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Expert's Report: Cryo-Save Group NV

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CELS Business Services Ltd
Bioscience Centre
International Centre for Life
Times Square
Newcastle upon Tyne
NE1 4EP
Tel 0191 211 2626
Fax 0191 211 2596

Contacts:

Dr Carolyn Horrocks
carolyn.horrocks@celsatlife.com
Tel 0191 211 2640

Dr Mike Nicholds
mike.nicholds@celsatlife.com
Tel 0191 211 3822

1. Summary

The core business of the Cryo-Save Group is the processing and cryogenic preservation of umbilical cord stem cells. The basic value offering of cord blood banking to parents is that the storage of stem cells present in a newborn's cord blood provides a source of therapeutic material that can be used in the event that the child or sibling develops a disease that can be treated using stem cells present in cord blood.

Stem cell biology provides an understanding of the body's capacity for regeneration which is driving the growth of the stem cell market[1]. Umbilical cord is a valuable source of stem cells due to its ease of collection, lack of ethical issues and the variety of adult stem cells (ASC) types which include haematopoietic stem cells (HSC: blood-forming) and mesenchymal stem cells(MSC connective tissue-forming: bone, cartilage, muscle). Additional sources of ASC include bone marrow, skin and adipose (fat) tissue.

Cryo-Save's core product, branded as Cryo-Cord offers parents a complete service including a collection kit, training material for midwives, logistics, processing and storage to enable the safe storage of cord blood HSC using accredited techniques and procedures.

Cryo-Save is the largest private cord blood bank in Europe, well established with a good reputation in the expanding market for cord blood storage. The company's strategy in the short-term is to grow by expanding the geographical coverage of its cord-blood banking operations, and in the medium term to introduce new products which will leverage the existing logistics, processing and storage infrastructure.

Stem cell therapy remains a sensitive issue. Although heavily regulated in the EU, control is much less stringent in territories such as Asia. Adverse events (infection, cancer, and ethics) in these areas would have a detrimental effect on public confidence in the entire industry. The EU has ethical concerns over the commercialisation of human material. To allay these concerns Cryo-Save operates to the highest international quality standards and is accredited by national and international organisations. In addition, Cryo-Save works with public banks in areas, such as Italy, in which private stem cell banking is much more stringently regulated. The focus on the implementation of stringent quality procedures indicates that Cryo-Save is aware of these critical issues.

Cryo-Save's new product development strategy involves the development of techniques to expand the stem cells present in each sample of cord blood. This will potentially increase the success rate of HSC transplantation and extend the use of cord blood from primarily paediatric to adult patients. The company has developed collaborations with institutions in Europe with expertise in this area and has indicated that it plans to acquire cGMP facilities, which would be necessary to implement this technology. If successful this technology would significantly enhance the company's offering. This area is, however, the subject of extensive research and patenting around the world, and contains a degree of technical risk.

Cryo-Save is adapting its existing processes and technology to store MSC derived from cord tissue. This would increase the utility of each cord sample because HSC and MSC have different applications for the treatment of both childhood and adult diseases. Development of this product utilises known technology combined with Cryo-Save's existing infrastructure and hence represent low technical risk.

Cryo-Save has indicated that it also intends to expand its offering to include Cryo—Lip, the collection, processing and storage of MSCs derived from lipo-suction procedures. These techniques are known within the industry and therefore represent a low technical risk. This product would however target a different set of customers than that for cord blood requiring the company to secure an appropriate route to market.

[1] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

Within the stem cell market the demand for products and services associated with cord blood is being driven by a number of factors. Parents are becoming increasingly aware of the potential of stem cells as therapeutics and are increasingly willing to invest in this form of biological insurance. Adults are also realising the potential of storing stem cells as a form of biological insurance. Cord blood provides an ethically non-controversial and easily obtainable source of HSC and MSC with the potential to regenerate both the blood and connective tissues.

Although routine use of cord blood for adult HSC transplantation is limited by the small size of the cord blood donation, this is changing rapidly due to recent improvements in transplant protocols and the development of stem cell expansion technology. Future non-haematopoietic uses of cord blood may also include such large markets as ischaemic heart disease and orthopaedics. Worldwide there over 50 stem cell therapies under investigation of which 6 use cord blood.

US companies with their longer experience and investment in new technology represent a threat by entry to the European market. However US companies are not heavily targeting the European market due to the varied regulatory regimes, the ethical debate over private versus public banks, and the higher growth rates in the US and Asian markets. Cryo-Save's major EU competitor is therefore German-based Vita34. As the market becomes more competitive companies are developing differentiated offerings. This includes technology to expand HSCs and improved technologies for collection/storage of stem cells. Cryo-Save is also filling its product pipeline by forming academic collaborations across Europe to develop improved cryopreservation and expansion technology.

2. Stem Cell Biology and Applications

2.1 Introduction

A stem cell is a cell capable of self-renewal over long periods of time and able to differentiate into specialised cells under the appropriate conditions. This is the basis of the body's capacity to continuously replenish tissues, such as blood, and to heal injuries. The combination of stem cell science with cell production under regulated conditions plus transplant technology raises the possibility of repairing damaged tissues and hence developing cures for previously intractable conditions. As parents become increasingly aware of successful and potential treatments using stem cells, they recognise the value in storing their newborn child's cord-blood which contains a number of stem cell types.

