

DEC 10 1999

## 510(k) Summary

### Custodiol® HTK Solution

Common/Classification Name: Isolated Kidney Perfusion and Transport System and Accessories, 21 CFR 876.5880

Dr. Franz Kohler Chemie GmbH  
Postfach 1117  
D-64659 Alsbach-Hahnlein  
Germany

Contact: E. Schaffner, M.D. Prepared: June 16, 1999

#### A. LEGALLY MARKETED PREDICATE DEVICES

The **Custodiol HTK Solution** is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996.

#### B. DEVICE DESCRIPTION

The HTK solution is intended for perfusion and flushing donor kidneys prior to removal from the donor and for preserving the kidney during hypothermic storage and transport to the recipient. HTK solution is based on the principle of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intensive buffering of the extracellular space by means of histidine/histidine HCl, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen supply. Only a small portion of the osmolality of the HTK solution is due to the sodium and potassium. The composition of HTK is similar to that of extracellular fluid. All of the components of the HTK solution occur naturally in the body.

The HTK solution is relatively low in potassium concentration so that residual solution in the transplanted organ poses no danger to the recipient. This is particularly important in organs that take up relatively large amounts of the perfusate, which may find its way into the recipient's circulation.

The HTK solution has a low viscosity, even at low temperatures. This characteristic assures rapid flow rates during initial perfusion, allowing the organ to be quickly cooled.

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**C. INDICATIONS FOR USE**

Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

**D. SUBSTANTIAL EQUIVALENCE SUMMARY**

The **Custodiol HTK Solution** is a medical device, and it has a similar indications for use as the legally marketed predicate device. While the indications for use statement is not identical to that of the predicate device, the intended use is clearly the same.

The **Custodiol HTK Solution** has the same technological characteristics as the predicate devices. However, the characteristics may not be sufficiently precise to assure equivalence through a point by point comparison. Therefore, extensive clinical data has been collected by the sponsor and others. The performance data clearly demonstrates equivalence.

**E. TECHNOLOGICAL CHARACTERISTICS**

Both the Custodiol HTK Solution and the predicate device are solutions containing electrolytes, buffering agents, and other materials occurring naturally in the body. Both solutions are intended to reduce metabolism and preserve physiological conditions of explanted organs and tissue during cold storage.

**F. TESTING**

Several clinical studies have been reported that compared the performance of Custodiol HTK Solution with the Viaspan Belzer UW Solution. These studies have compared survival rates and other outcome measures. The primary evidence for the equivalence of Custodiol and UW solutions has come from the 47-center randomized clinical study carried out under the guidance of the Eurotransplant organization of Leiden, The Netherlands. Over a thousand kidneys were included in the study.

This study showed that the HTK solution performs as well as the UW solution and significantly better than EC solution for kidney transplants. The overall kidney survival rates from the 47-center study for HTK versus UW at four time points were:

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	<u>HTK</u>	<u>UW</u>
1 Month	91%	91%
12 Months	83%	82%
24 Months	77%	74%
36 months	74%	68%

#### **G. CONCLUSIONS**

The clinical and other performance data amply demonstrate that Custodiol performs as well as the predicate device. This pre-market submission demonstrates Substantial Equivalence as defined and understood in the Federal Food Drug and Cosmetic Act and various guidance documents issued by the Center for Devices and Radiological Health.

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

DEC 10 1999

 Food and Drug Administration  
 9200 Corporate Boulevard  
 Rockville MD 20850

 Dr. Franz Kohler Chemie GmbH  
 c/o T. Whit Athey, Ph.D.  
 Senior Consultant  
 C.L. McIntosh & Associates, Inc.  
 Medical & Regulatory Affairs Services  
 12300 Twinbrook Parkway, Suite 625  
 Rockville, MD 20852

 Re: K992209  
 Custodiol® HTK Solution  
 Dated: October 21, 1999  
 Received: October 21, 1999  
 Regulatory Class: II  
 21 CFR §876.5880/Procode: 78 KDN

Dear Dr. Athey:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4613. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

 CAPT Daniel G. Schultz, M.D.  
 Acting Director, Division of Reproductive,  
 Abdominal, Ear, Nose and Throat,  
 and Radiological Devices  
 Office of Device Evaluation  
 Center for Devices and  
 Radiological Health

Enclosure

STATEMENT OF INDICATIONS FOR USE

510(k) Number (if known): K992209

Device Name: Custodiol HTK Solution

Indications For Use:

Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

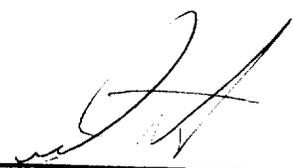
(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use    
 (Per 21 CFR 801.109)

OR

Over-The-Counter Use



(Division Sign-Off)  
Division of Reproductive, Abdominal, ENT,  
and Radiological Devices  
510(k) Number K992209/S<sup>001</sup>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
Document Mail Center (HFZ-401)  
9200 Corporate Blvd.  
Rockville, Maryland 20850

October 20, 1999

DR. FRANZ KOHLER CHEMIE GMBH  
C/O C.L. MCINTOSH & ASSOCIATES  
12300 TWINBROOK PARKWAY  
SUITE 625  
ROCKVILLE, MD 20852  
ATTN: T. WHIT ATHEY

510(k) Number: K992209  
Product: CUSTODIOL

Extended Until: 23-NOV-1999

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman  
Supervisory Consumer Safety Officer  
Premarket Notification Section  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

part of the Celeris family  
12300 Twinbrook Parkway  
Suite 625  
Rockville MD 20852  
toll free 1 888 770 9590  
phone 301 770 9590  
fax 301 770 9584

CL MCINTOSH

October 18, 1999

Center for Devices and Radiological Health  
Food and Drug Administration  
Document Mail Center  
9200 Corporate Blvd  
Rockville, MD 20850

Re: K992209, Request for Additional Information Dated 23 October 1999  
Custodiol HTK Solution by Dr. F. Kohler Chemie GmbH

Dear Sir or Madam:



On behalf of our client, Dr. F. Kohler Chemie GmbH, we request 30 days additional time to respond to your request for more information concerning K992209. The current deadline for response is October 23, 1999.

Thank you for your consideration of this matter. If you require any additional information or clarification, please call or FAX the undersigned at 301-770-9590 (voice) or 301-770-9584 (FAX).

Sincerely yours,

T. Whit Athey, Ph.D.  
Senior Consultant

RECEIVED  
20 Oct 99 08 11  
FDA/CDRH/OCE/DMC

## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

DEC 10 1999

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Dr. Franz Kohler Chemie GmbH  
c/o T. Whit Athey, Ph.D.  
Senior Consultant  
C.L. McIntosh & Associates, Inc.  
Medical & Regulatory Affairs Services  
12300 Twinbrook Parkway, Suite 625  
Rockville, MD 20852

Re: K992209  
Custodiol® HTK Solution  
Dated: October 21, 1999  
Received: October 21, 1999  
Regulatory Class: II  
21 CFR §876.5880/Procode: 78 KDN

Dear Dr. Athey:

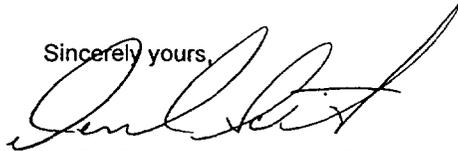
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This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4613. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,



CAPT Daniel G. Schultz, M.D.  
Acting Director, Division of Reproductive,  
Abdominal, Ear, Nose and Throat,  
and Radiological Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

STATEMENT OF INDICATIONS FOR USE

510(k) Number (if known): K992209

Device Name: Custodiol HTK Solution

Indications For Use:

Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use   
(Per 21 CFR 801.109)

OR

Over-The-Counter Use



(Division Sign-Off)  
Division of Reproductive, Abdominal, ENT,  
and Radiological Devices

510(k) Number K992209/5001

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

Memorandum

From: Reviewer(s) - Name(s) Miriam C. Provost, Ph.D.

Subject: 510(k) Number K992209/S1

To: The Record - It is my recommendation that the subject 510(k) Notification:

- Refused to accept.
- Requires additional information (other than refuse to accept).
- Is substantially equivalent to marketed devices.
- NOT substantially equivalent to marketed devices.

De Novo Classification Candidate?

YES  NO *NA*

Other (e.g., exempt by regulation, not a device, duplicate, etc.)

- Is this device subject to Postmarket Surveillance?  YES  NO
- Is this device subject to the Tracking Regulation?  YES  NO
- Was clinical data necessary to support the review of this 510(k)?  YES  NO
- Is this a prescription device?  YES  NO
- Was this 510(k) reviewed by a Third Party?  YES  NO
- Special 510(k)?  YES  NO
- Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers  YES  NO

This 510(k) contains:

Truthful and Accurate Statement  Requested  Enclosed  
(required for originals received 3-14-95 and after)

A 510(k) summary OR  A 510(k) statement

The required certification and summary for class III devices *NA*

The indication for use form (required for originals received 1-1-96 and after)

Material of Biological Origin  YES  NO

The submitter requests under 21 CFR 807.95 (does not apply for SEs):

- No Confidentiality
- Confidentiality for 90 days
- Continued Confidentiality exceeding 90 days

Predicate Product Code with class:

Additional Product Code(s) with panel (optional):

78 KDN 876.5880 Class II

Review: Carolyn Y Newland GRDB  
(Branch Chief) (Branch Code)

12/8/99  
(Date)

Final Review: [Signature]  
(Division Director)

12/9  
(Date)

12/9/99  
gmz

Revised: 8/17/99

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**K992209 "SUBSTANTIAL EQUIVALENCE" (SE) DECISION-MAKING DOCUMENTATION**

**Reviewer:** Miriam C. Provost, Ph.D. **Division/Branch:** DRAERD/GRDB, HFZ-470

**Trade Name:** Custodiol® solution  
**Common Name:** Isolated kidney perfusion and transport system and accessories  
**Classification:** Class II, 21 CFR §876.5880 **Date:** November 24, 1999  
**Product Code:** 78 KDN

**Product To Which Compared:** ViaSpan® solution (K883782)

**Contact:** Dr. Whit Athey (consultant) **Phone:** (301) 770-9590  
 C. L. McInstosh

	<b>YES</b>	<b>NO*</b>	
1. IS PRODUCT A DEVICE?	<u>✓</u>	—	IF NO STOP
2. DEVICE SUBJECT TO 510(K)?	<u>✓</u>	—	IF NO STOP
3. SAME INDICATION STATEMENT?	<u>✓</u>	—	IF YES GO TO 5
4. DO DIFFERENCES ALTER THE EFFECT OR RAISE NEW ISSUES OF SAFETY OR EFFECTIVENESS?	—	—	IF YES STOP → NE
5. SAME TECHNOLOGICAL CHARACTERISTICS	—	<u>✓</u>	IF YES GO TO 7
6. COULD THE NEW CHARACTERISTICS AFFECT SAFETY OR EFFECTIVENESS?	<u>✓</u>	—	IF YES GO TO 8
7. DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH?	—	—	IF YES STOP → SE IF NO GO TO 10
8. NEW TYPES OF SAFETY OR EFFECTIVENESS QUESTIONS?	—	<u>✓</u>	IF YES STOP → NE
9. ACCEPTED SCIENTIFIC METHODS EXIST?	<u>✓</u>	—	IF NO STOP → NE
10. PERFORMANCE DATA AVAILABLE?	<u>✓</u>	—	IF NO REQUEST DATA
11. DATA DEMONSTRATE EQUIVALENCE?	<u>✓</u>	—	

\* "yes" responses to 4, 6, 8, and 11, and every "no" response requires an explanation below

**NARRATIVE DEVICE DESCRIPTION****1. INTENDED USE:**

Custodiol HTK solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

**2. DEVICE DESCRIPTION:**

The device is a sterile solution for use in flushing, storing and transporting donor kidneys intended for transplantation. The predicate device (ViaSpan®) is also a cold storage solution, and is intended for use in preserving kidneys, livers and pancreata. The proposed device is packaged in either glass bottles or polypropylene containers. The predicate device was packaged in plastic bags.

The following table shows a comparison between the chemical composition of Custodiol HTK and ViaSpan.

Additive type	Custodiol HTK Solution	ViaSpan
Impermeant	_____	Pentafraction (hydroxyethyl starch) 50 g/L
Impermeant	_____	Lactobionic acid 35.83 g/L
Electrolyte	Histidine 27.9289 g/L Histidine-HCl H <sub>2</sub> O 3.7733 g/L	Potassium phosphate monobasic 3.4 g/L
Electrolyte	Magnesium chloride Hexahydrate 0.8132 g/L	Magnesium sulfate heptahydrate 1.23 g/L
Impermeant	Mannitol 5.4651 g/L	Raffinose pentahydrate 17.83 g/L
Electrolyte	Potassium chloride 0.671 g/L	Potassium hydroxide 5.61 g/L
Electrolyte	Calcium chloride 0.22 g/L Sodium chloride 0.8766 g/L	_____

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Additive type	Custodiol HTK Solution	ViaSpan
Metabolic substrate	Potassium hydrogen 2-ketoglutarate 0.1842 g/L	Adenosine 1.34 g/L
Antioxidant	_____	Allopurinol 0.136 g/L
Antioxidant	Tryptophan 0.4085 g/L	Total glutathione 0.922 g/L
pH	Potassium hydroxide (adjust pH to 7.02 to 7.2)	Sodium hydroxide (adjust to pH 7.4)
	Water for Injection	Water for injection
Osmolality	310 mOsm	320 mOsm

**5. Explain different technological characteristics.**

As shown by the table above, the predicate and proposed device have a different chemical composition.

**6. Explain why the new characteristics could or could not affect safety or effectiveness**

The new characteristics could affect safety or effectiveness. The difference in chemical composition may not provide adequate preservation of the donor kidney or may actually damage the organ.

**8. Explain why there are or are not new questions of safety and effectiveness**

The questions of safety and effectiveness for the proposed device are the same as the predicate device, i.e., whether the mixture of chemicals provides adequate preservation of the donor organs when used at hypothermic temperatures.

**11. Explain how data demonstrate equivalence**

The sponsor has pre-clinical and clinical data to support the substantial equivalence of the proposed device. The preclinical data support the safety of the materials used to package the device and also demonstrate that the product is stable over its labeled shelf life.

Clinical data was submitted from two randomized, controlled multi-center studies in Europe. These studies compared kidney graft preservation with Custodiol HTK, ViaSpan (UW) and Euro-Collins. The studies were performed at 47 institutions in Austria, Belgium, Germany and the Netherlands between July 1990 and September 1992. In the UW (i.e., ViaSpan)-HTK study, 342 donors and 611 transplants were included, and in the Euro-Collins (EC)-HTK study, 317 donors and 569 transplants were included. The endpoint of the study was the incidence of delayed graft function (DGF), defined as the absence of life-sustaining renal function, requiring dialysis treatment on two or more occasions during the first week after transplantation (in kidneys that survived at least 48 hours).

In the UW-HTK study, 33% (105/314) of the transplanted kidneys in the HTK group had DGF, as compared to 33% (99/297) in the UW group. In the EC-HTK study, 29% (85/292) of the transplanted kidneys in the HTK group had DGF as compared to 43% (119/277) in the EC group. This difference was found to be significant ( $p=0.001$ ).

In the UW-HTK study, overall graft survival at 1, 2 and 3 years after transplantation for the HTK group was 83, 77 and 73% respectively, compared to 81, 73 and 68%, respectively, for the UW group. These differences were not significant. In the EC-HTK study, the overall graft survival at 1, 2 and 3 years after transplantation for the HTK group was 80, 76 and 70%, respectively, compared to 78, 71 and 67%, respectively, for the EC group. These differences were not significant.

The data demonstrate that Custodiol HTK solution is equivalent to ViaSpan for preservation of donor kidneys for transplantation.

Other legally marketed devices are similar to the device described in this submission and the differences identified between the device included in this submission and the predicate devices to which equivalence is claimed would not affect safety and effectiveness. Labeling has been provided which includes instructions for use and an appropriate prescription statement as required by CFR 21.807.87 (e). In compliance with the SMDA of 1990, a 510(k) summary has been provided. The Truthful and Accurate statement and the Indications for Use form have been provided. As long this product is manufactured under GMP's, it should be as safe and effective for its intended use as other similar legally marketed devices.

	YES	NO
Is the device life-supporting or life sustaining?	<u>  </u>	<u>  ✓  </u>
Is the device implanted (short-term or long-term)?	<u>  </u>	<u>  ✓  </u>
Does the device design use software?	<u>  </u>	<u>  ✓  </u>
Is the device sterile?	<u>  ✓  </u>	<u>  </u>
Is the device for single use?	<u>  ✓  </u>	<u>  </u>
Is the device for home use?	<u>  </u>	<u>  ✓  </u>
Is the device for prescription use?	<u>  ✓  </u>	<u>  </u>
Does the device contain a drug or biological product as a component?	<u>  </u>	<u>  ✓  </u>
Is this device a kit?	<u>  </u>	<u>  ✓  </u>

**Recommendation: Substantially equivalent to other Class II devices described in 21 CFR part §876.5880.**

  Miriam C. Provost    
Miriam C. Provost, Ph.D.

  12/2/99    
Date

Concur

  Carolyn Y. Neuland    
Carolyn Y. Neuland, Ph.D., Chief  
Gastroenterology and Renal Devices Branch

  12/18/99    
Date

**MEMORANDUM**

**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND  
RADIOLOGICAL HEALTH  
OFFICE OF DEVICE EVALUATION**

**DATE:** November 24, 1999

**FROM:** Miriam C. Provost, Ph.D., Chemical Engineer  
Gastroenterology and Renal Devices Branch

**SUBJECT:** K992209/S1, Custodiol HTK® solution for flushing and cold storage of donor kidneys

**TO:** The Record

The following is review of a 510(k) submission for the above device. This is my second review of this submission. It now contains the responses to our deficiency letter of September 23, 1999. I would like to point out that a 510(k) was previously submitted for the same device (K983103), but the previous submission included indications for the preservation of hearts, livers, pancreatic islet cells and venous grafts. A "Cannot Respond" letter for the previous submission was issued on April 29, 1999. The sponsor has indicated that the current submission addresses all of the deficiencies raised in the previous letter. As noted below, the solution is now limited to preservation of donor kidneys, only.

