Classification of IVF media under the MDD

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Abstract
The issue of the regulation of in-vitro fertilisation (IVF) media used in the assisted reproductive technologies (ART) process has been a matter of discussion at a European level for a substantial period of time, and the regulatory process for IVF media is very recent and still evolving. The following provides a brief overview of the history of ART and the current guidance regarding the classification of IVF media as a medical device under Directive 93/42/EEC.

History of assisted reproductive technologies
Since the first live birth following IVF treatment of Louise Brown, in Oldham, Greater Manchester, UK, in 1978, the assisted reproductive technologies (ART) process has provided treatments for many types of infertility found in women and men. Its practice occurs in many countries around the world and it is now beyond doubt that this approach provides a realistic option for infertile people wishing to form a family. While the subject of ART is a highly emotive one, raising many moral and ethical questions, the result of an early start of monitoring of both efficacy and safety of these procedures is the high public acceptance of the techniques used and a general reassurance in the general public that the IVF technique is reasonably safe for both mother and child.

In the early days of IVF, enthusiasm among ART scientific teams across the world was contagious, with a sharing of learning points, such as some tiny item for the recipe or some small detail which allowed this or that step of progress. At the time, of course, there were no regulations governing reproductive medicine with the emphasis focused on the moral and ethical aspects of the technology and its impact on mother and child.

Historically, one of the major problems in IVF from the outset has been the culture conditions and culture media. Few media fulfilled the requirements for successful blastocyst development, at least not with the right timing dynamics, and for such reasons short in vitro culture was recommended (1–3 days). Typically most laboratories made their own media, based on information shared across IVF laboratories, with the effectiveness of a media formulation evaluated against success rates for blastocyst development and subsequently live birth rates. With very limited regulatory guidance during the early years of IVF, bovine serum was used in most media; the use of bovine serum has since been replaced with human serum albumin (HSA) for safety reasons. In recent years, the emergence of biotechnology companies experienced in the development of laboratory reagents and media, with a focus on providing IVF media to the market, has led to a demand for clear regulatory guidance for the quality assurance and quality control of these products.

Challenges for the regulation and classification of IVF media
Considering it is now 32 years since the first live birth following IVF treatment, it is surprising that the classification and regulation of media used in the IVF process within the EU was only clarified as recently as May 2008.

IVF and ART products are diverse and are used in a wide range of in vitro procedures, involving sperm, oocytes, eggs, blastocysts and embryos. The intended use of IVF media may range from maintenance of the physiological homeostasis required to support and promote fertilisation in vitro, to the maintenance of the physiological homeostasis of the cells during the cryopreservation process and the minimisation of cellular damage during the freezing process. IVF media products are comprised of a cocktail of physiological inorganic salts, energy sources, amino acids and proteins, and there is a range of different formulations available. Some media manufacturers, based on historical information, include the broad spectrum antibiotic gentamicin sulphate, to prevent microbial contamination of the media. Others include HSA, to act a chelating agent for heavy metals that may be present in minute quantities in the micro-environment and also as a surfactant to facilitate embryo and gamete manipulation by preventing them from sticking to glass or tissue culture ware.

There have been a number of challenges relating to the classification of these products, as follows:
1. The intended use of IVF media products does not strictly comply with either the medical device or medicinal product definition, and there was no guidance available for the definition and regulatory control of such products.

The definition of a medical device (reference Article 1(2)a of Directive 93/42/EEC, as amended) is as follows:

‘Medical device means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

• Diagnosis, prevention, monitoring, treatment or alleviation of disease
• Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
• Investigation, replacement or modification of the anatomy or of a physiological process

Control of conception
and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

The definition of a ‘medicinal product’ (reference, Article 1(2) of Directive 2001/83/EC, as amended) is:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

It is not clear that the concept of ‘intended by the manufacturer to be used for human beings’ applies to IVF media. The definition of a human being and the stage at which human life begins is a very sensitive topic, and the definition of when human life begins varies across the EU member states, depending on religious beliefs and legal definition. In the UK an embryo is not legally considered a human being. Therefore the media is intended to be used on cells/embryos and not a human body and from a legal perspective such IVF media products could not meet the definition of either a medical device or medicinal substance.

Another factor for confusion regarding the appropriate regulatory route for the control of IVF media is that a number of IVF media products also contain substances which, if used separately, can be considered to be a medicinal products as defined in Article 1 of Directive 2001/83/EC, such as gentamicin sulphate and HSA. The difficulty arises when trying to apply rule 13 of Annex IX from the medical device directive to these substances, as these substances are not liable to act on the human body and are only included because of the needs identified in the early days of IVF media and ART development.

A lack of regulatory clarity
The lack of a clear regulatory route and clarity on classification of IVF media has led to an inconsistent approach to the regulation of IVF media. Some countries regulate these products as medical devices while some member states within the EU have placed no restriction on the usage of non CE-marked IVF media products. This has led to an inconsistent approach across the EU, with requests for clarification from the borderline working group from both manufacturers and notified bodies. It is also important to note that many IVF media manufacturers have developed from a background in laboratory media preparation, with only the minority having expertise in medical device development.

