NOFSA statement on generic bisphosphonates

To the Editor: We wish to set the record straight in terms of inaccurate and irrelevant comments in the National Osteoporosis Foundation of South Africa's letter.[1]

NOFSA should have availed themselves of the facts leading up to the 'Notice of rejection' of an old application which is not linked to the current 10 mg and 70 mg registrations (even the formulations are different). The old application was rejected precisely because the Medicines Control Council was doing its job. They wanted *bioequivalence data*, and because this was not possible in 1998/1999 we attempted to register the product on *dissolution data alone* (based on the unique physicochemical and pharmacokinetic properties of alendronate). The MCC insisted on bioequivalence data, which became available later and were submitted with the *new* applications.

NOFSA admits the 'limitations' of the Epstein studies, but justifies its inclusion because 'differences exist in dissolution profiles of different alendronate preparations' and because they are 'the only dissolution data published'. Cipla Medpro's view is that this statement is not justified. Firstly, we are led to believe that if an article has been published, it does not matter how limited, how small, how biased, how irrelevant or how flawed it is, it can be 'reliably referenced'. Secondly, a Medline search would have yielded a number of peer-reviewed publications on alendronate generics with similar dissolution profiles and bioequivalence which should also have been 'reliably referenced'.[2-4] It is important to note that *in vitro* data alone are not sufficient in the case of alendronate to infer *in vivo* equivalence or inequivalence. Final conclusions on the bioequivalence (and interchangeability) of alendronate-containing products need to be drawn from properly designed *in vivo* bioequivalence studies. This is why the innovator also chose to use bioequivalence data (in normal healthy volunteers), and no additional clinical efficacy and safety data, to register a completely different alendronate formulation (their oral solution) in the USA.[5]

NOFSA's contention that the MCC has 'similar concerns regarding bioequivalence and lack of information on the long-term clinical efficacy and safety of generic alendronate preparations' puzzles us, as we have no knowledge of such concerns. The MCC has *never* explained or justified the inclusion of alendronate on this list. NOFSA also conveniently uses general statements from the MCC's 'Generic Substitution' document as if they apply specifically to alendronate.

Furthermore, the Non-Substitutable List is being revised, as officially acknowledged by the Registrar.[6] Therefore, instead of hiding behind the notion that it is 'the only source of information', NOFSA should rather, in the interest of all osteoporosis sufferers in South Africa, be asking why this molecule is on this list if there is no compelling scientific reason for its inclusion.

It is evident, from comment on Epstein et al.'s article and other publications,[7-9] that the mechanism of bisphosphonate oesophageal irritation is not yet properly established. It is far more complex than previously thought and probably a combination of both systemic and pre-systemic effects. It is therefore inappropriate to ascribe the bisphosphonate oesophagitis only to its potential 'pre-systemic' local irritant effect.

While we acknowledge the expertise of 'leaders in the field of metabolic bone diseases' and 'international experts on osteoporosis', we respectfully submit that these and even clinical pharmacologists (if not steeped in regulatory matters) are probably not appropriate experts on regulatory science.

We accept that the onus is on us to prove the efficacy and safety of our product, Osteobon. We have done this according to international norms, standards and guidelines, and this is why both the MCC and the Food and Drug Administration (FDA) have approved the product. NOFSA, on the contrary, still has no evidence of a lack of efficacy and safety of Osteobon.

It is therefore disturbing that NOFSA chooses to question the integrity and credibility of the MCC, who approved the efficacy and safety of generic alendronates for the indications applied for, and who strive to match the regulatory standards of developed countries. We respectfully suggest that NOFSA should rather focus on the goals of its own organisation and acknowledge the benefits that generic alendronate can offer to the thousands of osteoporosis sufferers in South Africa who may not be receiving appropriate treatment due to the high cost of medicines.