**Intended Use**

Custodiol HTK solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

**Device(s) to which equivalence is claimed:**

ViaSpan cold storage solution (K883782)

**Description of Device**

The device is a sterile solution for use in flushing, storing and transporting donor kidneys intended for transplantation. The predicate device (ViaSpan®) is also a cold storage solution, and is intended to be used to preserve kidneys, livers and pancreata.

The following table shows a comparison between the chemical composition of Custodiol HTK and ViaSpan.

10

Additive type	Custodiol HTK Solution	ViaSpan
Impermeant	—————	Pentafraction (hydroxyethyl starch) 50 g/L
Impermeant	—————	Lactobionic acid 35.83 g/L
Electrolyte	Histidine 27.9289 g/L Histidine-HCl H <sub>2</sub> O 3.7733 g/L	Potassium phosphate monobasic 3.4 g/L
Electrolyte	Magnesium chloride Hexahydrate 0.8132 g/L	Magnesium sulfate heptahydrate 1.23 g/L
Impermeant	Mannitol 5.4651 g/L	Raffinose pentahydrate 17.83 g/L
Electrolyte	Potassium chloride 0.671 g/L	Potassium hydroxide 5.61 g/L
Electrolyte	Calcium chloride 0.22 g/L Sodium chloride 0.8766 g/L	—————
Metabolic substrate	Potassium hydrogen 2- ketoglutarate 0.1842 g/L	Adenosine 1.34 g/L
Antioxidant	—————	Allopurinol 0.136 g/L
Antioxidant	Tryptophan 0.4085 g/L	Total glutathione 0.922 g/L
pH	Potassium hydroxide (adjust pH to 7.02 to 7.2)	Sodium hydroxide (adjust to pH 7.4)
	Water for Injection	Water for injection
Osmolality	310 mOsm	320 mOsm

The sponsor has not explained the specific mechanism of action for each component of their solution. A review of the previous submission for this product was provided by Dr. Brian Harvey, medical officer for GRDB. In his review, dated November 16, 1998, Dr. Harvey discusses the theoretical rationale for the inclusion of many of these

components. For example, Dr. Harvey stated that histidine "makes a good choice for a physiologic buffer." He believes that it makes theoretical sense to include ketoglutarate and tryptophan, since "both compounds play a role in cellular metabolism and amino acid biosynthesis which could aid in prolonging cell viability in the organ to be transplanted." Dr. Harvey also stated that the presence of a lower concentration of potassium (than in the predicate device) makes clinical and biochemical sense since it will minimize the danger to recipient if any solution is left in the organ vasculature at the time of transplantation. The small amount of calcium has "the potential to aid in increasing membrane stability and participate in ion channel gated functions." According to Dr. Harvey, the choice of mannitol over lactobionate/raffinose probably makes little physiological difference. However, Dr. Harvey does believe that the effect (if any) of the difference in osmolality between the proposed and the predicate device should be demonstrated with *in vitro* and/or *in vivo* data.

### **Biocompatibility**

The sponsor has provided some information on the purity of the solution components. The histidine, sodium chloride, magnesium chloride hexahydrate, potassium chloride, mannitol, and tryptophan are all specified as USP grade. The histidine hydrochloride monohydrate, potassium hydroxide and calcium chloride dihydrate appear to be EP or European Pharmacopeia grade. The purity of the ketoglutaric acid (also called 2-oxoglutaric acid) is listed as "in-house, not compendial" and the sponsor has explained that a USP or EP specification for this chemical does not exist. The company specifications were provided and compared to other amino acids that do have USP specifications (i.e., glycine and histidine). The specifications for 2-ketoglutaric acid appear to be similar to the USP specifications for the other amino acids, especially with regard to impurities such as heavy metals or iron. For the components that follow EP specifications (i.e., histidine hydrochloride monohydrate, calcium chloride dihydrate and 2 N potassium hydroxide) a comparison was given between the EP and USP specifications for these chemicals. In all cases, the EP specifications are similar and should be adequate for this intended use.

The solution is packaged in either 1 L infusion bottles of type II hydrolytic glass or 5 L polypropylene containers. The polypropylene was identified as "Vestolen P 6500." This material apparently complies with "EP V1.1.2.2.3, Polypropylene for containers for filling with parenteral preparations." In our deficiency letter, we requested additional information on the European standard and asked the sponsor to compare it to the appropriate USP standard. The sponsor stated that the European standard is specific to polypropylene while the USP standard is applicable to all plastic containers. A complete explanation of the EP standard was provided. The standard appears to address all issues regarding the purity of the materials for this intended use.

The bottles are sealed with an "elastomer stopper" (described as bromobutyl with

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aluminum silicate filler) with an aluminum cap overseal. The sponsor has indicated that the stopper meets the requirements of ISO 8871/A1, "Elastomeric parts for aqueous parenteral preparations." This standard includes tests for pyrogenicity, hemolysis and compatibility. Since this material is apparently acceptable for use in packaging parenteral solutions, it should not leach any chemical contaminants and should be acceptable for this use.

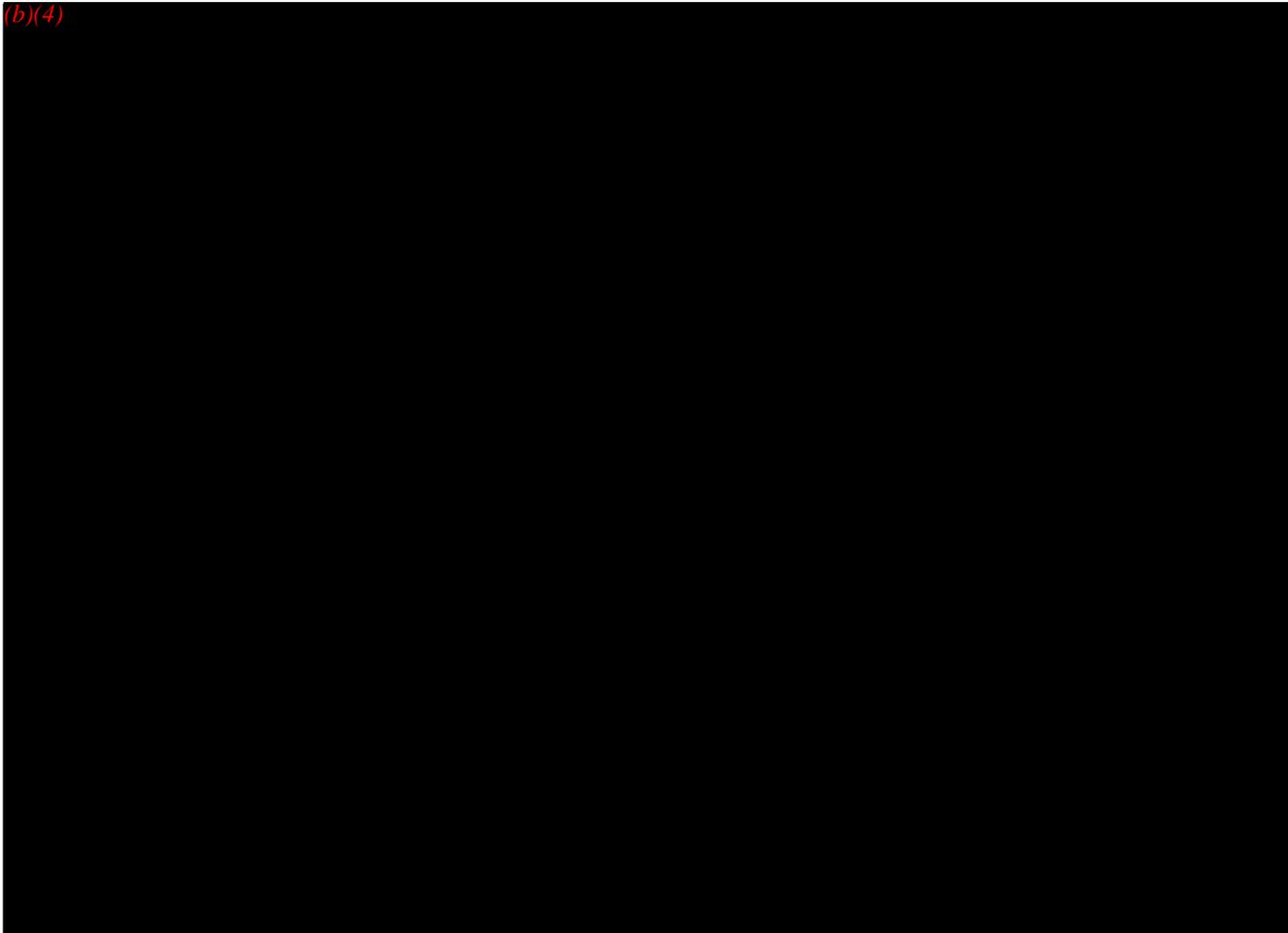
### **Sterilization**

(b)(4)

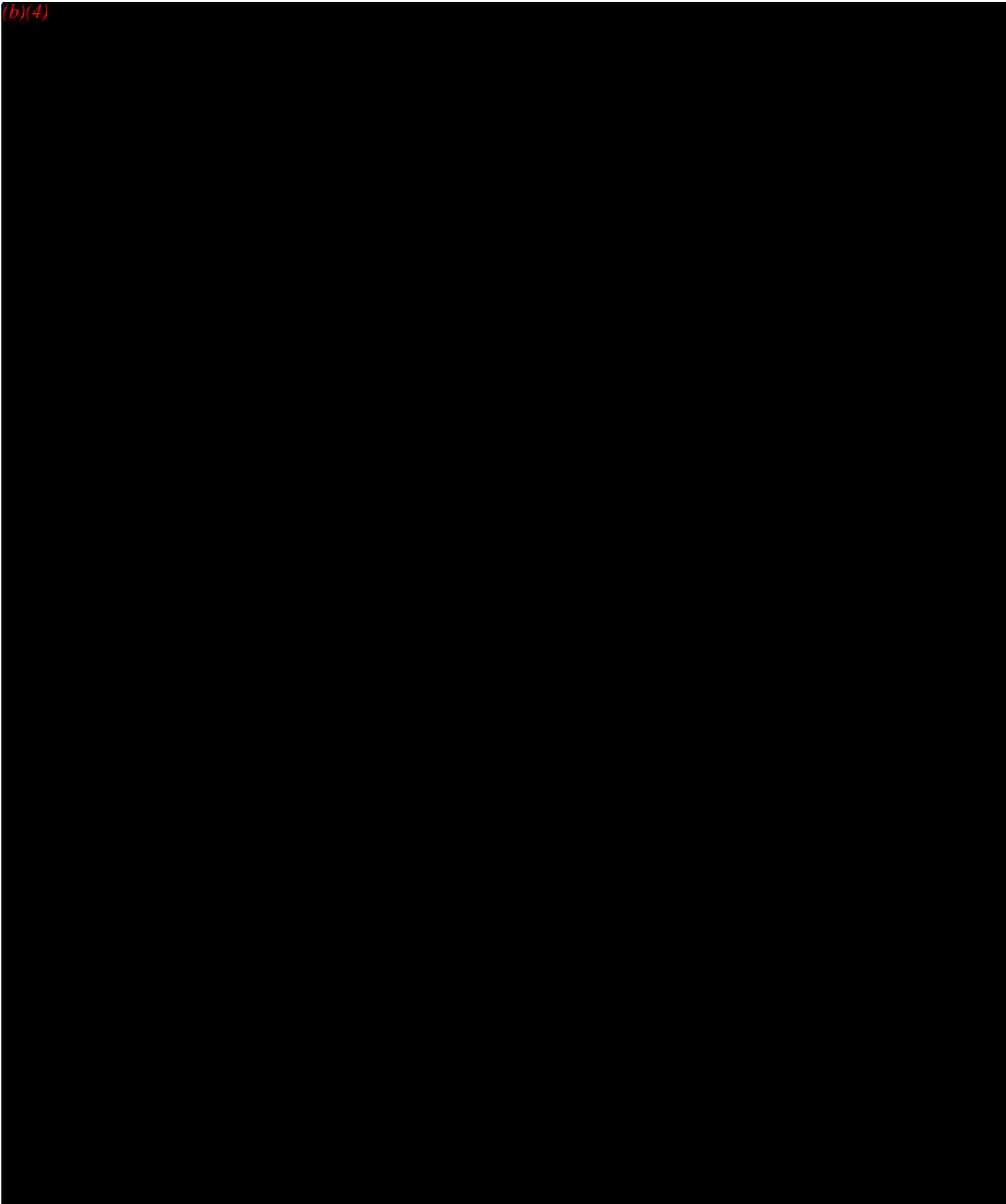


### **Laboratory Testing**

(b)(4)



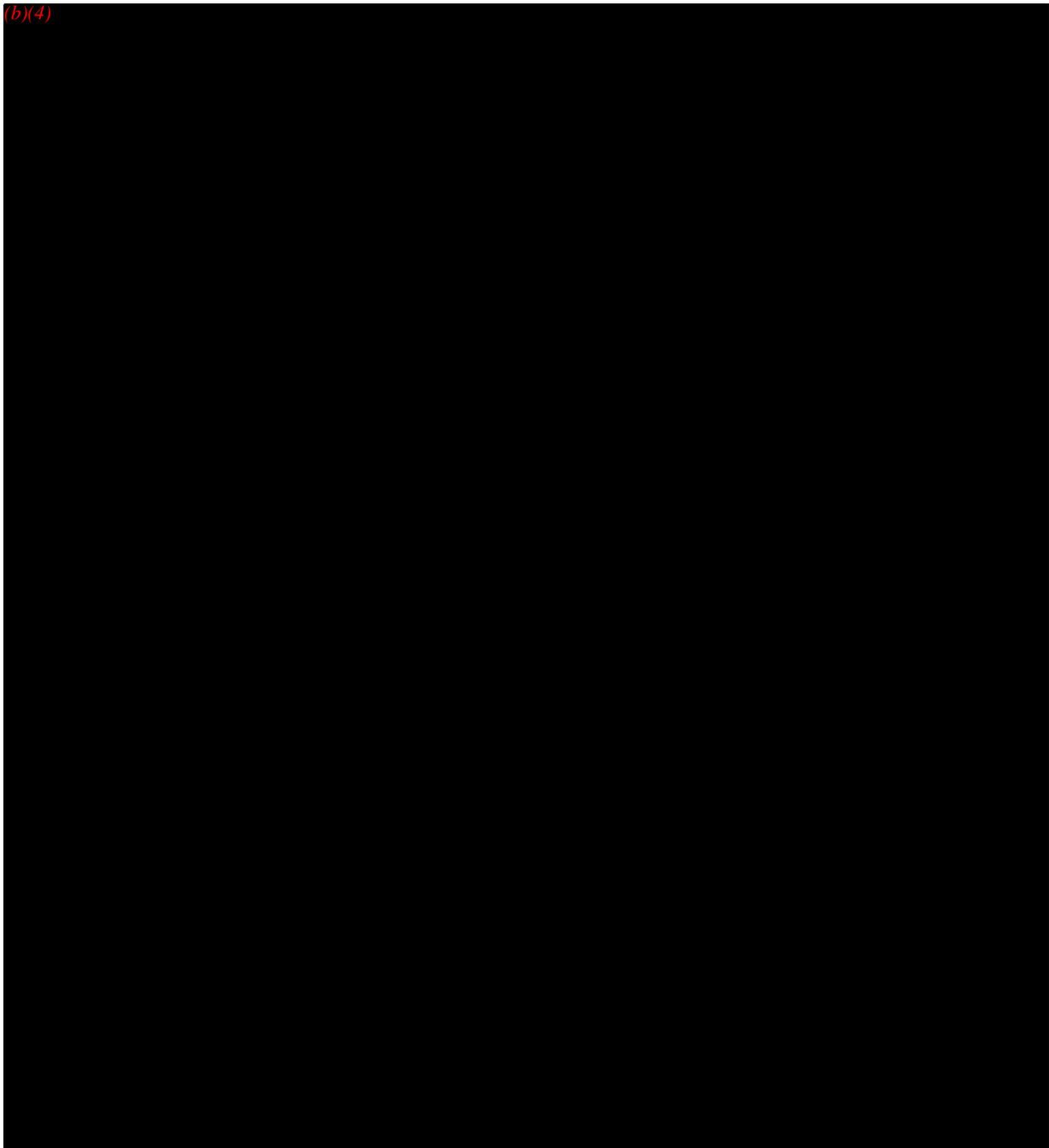
(b)(4)



14

## Clinical Testing

(b)(4)



15

## Labeling

A copy of the instructions for use (package insert) and promotional labeling have been provided. The indication in the package insert agrees with that submitted in the indications for use form.

Under "Warnings" it states, "Custodiol® is not indicated for intravenous or intraarterial administration. It is indicated only for selective perfusion of the kidney as for cooling of the surface areas, i.e., for the preservation of the donor organ during the transport from donor to recipient. Custodiol may not be used for systemic infusion." It also states "The product must be used before the expiration date on the package", and "The product must be stored according to the recommendations prior to use." The storage conditions are given as 8 to 15 °C.

The labeling includes a section called "Clinical Experience" that summarizes the multicenter trial discussed above. The labeling accurately summarizes the relevant data.

The sponsor has also provided a copy of an advertising brochure for their product. The brochure discusses the use of the product for preservation of kidney function. The following claims are now included:

- Rapid graft function
- Low frequency of post-operative dialysis

Data (based on the multicenter study) is given in the brochure to support these claims. A list of references is given and these appear to be limited to the use of Custodiol HTK solution for preservation of donor kidneys.

