived (by colleagues and patients) as the first step towards emigration. These fears must be countered by openly capitalising on the reality that medical mobility is an international phenomenon driven by a world shortage of experienced doctors. Gaining overseas experience and earning foreign exchange from short-term locums are laudable activities; in addition one has the opportunity to reflect on medical facilities at home.

My experiences have been gained from general practice in Ireland, a beautiful and hospitable country. Currently it is possible for South African medical graduates to gain lifelong full registration without any need for examinations. This status is now under threat and this door of opportunity, like many others over the past three decades, is likely to close soon as the Irish Medical Council, in its perceived wisdom, has recommended that this privilege be rescinded.

Your last chance to register is now.
Be entrepreneurial, you will have no regrets.

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2010, HIV and international public health issues

To the Editor: South Africa's capacity to hold a successful World Cup event in 2010 has been widely discussed. However, I have not seen anything on the public health issues of our hosting such an event, although these issues seem to be considerable.

Images and reports of the World Cup in Germany lead one to expect that very large crowds will attend. They also lead one to expect that there will be extensive celebrations in the streets and stadiums. Large sections of the crowd will be foreign tourists, exposed to cultures very different from their own. They will have all the disadvantages of displaced persons. These include a reduced resistance to engaging in behaviour patterns they would regard as unacceptable in their own milieu.

The combination of a large number of displaced persons partying and celebrating with free use of alcohol in a country with (at present) weak policing makes one expect that our emergency services will be stretched to their utmost coping with immediate consequences, such as violence, rape and alcohol- and drug-related emergencies.

But there is another issue which must be thought through. The injection of huge numbers of HIV-naïve partying people into a nation with one of the highest incidences of HIV infection, and definitely the highest incidence of rape, in the world can be expected to result in large numbers of newly infected people returning to nations with very low HIV prevalences. That is especially true if they make use of local prostitutes. If the press is to be believed, prostitutes in Germany and neighbouring countries did a very brisk trade in Germany during the last World Cup. It seems to me that this latter danger is so great that it should make us pause in our enthusiasm about hosting the 2010 event. Perhaps, for the sake of international public health we should suggest that another nation take on the task. What a dreadful thought!

If these considerations are not enough to make us suggest that another nation provide the venue, at least they require that we mount an enormous campaign to protect soccer tourists with a lot more than a condom message! Education campaigns aimed at preventing new HIV infections in our country have been singularly unsuccessful. That fact should perhaps make us limit our options even further. Perhaps the event should go to a country with a low incidence of HIV and rape!

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