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Rural doctors given fresh hope

To the Editor: The Izindaba article by Chris Bateman refers.[1] It was indeed refreshing to hear that we have somebody, in the person of Nozizwe Madlala-Routledge, Deputy Minister of Health, who seems to be understanding and willing to honestly face the current crisis in health care and make a commitment to action. It is long overdue that someone from the Department of Health should come out of the closet of denial and say, 'These are the facts, let's act on them.' To boldly and humbly admit that we have a problem is the first step towards a solution. Also, to be open and willing to acknowledge your mistakes seems to be a novel, but praiseworthy, way of conducting politics. The response by the Deputy Minister at the recent Rudasa congress reminds me of the words of John Ruskin, written in the late 19th century: 'Your honesty is not to be based either on religion or policy. Both your religion and policy must be based on it.'[2] If the words spoken are followed by the promised action, there remains a chance that some of the lost hope and trust in the Department of Health may be rekindled.

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Paediatric surgery in the Third World

To the Editor: Third-World nations are characterised, if not defined, by a colonial past, poverty, poor educational standards, particularly among women, and limited health care resources.[1]

In most Third-World countries children constitute more than half of the population[1] and Africa's population is predicted to increase by 1 000 million over the next 45 years, despite the ravages of HIV/AIDS, war and famine.[2] The number of children, including children with surgical disease, will therefore increase dramatically. But clinicians attempting to provide surgical services to children in Africa are faced with many problems including a lack of human and material resources.[3] Of the world's least developed countries, 70% are in sub-Saharan Africa.[1] Debt repayment, housing, education, and social service and health provision are near-impossible tasks faced by many African countries; some maintain that this confirms Africa's 'basket case' status.[4]

Primary health care has rightly been emphasised by cash-strapped societies, but HIV/AIDS has introduced new challenges for communities, clinical practice and health economics. It adds to the internecine battle for resources and has become a funding 'black hole' from which nothing escapes, while secondary and tertiary care, which include paediatric surgery, remain underfunded. Yet 85% of children in the Third World require surgery of some sort before their 15th birthday.[3] Most require simple surgery that is within the compass of appropriately trained general surgeons who must provide paediatric surgical services because of the paucity of paediatric surgeons in Africa.[3] Such 'multi-skilling' will remain the basis of surgical services in the medium term and mandates that the training of general surgeons must include paediatric experience, along with obstetric and trauma surgery.[5]

In Europe there is a paediatric surgeon for every 50 000 of an ageing population. In South Africa there is only 1 for every 2 669 000 people,[6] most of whom are children. However compared with most African countries, South Africa is enviably endowed with paediatric surgeons.[5] In the UK there are some 6 000 live births per annum per paediatric surgeon and in South Africa about 35 714.[6]

Surgical conditions in children constitute a significant public health problem and fully justify an increase in the number of appropriately trained surgeons.[3] Given the projected increase in the number of births, inaction is inexcusable. Clearly it is also important to develop nursing services in order to improve quality of care and minimise morbidity. Human resource difficulties are exacerbated by the loss of trained medical and nursing personnel to developed countries. Africa must strive harder to retain her academic clinicians and nurses to provide tertiary services to African children and training to African surgeons.

The tradition of sending surgeons and nurses from former colonies to Europe for higher training is expensive and results in largely irrelevant experience. Training for African surgeons should take place in Africa where children with relevant disorders abound. Few hospitals can afford to have surgeons away from their posts while gaining experience in paediatric surgery and fewer surgeons can afford to live without a stipend. Training capacity in Africa exists[7] and a growing need exists, but this requires funding.

Europe's awakening to the relevance of Africa in their own development will not solve Africa's economic problems. However this provides an opportunity for governments and other funding agencies to confront the looming catastrophe and to urgently train and develop surgeons with paediatric experience who can deal with the surgical problems of the extra 1 000 million people to whom Africa will soon be home.

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Separation-survivability – the elusive moral cut-off point?

To the Editor: De Roubaix and Van Niekerk[1] correctly point out that the utilitarian position holding that fetal life has no value cannot be defended, and argue that the Choice on Termination of Pregnancy Act is ethically deficient because it does not accord the fetus any moral significance. The notion of sentience as a measure of value is simply not defensible. Their argument that separation-survivability is the absolute moral cut-off point for termination of pregnancy is compelling and should inform our profession and bring pressure to bear on redrafting this Act.

