

Bioethics Advisory Committee

Opinion No 42 of 16 April 2007 on umbilical cord blood banks

***Request for opinion dated 26 October 2005,
from Ms Anne-Marie Lizin, chairperson of the Senate,
On umbilical cord blood banks***

CONTENT OF THE OPINION

Question put to committee

General introduction

Chapter I. Scientific fundamentals

I.1. Introduction

I.2. Objective of the use of umbilical cord blood cells

A. Therapeutic purpose

B. Research

I.3. More specific questions dealt with by the select committee with the experts consulted

I.4. The current situation in Belgium

I.5. Advantages and disadvantages of the clinical use of umbilical cord blood: summary

Chapter II. The current legal framework at national and European level

II.1. At national level

II.1.A. Regulations

II.1.B. Opinion papers and recommendations

II.1.C. Summary at national level

II.2. At European level

II.2.1. Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices

II.2.2. Directive 2002/98/EC of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components

II.2.3. Directive 2004/23/EC of 31 March 2004 (relating to human tissues and cells)

II.2.4. Opinion No. 19 of the European Advisory Group on Ethics of Science and New Technologies (EGE) of 16 March 2004 (Ethical aspects of umbilical cord blood banks)

II.2.5. Summary at European level

Chapter III. General ethical discussion on the use of umbilical cord blood

Introduction

III.1. Allogeneic use versus autologous use

III.1.1. On the legitimacy of storage for the individual's own use

III.1.2. On the non-legitimacy of storage for the individual's own use in the case of umbilical cord blood

III.2. Public banks versus commercial private banks

III.2.1. Impact of commercial private banks on the use and storage of umbilical cord blood

*III.2.2. **Clinical** arguments against the establishment of commercial private umbilical cord blood banks*

*III.2.3. **Ethical** arguments against the establishment of commercial private umbilical cord blood banks*

*III.2.4. **Immunological** and **epidemiological** arguments against the establishment of commercial private umbilical cord blood banks*

III.2.5. Conclusions

Chapter IV. Ethical, logistical and legal implications of the collection of umbilical cord blood

IV.1. Introduction

IV.1.1. Irresponsible action on the part of the therapist

IV.1.2. Disruption of traditional clinical practice

IV.1.3. Use of non-validated techniques

IV.2. Practical consequences for the collection of umbilical cord blood

IV.2.1. Logistical aspects

IV.2.2. Legal implications of the parental request for umbilical cord blood to be collected

IV.2.3. Fair access

Chapter V. Advice and recommendations

V.1. Coherent legislative framework

V.2. Conceptual legal framework

V.3. Storage and use of umbilical cord blood

V.4. Information provided by the government

V.5. Information provided by hospitals

V.6. Triangular relationship between patient, doctor and umbilical cord blood bank

V.7. Relationship between the umbilical cord blood bank and the future beneficiary/recipient

Question put to Committee

The following question was raised by Ms Anne-Marie Lizin, chairperson of the Senate, on 26 October 2005:

“In application of Article 8 of the cooperation agreement of 15 January 1993 on the creation of an Advisory Committee for Bio-ethics and pursuant to the request of at least ten senators, I ask you to give me the Committee’s opinion on the project of bill aimed at regulating umbilical cord blood banks (Doc. No. 3-1309).

In addition to a general opinion on the philosophical aspects and principles adopted in the bill, the commission would more specifically like to be informed of the Committee’s opinion on the expediency of private banks encouraging, via uncontrolled advertising and without mentioning the existence of public banks, autologous donations in exchange for the payment of large sums of money, and without it being specifically proven that such donations systematically deserve preference over donations of heterologous cells.”

This question was considered in the Committee’s plenary meeting of 7 November 2005 and the analysis of this question was entrusted to the 2006/2 select committee.

During the meeting of 27 February 2006, the 2006/2 select committee decided to focus, in an initial opinion, on the following specific questions that were raised:

- on the one hand, the setting up of chiefly private banks for autologous umbilical cord blood with a possible *deferred personal* therapeutic purpose,
- and on the other hand, the development and support of public banks aimed at storing the umbilical cord blood of as many people as possible for *allogeneic* use with a *joint and several* (altruistic) therapeutic purpose.

General introduction

Up until recently umbilical cord blood and placenta were considered as post-natal products with the status of waste. However, recently we have seen a practice arise whereby the mother of a newborn infant has been allowed to pay for the removal and storage of these products. The question that can therefore be raised is: what development explains the shift from a status of post-natal waste to a status of valuable medical product, both for the patient and for society? The answer is simple: for scientific and technical reasons, these waste products have acquired the status of a valuable product, more especially as a source of stem cells which may have haematopoietic characteristics for patients who would otherwise have to resort to bone marrow transplantation. The acquisition of this new status has also led to new commercial strategies having developed, which can be found in maternity clinics and among obstetrics departments. Given that the context of “market-based medicine” is gradually broadening and financial efficiency is threatening to replace ethics as a touchstone for medical practice, it is not surprising to see medical waste (which possibly has a value) being turned into a commercial good.

For this reason the continuing legal vacuum surrounding the status of umbilical cord blood is alarming. After all, legally speaking that status is still more or less that of waste, of a “*res delicata*”, and consequently the collection and intended end use thereof could get out of hand.

In its Opinion No. 24 of 13 October 2003 on human stem cells and therapeutic cloning, and also in respect of the questions raised by the request for an opinion made by the chairperson of the Senate, the Committee points to the persistent problems of the legal vacuum for umbilical cord blood banks.

Moreover, in its Opinion No. 11 of 20 December 1999 on the removal of organs and tissues from healthy living people with a view to transplantation, the Committee already advised that “*the legal status of stem cells both from **peripheral blood** and from **umbilical cord blood**, should be clarified*”. However, the legislative work that could have drawn inspiration from the Committee’s Opinions Nos. 11 and 24, specifically as regards umbilical cord blood, has been marking time since 1999.

Therefore, this opinion makes reference to the content of Opinions 11 and 24.

For that matter, the Committee is acquainted with Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 (setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells). This directive makes provision for a European legal framework for the securing of permission, the granting of licences, the obtaining of official approval, for inspections and controls, for promotion and advertising, and for the necessary experience of the staff. This directive specifically mentions stem cells deriving from umbilical cord blood.

The Royal Decree of 23 December 2002 (on the removal, storage, preparation, import, transportation, distribution and delivery of human tissues and on the banks for human tissues) espoused the same aim. But after a private firm appealed against it, the Council of State suspended the decree in question further to judgement 116.329 of 24

February 2003, and rescinded the Royal Decree on 24 February 2005 (judgement 141.137).

This opinion also refers to Opinion No. 19 of 16 March 2004 of the European Commission's European Advisory Group on the Ethics of Science and New Technologies, which welcomes the above-mentioned directive 2004/23/EC.

Chapter I. Scientific fundamentals

This chapter contains a summary of the information gathered from the experts who were consulted by this Committee, the Opinion Paper of June 2006 of the British Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists (RCOG)¹, Report No. 74 of the French CCNE of 12 December 2002, and various, recent scientific publications.

1.1. Introduction

Stem cells can be isolated from blood collected from the placenta during childbirth or from blood from the blood vessels of the umbilical cord². Umbilical cord blood is only available in small quantities but yields stem cells that are very immature and liable to active proliferation. What is particularly important, however, is that these stem cells are more immuno-compatible³ than the mature cells from bone marrow or from blood. Various laboratory studies are aimed at stimulating the proliferation of these cells from the umbilical cord in order thereby to be able to increase the number of stem cells available.

The use of stem cells from umbilical cord blood is an alternative to bone marrow transplantation, especially for certain haematological, immunological or metabolic disorders in children and young adults. The collection and storage of umbilical cord blood should be effected in optimal safety conditions and in accordance with the European Directive of 31.03.04 setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (Directive 2004/23/EC) and in accordance with the various Belgian laws which, in the future, should clearly take into account the status of umbilical cord blood and placenta blood.

In the future stem cells from umbilical cord blood (which are a source of haematopoietic precursors) could also be a source of precursors of mesenchymal cells or neurological cells. They can indeed develop and differentiate into different cell types and tissue types. However, research in this field is still at a very early stage and at the moment the therapeutic role of these cells basically remains speculative.

Bearing in mind the fact that umbilical cord blood is not available other than at birth, these stem cells can only be used in a therapeutic perspective if the blood is stored in the framework of an “umbilical cord blood bank”.

¹ Opinion Paper 2 of the RCOG on Umbilical Cord Blood Banking. This opinion replaces the RCOG’s opinion of October 2001.

² Although it is not directly the subject of this opinion, the Committee points out that foetal waste, obtained after a miscarriage, can also be used to obtain *multipotent* stem cells. In the context of Parkinson’s Disease, there have been ten years’ clinical (though still experimental) studies in people with neuronal stem cells isolated from foetal brain tissue.

³ The immature character of these stem cells from umbilical cord blood reportedly reduces the risk of immunological rejection, even in the case of insufficient compatibility of the tissue (i.e. the HLA [Human Leucocyte Antigen] compatibility) and reportedly also lowers the risk of so-called “graft versus host disease”.

Several programmes are also aimed at setting up umbilical cord blood banks and developing a follow up network of the results obtained with the transplants carried out.

1.2. Objective of the use of umbilical cord blood cells

The **deferred** use of stem cells from umbilical cord blood can basically occur for two purposes: therapeutic purpose and research.

A. Therapeutic purpose

The **allogeneic**⁴ therapeutic use of umbilical cord blood is usually a *non-targeted or altruistic donation* and should thus be distinguished from an **autologous** use intended for the donating child or a family member. In this sense a distinction can be made between three possible uses for umbilical cord blood:

1) The joint and several therapeutic objective by means of allogeneic, non-targeted, altruistic use

The joint and several therapeutic objective involves the storage of umbilical cord blood of a large number of individuals with the aim of *allogeneic* use, i.e. use to the benefit of someone else and solely in function of the criteria for immunological compatibility (such as is the case for organ transplantation).

The allogeneic use of stem cells is limited by the fact that an HLA-compatible donor has to be found. For patients needing a bone marrow transplant who have no family member with compatible bone marrow, or cannot avail themselves of any other donor with compatible bone marrow (i.e. having the same HLA groups), umbilical cord blood of registered and listed donors is available in umbilical cord blood banks to achieve or facilitate adequate HLA matching. At the moment more than 10,000,000 bone marrow donors have been listed. By way of comparison: the **Netcord Foundation** (international network of umbilical cord blood banks⁵) contains around 85,000 deep-frozen units in storage that are available for clinical use. And this only covers the approved umbilical cord blood banks.

In the United Kingdom, allogeneic umbilical cord blood banks were selected on the basis of **ethnic variability**⁶ of the local population. Indeed, a varied ethnic scale of umbilical cord blood would enable patients from ethnic minorities to access this kind of transplant by statistically improving the diversity of the HLA groups. It is worth noting that only 3% of bone marrow donors come from ethnic minority groups, whilst 40% of the donations of umbilical cord blood come from these ethnic groups.⁷

⁴ Autologous use means use in the person's own body; allogeneic use means use in the body of another person.

⁵ www.netcord.org

⁶ When the adjective "ethnic" is used in this opinion (variability, group, ethnic diversity), this refers only to the importance of ethnicity for ensuring that the diversity of the HLA groups is guaranteed in the political choices made in the field of public health. This term refers to the statistic of genetic diversity and not to the statistic of diversity of the racial population groups.

⁷ Opinion Paper 2 of the RCOG on Umbilical Cord Blood Banking. Op cit.

2) The familial therapeutic objective through autologous use in the context of families with an increased risk of disorders that can benefit from a later transplantation of umbilical cord blood

In this familial therapeutic objective the recipient can be the child itself or a family member of the risk family.

Some British transplantation centres recommend the storage of the umbilical cord blood of children born in a family where there are known genetic anomalies which could later lead to a transplantation of stem cells. If the umbilical cord blood cells are HLA compatible, they could be used for the sick child or for another sick child who is also HLA compatible.

If the newborn baby itself develops the illness, its own stem cells are available for later somatic gene therapy, provided of course that adapted techniques are developed.