2.2 Basic Stem Cell Biology

The common characteristics of all types of stem cells include: (a) Self-renewal to maintain identical stem cells over many years (b) differentiation to cells with different functions and (c) long-term repopulation of a tissue upon transplantation.

Differentiation is the process by which stem cells respond to physiological signals to generate fully functional mature cells (e.g. HSC mature into red and white blood cells). In this way cells in organs, such as the skin, blood and even the brain, are constantly replenished by a few resident adult stem cells. Many organs contain more than one cell type, each with its own specialised role, and hence may contain more than one stem cell e.g. skin contains epithethial (epidermis), mesenchymal (fibroblast) and endothelial (blood vessel) cells.

Adult (or somatic) stem cells can be isolated from many tissues, including umbilical cord, bone marrow, brain, hair follicles and adipose tissue. In general, ASC can only differentiate into the cell types of their tissue of origin, for example neural (brain) stem cells into nerves, glia and oligodendrocytes which together make up the brain.

The most common source of adult stem cells is the bone marrow, located in the centre of some bones. Since it was first demonstrated in 1956 that injected bone marrow can regenerate the complete blood forming system, bone marrow transplantation has become the most widely used example of stem cell therapy with 40,000-50,000 bone marrow transplants conducted annually in

the US and Europe[2]. There are 2 approaches to transplantation: autologous (common approach of private banks) in which the patients own cells are used; and allogeneic (common approach of public banks) where cells from a tissue-typed matched donor are used.

The ability of bone marrow to regenerate the blood forming system is due to the presence of HSC which are present at a frequency of 1 in 2 million cells. Many blood cells are short-lived and need to be replenished continuously; the average human requires approximately one hundred billion new haematopoietic (blood) cells each day. The bone marrow also contains MSC at a frequency of 1 in 100,000 cells which are responsible for repair and replenishment of connective tissues including bone, cartilage, tendon, muscle and fat.

2.3 Cord Blood derived cells

The product offering of Cryo-Save to its customers assumes that the stem cells contained within cord blood have unique advantages over other stem cell sources, such as bone marrow.

Cord blood has been identified as an additional source of HSC and its use has increased greatly in recent years. Cord blood also contains endothelial (blood vessel) and MSC. Since the first cord blood transplant was performed in 1988, cord blood has been shown to have several advantages compared with bone marrow. These include: easy availability, lower risk of infectious disease transmission and lower risk of graft versus host disease (GVHD: immune cells in the donor tissue attack the recipient's tissues).

The most common source of MSCs is the bone marrow, but aspirating bone marrow from donors is an invasive procedure. In addition, the number and the differentiating potential of bone marrow MSCs decreases with age. Therefore, alternative sources of MSCs are of significant value. The solid tissue of the umbilical cord and the placenta are a rich alternative source of MSC, as is skin and adipose tissue.

The fact that the umbilical cord is a source of multiple types of stem cells (predominantly HSC and MSC) with the potential to regenerate a wide variety of tissues, coupled with their relatively easy collection has led to significant research on their isolation, storage, biology and application.

2.4 Adipose tissue derived stem cells

Adipose (fat) tissue contains numerous types of regenerative cells. These include MSC, blood vessel stem cells and other cell types. These cells collectively contribute to healing and repair through a variety of mechanisms that involve promoting blood vessel growth, keeping alive injured cells and differentiating into several tissue types, such as bone, cartilage, fat, skeletal muscle, smooth muscle and cardiac muscle. Some evidence shows that adipose tissue may contains a higher proportion of stem cells than bone marrow (1:100 compared to 1:100,000). With the advent of cosmetic surgery and liposuction the collection techniques for adipose tissue are well established making this another safe and readily available source of adult stem cells.

[2] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

The following table summarizes the strength and weaknesses of the three main sources of stem cells, and the maturity of the technology (described as time to market).

Stem Cell Source	Strength	Weakness	Time to Market
Bone Marrow	• Contains HSC & MSC • Not likely to form tumours • No socio-political issues • Well established clinical use • Repeat donation possible • Donor lymphocytes may kill tumours	• Difficult to harvest • Difficult to expand in culture • Requires extensive HLA matching • Few registered ethnic minority donors	• Existing market in HSC transplantation, • New therapies likely in <5years (cardio, Ortho, Immuno)
Cord blood	• Contains HSC and MSC • Tumours unlikely (Allogeneic donors) • Ease of collection • Stored product for immediate use • Reduced risk infection • Proven in therapy (HSC) • No socio-political issues • Reduced risk of GVHD • Potential donors for minority populations • Absence of donor attrition • 100,000 units currently available	• Difficult to expand in culture • Insufficient HSC for adults • Delayed HSC engraftment increasing risk of transplant failure • Potential presence of pre-existing leukaemic clones in autologous donations. • No possibility of lymphocyte donations to help kill tumours	• Existing market in HSC transplantation • New therapies likely in 5+yrs (cardio, Ortho, Immuno)
Embryonic	• Capable of differentiating to any cell • Capable of unlimited expansion in culture	• Difficult to control differentiation, purity & function of final product • Potential tumor formation • Major socio-political issues	• Long-term impact on market 10+ years