On the last page of the brochure, the following claims are listed:

- Rapid homogenous cooling due to low viscosity
- Superior recovery of function
- Excellent ischemic tolerance
- High buffering capacity
- Virtual absence of side effects
- Simple perfusion techniques
- Easier surgical handling due to excellent visibility

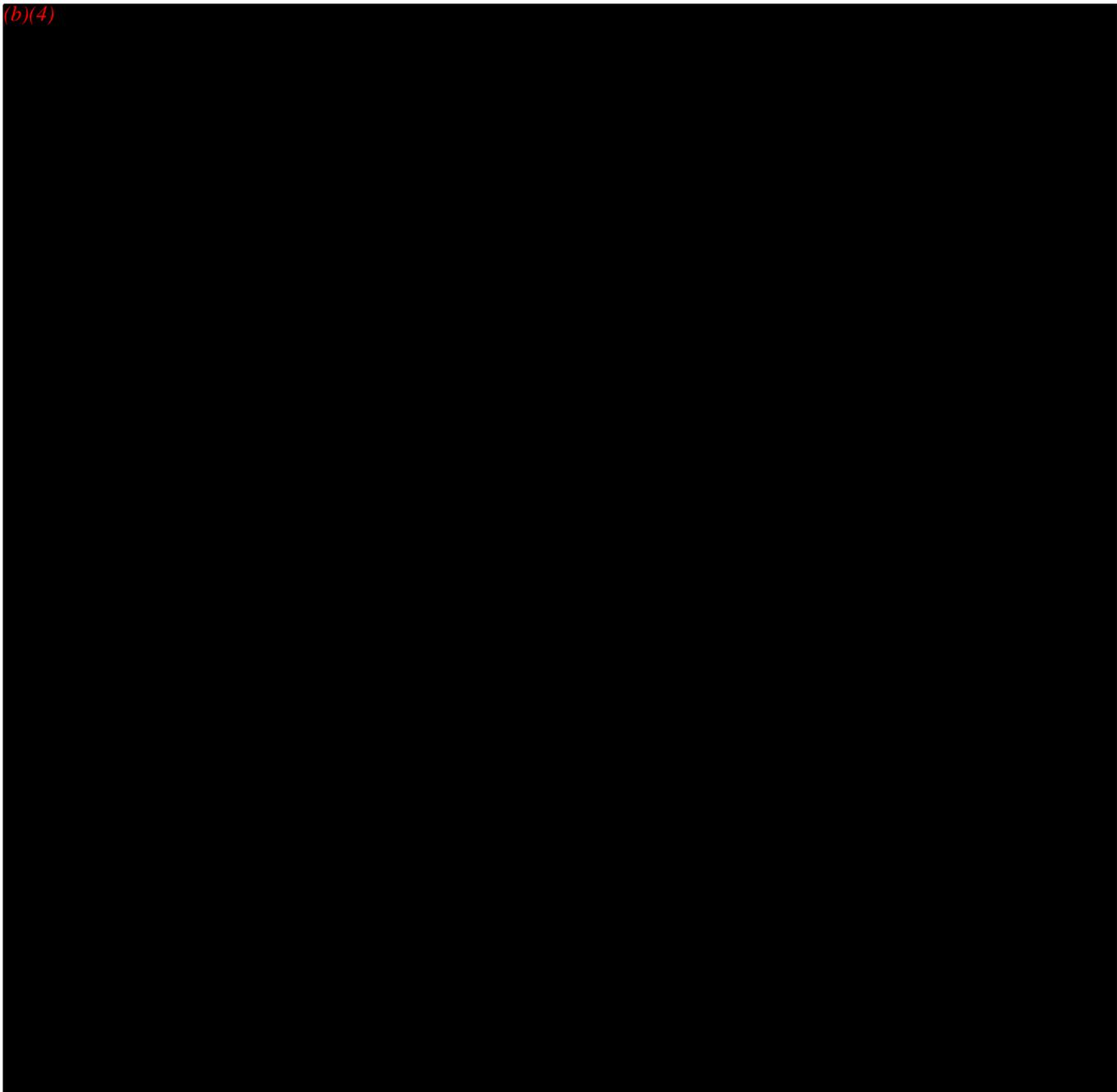
This claims appear to be reasonable, based on the data submitted from the multicenter clinical trial in Europe.

**Administrative**

The sponsor has submitted a "Truthful and Accurate" form, the "Indications for Use" form and a 510(k) summary.

**Response to Deficiencies in September 23, 1999, letter:**

(b)(4)



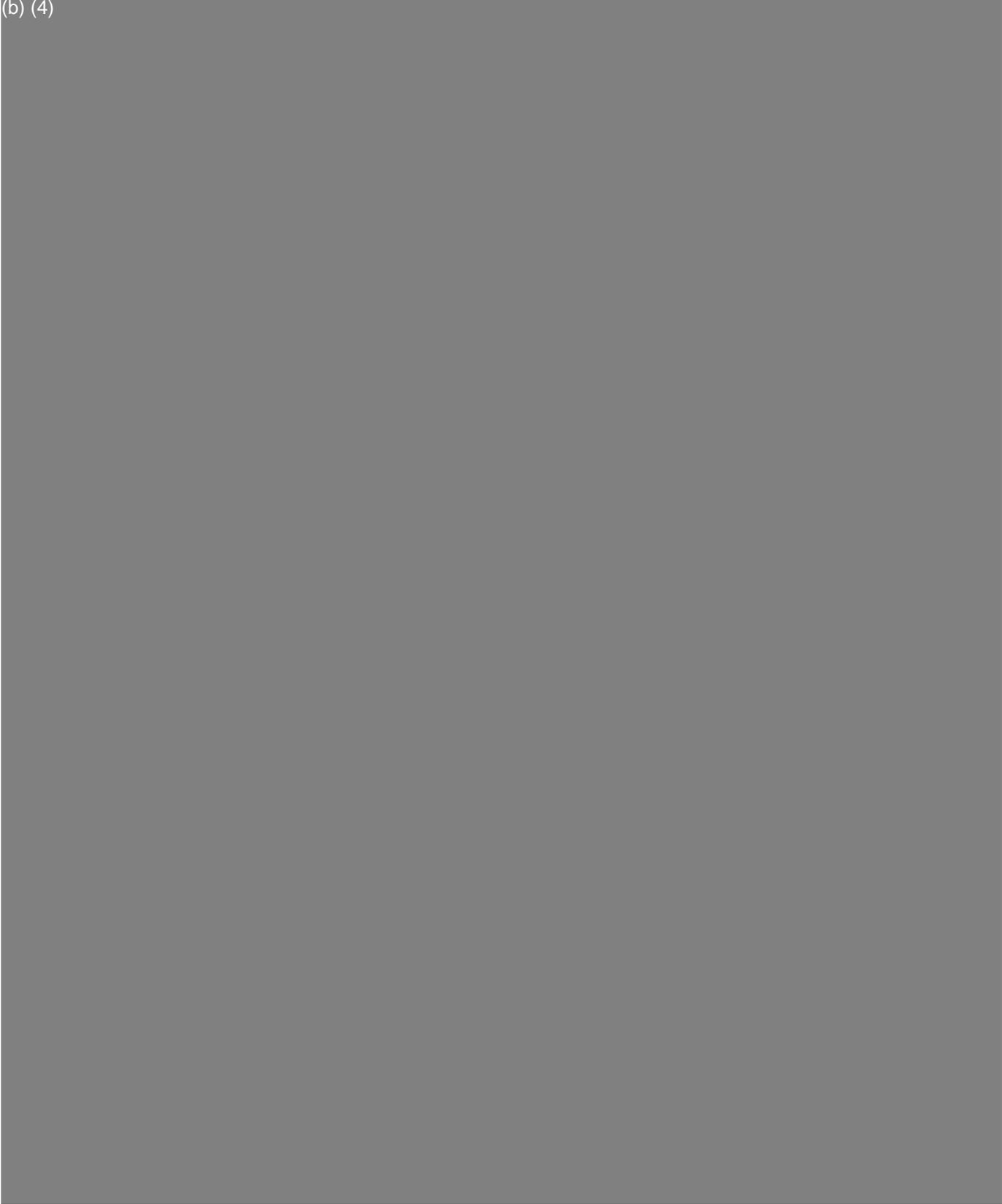
17

(b) (4)



18

(b) (4)



19

(b) (4)



20

(b) (4)



**Recommendation**

All outstanding deficiencies in this submission have been addressed. I recommend that this device be found substantially equivalent.

Miriam C. Provost  
Miriam C. Provost, Ph.D.

12/2/99  
Date

Concur

Carolyn Y. Neuland  
Carolyn Y. Neuland, Ph.D.  
Chief, Gastroenterology and Renal Devices Branch

12/8/99  
Date

21

K992209/A

**C.L. McIntosh**

**& ASSOCIATES, INC.**

**Medical & Regulatory Affairs Services**

12300 Twinbrook Parkway, Suite 625  
Rockville, Maryland 20852

Tel.: (301) 770-9590  
Fax: (301) 770-9584

November 29, 1999

Center for Devices and Radiological Health  
Food and Drug Administration  
Document Mail Center  
9200 Corporate Blvd  
Rockville, MD 20850

30 NOV 99 11 51  
FDA/CDRH/OCE/DID

ATTN: Miriam Provost, Ph.D.  
Gastroenterology and Renal Devices Branch, HFZ-470  
Division of Reproductive, Abdominal, ENT, and Radiology Devices

Re: K992209, K992209A1  
Dates of Submission: 30 June 1999, 24 October 1999  
Device: Custodiol® HTK Solution

Dear Dr. Provost:

We appreciate your prompt review of the additional information that we submitted on October 21, 1999. We also appreciate the opportunity to address the remaining issues in an interactive manner.

In your telephone call of November 25, 1999, you made two additional requests. In the following, I have first repeated your request in italics and then provided our response.

(b) (4)



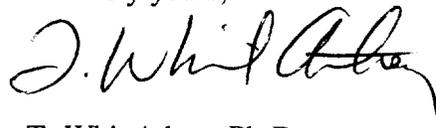
Dr. Miriam Provost, Page 2

(b) (4)



We believe that this additional information addresses the two remaining outstanding issues. If you have questions concerning this information, please call me at 301-770-9590.

Sincerely yours,



T. Whit Athey, Ph.D.  
Senior Consultant

Attachment: Revised Page of Package Insert

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(b) (4)



Dr. Franz Köhler Chemie GmbH  
P.O. Box 1117  
64659 Alsbach-Hähnlein  
Germany

part of the Celeris family  
12300 Twinbrook Parkway  
Suite 625  
Rockville MD 20852  
toll free 1 888 770 9590  
phone 301 770 9590  
fax 301 770 9584

CL MCINTOSH

# Fax

to	<b>Dr. Miriam Provost</b>	from	<b>Whit Athey</b>
fax	<b>301-594-2339</b>	pages	<b>4 (including cover sheet)</b>
phone		date	<b>11/29/99</b>
re	<b>K992209</b>	cc	

urgent   
 for review   
 please comment   
 please reply   
 please recycle

**Message:**

Attached is our response to your requests (by phone) for additional information in regard to K992209 on 25 November 1999.



**NOTICE OF CONFIDENTIALITY**

The information contained in this transmission is intended only for the addressee. It may contain legally confidential information which is protected under the law by a statutory privilege. Receipt by anyone is not a waiver of this or the work product privilege.

If you receive this transmission in error, please notify the sender immediately at 301-770-9590 and arrange for the return of this message and any documents. Thank you.

25

*J. J. McIntosh*

ASSOCIATES, INC.

*Medical & Regulatory Affairs Services*

*12300 Twinbrook Parkway, Suite 625  
Rockville, Maryland 20852*

*Tel.: (301) 770-9590  
Fax: (301) 770-9584*

November 29, 1999

Center for Devices and Radiological Health  
Food and Drug Administration  
Document Mail Center  
9200 Corporate Blvd  
Rockville, MD 20850

ATTN: Miriam Provost, Ph.D.  
Gastroenterology and Renal Devices Branch, HFZ-470  
Division of Reproductive, Abdominal, ENT, and Radiology Devices

Re: K992209, K992209A1  
Dates of Submission: 30 June 1999, 24 October 1999  
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Dear Dr. Provost:

We appreciate your prompt review of the additional information that we submitted on October 21, 1999. We also appreciate the opportunity to address the remaining issues in an interactive manner.

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26

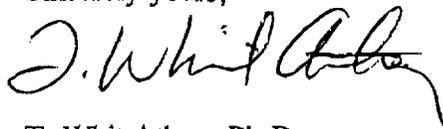
Dr. Miriam Provost, Page 2

(b) (4)



We believe that this additional information addresses the two remaining outstanding issues. If you have questions concerning this information, please call me at 301-770-9590.

Sincerely yours,



T. Whit Athey, Ph.D.  
Senior Consultant

Attachment: Revised Page of Package Insert

21

(b) (4)



Dr. Franz Köhler Chemie GmbH  
P.O. Box 1117  
64659 Alsbach-Hähnlein  
Germany

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
Document Mail Center (HFZ-401)  
9200 Corporate Blvd.  
Rockville, Maryland 20850

October 22, 1999

DR. FRANZ KOHLER CHEMIE GMBH  
C/O C.L. MCINTOSH & ASSOCIATES  
12300 TWINBROOK PARKWAY  
SUITE 625  
ROCKVILLE, MD 20852  
ATTN: T. WHIT ATHEY

510(k) Number: K992209  
Product: CUSTODIOL

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official.

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman  
Supervisory Consumer Safety Officer  
Premarket Notification Section  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

o

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**C.L. McIntosh**

**& ASSOCIATES, INC.**

K992209/S1

*Medical & Regulatory Affairs Services*

12300 Twinbrook Parkway, Suite 625  
Rockville, Maryland 20852

Tel.: (301) 770-9590  
Fax: (301) 770-9584

October 21, 1999

Center for Devices and Radiological Health  
Food and Drug Administration  
Document Mail Center  
9200 Corporate Blvd  
Rockville, MD 20850

RECEIVED  
21 Oct 99 14 22  
FDA/CDRH/OCE/DNC

ATTN: Miriam Provost, Ph.D.  
Gastroenterology and Renal Devices Branch, HFZ-470  
Division of Reproductive, Abdominal, ENT, and Radiology Devices

Re: K992209  
Date of Submission: 30 June 1999  
Device: Custodiol® HTK Solution

Dear Dr. Provost:

We are very disappointed in your letter of 23 September 1999. While you raise several legitimate points in regard to the labeling, many other points appear to be derived from some kind of clinical trial boilerplate deficiency template that ill suits the present case. The small ways in which the Eurotransplant study is different from the model that FDA prefers is far outweighed in importance by the size of the study and by the three-year follow-up period. For an important product such as the HTK Solution, a product that is used in every country in the world except the U.S., FDA should be looking for ways to facilitate its early clearance instead of finding ways to delay it. Luckily for the transplant community in the U.S., F. Kohler Chemie has been able to retrieve much of the additional clinical information that you requested from Eurotransplant.

Therefore, we are submitting this amendment to K992209 on behalf of Dr. F. Kohler Chemie GmbH. In the presentation below, we first repeat the requests from your letter of 23 September, followed by the response from F. Kohler Chemie.

(b) (4)



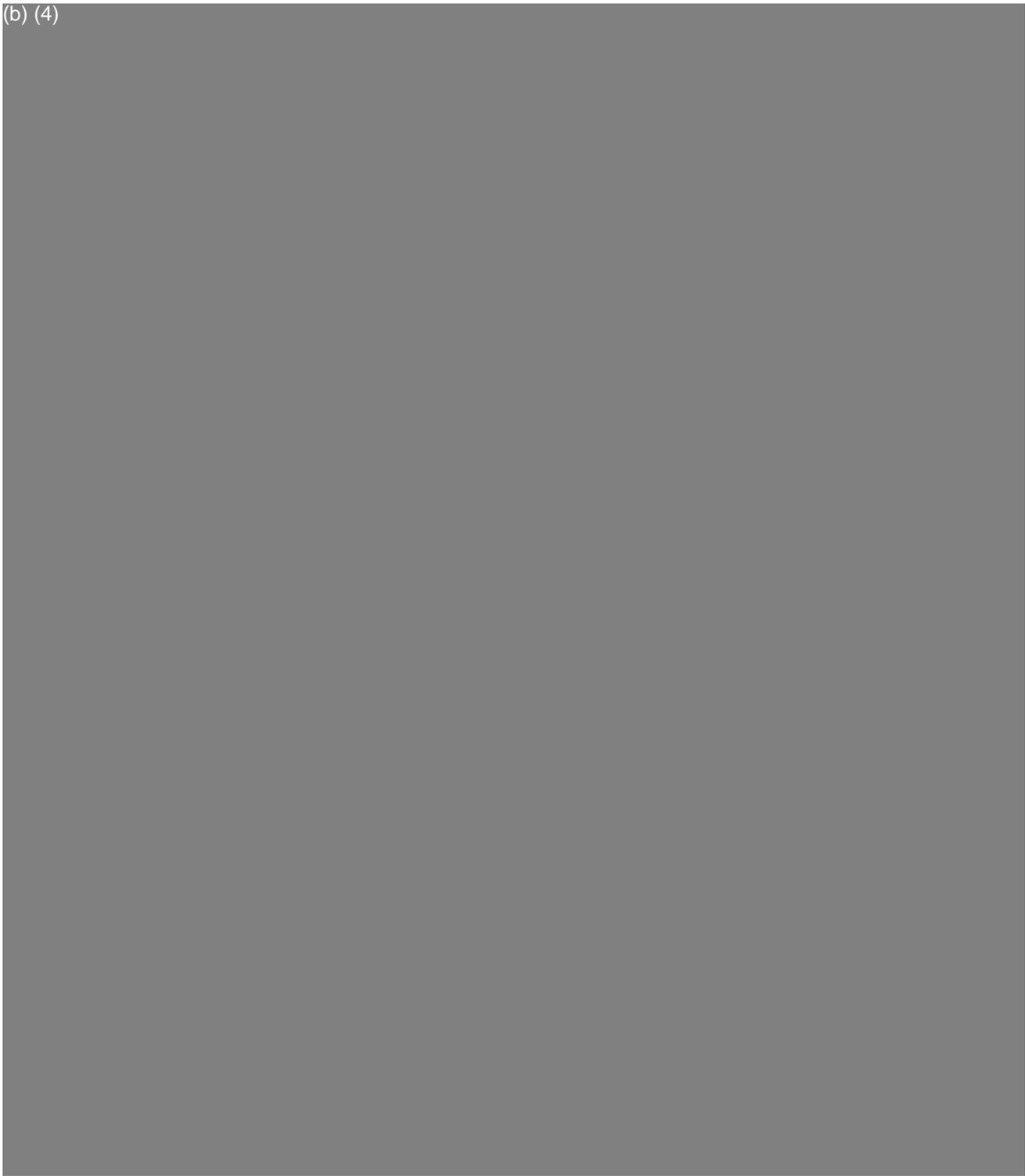
30

Handwritten initials/signature.

Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 2

Attachment A has stability data collected using the five liter container.

(b) (4)



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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 3

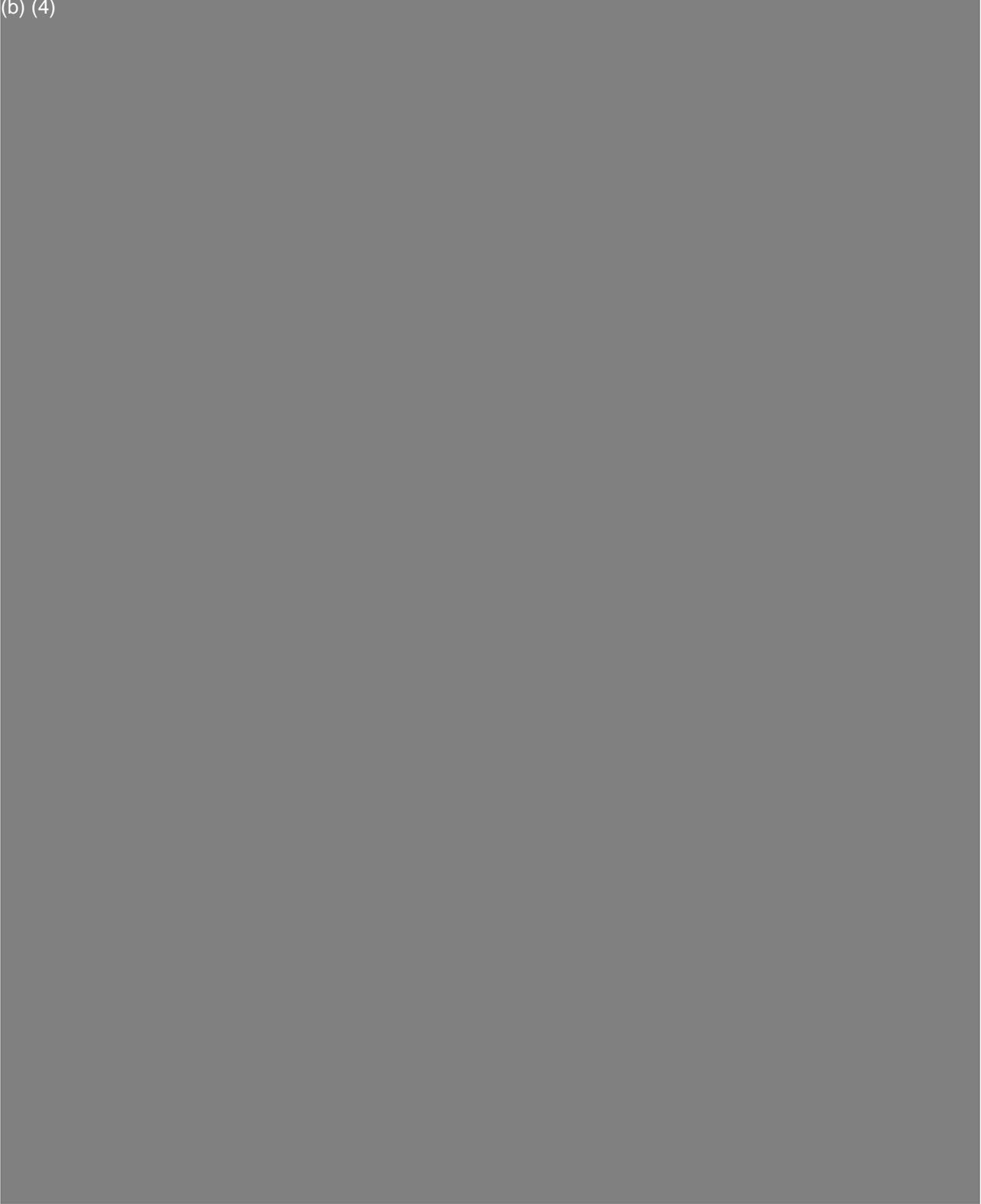
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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 4

(b) (4)



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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 5

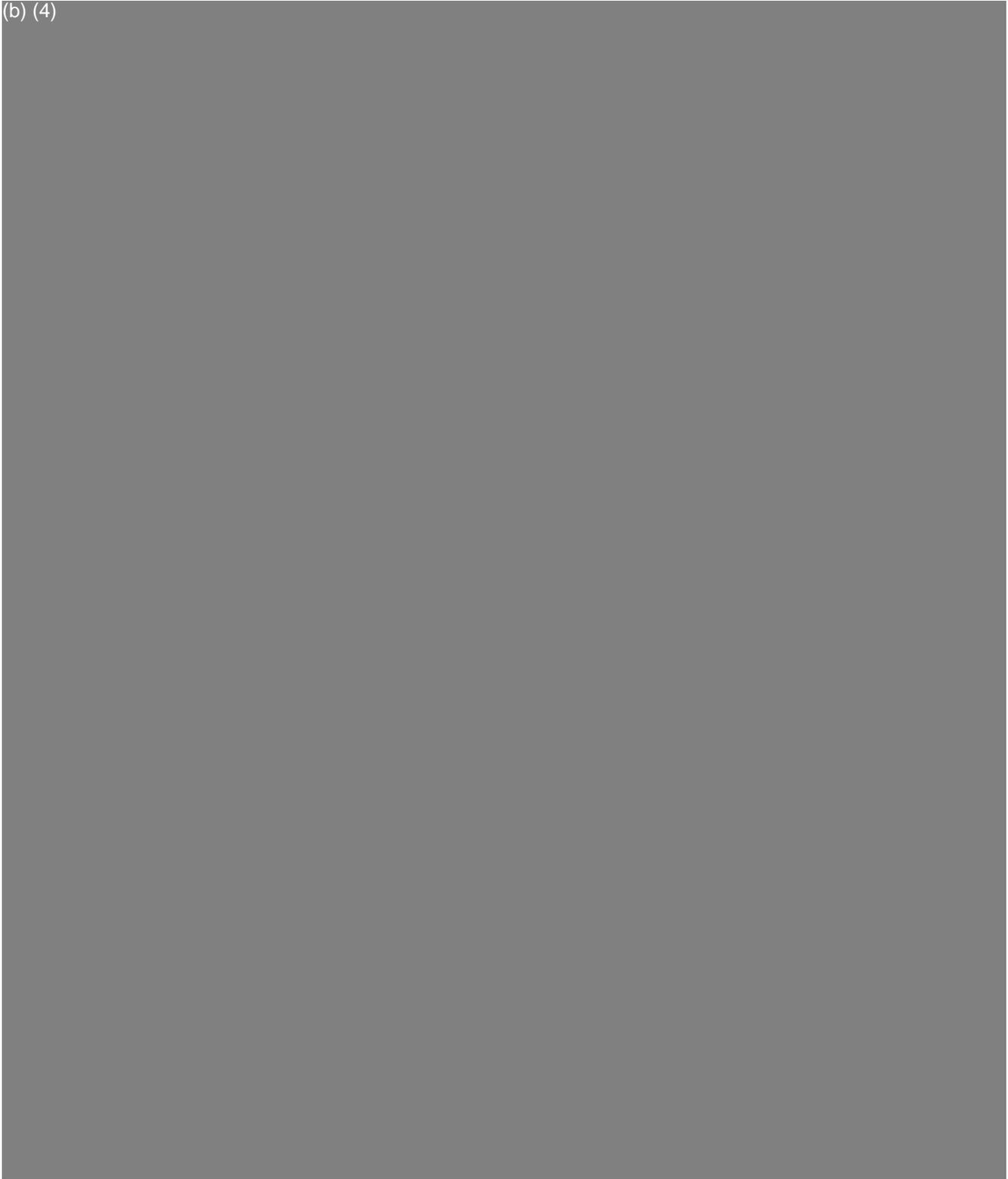
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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 6

(b) (4)



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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 7

(b) (4)



We would appreciate expedited review of the additional information that you requested, considering the history of this case. If you have any questions, please call me at 301-770-9590.

Sincerely yours,



T. Whit Athey, Ph.D.  
Senior Consultant

**Attachments:** Attachment A: Stability Data Using 5 Liter Container  
Attachment B: Comparison of USP and EP Standards  
Attachment C: Copy of EP Standard EP VI.1.2.2.3  
Attachment D: Additional Demographic Data from Eurotransplant  
Attachment E: Revised Package Insert  
Attachment F: Revised Promotional Brochure  
Attachment G: Article on Non-Heart-Beating Donors  
Attachment H: Form 3454

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Records processed under FOIA Request 2014-5611; Released 10/29/14

Records processed under FOIA Request 2014-5611; Released 10/29/14

Records processed under FOIA Request 2014-5611; Released 10/29/14



Records processed under FOIA Request 2014-5611; Released 10/29/14

Records processed under FOIA Request 2014-5611; Released 10/29/14



Records processed under FOIA Request 2014-5611; Released 10/29/14



Records processed under FOIA Request 2014-5611; Released 10/29/14































(Package Label)

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*fluted*

Labeling

1000 ml perfusion solution

Custodiol®  
Bretschneider HTK solution  
For kidney preservation

1000 ml perfusion solution contains

0,8766 g sodium chloride	=	15,0 mmol/l
0,6710 g potassium chloride	=	9,0 mmol/l
0,1842 g potassium hydrogen 2-ketoglutarate	=	1,0 mmol/l
0,8132 g magnesium chloride x 6 H <sub>2</sub> O	=	4,0 mmol/l
3,7733 g histidine x HCl H <sub>2</sub> O	=	18,0 mmol/l
27,9289 g histidine	=	180,0 mmol/l
0,4085 g tryptophan	=	2,0 mmol/l
5,4651 g mannitol	=	30,0 mmol/l
0,0022 g calcium chloride	=	0,015 mmol/l

in water for injections

Osmolality: 310 mosmol/kg

Anion: Cl 50 mEq

Indications for Use: Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

Do not use the solution if it is not clear or if the container is damaged!

Custodiol solution must be stored at  
the recommended temperature (8 °C – 15 °C)

Protect from light  
Sterile and pyrogen-free

Batch number: /expiry date:

Caution. Federal law restricts this device to sale by or on the order of a physician.

Dr. F. Köhler Chemie GmbH  
P.O. Box 1117, D-64659 Alsbach-Hähnlein  
Germany

WZ

## PACKAGE INSERT

### Bretschneider's HTK-Solution for kidney preservation

#### Description

Composition:

1,000 ml Custodiol<sup>®</sup> contain:

0.8766 g	Sodium Chloride	=	15.0 mmol
0.6710 g	Potassium Chloride	=	9.0 mmol
0.1842 g	Potassium hydrogen 2-Ketoglutarate	=	1.0 mmol
0.8132 g	Magnesium Chloride 6 H <sub>2</sub> O	=	4.0 mmol
3.7733 g	Histidine HCl H <sub>2</sub> O	=	18.0 mmol
27.9289 g	Histidine	=	180.0 mmol
0.4085 g	Tryptophan	=	2.0 mmol
5.4651 g	Mannitol	=	30.0 mmol
0.0022 g	Calcium Chloride	=	0.015 mmol

in sterile Water for injection

Anion Cl<sup>-</sup> 50 mval

Physical Properties:

pH 7.02 – 7.20 at 25 °C (pH 7.4-7.45 at 4 °C)

Osmolality: 310 mosmol/kg

#### Indications for Use

Custodiol<sup>®</sup> HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

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### **Contraindications**

Not for continuous perfusion.

### **Warnings and Precautions**

Warning: Federal law restricts sale of this device to or on the order of a physician or licensed practitioner.

Warning: Perfusion of the kidney should be carried out with a maximum hydrostatic pressure of 120 mm Hg.

Warning: Custodiol<sup>®</sup> is not indicated for intravenous or intraarterial administration. It is indicated only for selective perfusion of the kidney and for cooling of the surface areas, i.e., for the preservation of the donor organ during the transport from donor to recipient. Custodiol<sup>®</sup> may not be used for systemic infusion.

Warning: Keep out of reach of children.

Caution: The product must be used before the expiration date stated on the package.

Caution: The product must be stored according to the recommendations prior to use.

### **Adverse Events**

No side effects have been encountered that could be attributed to this product.

### **Interactions with other Medical Products**

Interactions with such therapeutic agents as glycosides, diuretics, nitrates, antihypertensives, beta blockers and calcium antagonists, which are used perioperatively, have not been reported.

### **Overdoses** (Symptoms, Countermeasures)

In the case of entry of the HTK solution into the general circulation, the resultant change in the concentration of sodium and calcium are very slight. After checking sodium and calcium levels in the extracorporeal circulation both of these electrolytes should be replaced if necessary.

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## Instructions for Use (Recommendations)

### Required Equipment:

Infusion apparatus with a Y piece for bottle or canister  
Infusion cannula tube 2.5 to 3 mm  
Tube clamp  
Infusion stand with a height setting of up to 200 cm with tape measure.  
Cooling Equipment (5 to 8° C) for use in cardiac surgery  
Infusion tube with an internal diameter of 6 mm  
Transport Container with sterile pouch for transport of the cooled organ from donor to recipient.

### Tolerance of Ischemia by the Kidney

The kidney may be stored with ice cold Custodiol solution at about 2 to 4° C with a period of (cold) ischemia of up to 48 hours. Warm ischemia time, that is to say the average time period required for the completion of anastomosis of the vessels, is usually 30 minutes. Taking this time as a basis, the organ recovers completely with optimal immediate function within 24 hours.

### Introduction of Renal Perfusion

Following successful laparotomy, the kidney is prepared by ligation of the capsular vessels. The perfusion catheter for selective kidney perfusion is fixed in the renal artery using a tourniquet. Perfusion is performed under hydrostatic pressure (maximum of 120 mm Hg). Within the first minute of perfusion, the renal vein is incised and clamped off adjacent to the vena cava. The escaping perfusate is removed from the abdominal cavity. After approximately 10 minutes of perfusion, the kidney is resected before transplantation.

Should the center decide to use the so-called aorto-single flush technique, the total amount of the preservation solution needed is perfused only via the aortal line. Once again, a pressurized infusion is not necessary. A Y-perfusion system is recommended in addition to perfusion tubing of the largest possible caliber and perfusion cannulae with an internal bore of at least Charrière 15 (5 mm).

### Transport of a Donor Organ

The transport of a donor organ to the recipient utilizes a sterile pouch accommodating the size of the kidney in an ice cold Custodiol solution. The organ must be completely

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covered by the solution. The pouch is sealed with adhesive tape and is placed into a second container which is also filled with Custodiol solution in order to prevent a breakdown of insulation and cooling by trapped air. The double-bagged organ is placed into a sterile plastic container and closed with a secure lid. The plastic bag is then placed into a transport container packed with ice for transport. Information about the donor, copies of the laboratory results and blood samples from the donor are also included. The transport of the donor organ in Custodiol solution must be accomplished as quickly as possible.

### Clinical Experience

A major multi-center prospective randomized clinical trial has been carried out in Europe comparing three perfusion and preservation solutions for use in kidney transplants<sup>1</sup>. The three solutions were the Custodiol HTK solution, the Belzer UW solution, and the Euro-Collins (EC) solution. Forty-seven centers participated and followed a strict protocol. Over a thousand kidneys were included in the study. In the HTK-UW study, there were 342 donors and 611 transplants (the UW group had 168 donors and 297 transplants, the HTK group had 174 donors and 314 transplants). In the HTK-EC study, there were 317 donors and 569 transplants (the EC group had 155 donors and 277 transplants, the HTK group had 162 donors and 292 transplants).

This study directly compared kidney survival in the HTK group with the UW group, and also with the EC solution, and showed that for kidney transplants, the HTK solution performs as well overall as the UW solution, and significantly better than EC solution for initial nonfunction. The average cold ischemia time in the HTK-UW study was 25.8 hours in the HTK group and 25.5 hours in the UW group. In the HTK-EC group, the average cold ischemia time was 24.1 hours in the HTK group and 24.2 hours in the EC group. The overall kidney survival rates from the 47-center study for HTK versus UW, and HTK versus EC, at four time points were:

	HTK	UW	HTK	EC
1 Month	91%	91%	85%	86%
12 Months	83%	82%	80%	74%
24 Months	77%	74%	76%	71%
36 Months	74%	68%	70%	67%

<sup>1</sup> de Boer J, De Meester J, Smits JMA, Doxiadis IIN, Groenewoud AF, Persijn GG (1999). Eurotransplant randomized multicenter study comparing kidney graft preservation with HTK, UW, and EC. *Transplantation* in press, publication about December 1999

clp

Delayed graft function that required two or more dialysis sessions during the first week was 20% (107/544) in the pooled HTK groups, 25% (66/266) for the UW group, and 32% (85/268) for the EC group. Initial nonfunction (INF) occurred in 33% of the kidneys in both HTK and UW groups, and in the other study, INF occurred in 29% of the HTK group and 43% of the EC group.

Kidney failure rates in the first 48 hours were comparable in all groups: UW-15/297 and HTK-18/314; EC-15/277 and HTK-13/272.

In the HTK-UW study, acute rejection episodes occurred in 99/314 (32%) in the HTK group and 105/297 (35%) in the UW group. In the HTK-EC study, acute rejection episodes occurred in 99/292 (34%) in the HTK group and 108/277 (39%) in the EC group.