Pre-implantation genetic diagnosis is currently the subject of ethical debates. Nonetheless, this technique is permitted, under certain conditions, in Belgium, Spain, the Netherlands and the United Kingdom. The autologous use of umbilical cord blood could be an alternative here for risk families.

3) The personal therapeutic objective of autologous use in the context of families with a low risk of a certain disorder that could draw benefit from a later transplantation of umbilical cord blood which was collected, preventatively, during birth

The personal therapeutic objective consists of the storage of the newborn baby's umbilical cord blood to enable the stem cells from the umbilical cord blood to be used at a later date (and if necessary). The establishment of *autologous* umbilical cord blood banks fits into the scheme of the promising regenerative medicine. The multipotency of the stem cells originating from umbilical cord blood could be applied for the purposes of curative medicine to the extent that these cells could in the future provide autologous replacement tissues produced from umbilical cord blood cells from the individual in question. In the context of our current knowledge, these autologous therapeutic applications are still only virtual and speculative.⁸

At this stage it is therefore very difficult to estimate what chance there is of an autologous donation possibly being useful for families with a low risk of a disorder and which in the future might derive benefit from a transplantation of umbilical cord blood that was collected at birth on account of any preventative possibilities. A number of future indications for the use of stem cells from umbilical cord blood remain extremely speculative. Internationally, the use for transplantation of autologous umbilical cord blood that was stored commercially is minimal, but this use appears to be on the increase under commercial pressure from private companies.

B. Research

Stem cells from umbilical cord blood can also be used for the purpose of research on these cells. Umbilical cord blood or placental blood could thus also be put to a more noble and advantageous use than commercial use in the production of cosmetics. The

⁸ *Les banques de sang du cordon ombilical en vue d'une utilisation autologue ou en recherche* (Umbilical cord blood banks with a view to autologous use or research), Report No. 74 of the French CCNE of 12 December 2002, p. 4.

possibility of umbilical cord blood being used for research should also be mentioned in the consent form handed to the mother.⁹

1.3. More specific questions dealt with by the select committee with the experts consulted¹⁰

1. Is it definitely established that a person's umbilical cord blood offers no benefit at all to this person in comparison with umbilical cord blood from an allogeneic bank and compatible with the person's immunological type? In other words, do the umbilical cord blood banks for autologous use give their donors a benefit and if so, what benefit(s) are we talking about?

A. A **first application** is to be found in the framework of transplantation of haematopoietic stem cells for hematopathies; in these cases it is indeed established that an allogeneic transplant is better than an autologous transplant since this allogeneic transplant corrects a genetic defect in the recipient or because an allogeneic transplant offers the recipient the necessary immunity to eliminate tumour cells (= GVL or antitumoral effect of the transplant).^{11 12}

This is confirmed by studies on twins^{13 14}, which show that stem cell transplants that came from a brother, sister or a third-party HLA compatible donor, score better than stem cell transplants from a twin with identical HLA. The immune system of the allogeneic donor indeed introduces an element that appears essential to eradicate the underlying disorder. Therefore complete compatibility would give less good results.

For aplastic anaemia – an auto-immune disorder of the marrow or induced by chemotherapy – it is currently impossible to assert that autologous use in this case would be better than resorting to an allogeneic transplant. After all, there are no studies on twins available in respect of this disease.

B. Regenerative medicine is seen as a **second possible medical application** for stem cells from umbilical cord blood, such as for example for Parkinson's Disease, Alzheimer's, heart complaints, diabetes, etc.

However, in this case the promises are harder to keep, because the cells are only stored for twenty years (e.g. Cryo-Save) and these disorders will in general only develop in the donor baby well beyond the period of storage, i.e. a lot longer than twenty years (reference: "French text PD").

⁹ Whilst there is no request for consent (and still less, information) when companies collect placentas in maternity clinics for the production of cosmetics! This only further heightens ambivalence as regards placental and umbilical cord blood: human tissue and human cells versus waste?

¹⁰ Interview with experts on 10.05.2006: D. Bron, M Sc of the J. Bordet Institute and Prof. C. Verfaillie of the Catholic University of Leuven.

¹¹ Horowitz M. et al. *GVL reactions after bone marrow transplantation*, Blood 1990; 75:555-62.

¹² Fefer A., Sullivan K. M., Weiden P., Buckner C. D., Schoch G., Storb R., Thomas E. D., *Graft versus leukemia effect in man: the relapse of acute leukemia is lower after allogeneic than after syngeneic marrow transplantation*. Prog. Clin Biol Res 1987; 244: 401-8.

¹³ Kroger N. et al. *Stem cell transplantation from identical twins in patients with myelodysplastic syndromes*. Bone Marrow Transplant. 2005; 35: 37-43.

¹⁴ Barrett A. J. et al. *Effect of nucleated marrow cell dose on relapse and survival in identical twin bone marrow transplant for leukemia*. Blood 2000; 95: 3323-7.

Studies from Germany¹⁵ on cultures of stem cells from umbilical cord blood of premature babies (32-38 weeks) suggest that these cells have a better intrinsic potential for pluripotent differentiation and would therefore be more efficient for regenerative therapy. But the removal of umbilical cord blood in premature babies can give rise to problems, both from a clinical and ethical standpoint (see point IV.2.1.).

C. A radiation accident could be a **third indication** for autologous transplantation. This is an exceptional case in which it can be assumed with certainty that the individual works in the nuclear industry once he is an adult and has been the victim of a serious radiation accident.

In such a case it is interesting to point out that it was suggested to the authorities in the nuclear sector that stem cells be removed from the blood of their workers and these cells be stored frozen in the event of an accident occurring. This proposal was turned down on the pretext that it would then become difficult to recruit staff.

Contracts of firms of the “Cordblood Banking” type are for 20 years. It is very unlikely that this umbilical cord blood would be needed before the age of 20, in the possible context of a radiation accident.

Summary

The experts agree that pertinent scientific data are currently not available to allow us to state that autologous use offers a significant advantage over allogeneic use.

2. Are there problems from a scientific standpoint associated with a deferred use of umbilical cord blood, either the donor’s immune system changing after a period of time or the storage of blood posing problems in the long run?

The freezing technique appears to guarantee the quality of adult haematopoietic cells for more than 30 years. At the moment we do not know whether the possibilities of storage of the functions of the stored stem cells remain intact after 20 years. There are no comparative studies on the quality of stem cells originating from umbilical cord blood after longer periods of storage.

*3. Is it possible to imagine an allogeneic umbilical cord blood bank where a system of traceability allows **priority** to be given to the donor? If it were assumed that this **traceability were guaranteed**, is the **availability** of the individualised stem cells then guaranteed at the desired moment for the donor, both as regards quantity (some of them may have been used for someone else) and quality (this again raises the question as to storage of the cells over time)?*

Traceability is possible in the umbilical cord blood banks. Umbilical cord blood can be traced comprehensively and qualitatively, as can control samples. If a sick child were to need his own frozen umbilical cord blood, this could be traced without any problem, given the accuracy of the HLA characterisation in the register.

¹⁵ Kogler G, Wernet P et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med 2004; 200:123-35.

However, we cannot overlook the possible danger of a system of *guaranteed traceability*, in which there is the possibility of a donor who has since grown to adulthood being approached for the removal of stem cells from his blood.¹⁶

Availability is a real problem. A sample of umbilical cord blood *from a birth* provides for an average amount of 50 to 100 ml with a specific quantity of stem cells. This sample can only be used once. Per treatment, an average of one sample of *50 to 100 ml* is needed for a patient with a maximum weight of 40 kg.¹⁷ Given that umbilical cord blood can only be used once, it is conceivable that it will have been used for another patient before the donor wishes to use it.

To sum up, even after the umbilical cord blood banks are anonymised, HLA characterisation today is very accurate and the donor's umbilical cord blood can be identified very quickly. However, it would be inappropriate to talk of "**priority**" since umbilical cord blood can in the meantime be used for another patient. The question of traceability therefore is not raised, other than for rare HLA groups.

4. *Would umbilical cord blood for autologous use rob fundamental research of a source of specific research material?*

The experts agree that what is available at the moment in the public banks is amply sufficient for scientific research. Unless the banks for autologous use were suddenly to prove very successful in the future, scientific researchers have enough research material. On the other hand half of the removals of umbilical cord blood are insufficient in terms of volume to be used therapeutically.

More questions should be posed on the relevance for private firms of carrying out publicity in this field in circuits and institutions involving services for obstetrics and maternity clinics (for example publicity in hospital maternity wards).

1.4. Current situation in Belgium¹⁸

A. Umbilical cord blood banks

At the moment there are five allogeneic public banks operational in Belgium (ULg, KULeuven, ULB, UGent, UCL) and probably one private bank.

By way of comparison: the list of around 20 allogeneic banks worldwide represents some 125,000 transplants. The system is based on international exchanges of transplants. This offers the greatest benefit for the community, whilst this option is also the most efficient from an economic standpoint and the most effective from a clinical standpoint.

¹⁶ "It has been also suggested that 'linkability' in research projects involving umbilical cord blood be maintained but that 'appropriate firewalls' be constructed to protect the donor's identity and privacy." Sugarman J., et al. *Ethical issues in umbilical cord blood banking*. JAMA 1997; 278: 938-43.

¹⁷ Since a weight of 40 kg is the maximum, it is worth pointing out that this weight is reached, according to paediatric tables, around the age of 11 or 12 for the percentile 50 in both sexes. Most indications for transplantation before this age are formed by genetic disorders such as haemoglobinopathies, immuno-deficiencies, and other disorders for which the stem cells of the umbilical cord blood do not offer any solution and may have the same genetic anomaly.

¹⁸ Information obtained from Professor Yves Beguin, director of research at the FNRS and associate department head at the haematology department of the CHU Sart Tilman, University of Liège.

B. Samples collection

The percentage of births where umbilical cord blood is collected remains low. The bank of the University of Liège, for example, receives 700 samples a year, of which around 100 are stored on the basis of a volume > 100 ml, with the aim of selecting the samples containing the most stem cells.

One thousand samples are collected at the Catholic University of Leuven (KUL) every year (150-200 samples are taken in situ, samples from other sources are transferred to the Leuven bank), of which one or two every month are used for transplantation of stem cells. The financing of the storage is almost wholly borne by private research funds.¹⁹

For all Belgian allogeneic public banks, it is currently estimated that together they receive around 3,000 samples every year, of which 500 to 1,000 are stored. No data is available as regards the private banks.

C. Cost price

The price asked by the private banks for the storage of the samples of umbilical cord blood is currently EUR 1,375 (for 20 years).^{20 21}

The amount of the fee offered to obstetricians per sample of umbilical cord blood removed during a birth is not known.

D. Use of umbilical cord blood

At the moment it appears that no sample of umbilical cord blood stored by private banks in Belgium is used for the transplantation of stem cells. Worldwide, that autologous use is not very prevalent.

For their part, the Belgian public banks have made it possible for 220 transplantations of stem cells to be carried out.

By way of comparison, every year 1,500 to 2,000 transplantations of stem cells are carried out worldwide, chiefly in patients who have no donor with compatible HLA bone marrow.

¹⁹ Information supplied by Pr.Dr em. E. Eggermont, Catholic University of Leuven.

²⁰ In: *Le point sur les banques privées de sang du cordon ombilical*. Document of 15 November 2006 of the Umbilical Cord Blood Banks of the ULg, ULB, UCL. "The cost price of an autologous freezing project of umbilical cord blood is absolutely disproportionate to the probability of that umbilical cord blood being used. The following calculation can be made. In Belgium there are currently approximately seven autologous transplants of haematopoietic stem cells per year for patients under the age of 20. That means that in the next 20 years 140 autologous transplants will be carried out in patients under 20. If we assume that none of these transplants can be carried out on the basis of stem cells from the patient himself and that autologous umbilical cord blood therefore has to be used, 140 units of autologous umbilical cord blood will be needed. If we assume that over this period of 20 years there will be 1,400,000 births, this means that every unit of frozen umbilical cord blood will have a 1/10,000 probability of being used for autologous transplantation. The cost price of each unit as offered by the private firms is of the order of €1,000 for a storage period of 20 years. That means that the total budget that has to be invested by Belgian families will be €10,000,000 per unit of umbilical cord blood used! This amount is a considerable under-estimate, for most autologous transplantations can be carried out with autologous stem cells from peripheral blood which offers the advantage of the transplantation occurring three times more quickly than with umbilical cord blood (10 as opposed to 30 days)".