A limitation of the paper is that it could not examine the moral impact on persons who make a utilitarian decision to end a fetal life that was entrusted to their protection. The potential or complete humanity of that life can be denied and the need to grieve repressed until some later event confronts such persons with its attendant grief and guilt. Many crises can break this cycle of denial, for example divorce or the death of a spouse or child, desire that the child from a later pregnancy should survive, and the sight of an ultrasound picture of a fetus of the same gestational age. They then discover what Raskolnikov found in Dostoyevsky's novel, *Crime and Punishment*, when he murdered the despicable old woman moneylender: that the most apparently useless individuals have value – have what theologians call the image of God upon them. The more prolonged the pregnancy, the more profound is this reaction, which supports De Roubaix and Van Niekerk's graded position on the value of prenatal life.

Health care workers who have to perform terminations of pregnancy face the same feelings of grief and guilt. That partly explains their frequent anger or distant stance taken against women seeking abortions – and why so many midwives burn out when they are compelled to do this work. Supervisors should provide counselling and support, and the opportunity to work in another area, rather than a disciplinary response.

Some hold that such grief and guilt are conditioned and should not be felt. Suggesting that the deep nurturing and protective drives in humans should not exist is dangerous for the effective nurturing of children, the sacrificial love needed for marriage, old age, and the sacrificial attitude to the sanctity of persons needed to be a good health care worker.

Grief and guilt are distressing to those affected, and for persons involved in terminations of pregnancies who experience it, healing only comes when it is honestly faced. Distress can affect family relationships before help is found. There is therefore a moral and ethical imperative of thorough counselling of persons seeking an abortion. None should be allowed to undertake it lightly without careful evaluation of the cost to their personalities and families. They should be assisted to find solutions to the problems created by the pregnancy, and options including adoption or foster care, getting employment, counselling of the couple together, ensuring maintenance is paid through pregnancy and childhood, and securing emergency housing and emergency financial aid should be explored.

No health care worker should be pressured to take part in or perform terminations of pregnancy against their conscience. The need for adequate pre-abortion counselling, and for health care workers to be free to follow the dictates of their conscience in this matter, should be written into any new legislation and acknowledged in our present practice.

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1. De Roubaix JAM, van Niekerk AA. Separation-survivability – the elusive moral cut-off point? *S Afr Med J* 2006; **96:** 623-626.

To the Editor: When arguing for a particular moral position, philosophers should provide a fair representation of the opponents' view – and in this case not focus solely on some weaknesses of *some* utilitarians.[1] Granted the authors' right to defend their essentially 'pro-life' stance, the use of an ideological vocabulary, such as feticide, killing and partial birth abortion, is disparaging for those who do not share their 'pro-life' position. Defending their own position they talk about viable fetuses, neonates, infants, babies and toddlers. It would be more appropriate to use the neutral medical vocabulary: zygote, embryo, fetus and neonate.

The argument is that 'separation-survivability is the only morally acceptable cut-off point' after which termination of pregnancy is morally unacceptable. The title ends with a question mark and adds the qualification that it is *elusive* (i.e. misleading). The argument from viability used as a legal cut-off dates back to the *Roe v. Wade* case in 1973 in the USA. In 1995, H J Gert made a philosophical argument against viability as a moral cut-off,[2] namely, 'it is far from clear why one's moral status would change as one develops the ability to survive on one's own'. Furthermore, the question was raised how an

outside factor such as medical technology can have a bearing on one's moral status?

In logic, premises are true or false. The conclusion is valid if supported by the premises. An argument is sound if it is valid and if the premises are true. The authors' conclusion states: 'a human being that can survive on its own has every right not to be killed'.[1] A 25-week-neonate cannot survive on its own but is entirely dependent on the availability of medical technology and expertise. Do the premises support the conclusion?

