Ethics, social, legal, counselling

A critical assessment of the impact of the European Union Tissues and Cells Directive (2004) on laboratory practices in assisted conception

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David Mortimer gained his PhD from Edinburgh University in 1977 and received post-doctoral training in Edinburgh, Paris and Birmingham before joining the faculty of the University of Calgary in 1983. There he continued his research on human sperm pathophysiology and was Scientific Director of the Infertility Programme. In 1991 he moved to Sydney IVF where he developed the novel sequential culture media and incubators that now constitute the Cook Culture System. He held positions at Sydney University and the Royal Prince Alfred Hospital, worked on the WHO's Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male, and was Programme Chairman for the 11th World Congress on IVF and Human Reproductive Genetics held in Sydney in 1999. By 2000 he had moved back to Canada and established an international consulting company based in Vancouver. Major consultancy projects since 1986 have included andrology labs, sperm banks and IVF units, and advice on accreditation, total quality management and risk management. He has 120 publications to his name, including two books, *Practical Laboratory Andrology* and *Quality and Risk Management in the IVF Laboratory* (with Dr Sharon Mortimer), and has given over 200 conference presentations worldwide.

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Abstract

The European Union's Tissues and Cells Directive (2004) establishes an extensive framework of standards for all tissue banks throughout the EU. This article considers how the requirements of the Directive might be expected to achieve the stated goals of promoting the safety of assisted conception treatments and/or facilitating the achievement of higher success rates. While there will certainly be some significant costs to implementing these systems, there are substantial benefits and returns, for example, quality improvement and risk minimization. However, there are grave problems with the feasibility, effectiveness, and probable adverse impacts of applying arbitrary clean room air quality standards to assisted conception facilities, especially IVF laboratories. This is likely to have negligible impact on the already low risks of both culture contamination and operator infection, but would severely compromise the ability to maintain gametes and embryos under optimum environmental conditions. Proper consideration must therefore be given to the particular circumstances that affect reproductive tissues (indeed, the same is true for all areas of tissue banking), to ensure that the final technical regulations are founded upon realistic expectations based on objective evidence from process-based systems. The creation of the highest quality embryos, and healthy children, must always remain the primary focus of assisted conception treatment.

Keywords: *clean rooms, embryo quality, government regulation, infertility, IVF, tissue banking*

Introduction to the Directive

On 31 March 2004, the European Parliament issued Directive 2004/23/EC entitled 'On setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells' ('the Directive'), which was published in the Official Journal of the European Union on 7 April 2004 (European Union, 2004a). The Directive was considered necessary due to the diversity of standards across Europe, the extensive exportation/importation of certain tissues (e.g. heart valves), the need to increase both the availability of donated tissues and the effective use of those tissues available, and to avoid errors arising from the multiple coding and classification systems in use across Europe. It applies to all human tissues and cells, including haematopoietic peripheral blood, umbilical cord and bone marrow stem cells, reproductive cells, fetal tissues and cells, and adult and embryonic stem cells, but excludes blood and blood products as well as human organs. The Directive also does not apply to tissues and cells used as autologous grafts within the same

surgical procedure and without being subjected to any 'banking process'.

In its preamble, the Directive identified its raison d'être as being "to safeguard public health and to prevent the transmission of infectious diseases via transplanted tissues and cells," and requiring that "all safety measures need to be taken during their donation, procurement, testing, processing, preservation, storage, distribution and use". It also states that the European Community should endeavour to promote the highest possible level of protection to safeguard public health regarding the quality and safety of tissues and cells. Article 28 of the Directive provides for the development of specific technical requirements for: (i) the accreditation, designation, authorization or licensing of tissue establishments; (ii) the procurement of human tissues and cells; (iii) a quality system, including training; (iv) selection criteria for donors of tissues and cells; (v) laboratory tests required for donors; (vi) cell and/or tissue procurement procedures and reception at tissue establishments; (vii) tissue and cell preparation processes; (viii) tissue and cell processing, storage and distribution; and (ix) the direct distribution to recipients of tissues and cells.

However, these matters were not covered specifically in the Directive, but will be published in a series of subsequent 'Technical Requirements' documents that are to be developed by one or more scientific committees.