²¹ For the record: R. Branson recently launched a new umbilical cord blood bank – the "Virgin Health Bank" – in which umbilical cord blood is stored for 20 years for a sum of EUR 2,270. R. Branson undertakes to give away, free of charge, 80% of every sample to a government bank which is accessible to everyone. *Journal du Médecin* - 13 February 2007.

E. Samples of umbilical cord blood

At the moment approximately 200,000 samples of umbilical cord blood are stored worldwide, around 12,000 of which in Belgium. That is not enough to cover the demand for transplants for all adults, since many samples do not contain the number of cells necessary per kilogram of body weight for the recipient affected by a disorder rendering him eligible for such a transplantation of cells.

To offset that shortfall, a project financed by the US government has been started up, with the aim of storing 150,000 new samples of umbilical cord blood in the space of three years.

F. Ethnicity

The British example, which consists in setting up banks that are more especially intended for certain ethnic minorities (for example people of Asian or African origin) is defensible, since the registers of adult donors voluntarily donating bone marrow (10,000,000 worldwide) are very under-represented as regards certain ethnic minorities. These will have far better chances of finding a donor who could be HLA compatible.

G. Opinions of the WMDA and of certain Belgian government banks

The opinion of the WMDA (World Marrow Donor Association)²² and an updated opinion of certain Belgian public banks (ULg, ULB, UCL)²³, distributed among French-speaking Belgian paediatricians and gynaecologists, contained a clear standpoint relating to the establishment of profit-making autologous private banks, the benefit from which for families and society is limited, and which moreover risks hampering the further development of allogeneic umbilical cord blood banks to which patients already have access.

H. International accreditation

The public banks are obliged to obtain international accreditation granted by the American body FACT and the European body Netcord together, which guarantees the quality of units that are stored in a bank in accordance with FACT/Netcord's international standards.

From 01/01/2008 no unit of allogeneic umbilical cord blood may be distributed in Europe or the US if the bank does not have FACT/Netcord accreditation.

It goes without saying that the same accreditation obligation (and therefore quality obligation) has to be required of the private banks. If their practice fails to take this quality standard into consideration, their operation should be banned.

I.5. Advantages and disadvantages of the clinical use of umbilical cord blood: summary

²² WMDA Policy Statement for the Utility of Autologous or Family Cord Blood Unit Storage (approved and adopted by the WMDA on 25 May 2006).

²³ *Le point sur les banques privées de sang du cordon*. Document of 15 November 2006 of the Umbilical Cord Blood Banks of the ULg, ULB, UCL. Op cit.

In an analysis carried out by the International Bone Marrow Transplantation Registry (IBMTR), it is estimated that since 1998 20% of transplantations of stem cells in patients under the age of 20 occurred on the basis of umbilical cord blood. The most common indications were lymphoblastic leukaemia or acute myeloblastic leukaemia.²⁴

The **advantages** of the use of umbilical cord blood include:

- Quicker availability: patients receiving a transplantation of cells from umbilical cord blood usually receive them more quickly than those who are treated with a conventional bone marrow transplantation.
- Extension of the donor pool: the transplantation of umbilical cord blood tolerates a greater mismatch of the HLA between donor and recipient than in the transplantation of bone marrow or cells from peripheral blood. And what is more, the umbilical cord blood banks work in a context of ethnic diversity and thus more frequently supply more varied HLD haplotypes than bone marrow stocks.
- The graft versus host reaction (rejection of the transplant) is less commonplace and is less serious.
- Viral transmission does not occur so often, in particular as regards the cytomegalovirus and the Epstein-Barr virus.
- When using umbilical cord blood there is no risk of unforeseen refusal, as in the case of a bone marrow donor who changes his mind.

The **disadvantages** of the use of umbilical cord blood:

- Less density of haematopoietic precursor cells and stem cells than in the bone marrow. This disadvantage is examined in studies to increase the pool of precursor cells. Recent research²⁵ into cultures of stem cells from umbilical cord blood in premature births (32-38 weeks) appears to show that these cells have a better intrinsic pluripotent differentiation potential. This would therefore be more efficient for regenerative therapy. But the removal of umbilical cord blood in premature babies could pose problems at both clinical and ethical level (see point IV.2.1.).
- The number of blood cells in umbilical cord blood constitutes an element of critical importance for the speed with which the transplant takes, and is thus related to survival, especially among adults. In the United Kingdom, at least 2×10^7 cells/kg body weight of the recipient is vitally important. In France, it is estimated that 80 ml and 0.37×10^8 cells/kg are needed if a unit of placental blood is to be used for a therapeutic purpose.²⁶ The average content of the cells supplied by a unit of umbilical cord blood is 1×10^9 . A single unit of autologous or allogeneic umbilical cord blood is therefore not enough for a person weighing 50 kg. At the moment research is under way aimed at the increasing the donor pool and strategies for increasing the dose of stem cells *ex vivo*. Research is thereby also being conducted into the possibility of transplanting several units of umbilical cord blood.

²⁴ Opinion Paper 2 of the RCOG on Umbilical cord blood Banking. Op cit.

²⁵ Kogler G., Wernet P et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J. Exp Med* 2004; 200: 123-35. Op cit.

²⁶ Opinion No. 74 of the National Ethics Advisory Committee (CCNE), 12 December 2002. *Les banques de sang du cordon ombilical en vue d'une utilisation autologue ou en recherche* (umbilical cord blood banks with a view to autologous use or research), p. 7.

- When the transplantation of cells from umbilical cord blood fails or when the recipient relapses, there are no more cells left from the umbilical cord blood of the same donor. We cannot overlook the possible danger of the guaranteed traceability of the donor, whereby the latter may be approached in the future with requests for stem cells to be taken from his peripheral blood or bone marrow.
- The use of stem cells from umbilical cord blood for the treatment of acute and chronic disorders is currently still very speculative. However, we do have more data on the use of foetal stem cells. Pre-clinical studies have also shown that the heart function improves after injection of stem cells from umbilical cord blood after a myocardium attack. The same is mentioned in a report on traumas of the spinal cord. The use of stem cells located in the Wharton's jelly²⁷ of the umbilical cord are at the experimental research state, in particular as regards the obtaining of hepatocytes. It is partly on the basis of these spectacular results, which are nonetheless very sporadic, that commercial banks (sometimes injudiciously) disseminate the results of preliminary studies that are still far from being clinically validated.

²⁷ "Wharton's jelly": mesenchymal tissue surrounding the blood vessels of the umbilical cord.

Chapter II. The current legal framework at national and European level

Confronted with a sometimes inaccurate technical and scientific terminology and with fields of research that are constantly changing, it is not surprising that the legal theories and concepts show two phenomena: a lack of maturity and a discrepancy between the rules and regulations and scientific reality.

As an example of lack of maturity, we cite the legal status of stem cells which has not been specifically laid down. The question can be asked as to whether their legal status should depend on the “source” of the cells (i.e. stem cells from peripheral blood, from umbilical cord blood, from embryos, etc.) and/or should be in function of their **possibilities for use** now or in the future with a therapeutic, commercial or research purpose.

As an example of discrepancy we again call to mind the Committee’s Opinion No. 11 of 20 December 1999 on the removal of organs and tissues from healthy living persons, with a view to transplantation, which stressed that: “*the legal status of the stem cells both from peripheral blood and from umbilical cord blood should be clarified*”. The technical and scientific uncertainties, especially as regards the autologous use of umbilical cord blood, are far from having been solved whilst the legal status of this blood is such as to contribute to a situation of lawlessness.

We can point out here that in its Opinion No. 24 of 13 October 2003 on human stem cells and therapeutic cloning (Chapter II), the Committee analysed the legal data that applied at that time to the fast-changing field of biotechnology in order to be able to fuel the subsequent ethical discussions, legislative initiatives and any recommendations. This analysis is brought up to date and supplemented here, taking account of the problem of private management versus public management.

II.1. At national level

II.1.A. Rules and regulations

II.1.A.1. The law of 5 July 1994 on blood and blood derivatives of human origin

Although Article 1 of this law states that it applies to human blood, independent of the source, the Committee is still of the view that the status of umbilical cord blood is not clear, given that umbilical cord blood is not extracted but merely collected. Moreover, umbilical cord blood and placenta have no medical importance in themselves other than that of the stem cells they contain.²⁸ But tissues and cells²⁹ fall under the law of 13 June 1986 as amended by the law of 22 December 2003. Therefore an analysis is presented of these latter legal provisions in points I.A.2 to I.A.5 below.

²⁸ Which can be considered as tissues.

²⁹ Note: We point out that stem cells appear to fall under the law of 5 July 1994; Article 17, para. 4 of this law makes indirect reference to them by stating: “The collection of trombocytes, leucocytes, neocytes and **stem cells** can also be effected by means of cytaferesis”. This results in stem cells (or at least stem cells from peripheral blood) falling under the law of 5 July 1994 and not under the 1986 law on organs.

The law of 5 July 1994 does not specify whether it is aimed at **autologous or allogeneic use**. Although it appears that allogeneic use is the most obvious, autologous use is not ruled out as such. In fact reference is made to it, for example in Article 9.³⁰

This law also does not rule on the **public or private character of the institutions** that are players in this field. All are obliged to comply with the principles and conditions laid down for the obtaining of ministerial approval, **including the voluntary nature of donations (donors are not remunerated)** and anonymity (but for extreme medical necessity, the donor and recipient do not know each other).

II.1.A.2. The law of 13 June 1986 on the removal and transplantation of organs

The law of 13 June 1986 does not give any definition of the terms “**organ and tissue**”. Only the Explanatory Statement states that the terms “organ and tissue” have to do with “*all elements of human origin, except blood and secretions*”. Given that this list has also been quickly outstripped, a sufficiently broad definition of the terms should be used (Senate, 1984-1985, No. 832/2, p. 4).

At this stage the legislator was thus aware of the necessarily evolving nature of removal and transplantation techniques, and of the probably temporary character of a prescriptive text in this field.

The programme law of 22 December 2003 extended the scope of this law to “cells” by replacing in every article “*organs and tissues of the body of a person*” by “*organs, tissue and cells of the body of a person*”.

This law excludes from its scope embryo transfer, the removal and transplantation of ***testes and ovaries*** and the use of ***ova and sperm*** (Article 1, para.2).

Before the amendment of 2003, ***this law was aimed at allogeneic grafts***, i.e. the removal of organs or tissues from the body of a person called the donor, with the purpose of transplanting these organs or tissues with therapeutic purposes into the body of someone else. The programme law of 22 December 2003 extended the scope to include ***autologous grafts*** (donor and recipient are one and the same in this case).

On the advice of the High Council for Health, the King can extend application of this law to include the post-mortem removal of organs or tissues that are indicated by the King with the purpose of preparing vital therapeutic devices for the treatment of serious disorders and deficiencies (Article 2).

This law authorises the King to set the rules and lay down the conditions for the removal, storage, transportation, distribution and delivery of organs and tissues (Article 1, para. 3) (See 1.A.3 and 1.A.4.)

Removal and transplantation should be carried out by a doctor ***in a hospital as established by the law of 23 December 1963 on hospitals*** (see Article 3). By way of a reminder: the law on hospitals, coordinated on 7 August 1987, defines *inter alia* the conditions for recognition of hospitals in Belgium, irrespective of whether their managers are ***public or private***.

³⁰ Article 9, para. 2 of the law of 5/7/1994: “However a blood extraction may occur [...] with a view to a programmed autologous transfusion”.

On the other hand the law of 13 June 1986 stipulates that parting with organs and tissues is *not permitted with a profit-making aim*, regardless of the parties between whom this is agreed (see Article 4, para.1). As is the case with the legal provisions on blood, the principle of non-commercialisation is also applicable here. We find explicit reference to this in point 1.A.6 on research into embryos *in vitro*.