3. Cryo-Save Products and Technologies

3.1 Existing Products

Cryo-cord

The core business of the Cryo-Save Group is the processing of cord blood and the cryogenic preservation of cord blood stem cells. The methods used for the processing and storage of cord blood stem cells are identical to those used by public stem cell banks. Cryo-Save is the largest private cord blood bank in Europe with approximately 65, 000 units stored and 5 released for successful transplantation for treatment, in line with the expected frequency of 1 in 20,000, thus illustrating the quality of their banking procedures

Based on the description of its procedures the company is operating to high quality standards as evidenced by it sites in Germany and Belgium receiving approval by the relevant authorities and recognizes the importance of the need to operate to these standards to maintain customer confidence and facilitate future use in cell based therapies. The splitting of samples between two sites also increases the security of the system.

The main Cryo-Save site in Belgium has been accredited by the Belgian accreditation body (BELAC) and has an ISO certificate (EN/ISO/IEC 17025). However the EU directive on human cells and tissues is yet to be transposed into Belgian law and hence further regulatory requirement may be made of this facility in 2007 when the transposition is expected to be completed. Similarly, the laboratories in Germany and Belgium are operating according to cGMP principles and are accredited by the appropriate competent authority in those states. The Dubai facility is in the process of accreditation by the AABB (American Association of Blood Banks) which is an

internationally recognised standard. Cryo-Save is also in the process of JACIE-FACT accreditation. Many clinicians recognise these standards and prefer to use material from accredited sources.

The processing methodology used by Cryo-Save meets current EU guidelines and involves preparing a Buffy coat containing only the white cells, using a fully automated closed system provided by BioSafe. This latter system is recognised as the standard equipment by JACIE-FACT and is used by most public blood and bone marrow banks. Cryo-save has shown that its kit is successful in 89% of collections (the average across all cord banks being 40-60%[3]).

The quality of the collection is ensured by use of this CE marked collection kit. A breach in quality may occur however if untrained persons use this kit. Most public cord blood banks provide trained staff present in the delivery room to collect the samples. Cryo-Save provides a training CD for midwives attending the birth but not specific technicians and this appears to operate satisfactorily.

Cryo-Save has an extensive logistics network which ensures that the cord blood is transported from the maternity unit to a Cryo-Save processing centre within 48hours of birth. Prompt processing and freezing has been shown to be a key factor affecting the quality of cord blood products.

The growth of Cryo-Save will primarily be driven in the short-term by geographical expansion. This is a feasible approach as it has been shown that cord blood banks using the same standard operating procedures achieve comparable results in terms of success of transplants, as shown in a study comparing two banks, in USA and Taiwan. If Cryo-Save is planning to attain additional JACIE-FACT accreditation at new locations this may impact upon Cryo-Save's timeline of 180 days to start-up new banks, although the existing quality systems and FACT-JACIE accreditation may mitigate this risk.

The Cryo-Save cord blood storage technology is the subject of a granted patent (WO2005095583A1 priority date 3 March 2004) plus a patent application (NL1031528C). These patents relate to the system of storage and retrieval of cells and relevant donor data. A further patent (BE1016380 publication date 2006-09-05) describes a similar system for storage and retrieval of umbilical cord tissue for later extraction of MSC. These patents do not represent novel technology for cryogenic storage of stem cells but rather innovative inventory systems. Patent activity is very high in this area with 814 patent applications in the Espacenet database describing methods of extraction, storage or use of umbilical cord and/or placenta for regenerative medicine.

Developments in the techniques of cryo-preservation will potentially enhance Cyro-Save's offering in stem cell storage. Their participation in the "Crystal" EU FP6 programme, which brings together a consortium of academic and industry scientists to develop new cryo-preservation technologies for cells, will enable them to access any appropriate developments.

3.2 Products in Development

Stem Cell Expansion

A major limitation in the use of cord blood stem cells is the relatively small size of the donation which makes a single cord unit unsuitable for adult HSC transplantation[4]. Therefore, for autologous use in adults or older children, expansion of HSC is essential. Many groups report expansion of the number of cells in cord blood but few have achieved this whilst retaining the transplantable HSC[5]. There is however significant research investment in this difficult challenge.

[3] Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program. Institute of Medicine of the National Academies Eds: Meyer, Hanna & Gebbie. The National Academic Press, Washington DC. (2005)

[4] Stem Cell Transplantation (Cord Blood Transplants) *Chao, Emerson and Weinberg Haematology(2004) page 354-371*

[5] *Boiron et* al Large-scale expansion and transplantation of CD34+hematopoietic cells: in vitro and in vivo confirmation of

Cryo-Save have formed alliances with European academic groups such as the French Blood Establishment Aquitaine-Limousin (EFSAL) in Bordeaux as well as the University of Cologne both of whom have expertise in the area of HSC expansion. In addition, Cryo-Save is a founder member of the International Tissue Engineering Research Association which is a network of over 40 mostly European scientists working in this field, giving them access to recognized expertise. However, this remains a key technical challenge, with a number of competitors investing in the area and with a number of patents issued. In particular, a number of patents cover key growth ingredients, such as cytokines, used in the expansion process which would need to be accessed if a process were to be commercialized.

