Dutch technical specification (NTA 8070) on devices for assisted reproductive technologies

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Abstract In 2006 the Dutch Society for Clinical Embryologists (KLEM) approached the Netherlands Standardisation Institute (NEN) for advice regarding the lack of safety and quality specifications for medical devices used in assisted reproductive technology. A project plan was drafted in accordance with NEN-standardized methods for the development of norms and Dutch technical specifications (NTA) and a working group was launched consisting of all interested parties. A framework was then set up to develop an NTA that focused on the safety of gametes, embryos and the unborn offspring. The three main parts of the NTA describe the classification of medical devices, the requirements for new and existing devices and testing methods. The content of the NTA can be considered mainly as a consensus of the participants in the working group from both industry and clinical embryologists (KLEM). A final draft was sent to representatives from or allied to the government and to a notified body, and NTA 8070, entitled Devices for Assisted Reproductive Technologies (ART), was issued in March 2008.

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Introduction

The Dutch society of Clinical Embryologists (KLEM) was founded in 1992. One of the main goals of this society was and continues to be to enhance the knowledge of its members and to ensure high standards of quality control in their laboratories. Therefore, soon after its foundation, the KLEM launched the first version of ‘Specific quality standards for in vitro fertilization (IVF) laboratories’. One of the paragraphs of this standard was dedicated to the quality of the devices used for IVF, stating that ‘all devices which directly or indirectly make contact with biological material should be considered as medical devices. These devices should meet the requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (CE Marking) and so should be tested for safety and quality in Mouse Embryo assays or Sperm Survival tests, or validated as already in use with good results in other IVF laboratories’. This paragraph has not been altered since that time, primarily because its purport was good. On the other hand, there has been repeated discussion about this paragraph, due to the fact that its ramifications had not been appropriately considered in depth.

Numerous regulations concerning assisted reproduction have been introduced over the past few years, focusing especially on laboratory matters. In 2004 the European Parliament and the Council of the European Union published EU Directive 2004/23/EC, which set standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (Directive 2004/23/EC, 2004). Subsequently, in 2006, Directive 2006/86/EC (2006) was launched as an implementation directive. Concerning equipment and materials, this directive formulates that ‘critical reagents and materials must meet documented requirements and specifications and when applicable the requirements of Council Directive 93/42/EEC of 14 June 1993 (Medical Device Directive, 1993) concerning medical devices and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices’ (IVD, 1998). In 2007 the Medical Device Directive (MDD) was amended and became effective, with more specific regulations for, amongst others, assisted reproduction devices. The application of these directives has led to the initiation of CE marking for assisted reproduction products. However, all of these directives describe the safety of these devices mainly in general terms (toxicity, sensitivity and irritation for the human body). In contrast to regulations of the US Food and Drug Administration (FDA, 1998), in Europe there are no well-described safety and quality standards for assisted reproduction medical devices focusing on safety of gametes, embryos and offspring. The Dutch embryologists recognized this as a shortcoming and discussions with suppliers of IVF laboratory devices and also between colleagues confirmed that there was a need for more clarity about this subject.

In 2006, the KLEM approached the Netherlands Standardisation Institute (NEN) for advice. After a short study, the NEN confirmed that there were no official standards available on this subject in Europe and that there was a gap between legislation and CE marking on one side and safety for gametes, embryos and offspring on the other. At this point, KLEM and NEN decided to fill the gap. This report describes the methods and results of the development of a Dutch technical specification (NTA) for assisted reproduction medical devices. In future, this NTA can be added to standards leading to CE marking.

Materials and methods

Working plan

NEN has standardized methods that are used to develop norms and Dutch technical specifications (NTA). First of all, support for the project was needed from the government. Secondly, a (N)EN-norm and a NTA had to be chosen and, finally, a working group had to be organized. NEN and KLEM composed a project in which the need for a standard was explained, choosing a NTA above a norm, since accomplishing a NTA is less complex and as a consequence would save time and money. Moreover, the extra value of a norm was relatively small. The project plan was sent to the Ministry of Health, who supported the need for a NTA and provided a grant to cover a substantial part of the costs. The remaining costs were to be provided by parties involved in the project team.

