ORGAN PRESERVATION
COMPETITIVE ANALYSIS

September 2003
Table of Contents

TABLE OF CONTENTS  2

COMPETITIVE SUMMARY  3

Human BioSystems (HBS) Solution  3
Euro-Collins or Collins Solution  4
Viaspan® or UW Solution  5
Custodial® or HTK Solution  5
Celsior® Solution  6

HBS ORGAN RESEARCH SUMMARY  7

Organ Preservation Research Findings Above Zero Degrees Centigrade  7
Organ Preservation Research Findings Below Zero Degrees Centigrade  8
The Organ Preservation Research Team  10

CONCLUSION  11
September 2003

COMPETITIVE SUMMARY

This document will identify the strengths and weaknesses of what we believe to be the major organ preservation solutions currently available in the U.S. and many other nations throughout the world. It also identifies opportunities for Human BioSystems (HBS) and its transplant product development team.

Increased organ preservation time has huge implications by potentially providing the recipient with the best functioning organ available and by enabling the organ to be transported further distances than is currently possible. Since the mid 1970’s, there have been two major preservation solutions dominating the market, starting with the Collins solution and followed by the UW Solution, which replaced the Collins in the U.S. in the mid 1980’s.

In the last five years, a new solution developed in Germany by Dr. Franz Kohler Chemie GmbH named Custodiol® HTK has become available in the U.S. market and, according to reports from many transplant centers, is beginning to take away market share from the UW Solution.

It is important to note that even to the present date, the development of preservation solutions has only been focused on preservation time, graft functions and survival. Consequently the current potential annual market value has been limited.

An additional requirement for organ recipients, the need to maintain the new organ with anti-rejection medicines, has resulted in many side effects such as damage to new kidneys due to secondary infections, malignancies, hypertension and diabetes. This factor could result in tremendous additional opportunities for HBS.

Human BioSystems’ approach and objective is to develop a superior preservation solution that will address the current problems associated with limited shelf life and to additionally have a solution that will ultimately reduce or eliminate the need for anti-rejection drugs. The potential savings in drug expenditures could be significant if the organ rejection problem is reduced or eliminated.

Human BioSystems (HBS) Solution
Target Price Range: $ 300 - $ 1,000 per liter

Under the direction of HBS Chief Medical Officer Luis Toledo, MD, PhD, HBS has recently started a research facility in Michigan with the goal to develop a new technology for organ preservation. The company has conducted preliminary kidney transplantation studies with rats. These studies, although in their early stages of research and development, have indicated that the HBS Solution and System performed as well, and in some cases superior to, the commonly used UW solution. In animal
research, Dr. Toledo and his team have made initial comparisons between the HBS Solution and the UW solution (generally considered to be the gold standard in this technology category) at 4°C, –20°C and –80°C preserved for 24, 38 and 48 hours. At 24 hours the HBS Solution and the UW Solution displayed equally positive results. When the preservation periods were extended to 38 hours the UW Solution failed, with the kidneys exhibiting organ damage. In preliminary studies, kidneys stored in the HBS Solution survived and exhibited signs of functionality. Kidneys stored at minus 20 degrees centigrade and minus 80 degrees centigrade in the HBS Solution showed some signs of viability.

**The potential benefits and major strengths of the HBS Solution are:**

- **Extension of Preservation time:** Early studies with rats have shown that 38 hours of kidney storage is feasible, potentially adding 14 hours of additional preservation time for kidneys, thereby potentially giving patients the opportunity to receive better organ matches.

- **Improved viability of transplanted kidneys:** This potentially will eliminate, and/or dramatically reduce post transplant dialysis treatments. The HBS Solution is light, low in viscosity and more stable, allowing it to withstand cold temperature without crystallization and therefore be able to protect the cell membranes from damage. This also provides additional benefits for safely transporting organs anywhere in the world.

- **Stability:** The HBS Solution is unique in its composition and is differentiated from the gold standard UW Solution, in that the HBS Solution is more stable and requires no flushing of the kidney prior to transplantation. This would define a simpler procedure than the process currently in use, saving time and expenses.

- **Immunomodulation:** There is evidence in previous research conducted by the HBS medical team and other investigators, showing that with long term cold storage there is a decrease in the immunogenicity of the transplanted organs. Potentially, with further research, the HBS Solution may modify the immunogenicity of donor organs, providing additional benefits in function and reducing rejection episodes.

**Euro-Collins or Collins Solution**

Price range $275 - $300 per liter

Developed by Dr. Geoffrey Collins in the mid ‘70’s, the Collins solution was used throughout the world and in most transplant centers in the U.S. for 20 years. The rights to market the solution were purchased by Fresenius, and it became known as the Euro-Collins Solution. It is still in use today at a few transplant centers to cold flush living donor kidneys after they have been removed.
Since the introduction of Viaspan (the UW Solution) in 1984, and the recent entry into the North American market by HTK-Custodiol, the competitive advantage of the Euro-Collins or Collins solution has diminished and therefore its competitive standing is now irrelevant.

