BELGIAN ADVISORY COMMITTEE ON Bioethics

Opinion no. 52 of 12 March 2012 on the ethical aspects of certain provisions of the European and Belgian regulations with regard to human tissues and cells used in the context of reproductive medicine

Referral

The question submitted to the "Ethics and regulation in reproductive medicine" commission was formulated on the initiative of the Bureau of the Advisory Committee on Bioethics itself on 26 February 2010.
More precisely, it concerns the issue of whether, as an ethical consideration, the new Belgian regulations following transposition of certain provisions of the European directives on human tissues and cells[1] include features that make the application of good clinical practices and principles of medical ethics more difficult with regard to medically assisted procreation.

The Committee decided in its plenary session of 8 March 2010 to take this question into consideration and entrusted the 2010/4 commission with examining it. In the light of this examination, the Committee has then carried out its own evaluation of the regulations.
This evaluation emphasises the Belgian situation, which has been compared successively to international consensus (via the experts consulted) and needs in the field (practitioners in Belgium).

I. Preamble

This opinion will not deal with issues covered by opinions previously issued by the Committee on the ethical problems raised by collections of human body material intended for academic research or used for commercial purposes, or by banks of organs, cells or tissues constituted with a view to autologous or heterologous transplantation for therapeutic purposes, or by banks of blood or its constituents for therapeutic purposes[2]. This opinion will also not deal with the use of gametes or embryos for purposes of scientific research[3]. It will concentrate on certain specific factors that hinder good clinical practice in centres for medically assisted reproduction (called "MAP Centres").

These centres are responsible for the use of gametes or reproductive tissues with a view to medically assisted procreation and in this capacity must apply the Belgian regulations in this regard, in particular the Royal Decree of 28 September 2009 concerning banks of human body material[4]. This is combined with the legislation on medically assisted procreation (MAP) and that on obtaining and using human body material[5], which must also be applied in the centres

[1] 1) Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; 2) Directive 2006/17/EC of the Commission of 8 February 2006 implementing directive 2004/23/EC of the European Parliament and the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells; 3) Directive 2006/86/EC of the Commission of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and 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.
[2] See in particular opinion no. 11 of the Committee of 20 December 1999 on collection of organs and tissues from healthy living subjects with a view to transplantation, opinion of the Committee no. 42 of 16 April 2007 on umbilical cord blood banks and opinion of the Committee no. 50 of 9 May 2011 on certain ethical aspects of the amendments made by the law of 25 February 2007 to the law of 13 June 1986 on organ collection and transplantation.
[3] See opinion of the Committee no. 18 of 16 September 2002 on research on the human embryo *in vitro*.
[4] Royal Decree of 28 September 2009 setting quality and safety standards for donation, collection, procurement, testing, processing, storage and distribution of human bodily material, with which banks of human bodily material, intermediate structures for human bodily material and production establishments must comply, hereafter designated as the Royal Decree "quality and safety standards (2009)", in particular Annex IV.
[5] Law of 6 July 2007 on medically assisted procreation and destination of excess embryos and gametes, hereafter designated "MAP (2007)" law.

concerned. From an ethical point of view, the opinions are based on the model of the four traditional principles of medical ethics. Analysis of the regulations shows that in several provisions, it contradicts these principles.
Thus, it is difficult to defend a position stipulating that in the event of manifest shortage of means, these valuable resources will be devoted to performing less useful technical examinations. The same reasoning also applies when the examinations to be performed prove to be detrimental to the persons examined.

II. Analysis

Interviews with some experts[6] have revealed certain concerns, specified below, with regard to both donations between partners other than for immediate use and donations other than those between partners.

The ethical analysis is based on the four principles of biomedical ethics[7]. We have considered whether the new regulatory provisions conflict with these principles. Two principles play an important role in this instance, namely beneficence and non-maleficence.
The principle of beneficence means that we must try to maximise the quantity of "good".
Applied to the medical context, this means that the costs incurred must be beneficial. Performing useless tests or those for which results are not conclusive is a waste of scarce resources. More "good" can be generated by this money on the basis of more judiciously allocated means.
The second principle is that of non-maleficence. A medical procedure that causes harm must be justified by a) a relative advantage compared to the application of another ethical principle; b) the certainty of preventing greater harm. Harm to the donor (testing, sampling) is justified by the concern for preventing harm (contamination) to the recipient. If it is obvious that the tests do not protect against any contamination or if another procedure can achieve the same result by causing less harm, then there is cause to amend the regulations as a consequence.

1. Donation between partners other than for immediate use

Is it necessary to conduct blood tests repeated at each collection of gametes in couples treated, even if sperm and autologous oocytes of the couple in treatment are used[8]?

According to the present regulations, virological analysis for HIV, hepatitis B and C (HBV and HCV) and syphilis is required (with or without PCR/NAT[9]) at each procedure involving oocytes

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Law of 19 December 2008 on procurement and use of human body material intended for human medical applications or for purposes of scientific research, hereafter designated as the "human body material (2008)" law.

[6] Cited on the last page of this opinion.

[7] Beauchamp T.L., Childress J.F., *Principles of Biomedical Ethics*, Oxford University Press, 6th ed., 2008 (French translation *Les principes de l'éthique biomédicale*, Paris, Les Belles Lettres, Médecine & Sciences humaines, 2008).