Project team

According to the NEN standard, the project team should consist of all interested parties. NEN itself is never one of these parties but participates to support and advise the project team by providing a link with other national and international standards. In order to bring together interested parties, NEN placed an advertisement in the NEN newsletter and on the website. This finally resulted in the project team as mentioned above.

Development of the NTA

The NTA was developed in the second part of 2007 and five meetings of the project team were necessary. During the first two meetings, the backbone of the NTA was set up and the team brainstormed about shortcomings in perspective of existing standards. These shortcomings were soon focused on safety of gametes, embryos and the unborn offspring, since this was missing in all other standards. Decisions were mainly based on consensus, however this was not a prerequisite of the NTA development.

After session 4, a first draft of the NTA was ready and this was sent to referees from or allied to the government (Netherlands Health Care Inspectorate, National Institute for Public Health and the Environment and Keuring Electrotechnische Materialen Arnhem (KEMA), a notified body). The NTA was divided into three important parts: (i) classification of devices; (ii) requirements for new and existing devices; and (iii) trial methods.

Results

Classification of medical devices

The devices were divided into six categories, A–F (Table 1), defined on the basis of their characteristics, e.g. no direct
The fifth category (E) is special, containing all types of media, media supplements and water, i.e. culture media, flushing media, sperm preparation gradients, denudation media, mineral oil, cryopreservation media, as well as all types of liquids/solids that can be added to these media (e.g. propanediol, polyvinylpyrolydone and heparin). Materials in this category have a direct function in processing, preservation and storage of gametes and embryos, and may even influence their metabolism, and therefore they require special conditions. Since many media used in assisted reproduction laboratories contain antibiotics or other drugs, it was difficult to decide whether this category could be considered as medical devices. Ultimately, the EU took the same stand and classified culture media as medical devices in the Medical Device Directive (1993).

The sixth category (F) is another special category, to include 'environmental' devices such as gases and laser equipment. Although this category of devices is mentioned, NTA 8070 does not incorporate quality requirements for it.

### Requirements for assisted reproduction medical devices

A starting point for the new requirements was the current (legal) regulations as described in several directives and guidelines (FDA, 1998; IVD, 1998; MDD, 1993; MEDDEV, 2001). In order to improve the safety of these devices for contact with embryos (pipettes, tubes, dishes) or invasive instrumentation (e.g. intracytoplasmic sperm injection needles). The fifth category (E) is special, containing all types of media, media supplements and water, i.e. culture media, flushing media, sperm preparation gradients, denudation media, mineral oil, cryopreservation media, as well as all types of liquids/solids that can be added to these media (e.g. propanediol, polyvinylpyrolydone and heparin). Materials in this category have a direct function in processing, preservation and storage of gametes and embryos, and may even influence their metabolism, and therefore they require special conditions. Since many media used in assisted reproduction laboratories contain antibiotics or other drugs, it was difficult to decide whether this category could be considered as medical devices. Ultimately, the EU took the same stand and classified culture media as medical devices in the Medical Device Directive (1993).

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gametes and embryos in vitro, this NTA contains additional requirements for assisted reproduction devices in the EU. New and existing devices were distinguished.

**New devices**

The first legal requirement is that the device should meet the requirements for CE marking. As explained in the introduction, the CE mark indicates a general safety for the intended use of the device, but is not specific to gamete and embryo safety during assisted reproduction treatment. New devices are sub-divided into three groups: (i) new developed products; (ii) products comparable with existing, CE-marked products of the same manufacturer; and (iii) existing CE-marked products of the same manufacturer but with a different scope of use.

Pre-market requirements of new developed products include a new technical file according to the MDD, complete risk analysis, clinical trials and specific tests (Table 2). This total package should lead to adequate CE marking with assisted reproduction treatment as intended use.

For new devices comparable with existing devices from the same manufacturer, the existing technical file can be used under the conditions that the main production steps are equal and the introduced limited changes do not affect the results of the risk analysis significantly.