The *argument from potentiality* states that from fertilisation (rather than conception) the zygote has the potential to evolve into a mature and rational human being. Whether this materialises or not is irrelevant. It is *potential* that gives the zygote-embryo-fetus its moral standing and the attached right to life. The authors reject the argument from sentience – only a presentient or insentient embryo-fetus can be aborted[3-4] – but propose the same gradualist approach (i.e. a pre-person has a right to life). In other words, before 25 weeks the embryo-fetus has no personhood (but the potential to become a person); from 25 weeks on it is a *pre-person* (until when?).

The second premise claims that the world cannot exist without human beings, a characteristically strict anthropomorphic position that is easily dispelled by looking at evolution. Man is a latecomer on this planet. The premise does not support the conclusion and is false.

The third premise is similar to the first, stating that the *pre-person* has the same moral importance as the term neonate. A pre-person is no more a person in the philosophical sense (i.e. rationality, command of language, self-consciousness, control or agency, moral worth)[5] than a term neonate. The premise only states what is the conclusion.

The fourth premise, the moral unacceptability of infanticide, is a conclusion and not a premise.

Although the term abortion does not appear in the title, the first sentence sets the stage: this is about abortion, which is 'the termination of pregnancy … before the fetus reaches viability (currently regarded as 24 weeks in the UK)'.[6] Hence, a pre-person can be terminated, not aborted. This is not just semantics. Termination after viability is usually practised for medical indications to prevent harm to the pregnant woman. One could even say that this no more morally justified than before viability (a topic not really addressed by the authors) unless it is from self-defence. However, self-defence requires an aggressor and the zygote-embryo-fetus is innocent.

The 'elusive cut-off' lends moral support to third-trimester fetuses. It illustrates the difficulty to convincingly argue for an intermediate position between pro-life and pro-choice. Moreover, it can be misleading (elusive). Personhood requires individuality; because individuality is not finalised before 12 weeks, the pre-embryo (much less a clone) cannot be a person. We know when personhood ends (irreversible coma, permanent vegetative stage), not when it starts. The *potential* for personhood is there from fertilisation; when it actualises is less definable. If a sliding scale were to start at 1 and end at 10, where on the scale is the pre-person?

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Dr De Roubaix replies: Dr Larsen makes a valid point on the necessity of adequate counselling. A grieving process similar to that following bereavement may occur after spontaneous and interventional abortion, since strong maternal bonds may be present before 12 weeks' gestation.[1] Moreover, spouses and partners may also experience a feeling of loss. Grieving is more likely following spontaneous than therapeutic abortion, and I would expect this to apply to TOP as well, when pregnancy is unplanned and unwelcome. But because of the complexity that surrounds termination and the need for rapid decision and action, guilt feelings may surface even some time after termination. Therefore counselling should be mandatory (at present Act 92 of 1996, the TOP act, only recommends it), though of course it would be difficult for the State to comply.

Dr Van Bogaert seems to be generally critical, with accusations of one-sidedness, that we attempt to support a pro-life position, the ideological use of vocabulary and the use of the word 'elusive' in the title. He is critical of the survivability cut-off argument, misunderstands our position on survivability, criticises the logic of our argument and voices some of the problems with the intermediate position on abortion. Our article is not a comprehensive critique of utilitarianism, whose concept of personhood has rendered influential support to the arguments for free choice in abortion (even though the central argument is female reproductive autonomy, as Act 92 of 1996 clearly sets out in the preamble). Peter Singer,[2] Michael Tooley[3] and John Harris[4] freely concede that consistent application of their personhood argument has the inevitable problematic of legitimising the killing of neonates since they, too, are not yet moral persons. This concession enables criticism of their argument, but that does not mean that we are pro-life in the accepted sense. Van Bogaert may have misread, or misunderstood, our argument. We believe that termination is always a moral matter, but also that the moral significance of prenatal life is not necessarily absolute and should be contextualised against a variety of other arguments. We do not argue that every pregnancy should necessarily proceed to

term, only that separation survivability might be a moral cut-off beyond which termination should only rarely be legitimate.