[8] See Art. 4.2. of Annex IV of the Royal Decree "quality and safety standards (2009)": "Blood samples must be collected upon donation" ("general conditions for determining biological markers") and Articles 2.1. to 2.6.; see also Art. 4.2. of Annex III of the aforementioned directive of 8 February 2006.

[9] PCR (polymerase chain reaction) designates a modern technique for DNA analysis lending itself to automation and using the molecular biology of *in vitro* DNA amplification. Polymerase or reverse transcriptase is an enzyme associated with carcinogenic viruses, those of some leukaemias and that of AIDS (HIV), and allows this RNA virus to incorporate itself into the chromosomes of the cell it infects and that are made of DNA. PCR allows for example a bacterium or virus to be identified or a gene mutation to be revealed to diagnose a genetic disease (*Dictionnaire Garnier-Delamare des termes de médecine*, Paris, Maloine, 30th ed., 2009, see "gene amplification" and "reverse transcriptase"). The Royal Decree uses NAT (Nucleic Acid Amplification Technology), which designates the same technique for nucleic acid amplification, instead of PCR.

or sperm in the two partners of a couple in the context of a medically assisted procreation procedure, in the case of other than immediate use. This high frequency is very difficult to defend and hardly feasible in practice:

A/ The risk of exogenous contamination by diseases during treatment is very low. This is moreover confirmed in international studies[10].

B/ Systematic monitoring in order to protect the laboratory personnel is meaningless, given that the entire procedure must take place in a completely sterile environment where the personnel must always observe standard sterility precautions[11].

C/ Systematic monitoring and repeated performance of blood analyses at each donation generate a resulting additional cost for the community. The additional cost for INAMI[12] in Belgium is approximately 4.8 million euro[13].

D/ Given that at present no contamination has been reported in major international studies[14], the investment of such a significant sum of public money for such a low benefit is difficult to justify from an ethical point of view.

E/ Physical and psychological pressure is also added to the financial factor, as the patients must submit to blood sampling and appear each time for a series of procedures.

F/ A recent study by the Belgian Society of Reproductive Medicine (BSRM)[15] has shown that various intervals between virological tests are assigned in the various countries of the European Union. They are as follows: Norway 12 months, Denmark 24 months, Finland and Sweden 12 to 24 months, Poland 6 months, France less than 6 months for the first cycle and then every 24 months. In Germany, examinations must take place one week before oocyte collection. In Italy, the period is 3 months; in Greece, screening is advised before the first sperm donation and after three to four cycles. Finally, in Latvia, a check is required every 6 months.
Moreover, a European bill exists to limit repetition of testing to one test every 24 months[16].

Recommendation

In the light of these aspects and on the basis of the information collected on the international scale, it is proposed that virological analysis for HIV, hepatitis B and C and syphilis be performed only at the first procedure and conducted afterward only at 12-month intervals.

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[10] Wingfield M., Cottell E., *Viral screening of couples undergoing partner donation in assisted reproduction with regard to EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC: what is the evidence for repeated screening?* E. Hum Reprod. 2010; 25(12):3058-65. Pepas L., Macmahon E., El Toukhy T., Khalaf Y. & Braude P., *Viral screening before each cycle of assisted conception treatment is expensive and unnecessary: a survey of results from a UK inner city clinic*, Human Fertility, 2011; 14(4):224-229.

[11] See Annex VII of the aforementioned Royal Decree "quality and safety standards (2009)" (text attached in the Appendix).

[12] The National Institute for Health and Disability Insurance.

[13] Estimate of Prof. Devroey P. at the 21st *BSRM meeting*, 30 January 2009, Elewijt Center, Zemst.

[14] Wingfield M. *et al., op. cit.*; Pepas L. *et al., op. cit.*

[15] Belgian Society for Reproductive Medicine, chaired by Prof. A. Delvigne.

[16] Summary Report of the Meeting of the Competent Authorities for Tissues and Cells, 23-24 June 2011, available at http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_mi_20110623_en.pdf "The NCAs group concluded that it was not needed to maintain the current testing requirements for partner donation as laid down in Annex III of Directive 2006/17/EC. This will require a future amendment of the Directive, through the regulatory procedure. It is the responsibility of the NCAs to ensure that ART tissue establishments have in place the appropriate safety and quality systems, which does not affect the safety and quality of reproductive cells and/or human health when donors are tested at up to 24 months time intervals".

This would correspond to the international consensus published in a number of scientific publications[17].

With this adaptation, a balance can be reached between greater safety on the one hand and costs and burdens on the donor/partner on the other hand. In this regard, reference can be made to an article from the American Medical Association: *The Harms of Screening, New Attention to an Old Concern*[18].

In a discussion of preventive diagnostic examinations, false positive results can never be forgotten, nor the burden of additional examinations. In this context, it should also be noted that these useless additional examinations sometimes represent a high cost to the community and thus uselessly squander the scant resources essential to the curative sector[19].

2. Sperm and oocyte donation, fresh or after cryopreservation, other than partner donation

2. 1. Virological analyses required for sperm donation other partner donation

2.1.1. Technical data

Current regulations require virological testing[20] at least for HIV, hepatitis B and C, syphilis and chlamydia (by PCR = NAT test or not) at each consecutive donation of sperm by the same donor[21].