Current guidance for the regulation of IVF media
To provide a clear regulatory route and classification of IVF media products, a review was conducted by the Medical Devices Expert Group's classification and borderline working group and assessed against the definitions available. The Medical Device Expert Group's classification and borderline working group came to a determination on the regulation of such products in May 2008, and it is now confirmed that IVF media products can be classified as medical devices. The consensus decision on these products has been published in the ‘Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices’, a copy of which may be obtained from the European Commission's website (see http://ec.europa.eu/enterprise/sectors/medical-devices/documents/borderline).

In essence this consensus agreement indicates that, in general, IVF/ART products may be qualified and regulated as medical devices provided that they meet the definition of a medical device as laid out in Directive 93/42/EEC, taking into consideration the principal intended action and intended purpose of the product. The concept of ‘used for human beings’ has been interpreted in the broadest sense as the whole IVF/ART procedure and related products would be seen as (indirectly) ‘(…) used for human beings for the purpose of (…) replacement or modification of (…) a physiological process’ by promulgating pregnancy. Therefore, the definition of medical devices can include IVF/ART products. Because of the variety of products that can be classified as medical devices, the advice from the borderlines group is that classification must be assessed on a case-by-case basis taking into account all product characteristics, however this consensus agreement indicates that in general IVF media will be considered as Class III medical devices under classification rule 13 as stated in Annex IX of the Medical Device Directive 93/42/EEC.

Examples of IVF products which could be qualified as medical devices, along with a preliminary classification are as follows:

- Devices, such as washing, separating, sperm immobilising, cryoprotecting solutions, which are liable to act with close contact on the inner or outer cells during the IVF/ART are likely to be considered as Class IIb medical devices, in particular by analogy of rule 3, ie, these products are considered to present the same level of risk as non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body
- Devices manufactured utilising animal tissues or derivatives rendered non-viable are considered as Class III medical devices according to rule 17
- Devices incorporating, as an integral part, (i) a human blood derivative or (ii) a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are considered as Class III medical devices according to rule 13. The assessment of the ancillary nature of the pharmacological, immunological or metabolic action of any medicinal product contained in IVF/ART products should be done on a case-by-case basis, taking also into account the purpose of the inclusion of this substance into the product. Although case-by-case analysis should always be performed, media intended for use in the IVF process to support the growth/storage of the embryo may generally be considered to be Class III medical devices and in case of doubt where taking into account all product characteristics, and provided that the concerned product meets both definitions of a medicinal product and of a medical device, Article 2(2) of Directive 2001/83/EC could apply.

Following the May 2008 clarification on IVF media classification, additional guidance has been sought regarding the requirement for consultation for media containing antibiotics (e.g. gentamicin), especially considering that the inclusion of the antibiotic within the media is intended as a media preservation constituent and at levels used within the media, it was felt that the antibiotic would not be liable to act on the mother. A clarification from the MHRA has recently been
received and the decision made that IVF media products containing antibiotics should be classified as Class III devices under rule 13, thus requiring a drug consultation in accordance with the medical device directive. Therefore for IVF media that contain both an antibiotic, such as gentamicin and HSA, two consultations will be required, one with a competent authority for the gentamicin and one with the EMA for the HSA. This ruling does raise some concerns, as IVF media manufacturers now need to comply with the expectations of a drug consultation and provide the necessary evidence to show control of the antibiotic and its inclusion within the media. Given that the antibiotic has historically been considered a media preservative, many manufacturers do not have the required level of information to satisfy the requirements of a drug consultation and the competent authority review.

Manufacturers have informally been advised that they will be given time to comply with the requirements of the medical device regulations for any products they may have which meet the criteria stated in the manual of borderline decision, and during this transition period manufacturers are permitted to continue to place their products in the market without the CE mark while they are going through the CE marking process. It should be noted though that the timeframe in which manufacturers must comply with the requirements of this decision was not defined following the borderline decision. Within the EU some countries having a lesser experience of medical device regulations have begun to insist that it is mandatory for IVF media products to be CE marked, while the UK has not yet defined the time period or set a deadline for CE marking. This lack of clarity has resulted in an inconsistent approach to these devices across the EU and the frustration of many manufacturers of these products.

Regrettably, in the case of the regulation of IVF media, there has not been a level playing field across the EU for all involved in the process. Some notified bodies issued CE certification well in advance of the borderline decision of May 2008, while others were left unable to provide a certification service due to the lack of a regulatory pathway. In addition, manufacturers are now being unfairly penalised by some member states if they have not yet completed the CE certification process. Considering that the regulatory timeline for CE marking could take months, if not years, from the point of preparing the required information for dossier submission to certification, it is inconsistent to penalise companies working in good faith towards this regulatory goal until regulators announce a target date for CE marking at a pan-European level, while also allowing manufacturers sufficient time to comply with the requirements. A pragmatic approach really is needed for a product that has been on the market and widely used for over 30 years.

References