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MEDICAL DEVICES: Guidance document

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Guidelines for conformity assessment of *In Vitro* Fertilisation (IVF) and Assisted Reproduction Technologies (ART) products

The present guidelines are part of a set of guidelines relating to questions of application of EU-Directives on medical devices. They are legally not binding. The guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interested parties in the medical devices sector.

I. Objective and purpose

This guideline concerns media, substances or mixture of substances used during IVF and ART procedures which fall under Directive 93/42/EEC (hereafter: "MDD") with the exception of objects such as receptacles, petri dishes, pipettes or syringes.

The medical devices described above are called “IVF/ART products” in this guideline.

This guideline is intended to promote the safety and a high level of performance of IVF/ART products. It aims at promoting a common approach of manufacturers of IVF/ART products and of Notified Bodies involved in the conformity assessment procedures according to the relevant annexes of the MDD. It also aims at assisting Member States’ authorities when verifying, during post market surveillance, that the device meets the essential requirements laid down in Annex I of the MDD.

This guideline describes the main requirements for affixing the CE mark on IVF/ART products, taking account of the current state of the art. It does not attempt to exhaustively cover the design of IVF/ART products. This guideline will be subject to the further evolution of the state of the art.

II. Background and legal basis

II.1. Background

Since the first reported live birth conceived by *in vitro* fertilization, the birth of Louise Brown in 1978, the IVF/ART products and techniques have become common practice for medical treatment for infertility all over the world. Many devices and products are necessary to apply these techniques. The heterogeneity of IVF and ART procedures should also be noted. The fluctuations of the pregnancy rates observed during the last decades could be partly due to these procedures or products.

II.2. Legal basis

As they make pregnancies more frequent, the IVF/ART products may be qualified and regulated as medical devices or medicinal products, depending on their principal mode of action. The qualification must be made on a case by case basis, taking the two modes of action and the intended purpose of the products into account.
When the IVF/ART products meet the definition of medical device, they should be classified according to the rules set out in Annex IX to Directive 93/42/EEC. With regard to classification, the present guideline should be read in conjunction with the Manual of borderline and classification in the Community regulatory framework for medical devices.

The verification of the conformity with the performance and safety requirements to be fulfilled under the normal conditions of use and the evaluation of side-effects and of the acceptability of the risk/benefit ratio must be based on a preclinical evaluation and an evaluation of clinical data. The objective of a clinical evaluation must be to verify that there is an overall positive risk/benefit ratio of the device under normal conditions of use (see MEDDEV 2.7-1). Effects on the gametes, on the embryo and on the mother-to-be shall be taken into account to this end.

Some IVF/ART products fall under class III according to rule 13 since they incorporate one or several medicinal product(s). For these products, a consultation procedure shall be conducted according to point 7.4 of the Annex I to Directive 93/42/EEC.

III. Relevant documents

- Council Directive 93/42/EEC concerning medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council
- Regulation EC/1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells
- EN ISO 10993: Biological evaluation of medical devices
- EN ISO 10993-3:2004: Biological evaluation of medical devices – Part 3: tests for genotoxicity, carcinogenicity and reproductive toxicity
- EN ISO 10993-5: Biological evaluation of medical devices - Part 5: tests for in vitro cytotoxicity
- EN ISO 10993-10: Biological evaluation of medical devices – Part 10: tests for irritation and skin sensitization
- EN ISO 10993-16: Toxicokinetic study design for degradation products and leachables
- EN ISO 14971:2007: Medical devices – Application of risk management to medical devices
- EN ISO 13824:2004: Sterilization of medical devices – aseptic processing of liquid medical devices
- EN ISO 14644: Cleanrooms and associated controlled environments
- MEDDEV 2.1/3: Interface with other directive – Medical devices/medicinal products
- MEDDEV 2.7.1 (2003): Evaluation of clinical data: A guide for manufacturers and notified bodies
- MEDDEV 2.12-1 (2009): Guidelines on a medical devices vigilance system
- MEDDEV 2.12-2 (2004): Guidelines on post market clinical follow-up
- Manual on borderline and classification in the community framework for medical devices: point 4.3 In-Vitro Fertilisation (IVF) and Assisted Reproductive Technologies (ART) products

IV. Hazards/Risks associated with the design and manufacture of the IVF/ART device

Medical devices must meet the essential requirements set out in Annex I to Directive 93/42/EEC which apply to them, taking into account the intended purpose of the devices concerned.

When a medical device is in conformity with the relevant national standards adopted pursuant to the harmonized standards the reference of which have been published in the *Official Journal of the European Communities* or the monographs of the *European Pharmacopoeia*, the device is presumed to conform to the essential requirements mentioned in the Annex Z of the standard. If the standard is not applied or if it is only partly applied, the manufacturer has to describe, in the technical documentation of the medical device, the solutions adopted to meet the essential requirements of the Directive.

The technical documentation must contain the grounds for incorporating each component in the final medical device. Taking account the utility of each component, each risk related to each component should be considered and should constitute an acceptable risk when weighed against the benefit to the gamete, to the embryo or to the mother-to-be. In addition, all risks combined must be acceptable when weighed against the benefit to the gamete, to the embryo or to the mother-to-be.
Among the essential requirements mentioned in Annex I to Directive 93/42/EEC, some risks have been particularly identified and listed below.