Often the methodology to expanded stem cells relies on specialized know-how that is contained in the personnel who developed the techniques. Therefore, if Cryo-Save moves to commercialise expansion technology developed by its partners it would need to ensure an efficient technology transfer into its operations.

Expanded stem cell products, unlike processed cord blood, are regulated by the FDA/EMEA and are considered by these agencies as biopharmaceutical products. As such they must be manufactured to cGMP standard in a certified facility and must undergo pre-clinical and clinical trials to determine safety and efficacy before they can be launched onto the market. Cryo-Save has indicated their intention to acquire GMP facilities which would allow them to produce expanded stem cell products. They will also be required to carry out pre-clinical and clinical trials with expanded products.

Cord MSC Storage

Cryo-Save plans to utilise its existing Cryo-Cord collection kit and logistics system to provide a cord MSC storage service. The new service will be marketed through the existing cord blood channels. Cryo-Save is currently conducting studies to determine the optimum method for collection, extraction and cryo-storage of cord MSC. The collection kit will then be modified and it is anticipated the product will be launched within 6 months. Cell and tissue freezing technology is now well established and hence testing the various available methods for use with cord MSCs should be a relatively low risk project bringing extra revenue from the existing customer base. There is some risk with culturing the cells prior to storage, as it is known that culture can profoundly affect function. There has been patenting in this area which may impinge upon Cryo-Save's ability to fully commercialise this product. In particular, WO20044072273 describes the extraction of MSC from the perivascular tissue (Wharton's jelly) of the cord. Companies such as Smith & Nephew and Advanced Tissue Sciences also hold patents in this area. Cryo-Save hold a patent application (BE1016380 publication date 2006-09-05) describing a system for storage and retrieval of umbilical cord tissue for later extraction of MSC. As with their cord blood storage patents this does not represent novel technology but protects their innovative inventory system.

Cryo-Lip

Currently most tissue obtained from cosmetic liposuction procedures is discarded. This material is, however, known to be a rich source of MSCs. Cryo-Save plan to use their existing storage facilities and know-how in logistics and cryo-preservation to create a service to store the MSCs derived from this adipose tissue. The techniques required for isolation and cryo-preservation of MSCs are known but would require testing and validation to determine the optimum conditions. Additional development would also be required to develop a kit, similar to the BioSafe systems, for customers to present to their physician. This appears to be a relatively low technical risk project.

Cryo-lip does however target an entirely new customer base (adults undergoing cosmetic procedures) and a different set of physicians (plastic surgeons). Cryo-Save would therefore need to develop a network of relationships within plastic surgery clinics and a new marketing strategy

neutropenia abrogation related to the expansion process without impairment of the long-term engraftment capacity
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to reach these new customers. Cryo-Save has begun this process via collaboration with Clinica Planas, a Barcelona plastic surgery centre.

Public-Private Banking

There is considerable ethical controversy surrounding the decision to store cord blood in private versus public banks. This issue can be resolved by creating a hybrid public-private bank in which samples can be split providing one half exclusively for family use and the remaining portion being available to any tissue-matched patient. This system is reliant upon developing methods for HSC expansion and also resolving issues regarding ownership and ethics. An alternative is to tissue-type and register all samples, including those privately banked. The parents can then choose to donate the cord blood should an unrelated matched patient need the unit. This is the approach adopted by Cryo-Save and is not reliant on development of HSC expansion technology.

In some territories private banking is not sanctioned (e.g. Italy and France) and hence public-private banks are essential. In addition, large public banks offer economies of scale which may become more significant as more stringent regulation is adopted throughout Europe. It is likely that private banks will begin to consolidate. Public-Private banks do however incur additional costs associated with the necessity for tissue-typing all donations.

Cryo-Save has already begun to develop business models that meet these ethical concerns via its collaboration with Osidea an Italian non-profit organisation. In addition, Cryo-save already offers tissue-typing at an additional fee.

4. Market Analysis

The total available market for cord blood banking is driven by two key factors; total number of live births and the percentage of parents able or willing to pay for the storage. In the core market for Cryo-Save which is Europe (here defined as the 27 countries within the European Union) there were 5.1m live births in 2005. Of this total only a low percentage <1% elect to store cord blood. Given that the live birth rates are relatively constant in developed regions like Europe the key drivers affecting the growth of the private market for cord blood banking are associated with parent's ability to pay (price), willingness (awareness of benefits, ethical concerns) and the extent of public cord blood banking provided by the government.

In the following sections, the factors and evidence that could drive market growth based on technical evidence and advances are summarized under the following headings; current clinical use, potential clinical uses, other technology based market drivers.