We have not intended to use any term pejoratively or as an ideological argument, as Van Bogaert seems to deduce. Though words often simply have meanings we ascribe to them, I take the word 'elusive' to mean 'difficult to find or catch, to understand', not 'misleading' as Van Bogaert suggests.[5]

The argument concerning separation-survivability actually precedes *Roe v. Wade*, which was a legal, not a moral position, such as ours, and not enforceable. The court suggested as a compromise that States of the Union, who so wished, could use separation-survivability as a cut-off to abortion. Several States allowed 'termination' of the fetus during labour at the crowning of the head, before it was actually delivered and became a 'person' with legally protected rights. President George B Bush recently stopped this. In response to Gert's supposition we suggest a moral coincidence between the separation-survivable fetus and the neonate, and that some of the recognition accorded the latter might also be applicable to the former. This is in accordance with general societal intuitions and legal practice, and may not be as inconsequential as Van Bogaert seems to think, since there are societies where termination of third-trimester fetuses is not frowned upon. As to the question about the influence of 'outside factors' on morality, is it not what responsible applied ethics is all about – the application of context and circumstance to moral thoughts and deeds? The challenge to bioethics is that we constantly attempt to make moral sense out of the application of (often new and innovative) scientific knowledge. Humankind is characterised by a constant inquisitive involvement with the world that surrounds us and with which we are inextricably entwined.

As to Van Bogaert's criticism of the construction of our argument, the point is not that a *25-week* fetus is *necessarily* separation-survivable; whatever the cut-off, we suggest that such a point exists. Our quest was to examine its moral significance. We do not disregard the moral significance of sentience, but separation-survivability probably precedes its advent, and the latter, not sentience (which it obviously would acquire later) would determine the fetus's possibility of entering into and survival in the world.

Van Bogaert's position on potentiality is unclear. It is certainly a significant argument, with three qualifications. Firstly, it needs to be of a moral nature (be human potentiality with the definite endpoint of the creation of a person capable of moral thoughts and deeds). Secondly, it is only relevant once twinning has ceased to be possible, since only then can one sensibly refer to the potentiality of a particular identifiable individual. Thirdly, extrinsic potentiality, i.e. a favourable environment in which to develop, is as important in our conception of potentiality as intrinsic, i.e. genetic, potentiality. We draw on insights from existential phenomenology to posit that speciesism (in a moderate guise) expresses fundamental aspects of human self-understanding and consequent self-esteem. The human species is essential for the possibility of sense-making and sense constitution in and of the world through its particular use of what Popper called the 'higher functions' of language. Without the essentially human phenomenon of valuation, a function of a personal reflective mode of being, in terms of which ethics and morality occurs in our world, it would be impossible to develop a consistent moral argument. The very possibility of morality is therefore dependent on humanity, arguments that some primates express (a rudimentary form of) morality notwithstanding. Of course this is anthropocentric, but can any animal, or can we, sensibly, convincingly argue to the contrary? But note that this is not an absolute 'right to life' argument for all 'human beings' (like anencephalic fetuses, irreversible comatose patients, etc.); nor is it an argument against 'animal rights' or in favour of cruelty to animals. It simply means that favouring 'our' species is inevitable for our mode of being.

I concede the moral challenge of the 'middle road', which in part motivated our article. But in practice many supporters of free choice actually follow this path, since they generally reject 'late' (third-trimester) termination and argue that one or more characteristics acquired during pregnancy preclude termination beyond a certain point. Individuation is usually regarded as having been confirmed at gastrulation (endometrial implantation). Psychological personhood, usually defined as the ability to value one's life, to be self-conscious, to be aware of one self as some sort of continuing substance of existence, is gradually attained some time after birth. We argue that in Van Bogaert's idiom perhaps 5 out of 10 is adequate for a 'right to life'.

These matters will be dealt with more systematically and comprehensively, and the applicable philosophical arguments developed more extensively, in our forthcoming article in the *South African Journal of Philosophy*.

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