Examples of risks associated with the aspect of quality:

- **In Annex I point 1 and in Annex I point 3**: *risks raised by the packaging of the final product*

Some products are provided in a large container for multiple IVF/ART procedures. In case of container for multiple procedures, special attention should be paid to contaminants dropped off unintentionally during a procedure. Considering this risk, the manufacturer should justify, in the technical documentation, that the selected packaging is ergonomic for the user and suitable for the function(s) assigned by the manufacturer.

The instruction for use must include information on characteristics and technical factors known to the manufacturer that could pose a risk when the container is for multiple IVF/ART procedures. It must also include the restriction of the number of procedures.

- **In Annex I point 2**: *solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles and users must be informed about the residual risks*

The selection of each component on IVF/ART products must be based on its safety. The information about residual risks, for example on allergic reaction against antibiotics, must be provided in the instructions for use.

- **In Annex I point 4**: *risks caused by the stability of the final product*

The IVF/ART product may not be adversely affected to such a degree that the clinical conditions and safety of the gamete, of the embryo, or of the mother-to-be are compromised during the lifetime of the device and under the normal conditions for use.
The following information shall be included in the technical documentation and in the instructions for use:
- Information on how to follow the evolution of the most unstable and the most crucial components (such as glutamine, pyruvic acid, vitamins …);
- Information on the storage conditions recommended by the manufacturer;
- Information on how to maintain, throughout the shelf-life of the device, the desired functionality of the devices.

Special attention should be paid to the description of the device's composition that contribute to the control of the stability of the final IVF/ART product and to the information which accompanied the device.

- **In Annex I point 7.1**: *risks raised by the choice of components used (development of the formulation)*

Special attention should be paid to the impurity profile of each component included in the formulation/product, considering that impurities could have an impact on the toxicity and on the performance of the final IVF/ART product.
Besides, special attention should be paid to the degradation profile of each component included in the formulation, considering that the degradation product(s) could also have an impact on the toxicity and on the performance of the final IVF/ART product. For example, glutamine, an amino acid, is degraded in ammonium ions.

In order to evaluate the overall risk due to the IVF/ART products, pre-clinical testing is necessary. If appropriate, the manufacturer should include the following biocompatibility testing:

a. When selecting tests among EN ISO 10993 series of standards, particular attention should be paid to local effects of the device, to the uterine tissue and also to the acute toxicity of the device
b. EN ISO 10993-3:2004 Biological evaluation of medical devices – Part 3: tests for genotoxicity, carcinogenicity and reproductive toxicity
c. EN ISO 10993-5: Biological evaluation of medical devices - Part 5 : tests for in vitro cytotoxicity
d. EN ISO 10993-10: Biological evaluation of medical devices – Part 10 : tests for irritation and skin sensitization
e. EN ISO 10993-16: Toxicokinetic study design for degradation products and leachables

- **In Annex I point 7.2**: *risks caused by contaminants and residues that could drop from the material constituents during to the manufacturing of the devices or during the transport, storage and use of the devices, whether they constitute risks for the gamete, for the embryo, for the patient or for other persons*

Thus, the level of endotoxins should be considered as acceptable to be used with gametes and embryos.

- **In Annex I point 7.4**: *risks caused by the incorporation of ancillary medicinal substance(s) or ancillary human blood derivative, as an integral part, in the medical device*

Irrespective of the concentration of the medicinal substance(s) and the direct contact with the mother-to-be, the conformity assessment procedure for the IVF/ART products which incorporate, as an integral part, a medicinal substance(s) must include the verification of the quality, the safety and of the usefulness of the substance(s).

First, the Notified Body has to assess the usefulness of any ancillary medicinal substance(s) with technical documentation provided by the manufacturer. To establish this statement on the usefulness, the Notified Body has to pay special attention to the contact of the ancillary medicinal substance with the gametes, with the embryo and with the mother-to-be. This statement has to be transmitted with the initial demand to a competent authority for medicinal products of the Member States or, as appropriate, to the European Medicines Agency (EMA). This competent authority or the EMA will evaluate the quality and the safety of the substance(s), including the clinical risk/benefit ratio for the addition of the substance(s) into the device. When issuing its opinion, the competent authority or the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.

Examples of ancillary medicinal substances are: antibiotics, human serum albumin

- **In Annex I point 7.5**: *risks linked to substances which are carcinogenic, mutagenic or toxic to reproduction*

If the IVF/ART solution incorporates substances which are known to be carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Regulation EC/1272/2008[1], the manufacturer must have duly justified their use in the formulation with regard to compliance with the essential requirements, in particular if these substances could be replaced by suitable alternatives. If a part of the device contains phthalates, the same applies. In addition, the labelling on the device or the sales packaging must mention this component and the instruction for use must also contain the information on residual risks and, if applicable, on appropriate precautionary measures.