**Viaspan® or UW Solution**  
Average Price $385 per liter

Viaspan, often referred to as the UW Solution, is a product of Barr Labs. It is ideally suited as a universal aortic flush and cold storage solution for the preservation of intra-abdominal organs, including the kidneys, liver, and pancreas. The UW Solution, considered to be the gold standard in the U.S. for preserving organs for the past decade, has recently been losing market share, primarily to the HTK solution.

Preservation solutions are one of the most important factors in transplant procedures for influencing positive patient results. Viaspan claims to offer the benefits of time, preservation and organ viability. Viaspan also claims it prolongs the preservation period for intra-abdominal organs. Advantages claimed include:

- Allows for kidney preservation time up to 48 hours\(^1\)
- Allows for liver preservation time up to 24 hours
- Allows for pancreas preservation time up to 24 hours
- Provides enough time to admit patients from distant locations
- Provides enough time to improve recipient matching
- Provides enough time to operate in a semi-elective situation

Flushing and storage with Viaspan improves the quality of organ preservation and may help to reduce post transplant complications. It is formulated to minimize organ damage upon initial perfusion and reperfusion, including cellular swelling, oxygen free radical injury, and cell membrane destruction.

Viaspan may help to reduce post transplant complications, which thereby contributes to positive patient outcomes. Organs preserved in Viaspan have a reduced occurrence of delayed graft function, improved graft function and extended graft survival.

**The major weakness of the Viaspan/ UW Solution** is that it must be flushed from the organ to prevent possible cardiovascular complications such as hyperkalemic cardiac arrest or bradyarrhythmia in the transplant recipient. Viaspan also requires additives, filtering, or premixing.

**Custodial® or HTK Solution**  
Price Range: $200 – $215 per liter

The HTK (Histidine-Tryptophan-Ketoglutarate) Solution for Multi-Organ

---

\(^1\) Our lab test indicated much less preservation time than claimed by Viaspan®.
Protection is used by leading transplant centers worldwide for the preservation of the kidney, liver, heart, lung, and pancreas. Custodiol, a product approved by the United States FDA as a Medical Device and a Multi-Organ solution, is also a popular choice for Non-Heart Beating Donors. The HTK Solution is eroding the UW Solution market share in the U.S. and has already gained acceptance in most European countries as the gold standard for preserving organs.

**Product Benefits:**
- Rapid homogenous cooling due to low viscosity
- Superior recovery of function
- Excellent ischemic tolerance
- Virtual absence of side effects
- Simple perfusion technique (ready-to-use, no additives or preparation)

Other notable benefits claimed by HTK are HTK’s much lower viscosity, which is nearly identical to water, and its biochemical makeup. These characteristics offer certain advantages that make it practical and easier to use. For instance, surgeons at the University of Pittsburgh Medical Center found it could penetrate the liver’s vessels and bile duct structures better.

HTK also claims that its lower viscosity makes it a better solution to use for livers recovered from non-heart beating donors because of its ability to flush out any residual blood left behind in vessels by the sudden stoppage of the heart.

**Celsior® Solution**

Distributed by SangStat in Fremont, California, Celsior is a storage solution for organs after removal from the donor and before transplantation into the recipient. It is a sterile, nonpyrogenic, extracellular solution for hypothermic flushing and storage of hearts. Early graft loss remains a significant problem associated with cardiac transplantation and damage to the heart tissue can occur due to inadequate preservation. Effective organ preservation includes initial flushing of the heart tissue during the recovery process and cold storage while the donor heart is transported to the recipient. Celsior® is the first and only flush and cold storage solution approved by the FDA, as a medical device for cardiac transplantation. It was designed specifically for cardiac transplantation to minimize myocardial edema, oxygen free radical-induced reperfusion injury, and diastolic stiffness.
HBS Organ Research Summary

Organ Preservation Research Findings Above Zero Degrees Centigrade

The graph below shows that laboratory rats died at 5 days when their kidneys were stored in the UW Solution for 36 hours at 4 degrees Centigrade before transplantation. The same experiment performed using the HBS Solution showing that the rats survived at 5 days and one even survived at 7 days.
Organ Preservation Research Findings Below Zero Degrees Centigrade

HBS Chief Medical Officer, Luis Toledo, M.D., Ph.D. and Fernando Lopez, M.D. and HBS Senior Research Scientist, have defined a new method to evaluate an organ’s viability titled the **Reperfusion Index**. An index number of 15 is considered to be a perfect organ while an index number of 1 is the worst rating, with no indication of viability or functionality.

**Reperfusion Index Scoring Criteria:**

The index was developed in order to find a measurable marker to evaluate the organs in the first 10 minutes of reperfusion after cold storage in preservation solutions.