II.1.A.3. The Royal Decree of 15 April 1988 on tissue banks and the removal, storage, preparation, import, transportation, distribution and delivery of tissues

The Royal Decree of 15 April 1988 finds its legal basis in the law of 13 June 1986, which was cited in point 1.A.2 above.

This Royal Decree does not define what tissues are and does not explicitly target stem cells. However, the Royal Decree was repealed and replaced by the Royal Decree of 23 December 2002 (see 1.A.4). But as a result of the suspension of the Royal Decree of 23 December 2002 by the Council of State on 24 February 2005 (see point 1.A.4 below), *the Royal Decree of 15 April 1988 is at the moment again³¹ in force*.

II.1.A.4. The Royal Decree of 23 December 2002 on the removal, storage, preparation, import, transportation, distribution and delivery of tissue of human origin, as well as on banks for tissues of human origin

The Royal Decree of 23 December 2002 defines “tissues” as “tissues and cells, elements that are taken out of or have come loose from the human body in the event of a deceased donor (whose heart was still beating or had stopped) for the purpose of *autologous or allogeneic* transplantation or implantation.

This Royal Decree contains an *Annex I which presents the list of tissues referred to in this decree*. The list enumerates “ocular tissue (cornea and sclera), musculo-skeletal tissue (bone, cartilage, osteo-chondral tissue, tendon, ligament and fascia, meniscus, smooth muscle and striated muscle), cardiovascular tissues (heart valve, vessels – arteries and veins, myoblast), skin, timpano-ossicular grafts, liver tissues, neurological tissues, endocrine tissues, teeth tissue, haematopoietic cells and stem cells (bone marrow and peripheral blood) and tissue of foetal origin (placenta, umbilical cord and umbilical cord blood), mesenchymal stem cells and embryonic stem cells”.

This Royal Decree does target umbilical cord and umbilical cord blood. According to the list included in the annex to this decree, the stem cells from this origin can be “stored” just as bone, cartilage or ligaments are stored in tissue banks to provide for needs for restorative orthopaedic surgery.

We can add that **Article 1, §2** of this Royal Decree **excludes** from these rules and regulations:

“**1.** peripheral blood, namely the components and derivatives thereof (*except stem cells*) that fall under the law of 5 July 1994 on blood and blood derivatives of human origin;

³¹ 12 April 2007.

2. elements which are separated off or produced by cell material exchange, used alone or in combination;
3. reproductive tissues, gametes and embryos; [...]

This Royal Decree³² *forbids* the use of tissues with deferred preventive ends (i.e. *deferred autologous use in time*).

This Royal Decree³³ reserves recognition *for hospitals, blood transfusion centres and non-profit making institutions. Both private operators and public services* can thus lay claim to the recognition insofar as they meet the regulatory requirements in this respect, *inter alia* the ban on any form of publicity **and the ban on striving for a profit-making goal**³⁴.

This Royal Decree was withdrawn by the Council of State (see 1.A.3). At the request of a private firm³⁵, the Council of State suspended the decree in question on 24 February 2003 (**judgement 116.329**) and annulled it on 24 February 2005 (**judgement 141.137**) on the grounds of it having no legal basis. There is no legal basis because the law of 13 June 1986 on the removal and transplantation of organs does not authorise the King to take executory measures for activities with autologous use or with a preventive character.³⁶

Further to this abolition, the Royal Decree of 15 April 1988 (see 1.A.3) is in force again.

II.1.A.5. The programme law of 22 December 2003 extends the scope of the law of 13 June 1986 and authorises the King also to regulate “autologous” activities in addition to organs and tissues.³⁷

Hitherto³⁸ no other implementing order has been adopted on the basis of the programme law of 22 December 2003. As described above, the Royal Decree of 15 April 1988 is applicable.

II.1.A.6. The law of 11 May 2003 on research into embryos in vitro

³² Article 2, point 3.

³³ See Article 3, para. 1, indent 2.

³⁴ See Article 2, points 5 and 6.

³⁵ The main activity of this firm is the establishment, in exchange for private payment, of a bank of foetal stem cells obtained from umbilical cord blood intended for autologous use. The customers are recruited internationally.

³⁶ We recall that in Belgium prevention in the field of public health falls under the authority of the Communities and not the federal government.

³⁷ **Article 156 of the law of 22 December 2003 states that:**

“Article 1, §1, first para. of the law of 13 June 1986 on the removal and transplantation of organs, is replaced as follows: “This law is applicable to the removal of organs, tissues or cells from the body of a person, referred to as the ‘donor’, with a view to the transplantation of these organs, tissues or cells, for therapeutic purposes, into the body of the same or another person, referred to as the ‘recipient’”.

Article 157 of this law states that.

“Article 1, §3 of the same law is replaced as follows:

“§3. The King can set rules and impose conditions or restrictions concerning the removal, storage, preparation, import, transportation, distribution and delivery of organs, tissues and cells. Each execution of the first paragraph after entry into force of the programme law of 23 December 2003 shall occur in a decree laid down after consultation in the Council of Ministers”.

³⁸ On 12 April 2007.

We only mention the law of 11 May 2003 by way of a reminder. Notwithstanding the adoption of this law, the legal status of stem cells has not been clarified. Since embryonic stem cells *in vitro* are concerned, this law simply forbids the use of *embryonic stem cells for commercial purposes* (Article 5.3).

Embryonic stem cells were isolated for the first time in 1998. This chronological factor should be taken into account in the re-reading and interpretation of certain legal provisions dating from before 1998 (points 1.A. 1 to 1.A.5), which can cover certain fields but leave a *legal vacuum in other areas and more particularly in the field of stem cells from umbilical cord blood*.

II.1.A.7. Bill on the removal and use of human body material for human applications or for scientific research (under study).

This bill is aimed at transposing Directive 2004/23 of the European Parliament and of the Council of 31 March 2004 (Directive on human tissues and cells) into Belgian law. The bill defines the legal framework for the procurement and use of stem cells from umbilical cord blood. However, these provisions are still at a design phase.

II.1.B. Opinion papers and recommendations

II.1.B.1. Opinion No. 11 of 20 December 1999 of the Belgian Advisory Committee for Bio-ethics on the removal of organs and tissues from healthy living persons, with a view to transplantation

Opinion No. 11 of 20 December 1999 recommends that “the legal status of stem cells from both **peripheral blood** and from **umbilical cord blood** should be clarified, given that umbilical cord blood is not removed but collected from the placenta when a child is born”. Therefore it is a kind of “*res delicata*”, without any function, and umbilical cord blood would “only require the simplest of legal procedures for its use to be promoted”. The opinion also recommends that: “only the mother’s permission should be requested, especially since she is also subsequently immediately asked to give additional information on her state of health. It therefore seems appropriate to give umbilical cord blood a status so that optimal use can be made of blood that is otherwise lost”.

We would point out that the possibility of an organ or tissue falling under the scope of both laws cannot be ruled out. One example is **placenta**, which falls under the field of application of the law of 1986 as organ or tissue, and under the law of 1994 on blood as a source of blood or blood derivatives.

II.1.B.2. Opinion of the Belgian High Council for Health of 7 December 2001 on the review of rules and regulations governing tissue banks³⁹

In its Opinion of 7 December 2001, the Belgian High Council for Health made the following recommendations:

- “*the umbilical cord and umbilical cord blood cells form part of the legislation on tissues and cells;*

³⁹ Internet: http://www.health.fgov.be/CSH_HGR/Francais/Avis/Avis Banques Tissus.htm

- *quality standards for umbilical cord banks should be worked out;*
- *autologous therapeutic use for preventive purposes with a deferred character should be prohibited.”*

In Annex II the High Council for Health lists the conditions for recognition and authorisation for activities related to tissue banks or cell banks. It stipulates *inter alia* that “every tissue or cell bank should be recognised by the Minister after a report by the competent department and after an opinion from the High Council for Health. This recognition may only be granted to non-profit making (...) bodies.

II.1.B.3. Statement of the Belgian Association of Physicians to gynaecologists and general practitioners⁴⁰

A statement made by the Belgian Association of Physicians runs as follows:

“The use of autologous umbilical cord blood is of no importance but for the interests of private firms, which of course see it as offering them the chance of securing financial gain from it.

It seems shocking that private firms could start operating in the commercialisation of organs and cells from the human body. The law prohibits the commercial use of human organs but unfortunately umbilical cord blood has not yet been categorised as such an organ. The minister is considering legal measures to stop the development of such private companies.

The possible failure of these firms will lead to very major ethical problems for the future of already frozen umbilical cord blood.

However, in the meantime the development of such profit-making banks (the advantage of which for family and society is very low) should not prevent allogeneic umbilical cord banks from further developing worldwide, and in Belgium more especially. This is a treatment which has proven its worth and for which a large number of patients from now on have a very real need.”

“Bearing in mind the discontinuation of the activities or failure of commercial umbilical cord banks, consumers should be informed and guarantees should be provided for the continuity of the storage and transfer of the samples to another bank or for compensation of the parties concerned”.

II.1.B.4. Opinion of the Belgian High Council for Health of 4 January 2006 on the bill on the removal, procurement and use of human body material for human applications or for scientific research (HGR No. 8147).

In its Opinion of 4 January 2006 the Belgian High Council for Health (HGR) supports the basic objectives of the bill for which an opinion was requested on 7 November 2005 by Minister R. Demotte (reference COHOP/05158/BP202396). The purpose of this bill is to transpose European Directive 2004/23/EC into Belgian legislation and to establish a legal basis to regulate the activities of cell banks and tissue banks.

This opinion recalls more especially that, in accordance with the provisions of Article 152 of the Treaty establishing the European Community, the legislator is authorised to incorporate into the scope of the law ethical requirements for which no provision is made in Directive 2004/23/EC.

⁴⁰ Internet: <http://www.ordomedic.be/braf/sangcordon.htm>

This national prerogative is confirmed in Article 4 §2 of Directive 2004/23/EC: “This directive shall not prevent a Member State from maintaining or introducing more stringent protective measures, provided that they comply with the provisions of the Treaty”.

As a result of this the members of the HGR’s working group stress the importance of certain fundamental ethical requirements being explicitly included in a future law constituting a framework in which the general principles are laid down.

These fundamental ethical requirements include:

- the principle of the voluntary and unpaid donation;
- the fundamental principle of a non-profit making goal;
- the principle of access to the relevant body material that is necessary for the production and research concerning the prepared products;
- strict compliance with the relevant provisions of the law of 22 August 2002 on patients’ rights;
- enforcement of the dispositions of the law of 13 June 1986;
- the binding references to the dispositions of the law of 7 May 2004 on human experiments, and those of the law of 11 May 2003 on research into embryos in vitro;
- the principles of general interest concerning absolute confidentiality and concerning the absence of rights and obligations between donor and recipient.

II.1.C. Summary at national level

Umbilical cord blood (which is merely collected and not removed like peripheral blood), stem cells and the umbilical cord itself (tissue that is simply left behind and possibly collected) have no clearly described legal status in Belgian law. The nebulous legal status of umbilical cord blood is alarming since the reception, storage and use thereof imply the possibility of all kinds of abuses.

If the placenta is described as tissue, it could fall under the law of 13 June 1986, but it could be asked whether this law applies to tissue “left behind” which is not “removed”.

If umbilical cord blood is merely considered as collected blood, or as a source of stem cells, then it is not self evident that the law of 5 July 1994 is applicable to it. The law of 13 June 1986 would then be invoked. Since the amendment by the law of 23 December 2003, this law is indeed applicable to organs, tissues and cells. But hitherto there have not been any application decisions.

Irrespective of the current legal situation described above, in Chapter III and IV the Committee presents arguments that could support a possible future legislation including the principle of non-remuneration of the donor and the possibility of allogeneic or autologous use.

II.2. At European level

II.2.1. Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices

Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices (including of human tissues) stipulates that the removal, collection and use of tissues, cells, and materials of human origin are regulated, as regards ethical aspects, by the principles listed in the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to application in biology and medicine (Bio-medicine Convention – Oviedo 1997) and by the rules that could exist on this in the Member States.