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[17] Bhargava P.M., *On the critical assessment of the impact of the recent European Union Tissues and Cells Directive.* Reprod Biomed Online, 2005; 11(2):161.
Hartshorne G.M., *Challenge of the EU 'tissues and cells' directive*. Reprod Biomed Online 2005; 11: 404-407.
Mortimer D.A., *Critical assessment of the impact of the European Union Tissues and Cells Directive (2004) on laboratory practices in assisted conception*, Reprod Biomed Online, 2005; 11(2):162-176. European Society of Human Reproduction and Embryology (ESHRE), *Statement 2009 on the European commission proposal of viral screening in assisted reproduction treatments* (www.eshre.eu). Hughes C., Emerson G., Grundy K., Kelly P., Mocanu E., *Is performing viral screening within 30 days of oocyte collection justified?*, Hum Reprod, 2010; 25:239.
Janssens P.M., *Rules and regulations in reproductive medicine: sensible requirements that should start with evidence*, Hum Reprod. 2010; 25(12):3055-7. 2010.
Wingfield M. *et al., op. cit.*

[18] Woolf S H., Harris R., *The Harms of Screening, New Attention to an Old Concern,* JAMA, 2012-Vol 307, No 6, p.565-566.

[19] N.B. We will not consider here examinations carried out with a view to treatment of the person himself (too-advanced preventive examinations) nor the harm caused by useless treatments (by the examination itself and also – this is not rare – through additional treatments that can lead to serious injuries). For this type of issue, one can refer to a (more general) article published in *Lancet*: *The perils of excessive medical care*, by Shangavi D.M., *Lancet*, 2011; 377, 1561-1562, and also the article *Overdiagnosed: Making People Sick in the Pursuit of Health,* M.D., 2011 by Welch H.G.G., Schwartz L.M., Woloshin S., which refers to the healthcare saga of Brian Mulroney, who was Prime Minister of Canada from 1984 to 1993. A preventive helicoidal scan of the thorax showed that he had two small nodules on the lung. A biopsy showed them to be completely benign. But the patient had to be hospitalised three months for this reason, and because of a complication due to the biopsy, developed life-threatening pancreatitis.

[20] Serology does not allow the virus itself to be detected. As for all diseases, it only allows the traces of its passage to be detected, that is, the antibodies that are produced by the body in response to its "attack". The antibodies produced are specific for each disease; a blood test detects only the antibodies for the disease that it is supposed to detect (see notably http://www.3trois3.com/experience_pratique_du_sdrp/5-interets-des-differentes-techniques-d-analyses-:-serologie-pcr-s_606/; Plantier J.-C. and Simon F. (UHC Charles Nicolle Virology Laboratory, Rouen), "Diagnostic sérologique des infections à VIH (*Serological diagnosis of HIV infections*)", Développement et Santé, no. 162, December 2002).

[21] Royal Decree "quality and safety standards (2009)", Art. 9 §2: *"Donors of gametes, gonads, fragments of gonads, foetal human body material and embryos are subject to the biological tests specified in items 1, 2 and 3 of Annex IV* (items 3.2 to 3.4, *cf.* text attached to this opinion). *The biological tests specified in paragraph 1 are conducted according to the general provisions of item 4 in Annex IV."*

We note that item 4.2 of Annex IV of the Royal Decree "quality and safety standards (2009)" reads as follows: "Les échantillons de sang doivent être prélevés **lors du don** (Blood samples must be collected **at** donation)"**,** while in the corresponding Dutch version we read: *4.2. "Bloedmonsters worden **op het tijdstip** van de donation afgenomen* (Blood samples are collected **at the time of** donation)"*.* This difference in translation gives rise to a divergence in interpretation.

These sperm donations generally take place twice per week, with repetition of the aforementioned tests each time, while the sperm is frozen each time. The reliability of the result of the PCR conducted immediately after contamination (in acute cases) is inadequate in this respect.

2.1.2. Precautions to be observed

A quarantine of a minimum of 180 days after the last sperm donation[22] must be observed, as has already been practised for years in all the approved centres. Only at the end of this quarantine period is the previously described viral serology again tested for the donor[23].

2.1.3. Recommendations

A/ Performance of tests repeated at each donation is rather meaningless when the standard quarantine period with separate collection is observed. It is much more sound to strictly observe the quarantine rule alone because, in this way, negative serology at the end of 180 days points to the absence of contamination.

B/ The obligation to conduct a short-term virological examination via PCR (called a PCR/NAT test) for each donor, at each donation, entails a significant additional cost for sperm donation. Moreover, the probability that the result is known at the time of cryopreservation of the sperm is relatively minimal.

C/ Repeated blood tests also have a dissuasive effect in the case of sperm donation. There is a significant shortage of candidate sperm donors at present in our country and every complication in the procedure only exacerbates this shortage.

The Committee thus also proposes that, for sperm donation other than partner donation, the standard method existing up to now be reinstituted. It involves conducting an in-depth virological and bacteriological test in a very short period before the first donation. The sperm samples donated are then frozen. There follows a quarantine period of 180 days, at the end of which a new clinical examination and serological test are performed in order to exclude in this way any risk. By combining these two factors, safe sperm donation can be maintained without additional and repeated blood tests.