4.1 Current Clinical Uses of cord blood stem cells

Haematopoietic stem cells

For parents considering storing their child's cord blood, particularly in a private bank, one of the key criteria is whether there is a proven potential benefit. Given that cord blood is a source of HSCs then the accumulated data from 40 years of experience showing that bone marrow transplants can successfully treat a range of illnesses gives parents positive information on the benefit of storage. There are currently in the region of 40,000 bone marrow transplants per year of which 5,000 are performed on children. This market has an estimated value of $4Bn and the total value of the HSC transplant market is currently $20Bn[6].

The first successful use of cord blood was achieved in 1988 and data accumulated since then have demonstrated that cord blood is an accepted source of stem cells for paediatric patients to treat a variety of malignant (e.g. leukemia, lymphoma) and non-malignant blood diseases[7]. Currently in

[6] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

[7] Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program. Institute of Medicine of the National Academies Eds: Meyer, Hanna & Gebbie, The National Academic Press, Washington DC. (2005)

the US and EU there are approximately 3,000 cord blood transplants per year, mostly unrelated donor (allogeneic) transplants in children[8].

The clinical criteria typically used for assessing the success of HSC transplantation is the time to engraftment (time taken for the transplanted cells to produce mature blood cells in the patient) and percentage of event-free survival. Data in the literature shows that cord blood performs well against the above criteria.

Where cord blood has been used in allogeneic (unrelated donors) therapy it has been shown to have advantages over bone marrow. In particular, the incidence of GVHD (graft versus host disease: donor cells attack the recipient's tissues) is lower and transplantation can be successful, even if the patient and cord blood donor are not perfectly matched. This latter observation increases the potential donor pool available and increases the potential use of cord blood stored in public or private/public banks.

Cord blood does have some disadvantages compared to other sources of HSCs, such as bone marrow or mobilized peripheral blood. The small volume of cord blood (typically 75-100ml) means that the number of HSCs is low and the use of cord blood HSC is therefore limited to children under 40kg. This means that currently in private banks the success rates for older children and young adults will be low. For allogeneic treatments this problem has been overcome by using multiple units of cord blood from different donors to treat each adult patient. In the last 5 years, several investigators have published the results of cord blood transplantations in adult patients using multiple allogeneic cord blood units. This issue could be overcome for autologous therapies by a process to reliably increase the population of stem cells by expansion.

Even when the optimal number of cord HSCs is given, cord blood shows slower engraftment (time for the HSC to produce mature blood cells). Opportunistic infection and organ failure rises when engraftment is slower. This limitation on the successful use of cord blood would be overcome by development of transplant protocols which promote transport of cord HSC to the bone marrow and subsequent engraftment.

Another disadvantage of autologous use of privately stored cord HSCs is the detection of leukaemic stem cells in the stored cord blood of some paediatric leukaemia patients. The significance of this observation is that prior to autologous cord blood treatment of childhood leukaemias extensive testing is required for the presence of the leukaemic cells. These techniques are available for use if needed.

Mesenchymal stem cells

The ability of MSC to differentiate into connective tissue cells such as bone, muscle, fat and tendon, gives them great potential in tissue engineering applications and this market is expected to grow significantly over the next 10 years[9]. Indeed, cell therapy is considered to be a disruptive technology in orthopaedics. There are already a number of products on the market or in late phase clinical trials which incorporate MSCs for wound healing, cosmetics and orthopaedics as well as cardiac and immuno-modulatory products. Furthermore there is increasing demand by the "worried well" for biological insurance to cover nuclear attack, sports injury and cosmetic therapies. These are summarised in the table below. Of the products in late phase development 6 utilize cord blood as the source of MSC.

4.2 Future uses of cord blood derived stem cells

The facts discussed above give parent's confidence that cord blood derived stem cells have demonstrated ability to treat a number of diseases that may occur in childhood and beyond. Even though the probability that a child will require a cord blood transplant for haematological conditions has been estimated as low as 1:200,000 (only 5 autologous transplants from private banks reported) the number of parents opting to invest in the insurance is increasing. Further

[8] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

[9] ibid

demonstrations of the utility and proven therapies using cord blood stem cells will likely serve to accelerate the acceptance and uptake of cord blood banking. Indeed stem cell banking is growing exponentially especially in Europe, central and south America. By 2005 there were 127 cord blood banks worldwide (40 of these are public) with an estimated value of the market of $300m[10].

The following table summarises the products currently in development.

Indication	US Patients	Company	Time to market	Cord Blood
Diabetes	2million	Gamida cell BioE	10yrs	X X
Orthopaedics	0.5million	Aastrom Cognate Mesoblast Osiris	<5yrs	
Spinal Cord Injury	0.25 million	BioE Stemcyte Saneron Sertoli	 10yrs	X
Ischaemic Heart Disease	12 million	Athersys Angioblast Osiris GamidaCell viacell endogenitor cytori Arteriocyte Bioheart	5-10yrs	 X X X
Immuno-modulation		Viacell		
HSC Transplant	18thousand	Hospitals Pluristem BioE	On market <5yrs <5yrs	X paediatric X X

4.2 Developments with positive impact on market

Improved Transplantation Protocols

A cord blood unit does not contain sufficient HSC to successfully transplant an adult or child over 40Kg[11]. The immunological properties of cord blood have recently allowed transplant physicians to pool 2 or more cord blood units to treat adult patients. Data indicates that these "double transplants" can be as successful as bone marrow and have the additional advantage of immediate availability[12]. In addition clinical researchers are developing novel cell delivery techniques to improve transport of cord HSC to the bone marrow in order to reduce engraftment time. These improvements in transplant protocols could make cord blood the standard HSC source for adult

[10] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

[11] Chao, Emerson, Weinberg. Stem Cell Transplantation (Cord Blood Transplants) Haematology (2004) page 354-371.