There are 4 parameters that are evaluated:

1) **Color:** **Color of the transplanted kidney during the first 10 minutes of reperfusion**
   - **4+** Fully pink-reddish
   - **3+** Few mottled areas
   - **2+** Partially perfused or dark red
   - **1+** Purplish
   - **0** No perfusion or pale-pink

2) **Timing of Reperfusion:** **The time that it takes the kidney to look fully reperfused immediately after the removal of the clamps at the end of the surgical procedure (actual transplant) connection of blood vessels**
   - **4+** Within 5 seconds
   - **3+** Within 15 seconds
   - **2+** Within 30 seconds
   - **1+** Within 1 minute
   - **0** No perfusion

3) **Urinary Output:** **The time that it takes the kidney to start to produce urine after the removal of the vascular clamps at the end of the surgical re-connection (anastomosis) of the blood vessels**
   - **4+** Urine within 1 minute
   - **3+** Urine within 3 minutes
   - **2+** Urine within 5 minutes
   - **1+** Urine within 10 minutes
   - **0** No Urine

4) **Macroscopic findings:** **How the kidney looks after 10 minutes of reperfusion. Every parameter is measured and then summarized - the score is as follows:**
• 3+ No edema or redness of perihiliar fat
• 2+ Some perihiliar edema and/or redish color
• 1+ Extensive perihiliar edema and/or hemorrhagic fat

**Reperfusion Index Total Score:**

- 12 – 15  Excellent
- 10 & 11  Good
- 7 – 9   Moderate
- 6 or less Bad

Using the Reperfusion Index as a guide, the graph below signifies that rat kidneys stored at –20 degrees Centigrade and at –80 degrees Centigrade for 48 hours in the HBS Solution demonstrate nearly 200% improvement of the Reperfusion Index number reading when compared to the UW Solution at –20 degrees, and more than 200% improvement at –80 degrees Centigrade.

This means that after storage the organ treated with the HBS Solution and Procedure is more viable than the organ processed with the UW solution at those temperatures. Two animals were used for each solution.

At the cellular level, the histopathology samples show better preservation in the HBS preserved kidneys with signs of viability (cell survival) compared to the damage and necrosis (death cells) observed in UW preserved samples.
The Organ Preservation Research Team

Luis Toledo, M.D., Ph.D. – Chief Medical Officer

Luis Toledo, M.D., Ph.D. joined HBS as Chief Medical Officer in March of 2000. Dr. Toledo is an internationally recognized authority on organ transplantation and preservation. He has authored 10 books on transplantation and related subjects, authored or co-authored 500 scientific publications, and contributed to chapters within 77 books. Dr. Toledo has held many medical staff positions in transplantation and research at Henry Ford Hospital, Mount Carmel Mercy Hospital and Borgess Medical Center. He is also currently the Director of Trauma, Surgery Research Sciences and Molecular Biology at the Borgess Research Institute and Professor of Surgery and Director of Research at Michigan State University-Kalamazoo Center for Medical Studies in Kalamazoo, Michigan.

Fernando Lopez, M.D. – Senior Research Scientist

Fernando Lopez, M.D., Senior Research Scientist at HBS, is a fully licensed medical doctor and surgeon in his home country of Mexico. He earned his medical degree in 1987 and was certified by the Mexican Board of Surgery as a Transplant Surgeon and Researcher in 1991. In 1996, Western Michigan University awarded Dr. Lopez a Master of Science Degree. In addition, studying under Dr. Toledo, he completed a Surgical Research Fellowship and Transplant Fellowship in June of 1995 for Borgess Hospital, which is located in Kalamazoo, Michigan. Dr. Lopez has held many medical staff positions including head of the transplant program and member of the research board at Western National Medical Center, Instituto Mexicano del Seguro Social (Mexican Institute of Social Health). He has earned several national and international awards in the fields of transplant and surgical research.
Conclusion

Human BioSystems is in the development stage of preservation technologies that could break through the scientific boundaries that have limited the shelf life of donor organs for several decades.

Although current HBS development efforts are concentrated on extending the shelf life of organs at a storage temperature of 4 degrees Centigrade, the company has demonstrated that rat kidneys stored at –20 degrees Centigrade using the HBS Solution remained unfrozen and produced urine when transplanted after re-warming.

Similar results were obtained after freezing kidneys at –80 degrees Centigrade, a temperature where the organ became completely frozen.

HBS believes that if the HBS Solution becomes commercially available, the implications can be profound and may change the way organs are stored and transplanted.

Contact: Harry Masuda, President, 650-323-0943, hmasuda@humanbiosystems.com
Bob Strom, VP Marketing, 760-883-5808, rstrom@humanbiosystems.com
Rich Kaiser, Yes International, 800-631-8127, rich@yesinternational.com
Website: www.humanbiosystems.com

DISCLAIMER

Certain statements contained herein are “forward-looking” statements (as such term is defined in the Private Securities Litigation Reform Act of 1995). Because such statements include risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Factors that could cause results to differ materially from those expressed or implied by such forward-looking statements include, but are not limited to, failure of independent test centers to duplicate or verify results of our Company’s tests, failure to obtain FDA or other necessary regulatory approval of the Company’s products, and those factors discussed in filings made by the Company with the Securities and Exchange Commission.