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[22]Royal Decree "quality and safety standards (2009)", Art. 12: "*Human body material is kept in quarantine until it can be released in application of Article 17".* And Annex IV, item 4.3*:* "*Donations of gametes, embryos, gonads and fragments of gonads other than partner donations, or donations of gametes intended for the use of surplus embryos, are put into quarantine for a minimum of 180 days, at the end of which period the tests must be recommenced*".

[23]See however Article 4.3. of Annex 3 of the directive of 8 February 2006: *"Sperm donations other than partner donations are put into quarantine for a minimum of one hundred eighty days, at the end of which period tests must be recommenced. If the blood sample collected at the time of donation is also tested for HIV, HBV and HCV using the nucleic acid amplification technique, it is not necessary to recommence the examination on another blood sample. Likewise, it is not necessary to recommence the examination when the processing procedure includes a validated inactivation step for the viruses concerned.*"

2. 2. Donation of fresh oocytes

As stated above, Annex III of the aforementioned directive of 8 February 2006 (Art. 4.2.) and Annex IV of the aforementioned Royal Decree of 28 September 2009 (Art. 4.2.) indicate, in the general conditions for determination of biological markers, that blood samples must be collected upon donation of oocytes. This also specifies the time when tests are conducted for HIV, HBV and HCV using the nucleic acid amplification technique (NAT).

The result of the PCR test can generally be obtained after approximately 72 hours at the earliest.

This is why the Committee puts forward the following recommendations:

Recommendations

A/ It would be preferable to perform this analysis within a certain time period before the donation of oocytes. This period can be 14 days to 3 weeks maximum. In this way, results would already be known at the time of implantation into the recipient. Clearly, the safety of the procedure would be increased.

B/ In this regard, the Committee declares itself in favour of vitrification[24], a preservation technique currently perfectly developed. Although this technique is still only authorised in six university centres, the Committee believes, on the basis of the current scientific data[25], that the vitrification technique should be preferred henceforth to donation of fresh oocytes, for the reasons that:

- there is no difference in viability or reproductive capacity between an oocyte transplanted after vitrification and a fresh transplanted oocyte (1),
- on the other hand, the safety of the transfer after 6 months of vitrification is greater than in the case of transfer of a fresh oocyte (2).

2. 3. Tests necessary in the case of donation and cryopreservation of oocytes for subsequent use

It is again[26] required that virological tests by PCR/NAT be conducted at each donation.

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[24]See the definition in the publication of the Superior Health Council no. 8630, Preservation of cells and reproductive tissues by vitrification, of 2 March 2011: "Water is vitrified by refrigeration to minus 130 °C. Vitrification of living cells, like slow freezing, involves preventing formation of intra- and extra-cellular ice crystals and survival of the cells after freezing/thawing (…). Vitrification of oocytes (or embryos) is a method of ultra-fast freezing that requires cooling and reheating rates of more than 2 °C per minute."

[25]According to the communication from R.-C. Chian, Royal Victoria Hospital, *Department of obstetrics and gynecology*, McGill University, Montreal, Quebec, Canada, 2007, summary to be consulted on the site http://www.em-consulte.com/article/138339. See also: Cobo A., Remohí J., Chang C.C., Nagy Z.P., *Oocyte cryopreservation for donor egg banking*, Reproductive BioMedicine Online (2011) Sep;23(3):341-6 (an abstract of which is available on the site http://www.ncbi.nlm.nih.gov/pubmed/21767989).
Cobo A., Meseguer M., Remohí J., Pellicer A., *Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial*, Hum Reprod. 2010 Sep; 25(9):2239-46. Epub 2010 Jun 30. Source: Instituto Valenciano de Infertilidad (IVI), University of Valencia, Valencia, Spain. (an abstract of which is available on the site http://www.ncbi.nlm.nih.gov/pubmed/20591872).
See also Herrero L., Pareja S., Losada C., Cobo A., Pellicer A., Garcia-Velasco J.A., *Avoiding the use of human chorionic gonadotropin combined with oocyte vitrification and GnRH agonist triggering versus coasting: a new strategy to avoid ovarian hyperstimulation syndrome,* 2011 Mar 1;95(3):1137-40. Epub 2010 Nov 3.
Mertes H., Pennings G., *Social egg freezing: for better, not for worse,* Reproductive BioMedicine Online (2011) 23, 824-829.

[26]In accordance with the general provisions of item 4 of Annex IV of the Royal Decree "quality and safety standards (2009)".

Recommendations

A/ It would be preferable that these tests rely on the same principles as those applicable to heterologous sperm donation.
Here as well, it seems desirable that a virological test performed 14 days to 3 weeks maximum before the collection procedure be the rule. This would offer greater safety than the provision specifying that the PCR be performed at the time of collection, as 72 hours generally pass before the result is known. Given the restricted time interval and the impossibility of always organising a quarantine, an additional possibility must obviously be provided for conducting the PCR if the oocytes must be used in the short term.

B/ It would be preferable that the quarantine period also be observed in the case of freezing (vitrification) (as for sperm donation).

3. The traceability requirement[27]

A requirement of complete traceability of gametes and embryos is justified and can certainly be satisfied. In addition to this condition, the new regulations have also introduced that of traceability for all solutions and equipment used[28]. This provides that each sample must be accompanied by extensive methodological traceability (in other words, by any useful information in connection with the products, materials and equipment used for processing and preservation).

The Committee entirely approves of this traceability requirement, to be applied at once and in the future. This can only increase the safety of the procedures and the commitment of the staff involved.