### **How Supplied**

Bottles of 1000 ml

Canister of 5000 ml

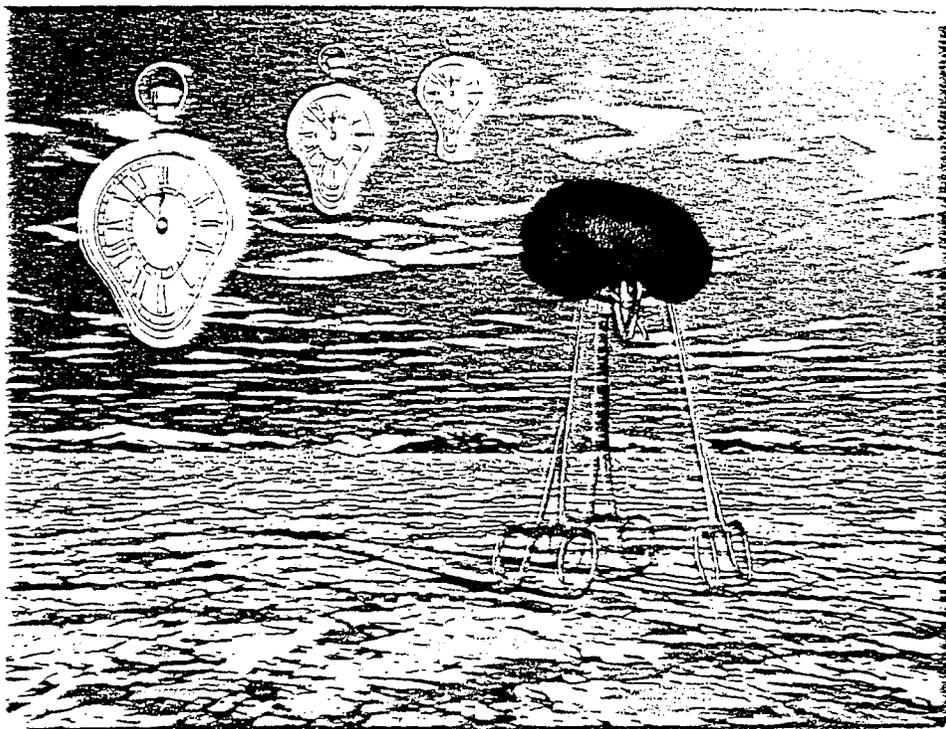
Store at +8 to +15° C and protect from light.

Dr. Franz Köhler Chemie GmbH  
P.O. Box 1117  
64659 Alsbach-Hähnlein  
Germany

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# CUSTODIOL<sup>®</sup>

*HTK Solution*



*THE EUROPEAN SOLUTION*

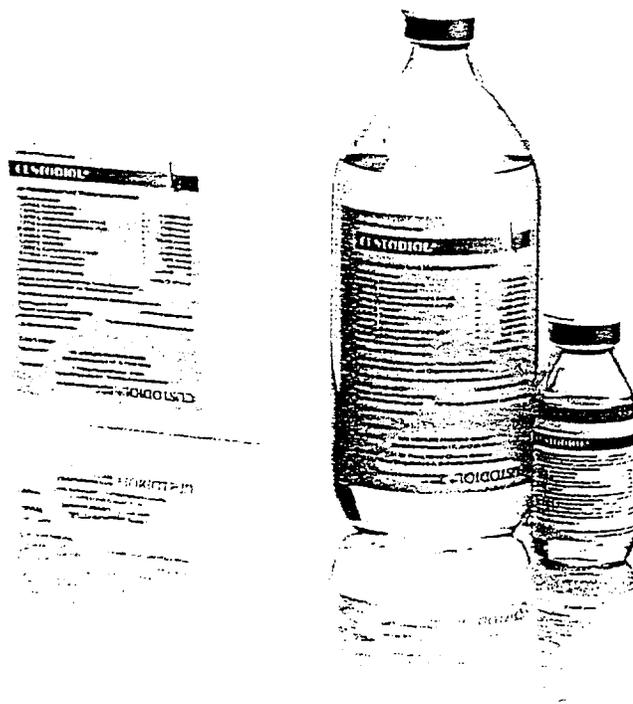
*FOR PROTECTION OF  
KIDNEYS FOR TRANSPLANT*



*CS*

# CUSTODIOL®

*Bretscheider's HTK solution for kidney preservation*



cep

## Pharmacology:

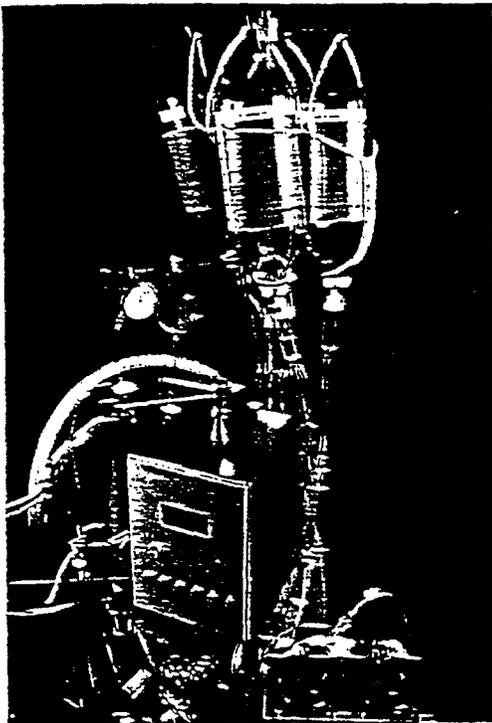
- *Organ protective* solution of intracellular type, based on an electrolyte mixture containing low sodium and potassium levels, as well as calcium at the low level found within the cell
- HTK solution produces its effects through inactivation of the cell function by virtue of extracellular sodium and calcium withdrawal, combined with intensive buffering of the extracellular space by means of histidine/histidine hydrochloride, leading to prolonged tolerance of the ischemic state
- Tryptophan is added to provide special membrane protection and enhances the buffering capacity. Alpha-ketoglutarate serves as a substrate for aerobic energy production
- The osmotic pressure is balanced by adding mannitol, counteracting cellular edema and scavenging or inhibiting active oxygen intermediates such as superoxide and free-hydroxyl radicals
- HTK is perfused as a cold solution, so that its hypothermic effect contributes to a decreased metabolic rate



## Pharmacodynamics:

1. General inhibition of all activation processes of muscular, nervous or incretory type in the stimuable membrane structures
2. Intensive buffering of the entire extracellular com-

# CUSTODIOL®



- partment, thus
3. Consequent postponement of critical intracellular acidosis.
  4. Prevention of the intracellular edema that may result from the breakdown of cellular osmoregulation.

## *Toxicology:*

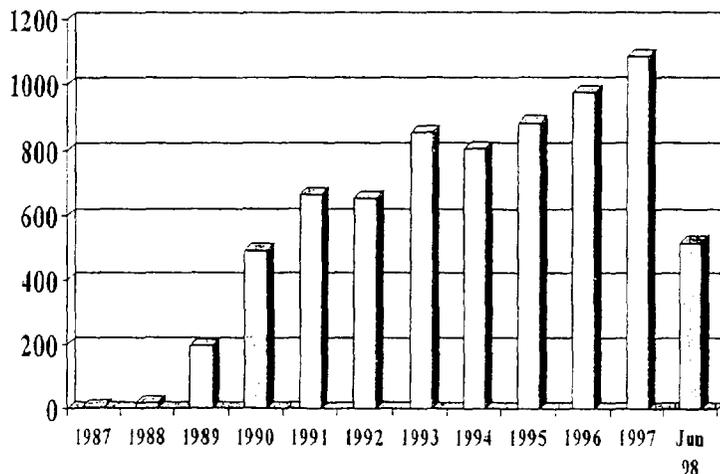
Because all the components of HTK solution are naturally occurring physiological substances except for the inert mannitol, no toxic effects have ever been observed

The calcium content of the solution is high enough to exclude any calcium paradox at low temperatures, but, on the other hand, is deliberately set too low to induce a calcium dependent stimulation of energy requirements with shortening of the ischemia time tolerated by the donor organ.

## *Therapeutic safety:*

HTK solution offers advantageous safety margins. . .

## KIDNEY Tx with HTK



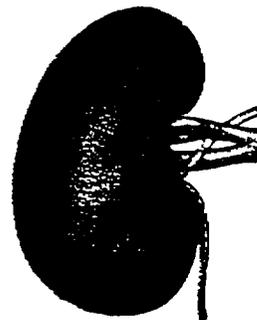
The very low viscosity allows rapid and complete equilibration.

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## CUSTODIOL<sup>®</sup>

- **Rapid graft function**

The Eurotransplant study of HTK, UW, and EC solutions showed that in kidneys functioning at 14 days, serum creatinine was cleared at a rate of 58 ml/min in the HTK groups, 49 ml/min in the UW group, and 38 ml/min in the EC group.



- **Low frequency of post-operative dialysis**

In the Eurotransplant study, the incidence of initial non-function, defined as lack of function requiring two or more dialysis sessions during the first week, was found to be equal for HTK and UW, but significantly greater in EC compared to HTK (29% versus 43%,  $p = 0.001$ ).

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# CUSTODIOL®

*Bretschneider's HTK solution for  
preservation of donor kidneys*

- In-situ and during hypothermic storage

## *Advantages:*

- Rapid homogenous cooling due to low viscosity
- Superior recovery of function
- Excellent ischemic tolerance
- High buffering capacity
- Virtual absence of side effects
- Simple perfusion technique
- Easier surgical handling due to excellent visibility

Distributed by:

Manufactured by:

Dr. F. Köhler Chemie GmbH



D-64665 Alsbach-Hähnlein · Neue Bergstraße 3 - 7  
Germany

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ORGANS AND TISSUES, (1), 19-22, 1999

## Non-heartbeating kidney donation, organisation and technical aspects

A.P. NEDERSTIGT, R.W.A. JACOBS, G. KOOTSTRA

Department of General Surgery, University Hospital of Maastricht, The Netherlands

**SUMMARY** - With regards to the growing shortage of donor organs, new donor sources must be considered. One of the most promising sources is the non-heartbeating (NHB) donor. In this article we explain the problems that can be expected, both technically and logistically, and how this category of donors can be successfully implemented. In our opinion adequate viability testing is a prerequisite for the safe use of NHB donors. If this is the case, the number of successfully transplanted kidneys may rise with figures up to 25%.

### BACKGROUND

Organ transplantation is generally accepted as the treatment of choice for end stage organ failure. Because of this wide acceptance, the demand for donor organs is increasing rapidly. The number of brain dead organ donors cannot keep up with this growing demand, resulting in longer waiting lists and higher mortality of patients on the waiting list. Especially the number of patients waiting for a donor kidney has been increasing very fast. Several proposals have been made to battle this organ shortage. A much discussed topic is the possibility of xenotransplantation. However, practical implementation of this form of transplantation seems to be some years away, so other strategies need to be devised. One of these strategies is the use of non-heartbeating (NHB) donors. These are donors who are declared dead after cardiac arrest, as opposed to brain dead organ donors where circulation remains intact until the moment of

organ perfusion. NHB donation is not new though, before the diagnosis of brain death was possible, the only way to declare death was after cardiac arrest. So explanation of organs for transplantation was only possible after the heart had stopped beating. In view of the expanding waiting lists and better preservation techniques, one can see a renewed interest in the concept of NHB organ donation.

### CATEGORIES

All NHB kidneys have one thing in common: the inevitability of sustaining a certain amount of ischemic damage. Of course this amount varies with the length of the warm ischemic time, the time between cardiac arrest and cooling. This amount also depends on the type of NHB donor. To clear things up, we have divided NHB donors into four "Maastricht" categories:

#### *Category 1 - Dead on arrival*

These are patients who are obviously already deceased when medical personnel arrives at the scene of the accident. No attempt will be made to resuscitate the patient, and normally he is brought straight to the mortuary. If the medical team is fast enough, and aware of the possibility of

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*Mailing address:* Arjen P. Nederstigt, Department of General Surgery, University Hospital of Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

NHB donation, these patients are potential kidney donors. The patient should then be brought to the emergency ward, where a preservation procedure can be started. Use of donors of this category demands a complete reroute of the normal logistic pathways, which may be troublesome at first. In our center NHB donors of this category form a strict minority.

#### *Category 2 – Unsuccessful resuscitation*

These are patients who suffer from cardiac arrest outside the hospital, and who are brought to the emergency ward for resuscitation. In some cases this will prove unsuccessful, and the resuscitation attempts will be stopped, regardless if organ donation is going to take place or not. If the family is present they can be asked to give consent for kidney donation, if so, the procedure can be started. With these donors we keep to a strict, ten-minute period of no-touch before starting any invasive procedures on the deceased. This is to make sure the donor is really deceased before the procedure is started<sup>1</sup>. The category 2 donors form the main part of our NHB donor procedures.

#### *Category 3 – Awaiting cardiac arrest*

These are patients who suffered a major cerebral bleeding or trauma, but who are not brain dead according to the accepted criteria. Therefore they cannot be used as multi-organ donors. However, in most of these cases the treating physician will decide to withdraw all treatment because of the bad prognosis. Shortly after the withdrawal of ventilation and medication the cardiac arrest will occur. If the family gives consent for a NHB procedure the catheter can be inserted after 10 minutes of no-touch. In this way the kidneys can be preserved for transplantation.

#### *Category 4 – Cardiac arrest while brain dead*

In these cases the patient is proven brain dead by the normal tests, but an irreversible cardiac arrest occurs before the explantation can take place. When resuscitation is fruitless, the only option left is commencing a NHB procedure. Please take note that in these cases there is no need for a 10-minute period of no-touch, and the procedure can be started immediately, if necessary, even in the Intensive Care Unit.

#### CRITERIA

For NHB donors almost the same criteria as for brain dead multi-organ donors are applicable. This means that there are the following contra-indications:

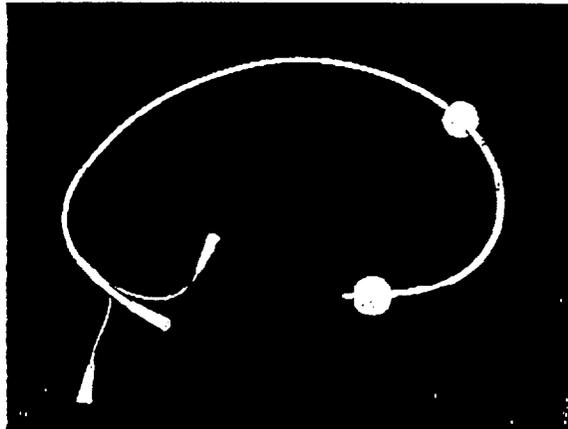


FIGURE 1 - A picture of DBTL-catheter, with the inflated balloons clearly visible.

- no signs of sepsis;
  - no known infection or risk group for HIV or hepatitis B;
  - no malignancies, except for some CNS tumours and basal cell carcinoma;
  - no history of malignant hypertension or kidney diseases.
- We accept only NHB donors not older than 65 years. Furthermore the period of circulatory arrest may be no longer than 45 minutes, without the period of reanimation. If a potential donor meets all these criteria and the family gives consent, the In Situ Preservation (ISP) procedure can be started.

#### ISP-PROCEDURE

It is very important to start the cooling of the kidneys as soon as possible after circulatory arrest, because the chance of Primary Non-Function (PNF) of the kidney will increase with a longer warm ischemic time. Therefore, we use a fast and simple method to preserve the kidneys, namely the Double Balloon Triple Lumen (DBTL) catheter (Porgès France, AJ 6516, Fig. 1). This catheter has two inflatable balloons with the purpose of isolating a length of abdominal aorta, including both renal arteries. The catheter in-between these two balloons has lots of openings through which the preservation fluid can pour into the renal arteries, thus almost selectively perfusing the kidneys. The procedure for introducing this catheter is as follows.

Both groin regions of the donor are shaved, disinfected and covered with sterile drapes. After that an incision is made in the region above the femoral artery and vein, and both vessels are isolated and cleared. An arteriotomy is performed of the femoral artery, and the catheter is in-

serted proximally into the bloodvessel, up to the red marker on the DBTL-catheter (this is approximately 60 cm). The distal balloon is then filled with 7 ml of a mixture of sterile water and x-ray contrastfluid, and then pulled back until it hooks on the bifurcation of the aorta. The balloon is then fully filled with an extra 5 ml of the mixture. The proximal balloon is now also filled with 12 ml of fluid and the perfusion is started through the middle lumen of the catheter. For preservation we make use of a Hystidin-tryptophan-keroglutarate (HTK) solution of 4° Celsius. After starting the perfusion a phlebectomy of the femoral vein is performed, and a Charrière 20 urine catheter system is inserted and fixated on the skin to secure a good outflow from the renal veins. To check the position of the catheter a high abdominal x-ray is made, on which the balloons of the DBTL catheter will be clearly visible because of the contrastfluid used. A large volume of HTK is needed to properly flush out the kidneys, approximately 15-20 litres. Reason for this is the fact that the superior mesenteric artery is flushed as well, thereby effectively flushing a part of the intestines. Perfusion is done with the aid of a pump, the first 5-7 litres are infused with a speed of 400 ml/min, then the speed is reduced to appr. 100 ml/min. One can check the temperature of the skin around the kidney region of the donor. If the skin is cold, then the kidneys are most probably flushed properly; the Kootstra sign is then called positive. After perfusion the kidneys are taken out as normal, under sterile conditions in the operating room.

### PRESERVATION

All NHB kidneys have sustained a certain amount of ischemic damage. This can be clearly seen from the high percentage of delayed function after transplantation (defined as the need for one or more dialysis sessions) when compared to kidneys with a first short warm ischemic period. This might pose some problems for the transplant physician because it can mask a period of acute rejection. However, these kidneys will eventually start functioning and keep the recipient off dialysis for some years. A bigger problem is the occurrence of PNF, this is an event that must be prevented at all costs. In order to prevent PNF, one must recognise the kidneys which are damaged beyond repair before transplantation. Different studies have proven the superiority of machine perfusion (MP) over cold storage (CS) when it comes to storing ischemically damaged kidneys until transplantation<sup>15</sup>. This is one of the reasons why we only use MP for NHB kidneys. The second reason for using MP is that it gives you the possibility of performing viability tests on the kidney while it is stored. With these viability tests you get an indication

of the amount of ischemic damage sustained. The kidneys are put on a perfusion machine (PF 200, Gambro, Lund, Sweden) in the operating theatre, and from thereon an eight hour testing program is started. During this program the flow, the intrarenal resistance and the temperature are constantly monitored. After 1, 2, 4, 6 and 8 hours samples are taken from the perfusate. In these samples we measure pH, LDH, alpha-Glutathione S-transferase (alpha-GST) and total GST. Especially the alpha-GST is a promising test. Alpha-GST is an enzyme restricted to the proximal tubuluscels in the kidney. These are cells with a very high aerobic metabolism, and therefore very susceptible to ischemic damage. When these cells die, the alpha-GST is released into the perfusate. There is a very good correlation between first warm ischemic time and alpha-GST in the perfusate<sup>6</sup>.

