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A bioethicist's view of the use of biosimilars

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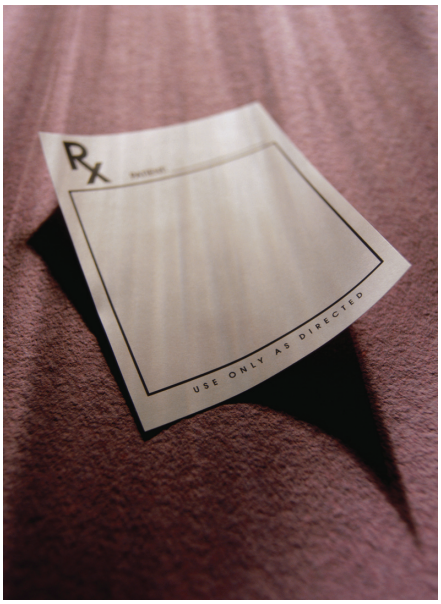

In recognition of the many ethically sensitive issues raised by the production and use of biosimilar medicinal products, the author imagines having to answer the non-multiple choice question 'From the ethical point of view, what is the most important issue raised by biosimilars?', and endeavours to explain why the proposed answer is 'safety'.

Keywords: Bioethics, drugs, ethics committees, legislation, risk, safety

The objective of this article is to discuss some of the ethical issues that arise when biosimilars are used in clinical practice.

As the Committee for Medicinal Products for Human Use states 'it should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established' [1]. For this reason the processes of evaluation and authorisation are more complex for biosimilars than for generic drugs and their quality, efficacy and safety need to be very thoroughly weighed [2].

The production and use of biosimilars involve a multitude of issues that range from those such as safety, risk, efficacy and informed consent, that concern individual users, to others that affect society at large, such as the organisation of healthcare services, the allocation of resources, industrial and commercial rights, conflicts of interest. All are ethically relevant.

A careful examination of the doxography of bioethics (from the seventies, when the term was coined [3] to the present) offers evidence of an evolution in the approach to this discipline. A probably early bias towards the principle of beneficence–the legacy of a centuries-old tradition of medical paternalism–was followed in the eighties by the emergence of greater emphasis on the principle of autonomy and its companions, individual freedom and self-determination. Today, at a time when organisation is a priority, the focus has perhaps shifted towards the principle of justice, the deal between providers and users of health care, negotiation. This is obviously a somewhat simplistic analysis, with all the limits that implies, since neither the various problems nor the various bioethical arguments are watertight compartments. The close interconnections are perfectly exemplified by the debate concerning the procedures for authorising the marketing of biosimilars [4, 5]. These procedures involve both 'collective' organisational issues (including questions of justice) and 'individual' clinical issues (which embrace such aspects as risk–benefit ratios).

Faced with such a varied scenario, a bioethicist might ask: 'What is the key ethical problem posed by biosimilars?'. There is no absolute answer to this question, as the weight of each problem will vary according to individual cases. At times the clinical aspect may seem the most important, while in different circumstances the legal aspect may appear to prevail. Notwithstanding this, if I were required to answer this question in a non-multiple choice quiz, my personal reply would be: 'The single most important issue is safety'.

While I believe that many aspects of so-called 'biolaw' are of great importance, for me the well-being of the individual must be the priority consideration. Establishing the level of acceptability of a risk is certainly a technical matter, but it is also a social problem. Sadly, scientific data are not always helpful, and it is sometimes extremely difficult to quantify the entity and probability of a given risk.

The whole question of risk acceptability is further compounded when biosimilars are used for the therapeutic benefit of somebody other than the person receiving them, as is the case with granulocyte-colony stimulating factor (G-CSF) for stem cell mobilisation in related and unrelated healthy donors [6]. This procedure raises a number of ethical questions [7]: i) the person being treated with a biosimilar product is

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not the person for whose therapeutic benefit the treatment is administered; ii) there could be concerns that a biosimilar G-CSF may be associated with greater risks than a brand product; iii) the main reason for using a biosimilar G-CSF is economic (the cost to the healthcare service will be lower than in the case of a brand-name drug).

There is no easy solution to these problems. It is some comfort that the regulatory authorities are generally of the opinion that the efficacy and safety of authorised biosimilars are comparable to those of the reference product [8, 9]. The Italian Medicines Agency (AIFA), in its Concept Paper 'Biosimilar Drugs' notes that 'biosimilar drugs are produced in accordance with the same quantitative standards that apply to other medicines' and therefore offer ample guarantees of safety [10]. However, long-term data are often not available and, as Dr Witts wrote, back in 1965, 'the final test of the safety of a drug is in fact its release for general use' [11].

The problem of risk is complex and there are no universal solutions, which is why we must be especially vigil in at least two areas.

The first is at the level of authorisation by regulatory authorities, in the knowledge that, as stated in a key document published by FDA, 'We are in the beginning of a new era for drug safety where protecting public health means that [the FDA's] responsibility doesn't end when we grant a product market approval; that is merely the first check point in ensuring safety' [12].

The second level is use. While the Concept Paper published by AIFA notes that 'the choice of treating with a biological or with a biosimilar drug remains a clinical decision entrusted to the specialist physician', it might be as well, where appropriate and feasible, for the specialist physician to receive advice from an ethics committee before making a final decision.

For patients

The processes of evaluation and authorisation are more complex for biosimilars than for generic drugs, and the ethical problems they raise are similarly more numerous and more complex. The present article points to safety as being of particular importance from the ethical viewpoint, and suggests that it should receive priority consideration when the admissibility of biosimilars is being assessed.

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