However, the new regulations also require that the same provisions be observed with regard to gametes and embryos collected in the past. Serious ethical objections are however raised.

A/ First of all, it is not admissible – at least for this type of provision – to introduce retroactive regulations[29].

B/ Given that the centres cannot fully observe these requirements, these regulations can have the effect that they are obliged to destroy thousands of cryopreserved embryos and gametes. These embryos and gametes can in fact, according to the terms of the law, only be used – with the agreement of the couple – for *in vitro* experimentation, never again for the couple themselves. From an ethical point of view,

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[27]Royal Decree "quality and safety standards (2009)", Art. 6. §1: *"Traceability of any human body material collected, procured, processed, stored or distributed must be ensured, as specified by Article 14 of the law. This traceability also involves all the pertinent data concerning the products and materials coming into contact with this human body material.*"

[28]"Human body material (2008)" law. Traceability is defined there in Article 2, 23°, as "*the ability to locate and identify the human body material at all steps of the process from procurement to distribution with a view to its use or destruction, including processing, testing and storage. This involves the ability to identify the donor and the structures or the production facility involved that receives, modifies or stores the human body material, and the ability to identify the recipients in hospitals that use the human body material. This also involves the ability to locate and identify all the pertinent data concerning the products and materials coming into contact with this human body material during the process*."

[29]Art. 43 of the "human body material (2008)" law (Transitional provisions and effective date): "*After the effective date of the present law (14 July 2010, under the terms of the law of 16 June 2009, Art. 46), human body material that was collected before this effective date and that is not traceable cannot be used for human applications but can be used for purposes of scientific research.";* Art. 44: *"Human body material collected before the effective date of the present law can be used for human application after the effective date of this law insofar as the provisions of the present law, with the exception of Articles 10, 12, 20 and 21, are observed."*

destruction is an option very difficult to defend; these gametes and embryos have in effect been entrusted by the patients with a view to later satisfying their desire for a child.

Recommendation

The Committee therefore requests that the regulations be amended. Strict regulations can have a very positive effect in the future, but with regard to the past, only traceability of the origin of the gametes and embryos can be provided, not information on the use of solutions and material.

III. Conclusions and recommendations

With this opinion, the Committee wishes to draw the attention of the competent authorities to the ethical problems raised in implementation of the Belgian law "human body material (2008)" and its implementing decrees by certain provisions applied to the Centres for medically assisted procreation.

1. Article 6, §1, of the Royal Decree "quality and safety standards (2009)", dealing with (1) the guarantee of traceability of all human body material (gametes and embryos) collected, procured, processed, stored or distributed, goes too far in that it also involves (2) all the pertinent data on the products and materials coming into contact with this human body material.

   Requirement (1) poses no problem; (2) does, due to the fact that traceability of the products and materials is required retroactively, which raises a significant ethical problem.

2. In the past, traceability of all these human body materials as well as the products and materials coming into contact with them has not been observed in practice.

3. The consequence of this is that thousands of cryopreserved gametes and embryos can no longer serve the purposes initially planned, those of satisfying a future desire for pregnancy, even in the patients from whom these human body materials come.

The Committee unanimously believes that, in this specific case, these regulations are not ethically defensible in their consequences. The request is therefore made to the legislator that transitional measures be taken so that these gametes and embryos can still be used. The current regulations impose the following biological tests[30]:

3.1. Concerning partner donation other than for immediate use as specified in item 1, the Royal Decree requires a series of biological tests for HIV, hepatitis B and C, syphilis and chlamydia to be conducted at each donation of gametes not intended for immediate use within a couple.

These requirements are not scientifically based and moreover impose an additional useless burden on patients, personnel and the healthcare budget. A sounder way of proceeding from a scientific and economic point of view would consist of repeating a test every 12 months after a first test of the biological markers (more precisely described in 2.2. above).

[30] With reference to Annex IV and to Section 3, Art. 9 §2 of the Royal Decree "quality and safety standards (2009)". In Chapter IV, Section 2, Art. 8 §1 on donor selection, in particular in item 2°, the selection criteria taken into account for donors of gametes, gonads, fragments of gonads and embryos intended for assisted procreation are listed.

3.2. With regard to donations other than between partners after cryopreservation, whether donation of sperm or oocytes, it is also required several times that tests be performed at each donation.

The Committee believes that it would be more reasonable – scientifically as well as ethically – to strictly apply the "quarantine principle". According to this, (1) biological testing takes place before collection(s), (2) the cells or tissues are frozen, (3) the results of the tests are communicated after an additional check of the biological tests (after 180 days).
In the present state of science, given the possibility of vitrifying oocytes and given that there is no difference in viability or reproductive capacity between an oocyte transplanted after vitrification and a fresh transplanted oocyte, and that the safety of the transfer is greater after 6 months of vitrification, the Committee believes that donation of fresh oocytes should no longer be practiced except in the case of lack of vitrified oocytes.

4. Moreover, the "bilingual" nature of the legal and regulatory texts sometimes gives rise to a lack of optimal consistency in the meaning of their terms. The Committee stresses the necessity of establishing rigorous correspondence between French and Dutch texts that deal with the same material.