In a retrospective study alpha-GST appeared to be the only parameter significantly different for functioning and non-functioning kidneys<sup>7</sup>. The problem with alpha-GST is that it is measured by means of an ELISA immuno-assay, which is very cost- and time-intensive.

Alpha-GST comes from a group of iso-enzymes, which together form the total GST. The other iso-enzymes are  $\pi$ -GST,  $\mu$ -GST and  $\sigma$ -GST. Because total GST can be measured much cheaper and quicker, we performed a study to find the correlation between alpha-GST and total GST. In a retrospective study the Pearson correlation between alpha- and total GST in the machine perfusate, 6 hours after MP, was 0,943 (unpublished data). Therefore total-GST has now replaced alpha-GST as the viability test of choice.

### RESULTS

With the aid of MP and viability testing we have been able to bring the percentage of kidneys which show PNF down to 7-8%. In the past it has been shown that the long term function of NHB kidneys does not differ from HB kidneys<sup>8</sup>. The percentage delayed function was higher in the NHB group, however this difference was no longer there after three months. As a direct result of our NHB program, we are able to procure an extra 20-40% more kidneys each year<sup>9</sup>.

### CONCLUSIONS

With the aid of machine preservation and proper viability testing, NHB kidneys are a very valuable source of donor organs in a time of scarcity, which may not be left unused. So far, the use of NHB kidneys seems to be the only effective way to fight the organ shortage<sup>10</sup>.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

Form Approved: OMB No. 0910-0396  
Expiration Date: 3/31/02

**CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

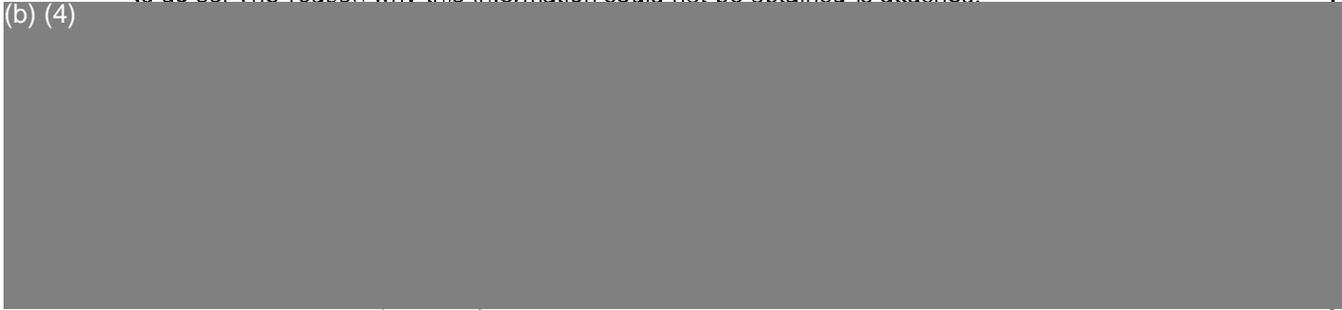
- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

(b) (4)



**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

SEP 23 1999

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Dr. Franz Kohler Chemie GmbH  
c/o T. Whit Athey, Ph.D.  
Senior Consultant  
C. L. McIntosh & Associates, Inc.  
12300 Twinbrook Parkway, Suite 625  
Rockville, Maryland 20852

Re: K992209

Trade Name: Custodiol® HTK Solution for hypothermic flushing, transport and storage of kidneys for transplantation

Dated: June 29, 1999

Received: June 30, 1999

Dear Dr. Athey:

We have reviewed your Section 510(k) notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate device based solely on the information you provided. To complete the review of your submission, we require the following information:

(b) (4)



81

Page 2 – T. Whit Athey, Ph.D.

(b) (4)



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Page 3 – T. Whit Athey, Ph.D.

(b) (4)



We believe that this information is necessary for us to determine whether or not this device is substantially equivalent to a legally marketed predicate device with regard to its safety and effectiveness.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (Act). You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence.

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Page 4 – T. Whit Athey, Ph.D.

Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

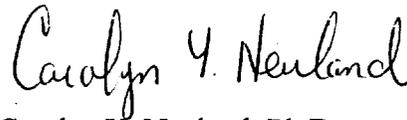
If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Document Mail Center (HFZ-401)  
9200 Corporate Boulevard  
Rockville, Maryland 20850

If you have any questions concerning the contents of this letter, please contact Miriam C. Provost, Ph.D. at (301) 594-1220. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or at (301) 443-6597, or at its Internet address "<http://www.fda.gov/cdrh/dsmamain.html>".

Sincerely yours,



Carolyn Y. Neuland, Ph.D.  
Chief, Gastroenterology and Renal  
Devices Branch  
Division of Reproductive, Abdominal,  
Ear, Nose and Throat, and  
Radiological Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

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**SEP 23 1999**

Dr. Franz Kohler Chemie GmbH  
c/o T. Whit Athey, Ph.D.  
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Page 2 – T. Whit Athey, Ph.D.

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Page 3 – T. Whit Athey, Ph.D.

(b) (4)



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Radiological Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Page 5 - T. Whit Athey, Ph.D.

cc: HFZ-401  
HFZ-404  
HFZ-470  
D.O.

MXP:mxs:09.23.99

FILE

AGUY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
Z-470	Provost	9/23/99						
AFZ470	Newland	9/23/99						

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food And Drug Administration

Memorandum

From: Reviewer(s) - Name(s) MIRIAM C. PROVOST, PH.D.

Subject: 510(k) Number L 992209

To: The Record - It is my recommendation that the subject 510(k) Notification:

- Refused to accept.
- Requires additional information (other than refuse to accept).
- Accepted for review 7-16-99.
- Is substantially equivalent to marketed devices.
- NOT substantially equivalent to marketed devices.

De Novo Classification Candidate?  YES  NO

Other (e.g., exempt by regulation, not a device, duplicate, etc.)

- Is this device subject to Postmarket Surveillance?  YES  NO
- Is this device subject to the Tracking Regulation?  YES  NO
- Was clinical data necessary to support the review of this 510(k)?  YES  NO
- Is this a prescription device?  YES  NO
- Was this 510(k) reviewed by a Third Party?  YES  NO
- Special 510(k)?  YES  NO
- Abbreviated 510(k)? Please fill out form on H Drive  YES  NO

This 510(k) contains:

Truthful and Accurate Statement  Requested  Enclosed  
(required for originals received 3-14-95 and after)

A 510(k) summary OR  A 510(k) statement

The required certification and summary for class III devices

The indication for use form (required for originals received 1-1-96 and after)

Material of Biological Origin  YES  NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

- No Confidentiality
- Confidentiality for 90 days
- Continued Confidentiality exceeding 90 days

Predicate Product Code with class:

Additional Product Code(s) with panel (optional):

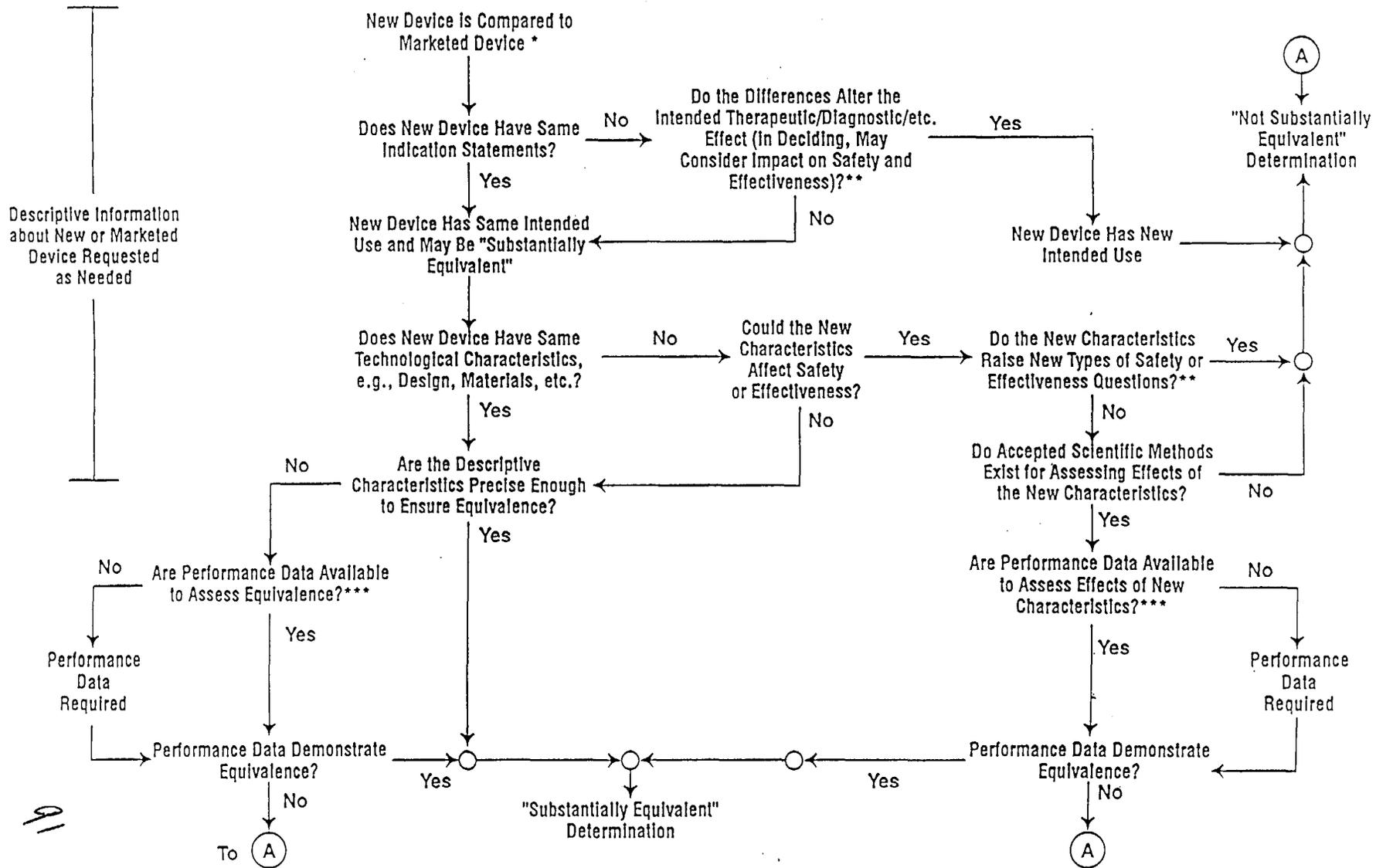
78 KDL 876.5880 Class II

Reviewed by: Carolyn Y Newland GRDB 9/23/99  
(Branch Chief) (Branch Code) (Date)

Final Review: \_\_\_\_\_  
(Division Director) (Date)

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## 510(k) "Substantial Equivalence" Decision-Making Process (Detailed)



\* 510(k) Applications Compare New Devices to Marketed Devices. FDA Requests Additional Information if the Relationship Between Marketed and "Predicate" (Pre-Amendments or Reclassified Post-Amendments) Devices is Unclear.

\*\* This Determination is Limited.

Normally Based on Descriptive Information Alone, But Additional Information is Sometimes Required.

\*\*\* Data May be from the 510(k), Other 510(k)s, The Center's Classification Files, or the Literature.



<b>USE OF MODIFIED DEVICE AS DESCRIBED IN ITS LABELING HAVE NOT CHANGED*</b>				
c) <b>STATEMENT - FUNDAMENTAL SCIENTIFIC TECHNOLOGY OF THE MODIFIED DEVICE HAS NOT CHANGED*</b>			* If no - STOP not a special	
d) Design Control Activities Summary				
i) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis				
ii) Based on the Risk Analysis, an identification of the verification and/or validation activities required, including methods or tests used and acceptance criteria to be applied				
iii) A declaration of conformity with design controls. The declaration of conformity should include:				
1) A statement signed by the individual responsible, that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met				
2) A statement signed by the individual responsible, that manufacturing facility is in conformance with design control procedure Requirements as specified in 21 CFR 820.30 and the records are available for review.				

	SPECIALS		ABBREVIATED		TRADITIONAL		✓ IF ITEM IS NEEDED AND IS MISSING
	YES	NO	YES	NO	YES	NO	
<b>4. ABBREVIATED 510(K): SPECIAL CONTROLS/CONFORMANCE TO RECOGNIZED STANDARDS - PLEASE FILL OUT THE STANDARDS ABBREVIATED FORM ON THE H DRIVE</b>							
a) For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type							
b) If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.							
c) For a submission, which relies on a recognized standard, a declaration of conformity to the standard. The declaration should include the following:							
i) An identification of the applicable recognized consensus standards that were met							
ii) A specification, for each consensus standard, that all requirements were met, except for							

inapplicable requirements or deviations noted below			
iii) An identification, for each consensus standard, of any way(s) in which the standard may have been adapted for application to the device under review, e.g., an identification of an alternative series of tests that were performed			
iv) An identification, for each consensus standard, of any requirements that were not applicable to the device			
v) A specification of any deviations from each applicable standard that were applied			
vi) A specification of the differences that may exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference			
vii) Name/address of test laboratory/certification body involved in determining the conformance of the device with applicable consensus standards and a reference to any accreditations for those organizations			
d) Data/information to address issues not covered by guidance documents, special controls, and/or recognized standards			

5. Additional Considerations: (may be covered by Design Controls)							
					y	N	Needed
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:							
i) component & material					✓		
ii) identify patient-contacting materials					✓		
iii) biocompatibility of final sterilized product					✓		
b) Sterilization and expiration dating information:							
i) sterilization method					✓		
ii) SAL					✓		
iii) packaging					✓		
iv) specify pyrogen free					✓		
v) ETO residues						✓	N
vi) radiation dose						✓	N
c) Software validation & verification:							
i) hazard analysis						✓	N
ii) level of concern						✓	N
iii) development documentation						✓	N
iv) certification						✓	N

Items shaded under "NO" are necessary for that type of submission. Circled items and items with checks in the "Needed & Missing" column must be submitted before acceptance of the document.

Passed Screening  Yes  No  
 Date: 7-16-99

Reviewer: Miriam Provost  
 Concurrence by Review Branch: Carilyn Newland

REVISED:3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K \_\_\_\_\_

Reviewer: \_\_\_\_\_

Division/Branch: \_\_\_\_\_

Device Name: \_\_\_\_\_

Product To Which Compared (510(K) Number If Known): \_\_\_\_\_

YES NO

	YES	NO	
1. Is Product A Device			If NO = Stop
2. Is Device Subject To 510(k)?			If NO = Stop
3. Same Indication Statement?			If YES = Go To 5
4. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NE
5. Same Technological Characteristics?			If YES = Go To 7
6. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 8
7. Descriptive Characteristics Precise Enough?			If NO = Go To 10 If YES = Stop SE
8. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NE
9. Accepted Scientific Methods Exist?			If NO = Stop NE
10. Performance Data Available?			If NO = Request Data
11. Data Demonstrate Equivalence?			Final Decision:

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

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1. Intended Use:
2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device for home use or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device:
2. Explain why not subject to 510(k):
3. How does the new indication differ from the predicate device's indication:
4. Explain why there is or is not a new effect or safety or effectiveness issue:
5. Describe the new technological characteristics:
6. Explain how new characteristics could or could not affect safety or effectiveness:
7. Explain how descriptive characteristics are not precise enough:
8. Explain new types of safety or effectiveness questions raised or why the questions are not new:
9. Explain why existing scientific methods can not be used:
10. Explain what performance data is needed:
11. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

ATTACH ADDITIONAL SUPPORTING INFORMATION

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**Internal Administrative Form** K992209

	YES	NO
1. Did the firm request expedited review?		✓
2. Did we grant expedited review?		
3. Have you verified that the Document is labeled Class III for GMP purposes?		NA
4. If, not, has POS been notified?		
5. Is the product a device?	✓	
6. Is the device exempt from 510(k) by regulation or policy?		✓
7. Is the device subject to review by CDRH?	✓	
8. Are you aware that this device has been the subject of a previous NSE decision?		✓
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.		
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		

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**M E M O R A N D U M**

**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND  
RADIOLOGICAL HEALTH  
OFFICE OF DEVICE EVALUATION**

**DATE:** September 16, 1999

**FROM:** Miriam C. Provost, Ph.D., Chemical Engineer  
Gastroenterology and Renal Devices Branch

**SUBJECT:** K992209, Custodiol HTK® solution for flushing and cold storage of donor kidneys

**TO:** The Record

The following is review of a 510(k) submission for the above device. This is my first review of this submission, although a 510(k) was previously submitted for the same device (K983103), but the previous submission included indications for preservation of hearts, livers, pancreatic islet cells and venous grafts. A "Cannot Respond" letter for the previous submission was issued on April 29, 1999. The sponsor has indicated that the current submission addresses all of the deficiencies raised in the previous letter. As noted below, the solution is now limited to preservation of donor kidneys, only.

**Intended Use**

Custodiol HTK solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient. *Note: the word "perfusion" should be deleted, since the product is to be used for flushing and not continuous machine perfusion.*

**Device(s) to which equivalence is claimed:**

ViaSpan cold storage solution (K883782)

**Description of Device**

The device is a sterile solution for use in flushing, storing and transporting donor kidneys intended for transplantation. The predicate device (ViaSpan®) is also a cold storage solution, and is intended to be used to preserve kidneys, livers and pancreata.

The following table shows a comparison between the chemical composition of Custodiol HTK and ViaSpan.