II.2.2. Directive 2002/98/EC of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components

Directive 2002/98/EC of 27 January 2003 recommends that an adequate system be set up for the comprehensive traceability of blood components and products from the donor through to the recipient.

At the current stage of research it is reasonable to demand that at national level, European level and possibly world level, a compulsory system of traceability be set up for oocytes and sources of stem cells. The reason for this are the fact that oocytes are being brought onto the market in an uncontrolled fashion and, on the other hand, the provision of follow-up enabling an oocyte to be traced in the event of genetic or cellular abnormalities that manifest themselves at a later stage. Such traceability falls under the principle of *prudence* and is part and parcel of a well-considered application of the *precautionary principle* in the field of public health. If we examine the scope of the therapeutic use of blood components and blood products, the application of such a *traceability system* for oocytes on the one hand and for sources of stem cells, on the other, appears feasible.

II.2.3. Directive 2004/23/EC of 31 March 2004

Directive 2004/23/EC⁴¹ relates to the setting of standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

Three aspects of this Directive deserve our attention:

- Firstly the Directive contains a number of elements that were listed in the Royal Decree of 23 December 2002 concerning the removal, storage, preparation, import, transportation, distribution and delivery of tissues of human origin and concerning banks for tissues of human origin, which was suspended and then annulled by the Belgian Council of State.
- Then the Directive specifically defines what is understood by “cells” and “tissues”. Article 3 states that “for the purposes of this directive, a) “cells” means individual human cells or a collection of human cells when not bound by any form of connective tissue; b) “tissues” means all constituent parts of the human body formed by cells.”
- Finally the Directive stipulates that it “should apply to tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone-marrow stem

⁴¹ Later than the Committee's Opinion No. 24 of 13 October 2003 and later than the Royal Decree of 23 December 2002.

cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells”.

II.2.4. Opinion No. 19 of the European Advisory Group on Ethics in Science and New Technologies (EGE) of 16 March 2004, on Ethical Aspects of Umbilical Cord Blood Banks

The EGE’s Opinion No. 19 reminds us of various fundamental ethical principles and values:

- the principle of respect for the dignity and integrity of the human being, including the principle of non-commercialisation of the human body;
- the autonomy principle or the right to self-determination on the basis of correct and comprehensive information;
- the principles of justice and solidarity as regards reasonable access to health care;
- the principle of charity or the obligation to do good for others, especially in the field of health care;
- the principle of not causing harm or the obligation not to cause harm to anyone, including the protection of vulnerable groups and individuals and respect for confidentiality and privacy;
- the principle of proportionality, which assumes a balance between resources and goals.

Opinion No. 19 also mentions that there are some conflicts of values. For example, the values of freedom and freedom of enterprise may indeed come into conflict with the principles of justice and solidarity on the grounds of which access to health care should be guaranteed on a fair basis in function of realistic needs and on the basis of the principle of the protection of vulnerable groups.

II.2.5. Summary at European level

In their Opinion No. 19 of 16 March 2004 the members of the European Commission’s European Advisory Group on Ethics in Science and New Technologies (EGE) welcome Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 (setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells).

This directive makes provision for a European legal framework governing authorisation, the granting of licences, recognition, inspection, control, promotion and publicity and the experience of the personnel.

In Belgium the content of the Royal Decree of 23 December 2002 (on the removal, storage, preparation, import, transportation, distribution and delivery of human tissues and on banks for human tissues) was of a similar ilk and ensured that Belgium was quickly able to align itself with the European directive. But, at the request of a private firm, the Council of State (see point 1.A.4) suspended the decree (pursuant to judgement 116.329 of 24 February 2003) and then annulled it (pursuant to judgement 141.137 of 24 February 2005).

Chapter III. General discussion on the *use* of umbilical cord blood^{42 43 44}

Introduction

The deferred use of stored stem cells from umbilical cord blood can basically serve two purposes: research and therapy. The therapeutic purpose can respond to a solidarity-based (altruistic) aim or a personal aim. In practice the therapeutic purpose usually leads to (public) blood banks being set up for allogeneic use or (generally private) banks being set up for autologous use.

Although the storage for an individual's own use of certain human products can be legitimised at a scientific level, and therefore be borne by the social security system, such scientific legitimacy is lacking in the autologous preservation of umbilical cord blood.

A therapeutic purpose should be based on objective scientific data. If these data are at hand, preservation with a personal and/or joint and several finality can be recommended. If the private purpose with therapeutic ends does not have scientific grounds, and therefore cannot be recommended, the question must be asked as to whether it can be pursued by umbilical cord blood banks, even where the costs are not covered by Belgian health care. If, on the other hand, the personal purpose is deemed legitimate at a particular time, it would be ideal for it to be covered in the framework of our social security system.

III.1. Allogeneic use versus autologous use

III.1.1. On the legitimacy of storage for an individual's own use

The preservation and storage of certain products of human origin for autologous use occurs in a whole range of medical fields, without this causing any real problems. It concerns personal preservation the legitimacy of which is in no way disputable, because its therapeutic effects are known: its financing is covered by our general solidarity system.

We can look, for example, at the case of the preservation of a man's own sperm before he undergoes a sterilising treatment (chemotherapy, radiotherapy, vasectomy). This has been carried out for decades. Preservation of an individual's own bone marrow in the context of an autologous transplantation is another good example, although the autologous preservation in that case is of short duration.

III.1.2. On the non-legitimacy of storage for an individual's own use in the case of umbilical cord blood

⁴² The discussion that follows is inspired inter alia by arguments resumed and developed in Opinion No. 19 of the EGE of 16 March 2002, Opinion No. 74 of the French CCNE of 12 December 2002, and considerations of Alain Fischer published in the "Cahiers du CCNE" of April 2003.

⁴³ Some of these arguments are also consciously resumed in the arguments advanced and the project of bill regulating umbilical cord blood banks tabled by senators Christine Defraigne and Jacques Brotchi.

⁴⁴ Finally the opinion of June 2006 of the British Scientific Committee of the Royal College of Obstetricians and Gynaecologists (RCOG) is also very useful to specifically situate various ethical questions in such a way as to avoid Utopian and moralising reflections.

Before making a judgement, the members of the Committee feel that it is important to give an answer (and one which is reliable in the long term) to a basic scientific question, namely: *“Is it certain that an individual’s umbilical cord blood does not offer that individual any extra benefit compared to the umbilical cord blood from an allogeneic bank which is compatible with his immunological type? In other words, do the umbilical cord blood banks for autologous use provide their donors with a benefit, and if so, what benefit or benefits are involved?”*

The experts who were questioned by the Committee⁴⁵ agree that at the moment there is no relevant scientific data on hand to affirm that autologous use offers a significant advantage over allogeneic use. Moreover, for regenerative medicine, thanks to the progress that has been made in the field of differentiation of the mesenchymal cells in neurones or liver cells, it can be predicted that the need for umbilical cord blood will decrease in the future.

At the moment there is therefore no clear and/or definitive scientific answer to the above question.

III.2. Public banks versus commercial private banks

III.2.1. Impact of commercial private banks on the use and storage of umbilical cord blood

The intervention of commercial private banks can influence the use and storage of umbilical cord blood in various ways.

1. Deception of the donor

There is a risk of the donor being deceived by the private firm – which promotes its services directly among pregnant women and bills them for the storage of the umbilical cord blood. The publicity carried out by most of these companies is accessible via the Internet. This direct and targeted marketing approach raises the question of misleading advertising (on account of details being left out or by extrapolation), and the question of the possible exploitation of the credulity of patients at a very vulnerable moment in their lives. Use of the term “biologic insurance”⁴⁶ is therefore inappropriate, given that the probability of autologous umbilical cord blood being needed in a family with a low risk of haematological disorders is close to zero (namely 1 in 20,000 during the first 20 years). And as was confirmed by the experts, autologous stem cells could be less efficient than allogeneic ones. It is thus not justifiable to saddle future parents with a feeling of guilt when they refuse “biologic insurance” or would be unable to pay for it.

2. Threat to the donor’s privacy

⁴⁵ Experts interviewed on 10/05/2006: D. Brown M Sc of the J. Bordet Institute and Prof. C. Verfaillie of the Catholic University of Leuven. The answers given by the experts interviewed by the Committee’s select committee are presented in Chapter I, point 3, of this Opinion under the title “More specific questions that were dealt with by the select committee with the experts consulted”.

⁴⁶ “As market-based medicine matures and efficiency threatens to replace ethics as the touchstone of medical practice, we are likely to see more schemes to transform medical waste into profit”, Annas G. J., *Waste and longing – The legal status of placental-blood banking*. *New Engl J Med* 1999; 340: 1 52124.

Clear and transparent information about the cost price is necessary for the patients. In the USA the initial costs for the patient for collection and storage of umbilical cord blood amount to \$1,500, followed by \$100 per year. The firm Lifebank asks for \$2,295 at the outset and then offers two extension plans for \$575 and \$495 respectively. These kinds of transactions are taking off: in 1999 the Californian private firm Cord Blood Registry declared that it had stored more than 10,000 samples of umbilical cord blood in three years, whilst the New York Blood Center in Manhattan (a public bank) had only stored 8,700 in the space of six years.

In the event of non-payment, certain private banks contractually become the owners of these samples of umbilical cord blood. They can sell them for research programmes provided they abide by the rules on confidentiality and protection of privacy.

However, allowing a private company that becomes the owner of the samples further to default on payment to sell them for therapeutic purposes can also create conflicts of interest between the company and the “recipient/purchaser”, who/which may later require clinical information about the donor – with the associated risks that this could raise as regards respect for the donor’s privacy.

3. Risks for the optimal medical treatment of the donor (mother/child)

The nature of the relations between the commercial private bank and the doctor treating the patient and/or monitoring her or assuming responsibility for collecting the umbilical cord blood during childbirth, is a basic question. Does this doctor act wholly independently of the private bank or as a temporary, contractual representative of the bank? Furthermore, the services offered for payment by these commercial banks and provided to the parents through the agency of doctors, could pose a problem of trust and/or lead to conflicts of interest. These conflicts of interest are illustrated in the CCNE’s Opinion No. 74: “The risks for the child in the removal itself, whereby the child itself and its mother are no longer the sole concern of the doctors at the time of childbirth. The need to collect a sufficient quantity of umbilical cord blood in good conditions could keep a part of the medical team busy. This (possibly remunerated?) task could be to the detriment of their care for the child and its mother”.

In the USA the firm Viacord, which is involved in the collection and storage of umbilical cord blood, has the patient sign an authorisation form under the terms of which the patient agrees never to take legal proceedings against Viacord. It can easily be surmised that this authorisation is obtained in circumstances in which some patients are, at the least, extremely vulnerable.

We might also wonder how the responsibility of the obstetrician or of every member of staff of the obstetrics ward should be assessed, since they are acting at least as agents of the company. In every case these contractual obligations do not relieve the obstetricians of their professional responsibility in the field of medical ethics and medical law.

III.2.2. Clinical arguments against the establishment of commercial private umbilical cord blood banks

There are various clinical arguments against the establishment of commercial private umbilical cord blood banks.

- The chance of an individual using his umbilical cord blood, which has been stored since his birth, for the treatment of a possible haematopoietic disorder before the age of 20, is very small. The estimates vary between five and 37 out of 100,000. For that matter, how many of those 37 people could be treated with an allogeneic source?
- There are alternatives for people who could receive an autologous transplantation of umbilical cord blood cells: the use of samples from international umbilical cord blood banks and bone marrow registers.
- The use of autologous cells cannot be suited to disorders with a genetic cause, including certain forms of leukaemia. In these cases the patients are helped more effectively with a **source other than** their stored autologous cells. Consequently, autologous umbilical cord blood banks are illegal in Italy and are not recommended in most other European countries. In 2004 the European Group for Ethics (EGE) pointed out, without recommending a ban on private banks, that at that time there was no well-founded therapeutic option at hand and that the activity of the private banks elicited severe criticism from an ethical standpoint.