The opinion was prepared in the select commission 2010/4 consisting of:

Joint chairpersons	Joint reporters	Members	Member of the Bureau
R. Rubens	R. Rubens	A. Beyers	P. Devroey
G. Schamps		N. Gallus	
		V. Geenen	
		I. Liebaers	
		G. Pennings	

Member of the secretariat
B. Orban

Experts interviewed
Prof. A. Delvigne, President of the Belgian Society for Reproductive Medicine (BSRM)
Prof. K. Vandewoude, Assistant Clinical Director, Intensive Care Department, Ghent University Hospital
M. P. Ballegeer, Head of the Health Products Division of the Federal Agency for Medicines and Health Products (*Agence Fédérale des Médicaments et des Produits de Santé*, AFMPS)
S. Ziebe, President of the Tissues and Cells Directive Task Force of the European Society of Human Reproduction and Embryology (ESHRE)

The working documents of the select commission 2010/4 – question, personal contributions of the members, minutes of the meetings, documents consulted – are stored as Annexes 2010/4 at the documentation centre of the Committee, and can be consulted and copied there.

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ANNEX

28 SEPTEMBER 2009. — Royal Decree setting quality and safety standards for donation, collection, procurement, testing, processing, storage and distribution of human body material, with which banks of human body material, intermediate structures for human body material and production establishments must comply
(*Belgian Official Gazette*, 23 October 2009).

CHAPTER III. – Traceability

Art. 6. §1. Traceability of all human body material collected, procured, processed, stored or distributed must be guaranteed, as specified by Article 14 of the law.
This traceability also involves all pertinent data concerning the products and materials coming into contact with this human body material.
§2. An unequivocal system of donor identification must be implemented, attributing a unique code to each donation and to each resulting human body material.
In the donor identification system specified in the preceding paragraph, the following data must be listed:
1° identification of the donation:
a) a unique code for the donation;
b) identification of the establishment;
2° identification of the product:
a) the product code;
b) the allotment number if applicable;
c) the expiry date.
The establishments have an effective and precise system for unequivocally identifying and labelling the human body material that they have collected, procured, and received and that is to be distributed.
The donation code specified in paragraph 2, 1° is linked to the name of the donor, and the key to this is kept by the manager of the human body material of the establishment specified in §4.
§3. Every human body material is identified by a label that is affixed to at least the primary non-sterile packaging and on which the information specified in the present article is indicated, or reference is made to it.
The establishments keep, in writing or in electronic form, the data necessary to guarantee complete identification at all stages, including the data specified in Annex I, for at least 30 years starting from:
a) either the clinical use of the human body material in the human body;
b) or distribution with a view to another possible use as specified in a);
c) the destruction of the human body material.
Application of the preceding paragraph cannot have the consequence that the specified data are preserved for more than 50 years.
§ 4. The data specified in §§2 and 3, paragraph 2, are kept in the procuring establishment immediately after collection.
In the event of application of Article 8, §2, paragraph 3 of the law, the data specified in §§2 and 3 are preserved by the bank of human body material responsible, as specified in Article 8, §2, paragraph 4 of the law.

Annex IV
Selection criteria and biological tests required for donors of gametes, embryos, gonads and fragments of gonads intended for assisted procreation

1**. Partner donations for immediate use** without storage or processing.
The donor selection criteria and laboratory tests do not apply in the case of a donation of male gametes between partners for immediate use.

2**. Partner donations other than for immediate use**, as specified in item 1.

Gametes, gonads, fragments of gonads and embryos that are processed and/or stored and gametes which will result in embryos that will be cryopreserved must fulfil the following criteria:
2.1. The treating physician of the donor must verify and document, on the basis of the medical history of the patient and the therapeutic indications, the justifications for the donation and the safety of the donation for the recipient and for any child that may be born from this donation.
2.2. The following biological tests must be performed to evaluate the risk of cross-contamination:
- anti-HIV-1, 2
- HBsAg
- anti-HBc
- anti-HCV
- a syphilis screening test.
In the case of sperm processed with a view to intrauterine insemination, not intended to be preserved, and if the establishment can demonstrate that the risk of cross-contamination and exposure of personnel has been taken into account through use of validated procedures, the biological tests are not necessarily performed.
2.3. If the results of the tests for HIV 1 and 2, hepatitis B or C are positive or not available, or if the donor proves to be a source of infectious risk, a separate storage system must be provided.
2.4. Tests for HTLV-I antibodies must be performed in the case of donors living in areas with a high incidence of this infection or originally from these areas, or whose sexual partners or parents originate from these areas.
2.5 In some circumstances, additional tests must be performed, depending on trips made by the donor, his exposure to risks, and the characteristics of the human body material donated (for example, RhD, malaria, CMV, T cruzi).
2.6. Positive results do not necessarily rule out partner donation.