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Additive type	Custodiol HTK Solution	ViaSpan
Impermeant	—————	Pentafraction (hydroxyethyl starch) 50 g/L
Impermeant	—————	Lactobionic acid 35.83 g/L
Electrolyte	Histidine 27.9289 g/L Histidine-HCl H <sub>2</sub> O 3.7733 g/L	Potassium phosphate monobasic 3.4 g/L
Electrolyte	Magnesium chloride Hexahydrate 0.8132 g/L	Magnesium sulfate heptahydrate 1.23 g/L
Impermeant	Mannitol 5.4651 g/L	Raffinose pentahydrate 17.83 g/L
Electrolyte	Potassium chloride 0.671 g/L	Potassium hydroxide 5.61 g/L
Electrolyte	Calcium chloride 0.22 g/L Sodium chloride 0.8766 g/L	—————
Metabolic substrate	Potassium hydrogen 2- ketoglutarate 0.1842 g/L	Adenosine 1.34 g/L
Antioxidant	—————	Allopurinol 0.136 g/L
Antioxidant	Tryptophan 0.4085 g/L	Total glutathione 0.922 g/L
pH	Potassium hydroxide (adjust pH to 7.02 to 7.2)	Sodium hydroxide (adjust to pH 7.4)
	Water for Injection	Water for injection
Osmolality	310 mOsm	320 mOsm

The sponsor has not explained the specific mechanism of action for each component of their solution. A review of the previous submission for this product was provided by Dr. Brian Harvey, medical officer for GRDB. In his review, dated November 16, 1998, Dr. Harvey discusses the theoretical rationale for the inclusion of many of these

components. For example, Dr. Harvey stated that histidine “makes a good choice for a physiologic buffer.” He believes that it makes theoretical sense to include ketoglutarate and tryptophan, since “both compounds play a role in cellular metabolism and amino acid biosynthesis which could aid in prolonging cell viability in the organ to be transplanted.” Dr. Harvey also stated that the presence of a lower concentration of potassium (than in the predicate device) makes clinical and biochemical sense since it will minimize the danger to recipient if any solution is left in the organ vasculature at the time of transplantation. The small amount of calcium has “the potential to aid in increasing membrane stability and participate in ion channel gated functions.” According to Dr. Harvey, the choice of mannitol over lactobionate/raffinose probably makes little physiological difference. However, Dr. Harvey does believe that the effect (if any) of the difference in osmolality between the proposed and the predicate device should be demonstrated with *in vitro* and/or *in vivo* data.

### **Biocompatibility**

The sponsor has provided some information on the purity of the solution components. The histidine, sodium chloride, magnesium chloride hexahydrate, potassium chloride, mannitol, and tryptophan are all specified as USP grade. The histidine hydrochloride monohydrate, potassium hydroxide and calcium chloride dihydrate appear to be EP or European Pharmacopeia grade. The purity of the ketoglutaric acid (also called 2-oxoglutaric acid) is listed as “in-house, not compendial” and the sponsor has explained that a USP or EP specification for this chemical does not exist. The company specifications were provided and compared to other amino acids that do have USP specifications (i.e., glycine and histidine). The specifications for 2-ketoglutaric acid appear to be similar to the USP specifications for the other amino acids, especially with regard to impurities such as heavy metals or iron. For the components that follow EP specifications (i.e., histidine hydrochloride monohydrate, calcium chloride dihydrate and 2 N potassium hydroxide) a comparison was given between the EP and USP specifications for these chemicals. In all cases, the EP specifications are similar and should be adequate for this intended use.

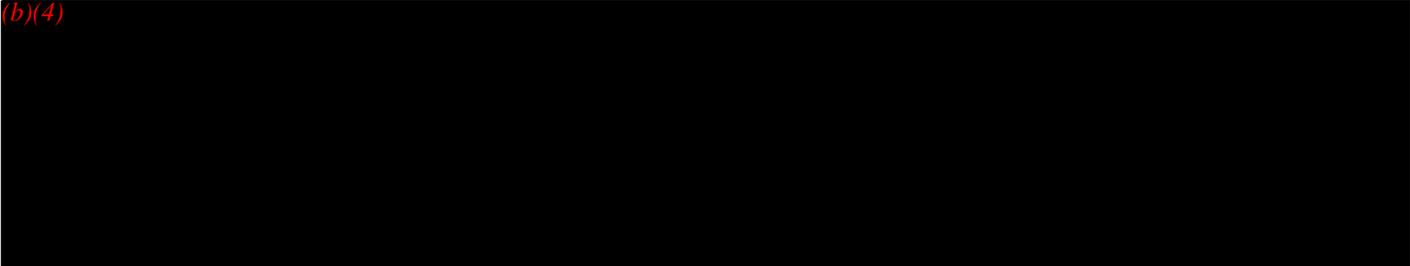
The solution is packaged in either 1 L infusion bottles of type II hydrolytic glass or 5 L polypropylene containers. The polypropylene was identified as “Vestolen P 6500.” This material apparently complies with “EP V1.1.2.2.3, Polypropylene for containers for filling with parenteral preparations.” *The sponsor has stated that this standard is equivalent to USP XXIII, however, a copy of the standard should be provided and a comparison with the USP standard should be given.*

The bottles are sealed with an “elastomer stopper” (described as bromobutyl with aluminum silicate filler) with an aluminum cap overseal. The sponsor has indicated that the stopper meets the requirements of ISO 8871/A1, “Elastomeric parts for aqueous parenteral preparations.” This standard includes tests for pyrogenicity,

hemolysis and compatibility. Since this material is apparently acceptable for use in packaging parenteral solutions, it should not leach any chemical contaminants and should be acceptable for this use.

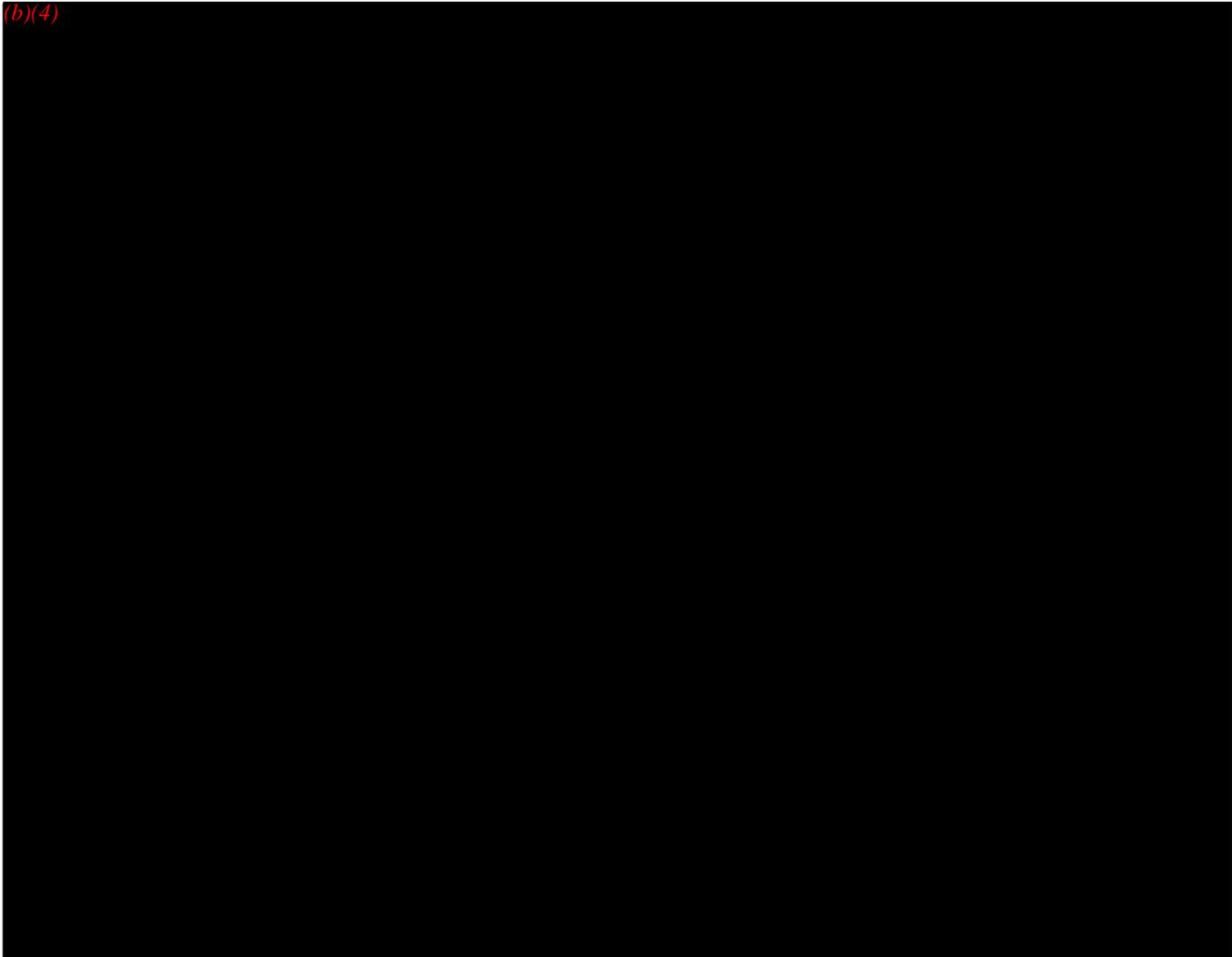
### **Sterilization**

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A large black rectangular redaction box covering the entire content of the 'Sterilization' section.

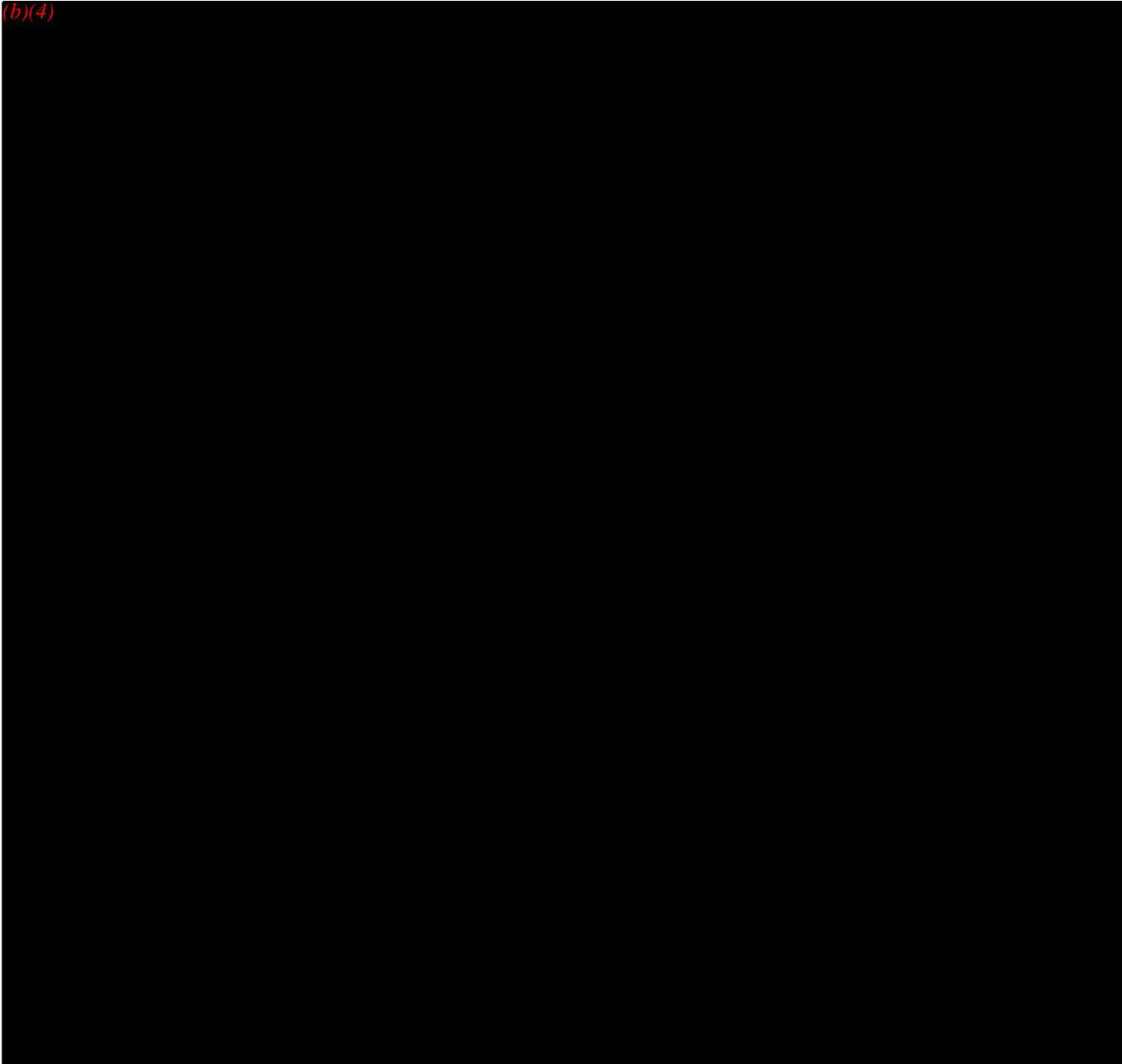
### **Laboratory Testing**

(b)(4)

A large black rectangular redaction box covering the entire content of the 'Laboratory Testing' section.

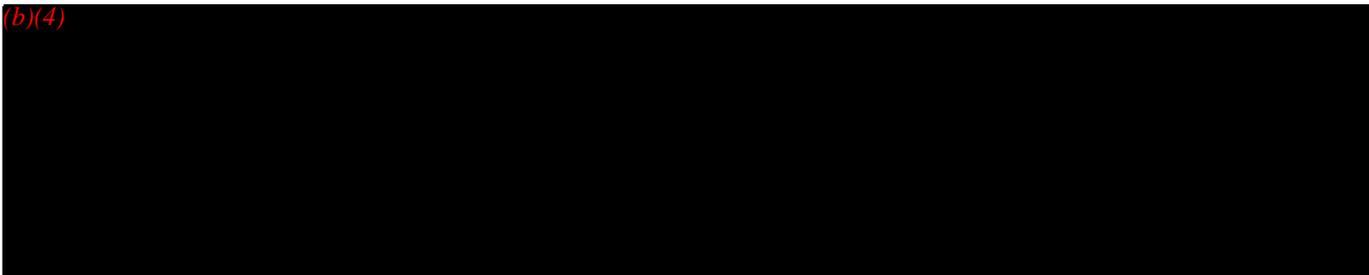
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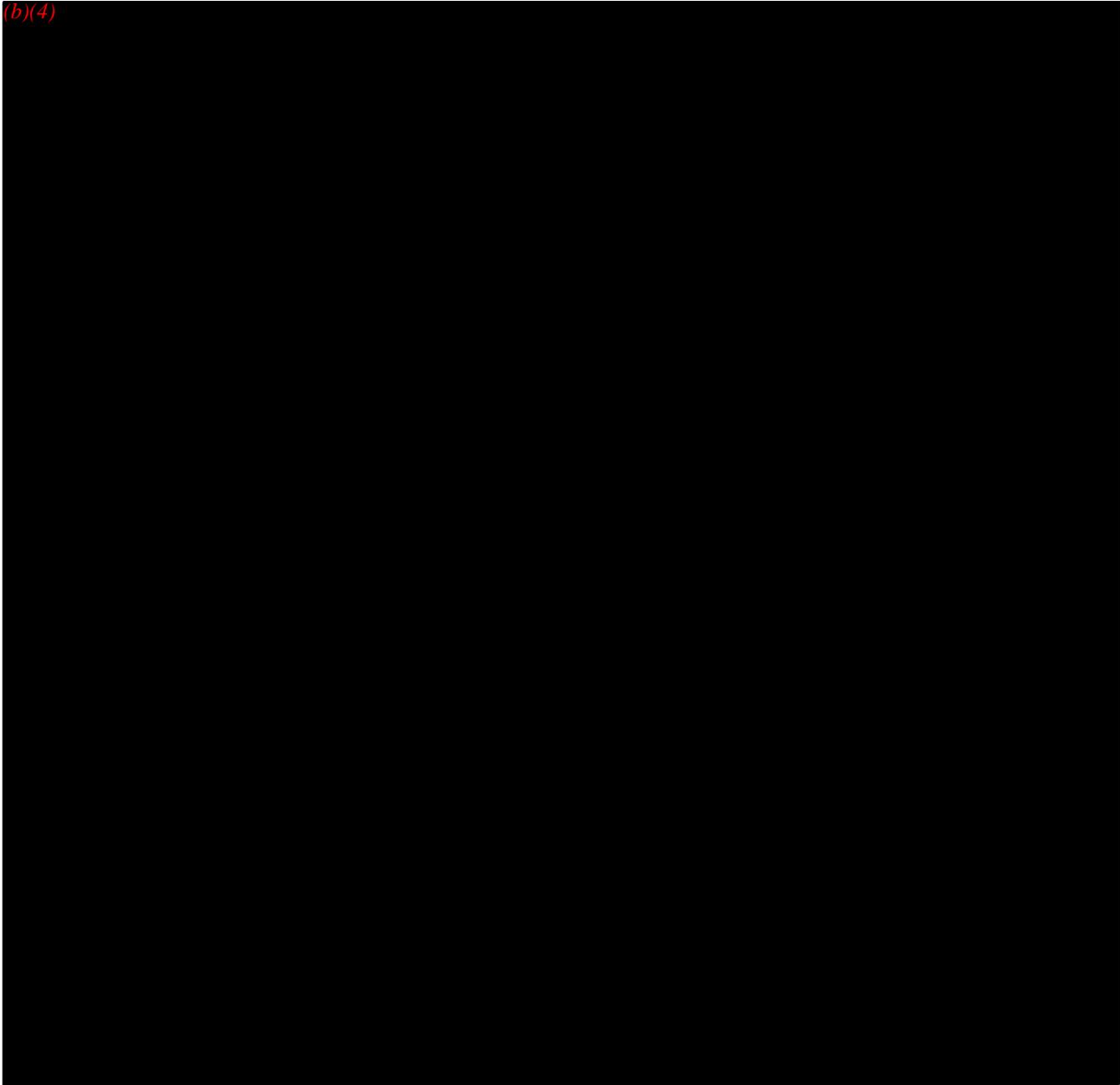
### Clinical Testing

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## Labeling

A copy of the instructions for use (package insert) and promotional labeling have been provided. The indication in the package insert agrees with that submitted in the indications for use form. However, the indication on the package label states: "Solution for perfusion in connection with kidney transplantation." *The sponsor is not seeking clearance for his product to be used for perfusion of kidneys, rather for flushing, transport and cold storage. As previously noted in my review, this should be changed. Also, the indication in the package label should match the indication in the instructions for use (package insert).*

Under "Special Precautions" it states, "Custodiol® is not indicated for intravenous or intraarterial administration. It is indicated only for selective perfusion of the kidney as for cooling of the surface areas, i.e., for the preservation of the donor organ during the transport from donor to recipient." It also states "The product must be used before the expiration date on the package", and "The product must be stored according to the recommendations prior to use." The storage conditions are given as 8 to 15 °C, however, under "Physical properties" it gives the pH as 7.02 to 7.20 at 25 °C. *The sponsor should justify why they have listed the physical properties at 25 °C (room temperature) when the product is to be stored at cool temperatures and used at cold temperatures.* Under a section called "Tolerance of ischemia by the kidney", it states "...by means of HTK protection of the kidney, the normo-thermal period of ischemia tolerance can be prolonged by a factor of 2 to 3." *The sponsor should provide an explanation of this claim and should submit data to support the ability of Custodiol HTK solution to permit prolonged ischemia times.* A brief summary of the clinical data was provided. *However, this summary does not provide sufficient details of the study, i.e., the number of patients enrolled, the number of investigational sites, the adverse events, average ischemia time, etc. In addition, it only lists the endpoints of 1, 12, 24 and 36 month survival. Results of other endpoints, such as delayed graft function, should also be provided. In general, the labeling should be written in the format recommended by the CDRH labeling guidance, i.e., the labeling should list (in order): Device description, intended use/indications, contraindications, warnings, precautions, adverse events, clinical studies, how supplied, directions for use. The proposed labeling does not include many of these sections.*

The sponsor has also provided a copy of an advertising brochure for their product. The brochure appears to include claims that are not supported by data in this submission, and also refers to indications that are not included in this submission. Specifically, the following issues have been identified:

- The cover of the promotional brochure includes a picture of a donor heart. This solution is not indicated for preservation of hearts, therefore, this picture should be

deleted.