The last group of new assisted reproduction devices consists of devices that are already available on the market, but for purposes other than assisted reproduction treatment. In this case a completely new technical file, including risk analysis, is obligatory. This file must be certified by a notified body in order to obtain CE marking.

**Supplementary requirements for new products**

The risk analysis is the main tool used to evaluate a product. Next to the general international standards, the risk analysis must include answers to the following questions: (i) What is the expected effect of the device on gonadal tissue, gametes and/or embryos? (ii) What is the expected influence on the fertilization process and embryo development in vitro? (iii) What is the expected influence on the implantation process? (iv) Is there a possible side effect for the offspring? If there is any doubt about one or more of these items, the supplier should decide not to put the device on the market, contact the KLEM for their opinion and/or perform further investigations to obtain better answers on the safety aspects, e.g. contact the KLEM to design a clinical trial.

The supplier must then demonstrate the advantages of the new product for the end user. For class-III CE-marked medical devices, this should be demonstrated as results of

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### Table 2 Test descriptions for medical devices intended for application in assisted reproduction treatment.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Preferred test method</th>
<th>Description/remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Chemical methods, e.g. calibrated auto analyser</td>
<td>The manufacturer defines specifications for each parameter in accordance with the clinical use, e.g. pH of culture media under specified CO₂ concentration</td>
</tr>
<tr>
<td>Physical parameters (osmolality, pH, viscosity in case of viscous fluids)</td>
<td>Osmometer, pH meter, viscosity meter</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Limulus amoebocyte lysate (LAL) test</td>
<td></td>
</tr>
<tr>
<td>Embryo toxicity test</td>
<td>Mouse embryo assay (MEA)</td>
<td>The MEA must meet the following requirements: description of test system (mouse strain, housing conditions, culture conditions), test method for specific device, description of start- and endpoint in hours post-ovulation, controlled design with correction for mouse variation and specification of test statistics, definition of cut off for toxicity, report of toxicity with confidence interval (CI), analysis of time trends in control group</td>
</tr>
</tbody>
</table>
clinical trials. These clinical trials must meet the legal standards, generally meaning that the trial has a prospective, randomized design. If possible, the following items must be specified: manner of randomization, statistical power (minimum 0.8), alpha level (maximum 0.05) and the means of calculating the number of included subjects/cases. Outcome parameters are related to effectiveness (e.g. fertilization rate, embryo quality and/or implantation rate) and safety (for gametes, embryos and (unborn) offspring).

**Discussion**

The NTA on medical devices for assisted reproduction gives criteria focused on gamete and embryo safety. It fills a gap between legislation and final testing and approval of these products. The NTA should be applied to essential materials only (see EU directive 2006/86/EG, 2006) as determined by the clinical embryologist or preferably by the national embryology society. Non-essential materials are not considered as medical devices and so require less stringent specifications. If an embryologist wants to use a material for assisted reproduction treatment, the pathway will be to determine: (i) whether or not the material is an essential material; (ii) if it is essential, the NTA category to which it belongs; (iii) whether or not it is a new application for assisted reproduction treatment of this material; and (iv) which tests are needed.

This NTA was developed as a consensus of participants from both industry and clinical embryologists (KLEM). Although this means that it has strong support, discussion about its content in some aspects is still possible. The present NTA can be seen as a kick-off for further definitions and requirements for the safety and effectiveness of assisted reproduction medical devices.

One of the points to reconsider is the classification of the products. As mentioned previously, only essential materials must be considered as medical devices and so need a CE mark with assisted reproduction treatment as intended use. It is up to the clinical embryology societies to establish rules about essential and non-essential devices. After finishing this process, it is possible that the categories within the NTA might change.

Another point for discussion is the freedom of handling for end users. At the moment it is possible for clinical embryologists to buy two or more products and to mix them to provide a new ‘device’. This situation occurs especially with products in the E category, e.g. the addition of DMSO to a buffered medium to obtain freezing medium for gametes or embryos. In this case, if the purchased products (DMSO and buffer) have separate legal specifications (CE mark) for IVF, the homemade mix no longer has the CE mark and, therefore, the supplier of the raw materials can no longer be responsible. The question remains as to whether further regulation is necessary on this point in order to protect not only patient and process but also the integrity of the embryologist.