3. **Donations other than partner donations.**
Aside from partner donations, use of gametes, embryos and gonads or fragments of gonads must fulfil the following criteria:
3.1. Donors must be selected as a function of their age, their state of health and their medical histories, on the basis of a questionnaire and an interview with a qualified healthcare professional trained to this effect. This evaluation must involve all the pertinent factors that can contribute to identifying and excluding persons whose donation could be hazardous to the health of another, notably the possibility of transmitting diseases (sexually transmitted infections, for example), or to their own health (for example, superovulation, sedation, risks related to harvesting ova, or psychological consequences related to the donation).
3.2. The HIV 1 and 2, HCV, and HBV tests and the syphilis test made on a serum or plasma sample from the donor in accordance with the provisions of Annex VI, item 1.1, must be negative for donors. In addition, chlamydia tests made on a urine sample using the nucleic acid amplification technique must be negative for sperm donors.
3.3. The HTLV-I antibody test must be performed for donors living in areas with a high incidence of this infection or originally from such areas, or whose sexual partners or parents originate from these areas.
3.4. In some circumstances, additional tests must be performed, depending on the history of the donor and the characteristics of the human body material donated (for example, RhD, malaria, CMV, T. cruzi).
3.5. For autologous donors, the provisions of Annex II, item 2.1.1 are applicable.
3.6. After consent to this effect has been granted:
a) genetic screening is performed for the autosomal recessive genes prevalent in the ethnic context of the donor, according to international scientific knowledge;
b) the risk of transmission of hereditary disorders known to be present in the family is evaluated.
The recipient is fully and intelligibly informed of the associated risks and of the measures taken to reduce them.

4. General conditions for determining biological markers.
4.1. Tests must be performed in accordance with Annex VI, items 2.1 and 2.2.
4.2. Blood samples must be collected at donation.
4.3. Donations of gametes, embryos, gonads and fragments of gonads other than partner donations or donations of gametes intended for use for surplus embryos are put into quarantine for at least 180 days, a period at the end of which the tests must be recommenced. If the blood sample from the donor at the time of donation is also tested using the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, it is not necessary to perform the tests on a second blood sample or to implement the quarantine specified above. Likewise, it is not necessary to recommence the test when the processing procedure includes a validated inactivation step for the viruses concerned.

Annex VII
Various provisions on the quality and safety of activities in the establishments

A. Organisation and management

1. A manager of human body material should be designated, equipped with the qualifications specified in the law as well as at least two years of practical experience in management of human body material, including quality, safety and traceability.
2. An establishment must have an organisational structure and standard operating procedures suited to the procedures for which approval is requested; an organisational chart must exist which clearly defines the lines of responsibility and the hierarchical structure.
3. The manager of human body material is responsible for the activities of the establishment such as donor selection, evaluation of clinical data on the human body material used or any interactions with clinical users.
4. A documented quality management system must be applied to the procedures for which approval is requested, in compliance with the standards set by the law and by the present decree.
5. It should be ensured that the risks inherent in use and handing of human body material are identified and reduced insofar as possible, while maintaining a level of quality and safety appropriate for the use for which the human body material is intended. These risks include notably those related to procedures, the environment and the state of health of the personnel within the establishment in question.
6. Agreements concluded between establishments and third parties must comply with the provisions of the law and of the present decree. Agreements made with third parties must specify the methods of collaboration and the responsibilities, as well as the protocols to be followed to fulfil the required performance demands.
7. A standard operating procedure must exist, supervised by the manager of human body material and serving to confirm that the human body material satisfies the required specifications with regard to safety and quality, for its release and distribution.
8. In the event of cessation of activities, the agreements concluded and the procedures adopted in compliance with the law include traceability data and information on the quality and safety of the human body material.
9. A standard operating procedure exists guaranteeing identification of each unit of human body material at all steps of the procedures.

B. Personnel

1. The personnel of the establishments must be available in sufficient number and be qualified for the tasks to be performed. The competence of the personnel must be evaluated at appropriate intervals specified in the quality system.
2. Clear job descriptions, documented and updated, must exist for all members of personnel. Their tasks, functions and responsibility must be clearly documented and well-understood.
3. The personnel must receive basic training and refresher training when a change in procedures or a development in scientific knowledge requires it, and be given appropriate opportunities for professional development in the area involved. The training programme ensures and provides documented proof that each individual:
a) has proven his competence in performing the tasks assigned to him;

b) has adequate knowledge and comprehension of the principles and/or the scientific and/or technical processes that are important for the tasks allotted to him;
c) understands the organisational framework, the quality system and the health and safety rules of the establishment in which he works;
d) is duly informed of the broader ethical, legal and regulatory context involved in his work.

C. Equipment and materials

1. All equipment and materials must be designed and maintained in such a way that they are suitable for the use for which they are intended, and must reduce insofar as possible any risk for the recipients and the personnel.
2. All critical equipment and technical devices must be identified and validated, and undergo regular inspections and preventive maintenance in accordance with the manufacturer's instructions. When the equipment or materials involve critical processing or storage parameters (for example, temperature, pressure, particle counting, levels of microbiological contamination), they must be identified as such and be subject to monitoring, alerts, alarms and appropriate corrective measures, if need be, to detect malfunctions and defects and guarantee that critical parameters are kept within acceptable limits at all times. All equipment with a critical measurement function must be calibrated on the basis of a standard if one exists.
3. New and repaired equipment must be tested upon installation and validated before use. The results of the tests must be documented.
4. Maintenance, inspection, cleaning and disinfection and decontamination of all critical equipment must be performed regularly; these procedures must be recorded.
5. Procedures must exist for the operation of each critical piece of apparatus, detailing the steps to be followed in case of malfunction or breakdown.
6. Procedures relating to the operations for which approval is requested must describe in detail the characteristics of all the critical materials and reagents. Specifications must in particular be defined for additives (solutions, for example) and packaging materials. Critical reagents and materials must fulfil the documented requirements and characteristics and, if necessary, the provisions of the Royal Decree of 18 March 1999 on medical devices and the Royal Decree of 14 November 2001 on medical devices for in vitro diagnosis.