The first Technical Requirements document on the donation, procurement and testing of human tissues and cells was made available for public consultation in August 2004 (European Union, 2004b), and its publication in final form is anticipated in the near future. The second Technical Requirements document was released for public consultation several weeks after the original submission of this manuscript. This opportunity for comment has now closed and the definitive version of the document is anticipated towards the end of the year. The delay in releasing the draft document was no doubt due to the diversity of the parties involved in its drafting and the range of technical complexities of its content.

Compliance with the Directive is required by 7 April 2006, although Member States can delay applying the requirements of the Directive for one year after this date to tissue establishments that were already bound by national provisions before the entry into force of the Directive. This 'derogation clause' means, for example, that those UK IVF clinics licensed by the Human Fertilization and Embryology Authority (HFEA) on 7 April 2004 will have until 7 April 2007 to comply. All clinics not licensed at that time, which includes transport IVF centres and centres performing only IUI treatment (see below), have to comply by 7 April 2006. Not only is this a very short compliance period for such far-reaching regulations but, at the time of writing (half-way through the 2-year compliance period), the technical requirements on the processing, preservation, storage and distribution of tissues and cells had still not yet appeared for public consultation, much less been published in definitive form.

It should also be noted that 'tissue establishments' whose activities are to be regulated by the Directive include not just IVF laboratories and sperm banks, but *any* premises where reproductive cells (gametes and embryos), as well as stem cells, are procured, processed, preserved or stored. In other words, every laboratory or doctor's office where a man's spermatozoa are washed for intrauterine insemination (IUI) treatment of his partner, or where donor spermatozoa are thawed and processed prior to insemination. Together, these treatments are hereafter referred to as 'assisted reproduction'. However, the precise definition of 'use' – which is not covered by the Directive – is still not absolutely clear: hence the insemination of cryopreserved donor spermatozoa directly from the packaging into the recipient might not be regulated under the Directive, although the immediately preceding cryostorage activity, or any post-thaw washing step, would be. Of course, in the UK the 'use' of donor spermatozoa is regulated by the HFEA and therefore must take place only in licensed centres.

The Directive requires that each tissue establishment have a comprehensive quality management system, including ongoing quality control and quality assurance activities, internal and external inspections and audits, document control, and an active quality improvement programme. Such requirements are completely normal under modern operational systems and accreditation schemes, e.g. ISO 9001:2000 and ISO 15189:2003 (ISO, 2000, 2003), and have been welcomed by many authorities in the assisted reproduction field (e.g. Wikland and Sjöblom, 2000; Alper *et al*., 2002; Mayer *et al*., 2003; Carson *et al*., 2004; Mortimer and Mortimer, 2005). While their implementation by all European assisted reproduction centres can only be seen as increasing the overall safety and effectiveness of treatment, estimates of the likely cost (primarily in terms of human resources needed) for centres to achieve their implementation remain elusive – but are generally accepted to be substantial, especially for the majority of centres where no such systems are in place already.

The Directive states that the quality and safety of transplanted tissues and cells should be ensured, and rightly focuses largely on the prevention of disease transmission from donor to recipient, as well as on the processing of donated tissues and cells. No-one denies the need to seek the highest possible standards of care, but this goal must reflect reality in terms of minimizing the risks of adverse events or outcomes while maximizing the success of treatment – in this case, a healthy child. Harmonized, pan-European safe practices governing gamete donation will be a real improvement, but the vast majority of assisted reproduction cases deal with helping couples who are unable to achieve a pregnancy without medical assistance, with no involvement of third-party donors. The Directive recognizes the existence of 'partner donation', i.e. donation of gametes between partners who have an intimate physical relationship, and only requires that testing for infectious organisms such as HIV 1 and 2, and hepatitis B and C be performed in such cases in order to assess the risk of cross-contamination (European Union, 2004b), not to regulate treatment. Hopefully, regulators will also recognize the differences between reproductive cells and stem cells, which are both highly labile and more sensitive to numerous extrinsic factors that can affect their functional competence (an obvious aspect of their 'quality'), than more 'static' tissues and cells such as corneas, skin or bone.

In this article, attention has been focused on the Directive's impact on the physical practice of assisted conception, i.e. the handling of gametes and embryos for the purpose of achieving a pregnancy [i.e. items (vi), (vii) and (viii) listed above]. The