The present NTA states that maintenance validation is performed more intensively during the initial period that a device is available and can be reduced after positive results are obtained. If negative results are obtained, the frequency of validation must be increased. Although the management of this process should be described in the products’ technical file, it is subject to interpretation by
the manufacturer and the notified body. Some cases in the different categories should be studied in collaboration with the embryology societies in order to reach the most appropriate definitions.

The next version of the NTA should also include more specific criteria for new culture/preservation media, which need better requirements particularly when clinical trials are undertaken. The present NTA focuses these on satisfactory power with respect to the pregnancy rate. In future, this will require extension with multicentre studies and standardization of follow up studies (e.g. data from parturition, complications during pregnancy and health of offspring).

Other aspects to be considered are the tests described in the NTA, especially specific tests for endotoxin and embryo toxicity. In the case of endotoxins, the necessity for the test can be questioned: if devices are produced in a specified controlled environment and with defined raw materials, the chance of endangering a patient will be close to zero. For the embryo, endotoxins appear to be harmless, e.g. high concentrations of endotoxins do not affect the results of mouse embryo development in the MEA (Punt van der Zalm, personal communication). This point needs further research and the input of test-laboratory representatives would be valuable for the next version of this norm. The MEA is one of the most important tests indicated in this NTA. This test should be the best surrogate indicator for embryo toxicity for the medical devices tested and, therefore, should always be performed on all assisted reproduction medical devices. However, this test has never been proved to have a correlation with the results of human assisted reproduction treatment and there is, therefore, resistance to its use. In addition, test performance has not previously been defined, which can lead to different test results being obtained in different test laboratories. Although the NTA working group distinguishes the shortcomings of the MEA (as listed by Punt van der Zalm et al., 2009 and Gardner et al., 2005), they are convinced that it is the best current alternative. The MEA incorporates testing of known factors (e.g. sterility and osmolality) as well as unknown factors that can influence safe and effective development of the embryo in vitro. Other tests, such as the human sperm survival test, are not well described and currently lack an adequate test protocol. Another alternative is to abandon these bioassays in general, but the NTA working group regards this as unethical. Punt van der Zalm et al. (2009) found that several batches of assisted reproduction devices, along with other devices from category E (media, medium supplements and water), do not pass the MEA. On further inquiry, in the majority of cases, the suppliers of these embryotoxic batches report small changes in raw materials or in the production process. Although it is unknown whether these batches affect the outcome of human assisted reproduction treatment, it is important to recognize any changes in products in order to prevent hazardous effects on results and offspring. From the animal point of view, there may be ethical considerations surrounding the number of mice needed to perform all of the tests. The NTA working group hopes that these ethical considerations will be taken into account and will lead to the extension of research on new, animal-free tests. In the meantime, the MEA is the best alternative under the (medical and ethical) condition that it is performed using a proper test protocol. Some general criteria were therefore described for the test. With reference to these criteria, it will be possible to define more specific standards, e.g. the accepted toxicity of a specific material. For example, this can be higher for a pipette than for culture media. Higher toxicity tolerance means that fewer embryos are required, saving animals and making the test cheaper. As an extension to this, it is also possible that some products need differing start- or endpoints for the tests. For example, some culture media are intended for culture from day 3 to day 5 and it would seem inconsistent or perhaps even impossible to do a MEA from day 1 to day 5 in this case. Specifications for each product will be outlined in a subsequent version of this NTA. It will also be necessary to extend the tests for completely new and challenging agents in culture media, which may require additional pre-clinical safety tests, e.g. to test genomic aspects or effects on organogenesis. Further, the NTA working group hopes that the human sperm survival test can and will be further developed, so that it can be implemented for semen related products in particular, such as tubes and sperm gradient media.

Finally, it is preferable that the next version of this NTA will evolve to a European (EN) standard. This would make it easier and more attractive for manufacturers to specify their products, leading to better, safer products with a reduction of costs. This should result in better safety for the patient during the treatment and better health for their children.

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