[12] Barker. Transplantation of 2 UCB units in adults. Blood. (2005)

patients which would greatly increase the demand for allogeneic (publicly banked) cord blood units[13].

Cell expansion

Enhancing HSC numbers prior to transplantation has so far been difficult to achieve. Many studies have shown massive proliferation of bone marrow or cord blood cells in cultures containing a cocktail of expensive protein growth factors. However expansion of transplantable HSC was very modest and usually did not exceed input levels by more than 2-fold and in many cases diminished HSC numbers. These preliminary results indicate that HSC expansion in culture is difficult but feasible and may eventually be used in the clinic following further R&D[14].

Similarly, for MSC, although cells are easily expanded in culture, they may not retain their functional properties. Currently MSCs expansion relies on uncharacterized animal products, such as foetal calf serum. These ingredients are subject to increased regulatory scrutiny which will increase the time and cost to develop usable therapies.

The expansion of stem cells exceeds the FDA's definition of "minimum manipulation" category and hence will be regulated in a similar manner to biopharmaceuticals requiring pre-clinical animal testing and clinical trials prior to market launch.

Other factors

Research spending by governments on the science of stem cell technology will continue to increase and in particular the situation in the USA is changing at the state level (e.g. Proposition 71 in California) and potentially at the federal level with the change in administration. Increased research will lead to further advances which will maintain the benefits of stem cell therapy in the public domain.

The implementation of EU regulations is assessed to have a positive impact on the market, giving the pubic confidence in the quality of cord blood banks. In the short-term this may cause a number of operations to close, but overall public confidence in the sector is likely to increase.

4.4 Developments with negative impacts on the market

Any adverse event (e.g. infection or cancer) induced by a cord blood derived therapy will have a negative impact on the whole industry. For this reason it is essential that all companies, wherever they are located, operate to the highest quality standards. This is especially the case for companies who operate in less stringently regulated territories such as Asia.

There is considerable ethical debate, in the EU, concerning the choice of private versus public banking. The principle of non-commerciality of body material, transmitted in an EU directive forbids profiting from body material. Thus, banks are forbidden from re-selling cord blood at a profit. It is, however, permissible for blood banks to charge fees for blood products which allow them to recoup their operating expenses and research costs. Many private banks, such as Cryo-Save, do not sell human cells but provide storage services for families and hence do not infringe this EU directive. Should government increase resources in public banking it could overtake private banks. Conversely involvement in the growth of public cord banks can be viewed as an opportunity for private banks.

4.5 Description of generic blood banking operation

The first operational cord blood banks were established in the early 1990s in New York, Milan, and Dusseldorf and created the protocols for collection, processing, and freezing of cord blood units.

[13] Ballen. New trends in umbilical cord blood transplantation. Blood. (2005)

[14] Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program. Institute of Medicine of the National Academies Eds: Meyer, Hanna & Gebbie, The National Academic Press, Washington DC. (2005)

Currently, Bone Marrow Donors Worldwide lists approximately 150 000 available cord blood units from 35 different cord blood banks in 21 countries, with nearly all units tissue-typed for matching.

Cord blood banking involves the following phases: recruitment, consent, and testing of maternal donors; collection of the cord blood unit; processing, freezing, and testing of the cord blood unit; and release of cord blood unit to transplant center[15].

Existing technology and standard methods for collection and storage of stem/progenitor cells from umbilical tissues have proven adequate for regenerative medicine as evidenced by the now large number of transplants. While a number of cord blood storage companies are developing new techniques and procedures to improve their offering, the current technology, when operated to high quality standards, has shown to produce similar results of transplant success in different locations.

The cord blood is processed to remove the red blood cells and plasma and the remaining Buffy coat, containing the HSC and white blood cells, is frozen. Ideally, this processing uses a closed system to minimize contamination risk. Freezing is at a controlled rate (1°C /minute) in the presence of a cryoprotectant, such as DMSO. The sample is then transferred to -80°C freezer, and finally to liquid nitrogen freezers, achieving a temperature of <-180°C, for long-term storage. This procedure has been shown to enable recovery of HSC in cord blood cells for up to 12 years[16].

Blood from the mother is tested for infectious agents including syphilis, human T-cell lymphotropic virus 1 (HTLV-1), HIV, hepatitis B, hepatitis C and cytomegalovirus (CMV). A sample of the cord blood unit itself is cultured, and HLA (tissue type for transplant matching) tested. Cells are count before and after processing and HSC content is tested on the cord blood product. About half of the cord blood units collected are discarded as they are too small even for transplantation of children. One advantage of cord blood as opposed to bone marrow is the speed of the search process, since there is no living donor to contact and test.