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF

- **In Annex I point 7.6**: *risks caused by the unintentional ingress of substances into the device during the manufacturing process*

The EN ISO 14644 series of standards can be used, where appropriate. In the technical documentation, the manufacturer must include elements on the manufacturing process and, more specifically, on the level of cleanliness of rooms where the manufacture takes place.

- **In Annex I point 8.1**: *risks caused by infection and microbial contamination (bacteria, bacterial spores, mycobacteria, fungi including sporing forms, yeasts, parasites and viruses)*

The standards EN 556-1 and EN 556-2 define the requirements for medical devices to be designated “STERILE”.
For medical devices which could not be terminally-sterilized, EN 13824 can be used. The sterilisation process must have been validated adequately and must have been documented in the technical file.
Considering the invaluable character of the gamete or of the embryo and the risk of their infection, these types of products are usually provided sterile. Where the device is exceptionally not sterile, the level of contamination by micro-organisms still deemed acceptable must be justified in the technical documentation.

The choice of the environment where the manufacture takes place (clean rooms, if appropriate) must be duly justified in the technical documentation and must correspond to the acceptable level of contamination defined for the device.

Where the device is manufactured utilizing animal tissues or derivatives rendered non-viable, the processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal safety. This essential requirement is also applicable where materials of animal origin are used in manufacturing processes without being in the final device. In order to eliminate or reduce as far as possible the risk of transmitting transmissible spongiform encephalopathies due to tissues of animal from bovine ovine and of caprine species, as well as of deer, elk, mink and of cats, the conformity assessment procedure shall include the evaluation of their compliance with Directive 2003/32/EC.
Examples are: bovine serum albumin used during the process of production of “synthetic” hyaluronic acid, hyaluronic acid extracted from the cock's comb.

- **In Annex I point 9.1 and Annex I point 13.6.c**: *risks caused by the use in combination with others devices*

During an IVF/ART procedure, different kind of devices have to be used on gametes and then on the embryo. The whole combination must be safe and may not impair the specified performance of the devices.
In application of point 13.6.c of Annex I to Directive 93/42/EEC, the manufacturer must describe the characteristics of its product in its instruction for use in order to identify the devices which must be used in combination to obtain a safe combination. In order to reduce the risk of combination error, the manufacturer must precisely indicate the references of the medical devices concerned in the instruction for use. Furthermore, the user shall be informed on known incompatibilities related to a combination with medical device(s) of other manufacturers in the instruction for use.

- **In Annex I point 13**: *risks caused by the information supplied by the manufacturer*

Considering that each device must be accompanied by the information needed to use it safely and properly and that the IVF/ART medical devices are usually composed of multiple components, their instruction for use should contain the whole qualitative composition of the device.

V. Classification

The Manual of borderline and classification in the community regulatory framework for medical devices gives some examples of classification for IVF/ART products: "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' is interpreted in the broadest sense. 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.

Examples of products which could be qualified as medical devices (classification is only indicative and must be assessed on a case by case basis taking into account all product characteristics):
- Devices that act in a physical or mechanical way intended to be used for IVF/ART (such as pipettes or syringes) should be classified according to the rules set out in Annex IX of Directive 93/42/EEC, depending mainly on their intended use;
- Devices, such as washing, separating, sperm immobilizing, 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[2].
- Devices manufactured utilizing 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.

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."

VI. Traceability

Special attention should be paid to traceability since incidents might be disclosed several months or years later, at the baby's birth or even later during its life. The instruction for use must inform the user on the need for traceability and, where appropriate, on the national legal requirements in this field.

[2] 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.

VII. Vigilance

In case of assisted reproduction, special attention should be paid to the causes of the death or deterioration of the gamete (spermatozoid, oocyte), of the embryo or of the mother-to-be. If the product could be involved in this deterioration or death of the gamete, of the embryo or of the mother-to-be, the manufacturer shall carry out an assessment and inform the competent authority. In case of doubt, incidents shall be notified to the relevant national competent authority.

Since Directive 2004/23/EC also applies to reproductive cells (eggs, sperm) and foetal tissues, a notification of serious adverse reactions and events can be required according to Directive 2006/86/EC.

VIII. Preclinical data and clinical data supporting CE marking including Post-Market Clinical Follow-up (PMCF)

The demonstration of conformity with the essential requirements must include a pre-clinical evaluation in accordance with Annexes II, III and VII to Directive 93/42/EEC and a clinical evaluation in accordance with Annex X to Directive 93/42/EEC.

A PMCF programme must be planned and can take the form of clinical investigations and/or registries. Postmarket surveillance should be carried out in “all comers” registries to better provide the clinical safety and performance data on the IVF/ART solutions’ use in the clinical practice.

IX. IVF/ART solutions’ modification

When the manufacturer does some subsequent modifications or when design iterations occur to an already marketed IVF/ART products, it is essential to evaluate, based on a risk analysis, preclinical data and clinical data, the impact of the modified characteristics. The results of this evaluation will determine the need for any new or additional testing.

For medical device of class III falling under rule 13 of the Annex IX of the Directive 93/42/EEC, each modification influencing the specified drug characteristics requires a consultation by the notified body of the Member State's Competent Authority for medicinal products or of the European Medicine Agency (EMA).