D. Facilities/premises

1. Establishments must have facilities appropriate for the performance of the procedures for which approval is requested, in compliance with the standards set by the present directive.
2. If, in the framework of the procedures, human body material is processed while exposed to the environment, this processing must take place in an environment with an established air quality and cleanliness in order to reduce the risk of contamination, including cross-contamination between donations, as much as possible.
The efficacy of these measures must be validated and monitored.
3. Except in the case of item 4, when human body material is exposed to the environment in the course of processing without undergoing a subsequent microbial inactivation procedure, an air quality characterised by a particle number and a microbial colony count equivalent to those of class A, as defined in Annex 1 of the current European guide to good manufacturing practice (GMP) and Annex IV of the Royal Decree of 14 December 2006 on medications for human and veterinary use should be ensured; the background environment must be suitable for the processing of the human body material concerned, but must be at least equivalent to class D in the GMP with regard to particle numbers and microbial colony count.
By derogation to the preceding paragraph, it is required that the number of microbial colony units in the background environment corresponds at least to class C of the GMP instead of class D in cases of cells that are exposed to the environment during processing, as well as for cardiac valves, blood vessels and musculoskeletal system transplants.
The condition specified in the preceding paragraph does not apply in the case of use of a closed functional system or for gametes; in this case, it suffices that the number of microbial colony units corresponds to at least class D of the GMP.
4. A less strict environment than that specified in item 3 with regard to class A is acceptable insofar as:
a) a validated microbial inactivation or final sterilisation procedure is used;

b) or it is demonstrated that exposure to a class A environment has a harmful effect on the required properties of the human body material concerned;
c) or it is demonstrated that the method and means of application of the human body material to the recipient involve a risk of transmission of a bacterial or mycotic infection to the recipient significantly less than that presented by transplantation of human body material;
d) or it is not technically possible to perform the required process in a class A environment, for example due to the necessity for having a specific piece of equipment that is not fully compatible with class A in the processing area.
5. In the situations described in item 4, letters a) to d), the environment must be specified. It should be proven, with supporting documents, that the chosen environment guarantees the required quality and safety, taking account at least of the planned use, the method of application and the immune status of the recipient. Appropriate clothing, personal protective equipment and hygiene facilities, as well as written instructions with regard to hygiene and apparel, must be provided in each section concerned within the establishment.
6. When the procedures for which approval is requested involve storage of human body material, the storage conditions necessary to preserve the required properties of the human body material, including key parameters such as temperature, humidity or air quality, should be specified.
7. Critical parameters, including temperature, humidity or air quality, must be controlled, monitored and recorded to prove their compliance with the required storage conditions.
8. The storage premises must ensure clear separation and distinction between human body material before release and in quarantine, human body material that has been released and human body material that has been rejected, in order to prevent any confusion and cross-contamination between them. In both quarantine areas and storage areas for released human body materials, physically separated areas or secure storage or isolation systems are to be provided for storing human body material fulfilling specific criteria.
The specific criteria cited are for example the fact that human body material intended for autologous or deferred use is kept, or that gametes intended for partner donation are involved.
9. The establishment must have written directives and procedures for controlling access to the premises, cleaning and maintenance, removal of waste and continuity of services in the event of an emergency.

E. Documentation and recording

1. A system characterised by clearly defined and efficient documentation, proper reporting and registers, and authorised standard operating procedures should be established for the procedures for which approval is requested. Documents must be regularly revised and compliant with the law and the present decree. The system must guarantee standardisation of the procedures performed and the possibility of retracing all the steps, that is, collection, codification, donor eligibility, procurement, processing, preservation, storage, transport, distribution or disposal or destruction, including aspects related to quality control and quality assurance.
2. For any critical activity, the materials, equipment and personnel involved must be identified and documented.
3. Any change in the documents must be checked, dated, approved, documented and executed without delay by authorised personnel in the establishments.
4. A procedure must be established for monitoring documents to provide the history of revisions and changes in the documents and to guarantee that only current versions of documents are used.
5. It must be demonstrated that the data recorded are reliable and constitute a faithful representation of the results.
6. The data recorded must be legible and indelible. They can be handwritten or recorded in another validated electronic system.
7. Without prejudice to Article 6, §3, paragraph 2 of the present decree, all the data recorded, including basic data, that are critical for the safety and quality of the human body material must be preserved in such a way that access to these data is guaranteed for at least ten years after the expiry date for clinical use or disposal.

F. Evaluation of the quality

1. An auditing system should be established for the activities for which approval is requested. Trained and competent persons must perform these audits independently, at least every two years, in order to ensure that the approved protocols and regulatory requirements are observed. The results and corrective measures must be documented.
2. Any breach in observance of the requirements provided by the quality and safety standards must result in documented investigations, along with a decision on any corrective and preventive measures. The fate of non-compliant body material must be decided in accordance with the written procedures, under the supervision of the person responsible, and recorded. All the human body material concerned must be identified and undergo the necessary measures.
3. Corrective measures must be documented, implemented and completed efficiently and within appropriate time periods. The efficacy of the preventive and corrective measures should be evaluated after they are applied.
4. The establishment must establish procedures allowing the efficacy of the quality management system to be evaluated in order to guarantee systematic and ongoing improvement.

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