4.6 Regulatory Requirements

In the EU it is (or soon will be) mandatory that Cord Blood storage facilities comply with the EU Cells and Tissues Directive (2004/23/EC) and must be licensed by the competent authority in the EU state in which they operate (Medicines & Health Regulatory Authority in the UK).

Most cord blood banks operate under strict guidelines, analogous to blood banks, and are instituted by either NETCORD, FACT (Foundation for Accreditation of Cellular Therapy), or AABB (American Association of Blood Banks). In addition, most public cord blood banks also comply with the voluntary codes set down by The Joint Accreditation Committee-ISCT & EBMT (JACIE-FACT). As of 2006, in Europe 35 centres have been inspected and, following correction of deficiencies, 28 have achieved full accreditation. Although FACT-JACIE accreditation is currently voluntary, many transplant clinicians will expect the donor cells to be from a JACIE-FACT accredited source. JACIE-FACT is currently working on global harmonisation of recommendations for cellular therapies. Until recently JACIE-FACT would license only public banks but have now begun to register private banks (e.g. StemCyte and Cryo-Save). The standards required to achieve accreditation to JACIE-FACT require investment in time and people. Those centres approved in Europe required at least 18 months to prepare for accreditation and 85% needed to employ a quality manager on an ongoing basis. JACIE-FACT is increasingly becoming a minimum requirement with some territories demanding full cGMP accreditation similar to that required for biopharmaceuticals. The cGMP compliant collection and storage becomes increasingly critical if the stored cells form the raw material for a biopharmaceutical product (e.g. expanded and/or differentiated cell therapy)

[15] Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program. Institute of Medicine of the National Academies Eds: Meyer, Hanna & Gebbie, The National Academic Press, Washington DC. (2005)

[16] ibid

4.7 Competition

The USA is the most developed market for private cord blood banking with 22 existing banks established over the last 10 years. The total capacity in the USA includes 18 public cord blood banks which offer processed materials for allogeneic transplants[17]. The US industry is therefore well established and probably leading the world in terms of the technology to collect, store and provide cord blood derived stem cells. Currently, there are few examples of US based companies directly entering the European market (UK cord blood bank is a subsidiary of New England Cord Blood Bank). In contrast, there are numerous examples of expansion into the Far and Middle East regions which are experiencing exponential expansion of cord blood banking. The fact that US companies are not heavily targeting the European market is probably related to the varied regulatory regimes within individual countries, the debate in Europe over ethics of private versus public banks, and the high growth rates for the US and eastern markets.

In the medium term, US companies with their longer experience curve and investment in technology may represent a threat by either direct entry to the European market or by partnering or acquisition.

In Europe, private cord blood banking has developed over the last 5-6 years and in the UK seven banks were founded between 2001 and 2006. In Europe there are currently 38 private banks operating, the market leaders being Crow-Save and Vita34, and of these 32% have released material for transplantation.

There is significant variation in the number of competitors per country in Europe, most notably in France there are no private banks as only public banking is allowed. In Europe private banking has generally been viewed as less ethical than public banking. Therefore in Europe public banking or public/private banking does represent a major competitor to purely private operations. If European governments increase the funding available for public banking then this could have a negative effect on the market growth for private banking.

In the UK, Virgin Health has recently launched a private/public cord blood banking system. In their business model the cord is split into private and a public samples with the latter available for general use by any HLA-matched patient. The Virgin model is based on the assumption that HSC expansion technology will be available in the near term as the half samples are currently too small for use in HSC transplantation. Virgin charges £1500 for processing and storage which is similar to the price offered by entirely private banks.

In the rest of Europe the major competitor to Cryo-Save is Vita34. Based in Germany and operating to the standards required by the German federal authorities, Vita 34 will have quality procedures that are likely to satisfy the requirements of the EU Cells and Tissues Directive (2004/23/EC). Vita34 store the cord blood containing the red blood cells which is likely to affect the quality of the product and is not the JACIE-FACT recommended procedure, Vita-34 have however released product for successful transplants.

Throughout the Middle East and Asia there are twenty-nine cord blood banks operating some of which are subsidiaries of or collaborate with EU or US banks. Of these six are AABB accredited. The higher birth rates, lower ethical concerns, often less regulation, and increase in living standards in these countries means they are high growth markets for private cord blood banking. The expansion of large US private banks into these markets indicates the relative attractiveness compared to Europe for the reasons discussed above. For example the large California based company StemCyte has expanded into Taiwan and has supplied over 500 units for transplantation, mostly for allogeneic use. StemCyte offers a hybrid model in which no charge is made for storage and donors can request their cord for family members free of charge. The cords are also available to any HLA-matching patient at a price in the region of €20,000 (compared with €10,000 from public banks).

[17] Opportunities in Stem Cell Research and Commercialization. Business insights Ltd (2006)

As the market for cord blood banking expands and more companies enter the market companies are beginning to develop differentiated offerings. This includes investing in technology to expand HSCs, newer technologies for collection of cord blood stem cells, storage of MSCs and other cells or tissue (e.g. placenta, adipose tissue, mobilized peripheral blood).