At the recommendation of the Institute of Medicine of the National Academies the US Congress voted through a budget of \$77 million for the establishment of a National Cord Blood Stem Cell Bank Network. The same occurred in the United Kingdom where the Royal College of Obstetricians and Gynaecologists strongly supports the establishment and suitable funding of an NHS (National Health Service) Cord Blood Bank for allogeneic storage of donated cord blood. The Belgian legislator could perhaps draw inspiration from such initiatives.⁴⁷

The setting up of commercial autologous private banks for low-risk families convinces few people. If the establishment of such banks is not banned, their establishment should meet well-defined criteria, namely:

- *Non-misleading information;*
- *Objective and fair commercial and publicity texts;*
- *Transparent information on the financial structures and an objective explanation of the costs.*

The collection and storage of umbilical cord blood should also comply with European Directive 2004/23/EC on tissues and cells. National legislation should also be followed and should, where necessary, be adapted and improved.

In the above-mentioned Opinion No. 11 of 20 December 1999, the Belgian Advisory Committee for Bio-ethics examined the use of umbilical cord blood. It conceded that “the bulk is made available to an international blood bank and thus is seldom used for recipients within the family. This harmless way of removing material is only carried out subject to the written agreement of the mother, who renounces all control over any subsequent use and who in principle agrees to blood being taken upon removal and for three months thereafter (in order to detect any transmissible diseases). She undertakes to keep the centre informed thereafter of her health problems in the future and those of her child.”⁴⁸

⁴⁷ Opinion Paper 2 of the RCOG on Umbilical Cord Blood Banking. Op cit.

⁴⁸ See the Committee’s Opinion No. 11 of 20 December 2002, point A.4.

III.2.3. Ethical arguments against the establishment of commercial private umbilical cord blood banks

The banks of umbilical cord blood for autologous use again question the ethical principle of non-profit voluntary donation intended for the treatment of other people or for research. Unlike the public banks, which assume a solidarity aspect and contribute to social cohesion, the commercial private banks of umbilical cord blood mainly have a profit-making goal. This situation reflects a general evolution in health systems. Initially based on solidarity and motivated by public health considerations (systems that are specific to Europe since the Second World War), they are moving towards a commercialisation of health care financed by the private sector or towards a mixed management system. However, a distinction needs to be made between commercial logic on the one hand (in name of the market economy), which forms the basis of the competitive evolution towards commercialisation of health care, and the indefensible exploitation of the concern and credulity of individuals and patients, on the other.

Given that the law often changes in the wake of ethical and/or technical/scientific progress, it is once more important to draw attention to the need to give umbilical cord blood a legal status. After all, continuing to describe umbilical cord blood as a “*res delicata*”, thereby rendering reappropriation possible, immediately reduces it to a “marketable good”. If the legislator does not adopt a standpoint in that sense, a part of the human body – although admittedly separate from it – will irrefutably fall into the category of “goods” that are liable for various rights and obligations (purchase – sale – donation – all possible service contracts). The Committee therefore recommends that umbilical cord blood be granted an unambiguous status, a status *sui generis*, the content of which will be established in the framework of a coherent legal regulation concerning all stem cells.

III.2.4. Immunological and epidemiological arguments against the establishment of commercial private umbilical cord blood banks

III.2.4.1. Diversity of the HLA groups

Public banks need a large diversity of samples that represent as many HLA types as possible in order to enable a compatible donor to be found for every possible interested party.

The techniques of marketing and persuasion used by some private banks may lead to a fall in the possible donors for the public banks. Indeed, a large number of donors might prefer to have the blood from the umbilical cord of their newborn child stored for autologous purposes, rather than gifting it to public banks. This could lead to the risk of the banks no longer being able to procure the critical mass of necessary samples.

If, on the other hand, the public banks receive sufficient blood samples, including rare or less frequent HLA types, and if their network develops further, each individual will statistically have a good chance of finding a compatible sample and be able to benefit from a transplantation that is essential for his treatment.

At the moment umbilical cord blood banks are being set up in various countries, meaning that registers can be maintained and thus national and international

exchanges can occur.⁴⁹ These exchanges should make it possible for the promises in respect of the use of stem cells from umbilical cord blood to be included in the framework of so-called allogeneic transplantations.

But the one-sidedness of the recruitment explains why the entire genetic diversity of the HLA system of the population is not optimally represented in the various registers of adult voluntary bone-marrow donors. The addition of allogeneic umbilical cord blood banks would help increase this diversity.

Moreover, the umbilical cord blood banks could help solve certain problems related to immunogenicity⁵⁰:

- 1) Less rigorous compatibility with cells of the umbilical cord blood is necessary, so that children with a less common HLA group can efficiently receive a transplantation originating from a donor who is not perfectly compatible.
- 2) HLA groups that are not commonplace in the registers, because their population groups do not often cooperate in voluntary collection, but do have an interest in transplantations, could be found more easily in placental blood banks.

The development of public umbilical cord blood banks for mainly allogeneic use is therefore also important in epidemiological terms, given that Europe's population is increasingly **multiethnic**.⁵¹ So if we are to achieve equal access to transplantation of stem cells from umbilical cord blood for as many citizens as possible who might need this, irrespective of their ethnic background, the competent authorities should decide to set up large sample banks and databases originating from various ethnic groups, covering the range of HLA types as comprehensively as possible. In the field of fairness, resorting to allogeneic grafts offers to the world population the possibility of having access to a future exchange between allogeneic banks worldwide. This would not be the case with commercial private banks for autologous blood intended for the richest countries, and even then in those countries only for those who have sufficient financial resources.⁵²

III.2.4.2.

Such a choice would make it possible to avoid people having in some cases to resort to IVF and PGD (Pre-implantation Genetic Diagnosis) children, referred to as "saviour siblings", since a histocompatible transplant from umbilical cord blood cells would then be available thanks to the large public banks. Such a solution would avoid people having to resort to the complex alternative of the saviour sibling, and thereby also save the time of the pregnancy before being able to start on the treatment of the patient concerned.

⁴⁹ <http://www.BMDW.ORG>

⁵⁰ Opinion No. 74 of the Comité Consultatif National d'Ethique (CCNE), 12 December 2002. *Les banques de sang du cordon ombilical en vue d'une utilisation autologue ou en recherche* (Umbilical cord blood banks with a view to autologous use or research), p.4.

⁵¹ The word "multiethnic" does not contain any pejorative connotation at all in this text, but is connected with the presence of genetic disorders that are specific to certain population groups, such as haemoglobinopathy in the area around the Mediterranean Sea. See footnote no. 6.

⁵² We recall here that in the United Kingdom public allogeneic umbilical cord blood banks were selected and that the ethnic variety of the local population was also used as a basis when this was done. Thanks to a varied ethnic spread of umbilical cord blood, patients from ethnic minorities should indeed be able to have access to this kind of transplant. We also recall that only 3% of bone marrow donations come from ethnic minority groups, whilst 40% of donations of umbilical cord blood come from these ethnic groups. Cf. Opinion Paper 2 of the RCOG on Umbilical Cord Blood Banking, Op. cit.

Of course this comment does not apply to the simple collection of umbilical cord blood at the time a child is born, which would be used for a family member who could benefit from it. This falls under the wholly legitimate framework of an intra-family allogeneic transplantation (see point I.2.A).

III.2.4.3.

For the **exceptional cases** of newborn babies in families with a heightened risk of specific disorders or for **uncommon HLA types**, the storage of umbilical cord blood with a view to subsequent autologous use, can perfectly be taken on board by the public banks, and at a lower cost price for the families concerned. Given that certain people will probably not be able to bear the cost price of such storage, it should be ensured that access to this also takes account of differences in financial resources.

In the context of the public umbilical cord blood banks for allogeneic use, the traceability of placental blood of a child with an uncommon HLA group is indeed possible. In the logic of immunogenetic diversification (i.e. diversity of HLA groups) of these banks, it is sufficient for the existing indications for the storage of placental blood to be extended, as a result of which autologous and family use become possible if this is necessary. Such an extension may not be compared to the establishment of systematic storage for exclusive, autologous use.

In France this storage of umbilical cord blood is mentioned in the child's booklet. Even if the donation is anonymous, the bank is nonetheless composed of traceable samples. In the event of the child in question suffering health problems, it will thus be possible to make use of his stored umbilical cord blood at a later stage.⁵³

In any case it is worth again recalling that the autologous use for a patient of his own umbilical cord blood is still hypothetical⁵⁴ at this stage in the development of regenerative medicine, for three kinds of reasons⁵⁵:

a) *Scientific* reasons

Future progress in research into stem cells and gene transfer will probably render unnecessary the need to resort to cells from umbilical cord blood for autologous use. In its opinion no. 74⁵⁶, the CCNE states that "the haematopoietic stem cells for autologous use are mostly from peripheral blood of patients and autologous indications mostly relate to adults and not children. It is probable that progress in our knowledge of stem cells from placental blood will in the future enable us to use them therapeutically for indications other than those adopted now. Control of the manipulation of stem cells from peripheral blood, or possibly from other tissue, will have evolved in parallel. If that is the case, preference will be given to the use of stem cells from the patient over and above those from placental blood which has been stored for years (we do not yet know anything about the survival of stem cells that are deep frozen for more than 20 years). Therefore it seems reasonable to wait for a

⁵³ Opinion No. 74 of the CCNE committee, 12 December 2002. *Les banques de sang du cordon ombilical en vue d'une utilisation autologue ou en recherche* (Umbilical cord blood banks with a view to autologous use or research), p. 4.

⁵⁴ In one case a girl of three could use an autologous transplantation of umbilical cord blood for the treatment of a recurrent lymphoblastic leukaemia to the central nervous system after systemic and intrathecal chemotherapy. Hayani A. et al. First report of autologous cord blood transplantation in the treatment of a child with leukaemia. *Pediatrics* 2007; 199: 296-300.

⁵⁵ Alain Fischer. *Une banque de sang du cordon ombilical pour usage personnel?* (An umbilical cord blood bank for personal use?) *Les Cahiers du C.C.N.E.* no. 35, 2003.

⁵⁶ Opinion No. 74 of the CCNE committee, op cit, p. 5.

convincing scientific demonstration before venturing to store placental blood for autologous use in the framework of regenerative medicine”.

b) *Technical* reasons

The possibilities for the storage of umbilical cord blood in the very long term (longer than 20 years) are unknown and therefore should fall under the principle of precaution and under the virtue of prudence.

In genetic disorders we do not see how cells can come to someone’s aid to the extent that they are bearers of the same mutation, other than with gene therapy which at the moment does not yet work and is not foreseen. For some of these disorders, an allogeneic transplantation in a family context or by unrelated persons, may be indicated.

c) *Ethical* reasons

In a community in which the health system is based on solidarity, the umbilical cord blood banks should, from now on and as far as possible, serve two objectives: (1) carrying allogeneic transplantation of haematopoietic cells for serious disorders of the bone marrow; (2) as research material to broaden our knowledge of stem cells.

III.2.5. Conclusions

A. Allogeneic use versus autologous use

Hitherto no scientific data has been available to conclude that autologous use offers a significant advantage over allogeneic use of umbilical cord blood.

Therefore it is important now that the government supports the establishment and operation of banks for allogeneic use, which are accessible for everyone.

B. Public banks versus commercial banks

Some members are of the view that the activities of autologous *commercial* private banks should simply be banned or at least discouraged.

Firstly because systematic storage for autologous purposes without special medical justification is currently not founded on any objective, scientific basis and could even constitute an obstacle for the establishment of allogeneic banks. Secondly, because the children whose umbilical cord blood has been stored remain potential users of the allogeneic banks. They would a priori draw a benefit from the others without reciprocity. Storage for autologous purposes for low-risk groups thereby denies the existence of the solidarity system, which is the basis of our health care system. Finally, it is important to remain aware that these autologous banks cannot be integrated into an allogeneic system and will thus remain in the field of trade.⁵⁷

Other members feel that a formal ban would constitute an attack on individual freedom and entrepreneurial freedom, even though the autologous therapeutic indications, with what we know at the moment, are almost virtual. However, taking account of the possible advantages that the banks for autologous use could imply in the future in comparison with the banks for allogeneic use, these members of the

⁵⁷ Bill, explanatory statement, p. 6; EGE opinion of 16/3/2004, point 2.2.