A number of companies are developing proprietary systems that claim to improve the quality and efficiency of cord blood processing (in terms of the recovery of HSCs). BioE Corporation has developed PrepaCyte(R)-CB Umbilical Cord Blood Processing System which has been shown to improve the recovery of cells from human umbilical cord blood when compared to traditional processing methods. An alternative approach has been patented by PharmaStem (formerly Biocyte) for cord blood processing. Many cord blood banks (e.g. New England Cord blood bank and LifeBank) have licensed this technology. The development of proprietary improved processing methodology potential creates a barrier to entry unless the product is made available on the market as a medical device, as is the case for Prepacyte, or is licensed for use.

A number of companies have recognised that the ability to expand HSCs and/or MSCs derived from cord blood would significantly increase the market for banking and also for therapies based on the derived stem cells. ViaCell is the only US cord blood bank which conducts its own in-house R&D into umbilical cord blood-derived stem cell expansion. ViaCell have licenses to stem cell growth factors and an option to collaborate with Amgen, Genzyme, GlasxoSmithKline and Johnson & Johnson (Centocor and Cordis) in development of these products.

Other cell therapy companies that do not operate banking facilities are also developing HSC expansion technologies. For example, Gamida Cell is developing cell therapies based on expanded stem cells for the treatment of blood cancers, cardiac disease and neurological disorders.

Expanded mesenchymal cells for tissue engineering have been introduced to the market by many companies such as Smith & Nephew (Dermagraft), Organogenesis (Apligraf) and Genzyme (Carticel). Osiris Therapeutics has developed a manufacturing process for the expansion of allogeneic bone marrow-derived MSC and has 47 issued US and 167 non-US patents.

The significance of therapy companies developing these expansion technologies to underpin their products is that these processes are often patented and therefore any cord blood company may be excluded from offering this capability unless they can circumvent or license the necessary patents. On the positive side as discussed previously the fact that technologies are being developed illustrates the technical feasibility of the approach. In addition, stored cells (such as cord blood) which form the raw material for these processes must be cGMP compliant.

Although there are over 100 companies worldwide which offer cord blood banking, at the current time we are aware of only two North Amercian companies, Create Cord Blood Bank (Toronto) and LifeCord (US), who are developing services for collection of MSCs from the cord tissue. This is an attractive compliment to expectant parents already storing umbilical cord blood stem cells. Similarly, we are only aware of BioMatrix in the USA developing collection and storage services for autologous adipose tissue derived MSCs. We are not currently aware of any companies in Europe offering these service. Another potential competitor to the storage of MSCs from adipose tissue is the extraction from a patient when required. Cytori's Celution™ System automates the process that releases MSC from adipose (fat) tissue. The adipose tissue is processed in an automated closed system delivering MSC within 1 hour for immediate re-administration to the patient without the need for further manipulation.

5. Risks

Based on information received regarding Cryo-Save and expert knowledge of the market, the following table summarises the key risks associated with the cord blood banking market and specific risks associated with the business plan of Cryo-Save. Where appropriate under the section of mitigation, actions or activities that Cryo-Save has indicated they are undertaking are referenced.

	Risk	Impact	Mitigation
Technical	Failure to develop HSCs expansion	Medium	Extensive academic collaboration (Bordeaux)
	Lack of in house R&D	Medium	Extensive academic collaboration
	Inexperience in GMP production	Medium	Acquire facility and expertise
	Failure to develop MSC expansion	Low	Extensive academic collaboration
Regulatory	Failure to maintain quality across the group	High	Centrally accredited and automated processing centres
	Failure to achieve cGMP accreditation	Medium	Current use of approved methods and equipment
	Changing EU regulations	Medium	Well networked with EU national regulatory bodies
Commercial	High cost of HSC expansion processes	High	Cost modeling and forecasting prior to commercialisation
	Failure to target new MSC customers	Medium	Work with existing channel e.g. plastic surgeons
	US competition in Asia	Medium	Quality and reputation of EU operation
	Competition from public banks in EU	Medium	Developing public/private banking to address EU ethical concerns.
	IP issues especially in stem cell expansion	Medium	License or develop own IP

6. Conclusions

The market for cord blood and other stem cells is expanding rapidly not only for treatment of serious haematological conditions but also into heart disease orthopaedics and cosmetic/wellness areas. Cryo-Save is in an excellent position to take advantage of this opportunity as they have significant expertise, infrastructure and reputation in this area. This field is however becoming increasingly competitive and more highly regulated.

To ensure that they remain competitive Cryo-Save are developing their product pipeline by establishing a number of collaborations with academic groups to access leading edge technology, such as stem cell expansion and cryopreservation. To penetrate the new markets in cosmetics/well-being they have begun to expand their clinical collaborations beyond haematologists to include cosmetic surgeons. They are also moving into the expanding Asian and Middle East markets using their considerable reputation for quality and expertise in regulatory compliance. This regulatory/ethical expertise places them in a strong position to maintain their lead in Europe by establishing alliances with Europe's increasing number of Public banks.

The regenerative medicine market is not however without risk. There are both technical and commercial risks in developing these disruptive technologies.