Committee are of the opinion that the government should take measures urging private initiatives launched in this field to be subject to suitable control. This control should first be financed by the **private bodies**, which would subsequently be given financial support by the government if necessary and even organised as **public services**, if scientific data were to prove their legitimacy. Such choices should nonetheless be made with respect for the principles of distributive justice, which, in a democratic society, forms the basis of decisions on the fair allocation of available resources for health care.

All members nonetheless agree that the organisation and accreditation criteria governing the banks relating to the storage of umbilical cord blood for autologous use should, as regards strictness and safety, be comparable with those laid down for the allogeneic public banks.⁵⁸

⁵⁸ EGE Opinion dated 16/3/2004, point 2.3.

Chapter IV. Ethical, logistical and legal implications of the collection of umbilical cord blood

IV.1. Introduction

New developments can lead to unforeseen situations. If we want medicine to continue to make advances, we should be receptive to a number of questions that these new developments could throw up.

IV.1.1. Irresponsible action on the part of the therapist

First and foremost the patient deposits considerable trust in his therapist, to the extent that when the latter innovates, the patient always expects that he is championing optimal care and not merely carrying out innovative research (which is sometimes associated with minimal care standards). However, there is the risk of the therapist no longer acting as the guardian of health when he applies innovative techniques rather than using traditional techniques validated by years of experience. This aspect of medicine can be illustrated by a daily example from surgery: the members of an operating ward form (or should form) a moral community with strict implicit and explicit standards thanks to which the patient can be protected from a surgeon or team member who applies non-validated or dangerous innovations. The same kind of protective measures should be taken by the technical and scientific community for the benefit of obstetrics departments and in maternity wards, in order to monitor the logistical, legal and ethical impact of the operating methods of private umbilical cord blood banks for autologous use.

IV.1.2. Upsetting the balance of traditional clinical practice

Secondly, there is the unbalancing effect of the innovative nature of a new technical approach on the safeguards developed by clinical competence and validated by traditional practice. In a market-driven economy the term “innovation” has indeed an alluring secondary meaning of added value ascribed to it. There is even a category of patients who are psychologically inclined to seek – and therefore accept – innovation because they erroneously assume that the latest technique is also necessarily the best. In clinical practice the patient’s preference cannot always be decisive, even in a society in which patients behave increasingly like consumers. Where umbilical cord blood banks are concerned, there is the risk of the commercial aspects being allowed to hold sway over scientific necessity. Therefore, instead of a concept of *innovation*, it would be better to talk of a *non-validated technique* when reference is made to a new procedure. The expression “non-validated technique” refers to the risk attached to the use of recent techniques (which are often in an experimental phase) in vulnerable patients, who sometimes deposit excessive trust in their therapists. The same semantic circumspection also implies that the medical community proves itself worthy of the trust deposited in it.

IV.1.3. Application of non-validated techniques

Thirdly it is absolutely vital to work systematically on the evaluation of a new technique or a new procedure before it is definitively recognised. All too often the pressure from the public and from patients, from the industry, from the market and from insurers, leads to a decline in the scientific and medical community's standards. This leads some to be tempted to surf on the waves of the innovations which, as it were, cannot be avoided. The indiscriminate application of non-validated techniques by some therapists in vulnerable patients who have placed their trust in them, points to a negation of the basic principles of medical ethics. It could also lead to clinical disasters.

These three ethical questions are partially included in Opinion No. 19 of the EGE of 16 March 2004 (cf. 2.3): "People could be inclined to take advantage of all the possibilities offered to them on health, even if these are not validated. What is more, pregnancy and childbirth are events in which women and parents can feel vulnerable. This vulnerability and the feeling of guilt on the part of the parents who want to do everything to ensure that things go well for their children (feelings attributable to incorrect or overly optimistic information) could prompt people to spend their money on something that they cannot really afford and on something that may not be worth the sums of money thus invested. If commercial umbilical cord blood banks are permitted, correct information should be given to the consumers who use their services. This information should point out that the chance of the sample being used to provide care for their child, is, at the moment, negligible and that the future therapeutic possibilities are still hypothetical and that hitherto there is no indication whatsoever that research will lead to specific therapeutic applications of cells from umbilical cord blood for autologous use. The information should also be especially explicit on the fact that autologous preservation is a matter of little account in the light of our current scientific knowledge. This information should be provided in all media, including the Internet, and should appear in all contracts binding the customers with the commercial banks".

These three ethical questions and the risks of abuse were described more specifically in the warning given by the French CCNE⁵⁹ concerning the systematic collection of umbilical cord blood during pregnancy with an autologous purpose; a purpose presented as a real benefit for the child. The routine collection of umbilical cord blood for autologous use "could have repercussions for the place where the baby is delivered, or even on the conditions and technique of the delivery. The delivery would then be accompanied by therapeutic proceedings for the future of the child and would no longer only consist of simply bringing the child into the world. These proceedings then risk disrupting the delivery itself. In the case of banks for allogeneic use, on the other hand, only non-complicated deliveries are chosen for the collection of umbilical cord blood, and the large number of births means it is possible to ensure that this only occurs if there is absolutely no danger for the birth.

When a great deal of attention is placed on the umbilical cord, the way it is ligated, and the care taken to ensure enough blood is collected, attention can be diverted from the delivery itself. This care can be important in the context of a better guarantee of a possibly efficient therapy for the child in the future. Indeed, it is estimated that 80 ml and 0.37×10^8 cells/kg is needed before a unit of placental blood can be used for

⁵⁹ Opinion No. 74 of the Comité Consultatif National d'Ethique (CCNE), 12 December 2002. *Les banques de sang du cordon ombilical en vue d'une utilisation autologue ou en recherche* (Umbilical cord blood banks with a view to autologous use or research), p.7.

therapeutic purposes. The impact of the timing of the clamping of the umbilical cord on the child could be even more important than anticipated, given that the quantity of blood required to collect as many stem cells as possible, could provoke a hypox⁶⁰ in the newborn baby unless great care is taken, on account of the desire to collect a larger volume of placental blood.⁶¹

In an extreme case a Caesarean section could even be proposed, with this purpose in mind, and without there being any obstetric indication.

If the amount of blood obtained is not enough for therapeutic purposes, account should also be taken of the anxiety or feeling of guilt that the mother may suffer because, on account of her delivery, she had not been able to protect her child against a (hypothetically) ominous future.

We should certainly not dramatise the removal of placental blood, a procedure which does not usually have any consequences and is extremely commonplace.” (end of quote)

However, first and foremost the question concerns the end purpose of this removal, which could indeed shift from a simple ligation of the umbilical cord without any importance, to a medical act with a therapeutic purpose, with the risk of the exclusive attention being diverted away from the child and the mother, on whom that attention should in fact be focused.

IV.2. Practical consequences for the collection of umbilical cord blood

IV.2.1. Logistical aspects

The scientific and medical community should set up control mechanisms in obstetrics departments and maternity wards to assess the logistical impact of the collection of umbilical cord blood.

The collection of umbilical cord blood in the context of a maternity ward constitutes an additional logistical burden placed on the obstetrician, the midwives and the hospital structure. In its Opinion No. 74 of 12 December 2002, the Comité Consultatif National d’Ethique (CCNE) already discussed several aspects of this problem. More recently, this logistical effect was conspicuously analysed in the report by the Royal College of Obstetricians and Gynaecologists:⁶²

- The informed consent procedure causes a not insignificant additional administrative workload for the medical and paramedical teams of the maternity clinics.
- The collection of umbilical cord blood should occur in the last stage of the delivery (i.e. in the third stage after the birth of the baby when the placenta is still in the uterus) or after this last stage (i.e. at a time when the risk of post-natal bleeding has practically disappeared and after the period in which mother and child have exclusive right to the provision of care).
- There may be pressure to collect a sufficiently large volume of umbilical cord blood, given that the chance of later transplantation of umbilical cord blood being successful is related to the amount collected and the number of cells collected.

⁶⁰ Hypox^y consists of a drop in the amount of oxygen in the arterial blood.

⁶¹ Van Rheenen P., Brabin B. J., *A practical approach to timing cord clamping in resource poor settings*, BMJ 2006; 333:954-958.

⁶² Opinion Paper 2 of the RCOG on Umbilical Cord Blood Banking. Op. cit.

- Umbilical cord blood can be infected by bacteria during collection unless strict precautionary measures are taken.
- The use of the medical and paramedical team of a delivery room for the collection of umbilical cord blood can divert the members of the care team from the care that should be dispensed to the mother and child.

More specifically the collection of umbilical cord blood can threaten the welfare of the mother and child insofar as:

- Normal delivery practice is altered or delayed in order to achieve an efficient collection of umbilical cord blood, for example by delaying the controlled traction on the umbilical cord to evacuate the placenta, whilst the mother has already experienced significant blood loss (for example during pre-eclampsia), with the aim of maximising the amount of umbilical cord blood whilst the placenta is still in utero.
- Monitoring of the mother and child is also neglected in order to collect umbilical cord blood by delaying the analysis of the mother's arterial blood and the venous blood from the umbilical cord to study the blood gasses when there is a problem of hypoxia. The logistical burden caused by the collection of blood may interfere with the work of the team on the maternity ward. Therefore the assertion made by some commercial banks that this would not be the case is incorrect, as is the claim that the woman's husband would be perfectly able to collect this kind of blood himself. Indeed, it has been possible to establish that the incidence of bacterial infection rises significantly with the inexperience of those collecting the umbilical cord blood, which incidentally is the case every time blood is taken.

The British Royal College of Obstetricians and Gynaecologists and the Comité Consultatif National d'Ethique also cite other different problems that could arise during the last part of delivery:

- In the event of a *premature birth*, the early clamping of the umbilical cord is unfavourable for the pre-term baby. A systematic overview of the Cochrane Database⁶³ of seven randomised studies shows that extending the period for the clamping of the umbilical cord by 30 to 120 seconds leads to fewer transfusions for post-natal anaemia. The moment at which the umbilical cord is clamped could also be important for children born at term. Clinical studies are currently being carried out and a Cochrane overview is also expected for children born at term.⁶⁴ Available controlled studies reveal that the neonatal haematocrit value falls when clamping occurs early, more especially in some groups of the population or among immigrants who have just arrived.
- When the child is born with a *circular umbilical cord* (i.e. when the umbilical cord has placed itself around the child's neck during expulsion) this should be severed quickly. In no circumstances should pressure be brought to bear on the obstetrician to try to draw off any umbilical cord blood.
- During a *Caesarean section* the standard procedure consists in the umbilical cord being clamped immediately and the child being handed over to a midwife, whereupon the placenta is removed by means of traction on the umbilical cord or

⁶³ Rabe, H., Reynolds, G., Diaz-Rossello J. Early versus delayed umbilical cord clamping in pre-term infants. Cochrane Database Syst Rev 2004; 42: 1261-67.

⁶⁴ Van Rheenen P., Brabin B. J. *Late umbilical cord-clamping as an intervention for reducing iron deficiency anaemia in term infants in developing and industrialised countries: a systematic review.* Ann Trop Paediatr 2004; 24: 3-16.

possibly manually, and then the incision in the uterus quickly sutured. Thereby blood loss suffered by the mother is minimised in this kind of surgical intervention. Any delay in this intervention, for any reason whatsoever, is inappropriate.

- During delivery the removal of umbilical cord blood may not interfere with the *rapid contact between baby and mother*.
- In the case of *twin or multiple* pregnancies the delivery team's attention may not be diverted from the risk of complications for the newborn babies and from the importance of minimising post-natal bleeding suffered by the mother. Incidentally, when umbilical cord blood is collected it is important to record accurately what umbilical cord blood corresponds to which child. This very important information in the event of subsequent autologous use, is not included in the procedure to be followed in some commercial banks. One good example of good practice is the way the NHS Cord Blood Bank works, whereby the umbilical cord blood is collected aseptically, after expulsion of the placenta, by competent staff of the National Blood Service and in the obstetrics ward, but outside the delivery room!

IV.2.2. Legal implications of the parental request for umbilical cord blood to be collected

A foetus becomes a legal person when it has come fully out of the body of the mother, and when it has come into the world alive and viable. Up until that moment the doctor is bound to respect the autonomy of the mother who has an unalienable right to determine what happens or will happen to her body. The placenta is a part of the woman's body, rather than a part of the child's body. Where each parent has to give their assent for a treatment for their newborn baby, only the mother may decide what will happen to her own body. This applies to the removal of umbilical cord blood, which is also placental blood. So if the mother wishes umbilical cord blood to be removed, the health care workers in the delivery room can decide whether they can meet that request, in complete safety and taking account of the circumstances at that time.

The phrase "meet that request, in complete safety and taking account of the circumstances at that time" should therefore be interpreted with the necessary common sense. Indeed, the mother's request may not interfere with any care dispensed to other patients as a result of which they would see a part of the technical infrastructure and personnel diverted because of her request. Therefore it is essential for hospitals with an obstetrics ward to develop a clear policy in this field and for patients to be informed of this beforehand. When hospitals judge that it is logistically and financially possible for them to offer this extra service to patients who ask for it, it is important to specify that the request to collect umbilical cord blood will depend on the local clinical and logistical possibilities that could change unexpectedly (in the event of an emergency situation or the temporary saturation of the obstetrics infrastructure) in time and space.

IV.2.3. Fair access

A. Networks and registers

Bearing in mind the possible number of collections of samples of umbilical cord blood in a small country such as Belgium, which is part of the larger whole of the European Union, the Committee insists on the need for a system to be developed that ensures access to as many samples as possible, so that a compatible sample can be found quickly for a patient having to receive a transplantation.

This system can be worked out in the form of networks and registers at various levels, whereby the European level appears to be the most functional. In that respect, both for ethical reasons and for reasons of clinical and operational effectiveness, the Committee ranges itself behind Opinion No. 19 of the European Group on Ethics, which states that “the promotion and support of such networks and registers clearly and rationally constitutes a medical and political priority”.

B. Central (European) umbilical cord blood bank

The objective for each patient of finding a compatible sample of umbilical cord blood could also be fulfilled by a single umbilical cord blood bank being set up at a level to be established. This bank would be entrusted with the storage of the samples once a written undertaking is given to the donor of the umbilical cord blood that the possible benefit contained in that sample is transferred to a person who is not identified by name in the document but who, at a certain time and in certain clinical circumstances, is the best recipient of the donation, with abstraction being made of any financial consideration. This alternative for the network exists in the United States under the name “Charitable Trust for Genomic Biobanks”.⁶⁵

Furthermore, the Committee focuses attention on the need for strict application of the rules concerning respect for privacy and the protection of personal data, and the rules on information and consent of the parties concerned, irrespective of the formula chosen. As in the case of organ or tissue donations, the donor should remain anonymous, on the one hand because it should not be made possible for any beneficiaries of umbilical cord blood to “approach” the donor again subsequently for any other treatment (for example, an initial failure), and on the other hand because the donor is not in a position to weigh up correctly the risks and benefits that his donation will imply for the beneficiary or for future research protocols.

⁶⁵ Winickoff D. E., Winickoff, R. N., *The charitable trust as a model for genomic biobanks*. N Engl J Med 2003; 349: 1180-84.

Chapter V. Opinion and recommendations

V.1. Coherent legislative framework

The Committee draws attention to the fact that a coherent body of laws is more than desirable. What happens to stem cells, regardless of their provenance, should not be dependent on different legal provisions governing the removal, transportation, processing, storage and use thereof. The Committee once again recommends a clarification of the legal status of placenta, umbilical cord blood and the stem cells thereof, in the light of an optimal and responsible use of umbilical cord blood.

V.2. Conceptual legal framework

For the transplantation of bone marrow the organ transplantation model is presented by *analogy*. Umbilical cord blood taken from children after birth falls more under the analogy with the model of blood donations for transfusion (of the blood or blood components). What is more, analogy with the blood donation for transfusion model also brings us closer to the example of the pre-donation of blood for (planned) elective surgery, given that pre-donated blood, if necessary, will be re-administered to the patient, just like umbilical cord blood. Adopting the analogy with the model of blood donation for transfusion for umbilical cord blood could thus help, conceptually and legally, to solve the problems arising from the removal, storage and use of umbilical cord blood.⁶⁶ This does not detract from the fact that, although this analogy can help solve the problems of product status and safety, it does not offer any solution for the risks associated with the commercialisation of umbilical cord blood by commercial private banks (profit-making banks), particularly in Europe and the United States.

V.3. Storage and use of umbilical cord blood

V.3.1. Allogeneic use versus autologous use

At the moment there are no persuasive scientific grounds on which to recommend the storage of umbilical cord blood for autologous use for low-risk families. Autologous use of stem cells from umbilical cord blood in non-haematopoietic indications is still very speculative.

Therefore only the storage of umbilical cord blood with an allogeneic purpose for the population in general, and with an autologous use for risk families, can be considered as a service of general benefit in which the stringent medical standards applied by Netcord are complied with.

It is therefore important that the government now only support the establishment and operation of banks for allogeneic use that are accessible to everyone, and banks for autologous use for risk families.

⁶⁶ In the USA, adoption of the transfusion model made it possible for the task of setting the criteria for the storage of umbilical cord blood to be assigned to the Food and Drug Administration (FDA), which is competent for the safety of human blood.

V.3.2. Public banks versus commercial banks

The question arises as to which structure is most appropriate for the collection and storage of umbilical cord blood.

Some members of the Committee are of the view that the principle of entrepreneurial freedom can justify the establishment of private banks.

Other members are of the view that entrepreneurial freedom cannot justify the establishment of (autologous) commercial private banks in a field of health care where a public financing system of care exists, and in which it is not acceptable for some of the effects and resources to accrue to private operators who select profitable activities (creaming) and reject the rest (dumping).

Although not all the members of the Committee are in favour of a ban on commercial private banks, all members nonetheless recommend that storage of umbilical cord blood should always meet internationally applicable quality standards⁶⁷ and take account of the impact that such collection can have in logistical terms for the obstetrics departments where these births take place.

V.3.3. Financing system

The Committee recommends that a financing system be worked out for the allogeneic storage of umbilical cord blood, both at national level and at European level. The same applies to the autologous storage of umbilical cord blood of families with genetic disorders or of families with an acquired disorder that could possibly be treated by a transplantation of human stem cells.

This would make it possible to provide fair and ample access for those who could use a transplantation of stem cells in already known indications or indications whereby a stem cell transplantation could offer a solution in the future.

V.3.4. Access and organisation

The Committee recommends the development of a system for collection of umbilical cord blood that guarantees that every patient who could receive a transplantation can quickly find a compatible donor, especially for Belgium where the annual number of collections of umbilical cord blood will always remain very low, bearing in mind the number of inhabitants.

A register and network system of existing banks or a system of banks with a wider field of action could offer a solution here.

V.4. Information provided by the government

V.4.1. Medical indications

All members are of the opinion that the government should offer people comprehensive and accurate information on collections of umbilical cord blood and the various possible intended uses thereof. More especially, this information should

⁶⁷ See point I.4.H.

highlight the very low probability of people in a low-risk family ever having to use their own stored umbilical cord blood.

Even so, it is the job of every obstetrician to explain this information, so that patients are able to decide, in full knowledge of the facts, on the intended use of the umbilical cord blood collected, bearing in mind their family situation.

V.4.2. Cost price

Clear and transparent information is needed regarding the cost price for patients.

V.4.3. Publicity

The advertising carried out by the commercial private firms maintains a twofold uncertainty, between the different sorts of stem cells on the one hand, and between autologous and allogeneic use thereof, on the other.

The use of the term “biologic insurance”⁶⁸ by a private firm – which directly advertises its services among pregnant women, offering the storage of their umbilical cord blood in exchange for payment – is misplaced, given that the probability of autologous umbilical cord blood being used in a family with a low risk of haematological disorders, is almost zero. It is therefore pointless and indefensible to saddle future parents, who might refuse such biologic insurance or be unable to afford it, with a feeling of guilt.

The Committee therefore recommends that the content of this kind of advertising be strictly controlled by the competent authorities.

V.5. Information provided by the hospitals

V.5.1. Policy of hospitals

Every hospital and every obstetrics department should clearly work out its own policy concerning requests by commercial private firms for collections and storage of umbilical cord blood, both from a financial and logistical point of view, bearing in mind the fact that clinical and logistical conditions may change in time and place (i.e. emergency situation, opening hours, strain of work among staff, etc.).

Bearing in mind the fact that some patients may have entered into financial and contractual commitments with commercial firms before even speaking about it with their obstetrician, the policy of the institution where the delivery takes place should be explained to the patients and their partners beforehand and in good time. Written information explaining the hospital’s policy should be made available to all patients when they are considering having their pregnancy monitored and/or upon their admission to the obstetrics ward.

⁶⁸ “As market-based medicine matures and efficiency threatens to replace ethics as the touchstone of medical practice, we are likely to see more schemes to transform medical waste into profit”, Annas, G. J., *Waste and longing – The legal status of placental-blood banking*. *New Engl J Med* 1999; 340: 1521-24.

V.5.2. Supervision of the hospital services

Departments thinking of collecting autologous umbilical cord blood should take the following guidelines into account:

- a) Under no circumstances may the department's care policy and operating procedures be altered during the various phases of delivery, more especially during the last phase which corresponds to that of evacuation of the placenta.
- b) The safety of mother and infant should be guaranteed at all times. Therefore, collection of umbilical cord blood for commercial purposes should occur from a placenta that has already been evacuated from the uterus.
- c) Umbilical cord blood should be collected by experienced members of staff using appropriate methods that meet the criteria of European Directive 2004/23/EC. The collection may not interfere with the clinical activities of the staff of the delivery room.
- d) The removal of umbilical cord blood may not be effected when the obstetrician is of the view that there is a contra-indication. This may be the case in the event of a premature birth, when the mother is bleeding, when the obstetrician is faced with a circular umbilical cord, or in the event of a twin or multiple pregnancy.
- e) The details of the hospital's policy should be made available to all patients beforehand.

V.6. Triangular relationship between patient, doctor and umbilical cord blood bank

The legal character of the relationships between all parties involved in the collection of umbilical cord blood during delivery (bank, patient, doctor collecting the umbilical cord blood, obstetrician, etc.) should be specified.

The collection of umbilical cord blood may not be invoked in order temporarily or partially to detract from the obstetrician's professional responsibility.

This is the case when either the doctor works independently of the umbilical cord blood bank or acts as a temporary contractual representative of this bank. The same applies when the prior consent of the patient was obtained by a bank in the framework of a previous contract.

V.7. Relationship between the umbilical cord blood bank and the future beneficiary/recipient

Allowing a private profit-making firm, which has contractually become the owner of the umbilical cord blood samples, to be able to sell them on for therapeutic use in the event of non-payment could lead to conflicts of interest between the company and the "recipient/buyer". The latter could demand clinical data on the donor, with all the risks that this could imply as regards respect for confidentiality and privacy of the donor (see the law of 8/12/1992 on the protection of privacy in respect of the processing of personal data, and the law of 22/8/2002 on patients' rights) or his family. Government-financed banks should also guarantee respect for confidentiality and privacy.

The Committee therefore recommends that the competent authorities lay down clear requirements in this respect.

The Opinion was prepared in select committee 2006/2, made up of:

Co-chairpersons	Co-rapporteurs	Members	Member of the Executive
L. Michel G. Van Overwalle	L. Michel G. Van Overwalle	M. Baum P. Cras A. Dieudonné J.-N. Missa G. Verdonk	J.-A. Stiennon

Member of the Secretariat: M. Bosson

Exerts interviewed.

- Dominique Bron, M Sc, Jules Bordet Institute
- Prof. Catherine Verfaillie, M Sc, Catholic University of Leuven

Expert consulted

- Prof. Yves Beguin, University of Liège

The working documents of select committee 2006/2 (questions, members' personal contributions, minutes of the meetings and documents consulted) are kept in the form of Appendices 2006/2 in the Committee's documentation centre, where they may be consulted and photocopies taken.