- The third page of the brochure includes a graph showing the number of units of Custodiol sold over the years 1981 to 1996, and it states "Utilized in more than 300,000 surgical procedures." This figures should be removed or modified, since the sponsor indicated that the solution has been used for only 7,153 kidney transplantation surgeries.
- On the fourth page of the brochure, the following claims are listed:

Rapid graft function  
Prolongation of ischemic tolerance  
Lower frequency of post-operative dialysis  
Shortened hospitalization  
Good structural protection even at 25 °C

Data should be submitted to support all of these claims.

- On the 5<sup>th</sup> page of the brochure, under "References" most of the listings have been scratched out by hand. However, one of the references appears to indicate that Custodiol solution can be used to retrieve kidneys from non-heart beating donors. Since the sponsor is not seeking a claim for this intended use, this reference should be eliminated.
- On the 6<sup>th</sup> page of the brochure, the following claims are listed which require additional supporting data:

Superior recovery of function  
Excellent ischemic tolerance  
Virtual absence of side effects  
Reduced risk of postaggression syndrome  
Shortened postoperative intensive care period

### **Administrative**

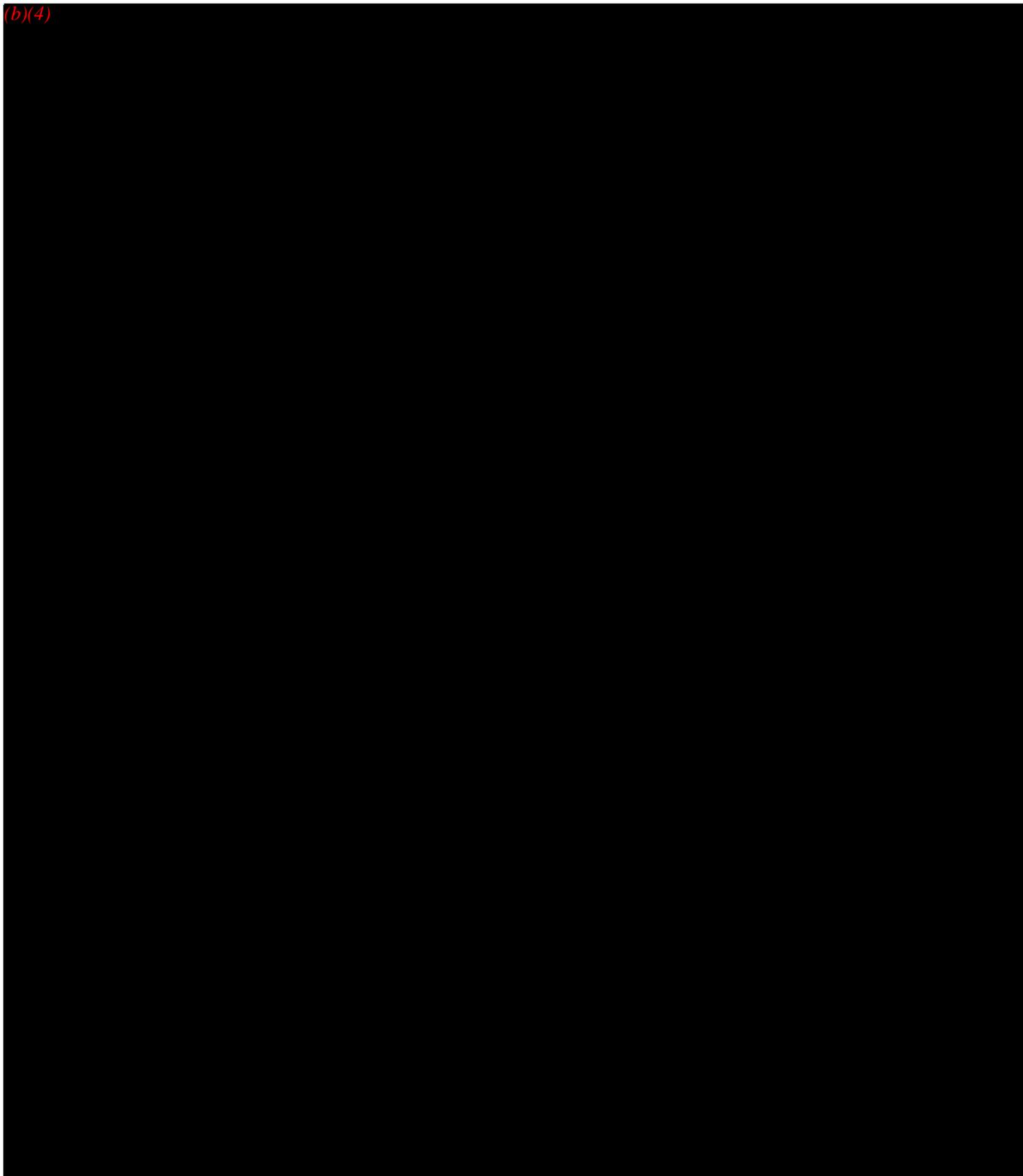
The sponsor has submitted a "Truthful and Accurate" form, the "Indications for Use" form and a 510(k) summary.

### **Recommendation**

There are a number of deficiencies that must be addressed before a finding of substantial equivalence can be made. I recommend that we place the submission on

hold and that the sponsor be asked to address the following deficiencies:

(b)(4)



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(b) (4)



107

(b) (4)



Miriam C. Provost

Miriam C. Provost, Ph.D.

9/17/99

Date

Concur

Carolyn Y. Neuland

Carolyn Y. Neuland, Ph.D.

Chief, Gastroenterology and Renal Devices Branch

9/23/99

Date

**Office of Device Evaluation**

**From:** Brian E. Harvey, M.D., Ph.D.  
Medical Officer  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

**To:** Miriam C. Provost, Ph.D.  
Primary Reviewer  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

**Through:** Carolyn Y. Neuland, Ph.D.  
Branch Chief  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

**Subject:** K983103  
Custodiol® HTK solution  
Dr. F. Kohler Chemie GmbH, Germany

**Date:** October 21, 1998 (Draft)  
November 16, 1998 (Final)

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**New Submission**

This clinical evaluation is for a review of a new submissions for the 510(k) identification number K983103, the Custodiol® HTK solution, by Dr. F. Kohler Chemie GmbH, Germany, under 21 CFR § 876.5880 (procode: KDL). The sponsor described their product as a “preservation/protective and storage medium for organs for transplant. The product is presently registered for use for this intended use in Europe, Latin American, and throughout the rest of the world...” (sponsor’s submission, p. 1). The sponsor added that the “HTK” in the name “refers to three of its constituents, histidine, tryptophan[e], and ketoglutarate” (sponsor’s submission, p. 6).

The sponsor stated that the “Custodiol HTK Solution is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866” (sponsor’s submission, pp. 1, 3).

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The sponsor has provided the following proposed Indications for User statement:

“Custodiol HTK solution is indicated for perfusion and flushing donor organs, including heart, kidney, liver and pancreas, prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient. Custodiol HTK Solution is also indicated for preservation of the pancreas until islet cells may be separated” (sponsor’s submission, p. 43B).

### **Background**

The sponsor has provided the following information on the scientific basis for the composition of their organ preservation/protective/storage medium: “The HTK solution is based upon the principle of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intensive buffering of the extracellular space by means of histidine/histidine HCL, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen supply. Only a small portion of the osmolality of the HTK solution is due to the sodium and potassium. The composition of HTK is similar to that of extracellular fluid. All of the components of the HTK solution occur naturally in the body. The HTK solution is relatively low in potassium concentration so that residual solution in the transplanted organ poses no danger to the recipient. This particularly important in organs that take up relatively large amounts of the perfusate, which may find its way into the recipient’s circulation. The HTK solution has a low viscosity, even at low temperatures. This characteristic assures rapid flow rates during initial perfusion, allowing the organ to be quickly cooled” (sponsor’s submission, p. 1).

### **Data & Analysis**

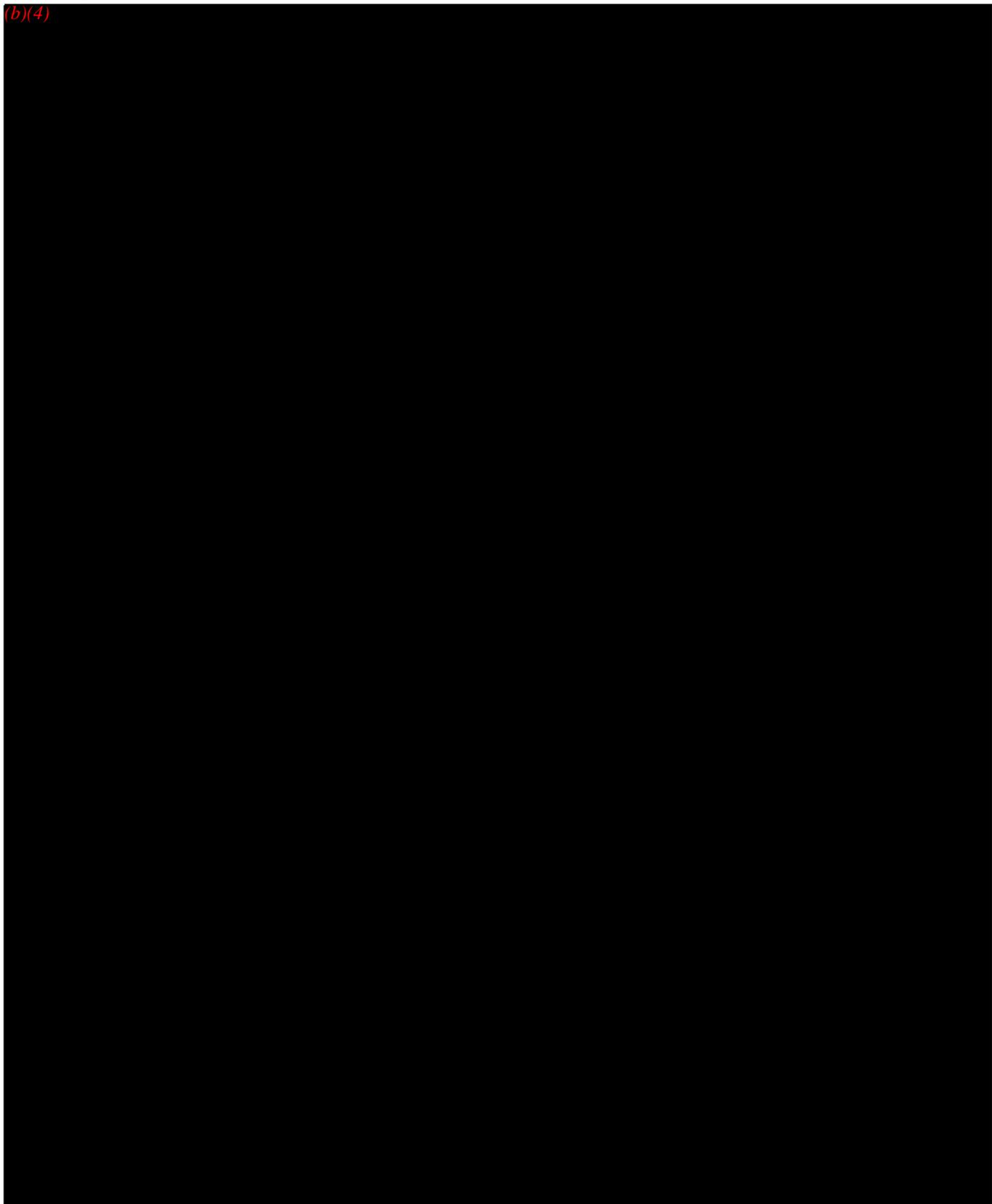
The sponsor has provided the following composition information for the Custodiol® HTK solution. “Each liter of aqueous sterile solution contains the following:

0.8766 g	Sodium chloride (15.0 mmol)
0.6710 g	Potassium [Potassium] chloride (9.0 mmol)
0.1842 g	Potassium [Potassium] hydrogen 2-ketoglutarate (1.0 mmol)
0.8132 g	Magnesium chloride • 6H <sub>2</sub> O (4.0 mmol)
3.7733 g	Histidine • HCl H <sub>2</sub> O [Histidine HCl • H <sub>2</sub> O] (18.0 mmol)
27.9289 g	Histidine (180.0 mmol)
0.4085 g	Tryptophan (2.0 mmol)
5.4651 g	Mannitol (30.0 mmol)
0.0022 g	Calcium chloride (0.015 mmol) (sponsor’s submission, pp. 6, 38).

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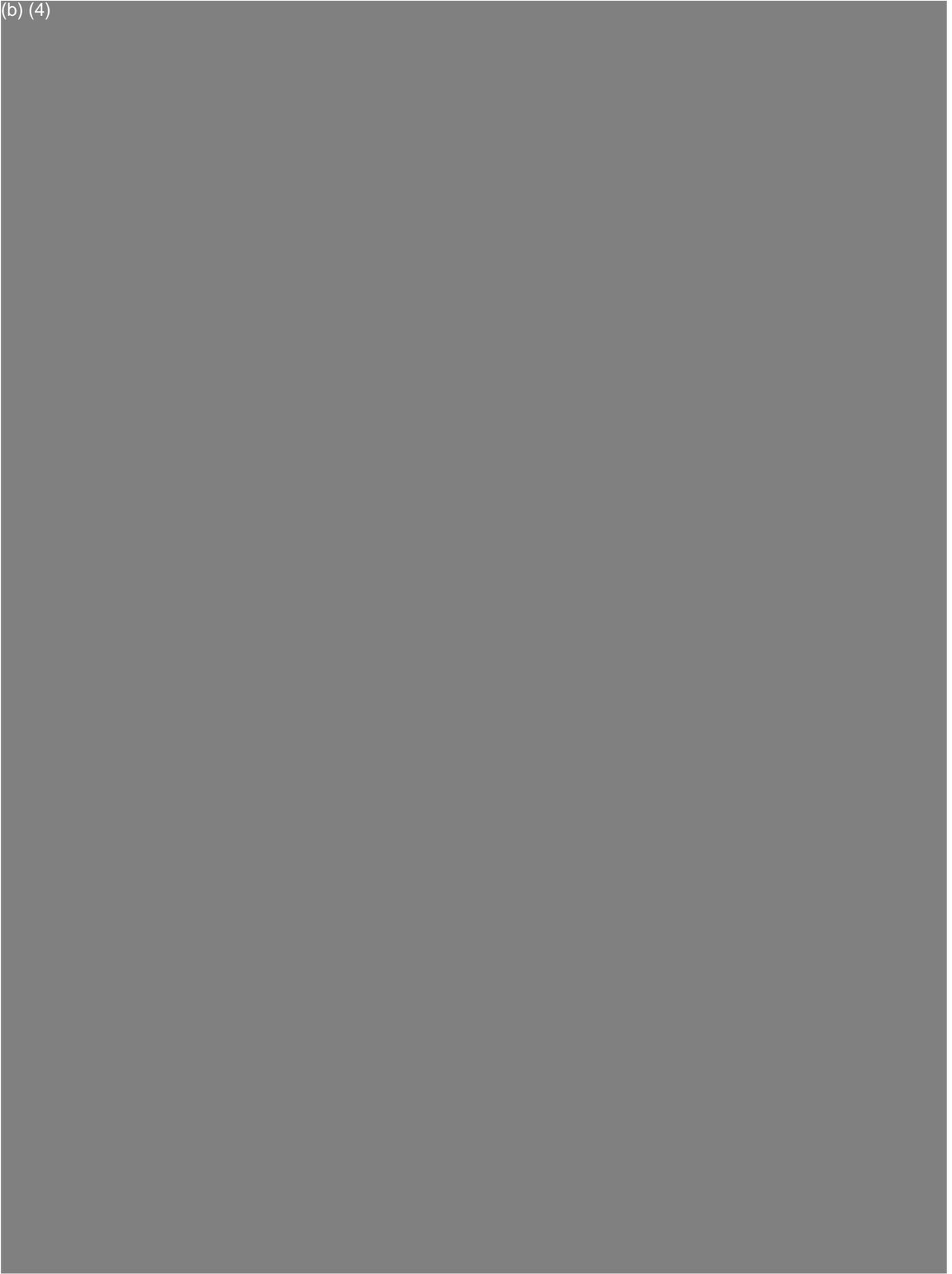
There are several major differences between the Custodiol HTK Solution, and the proposed predicate, the Viaspan Belzer UW Cold Storage Solution:

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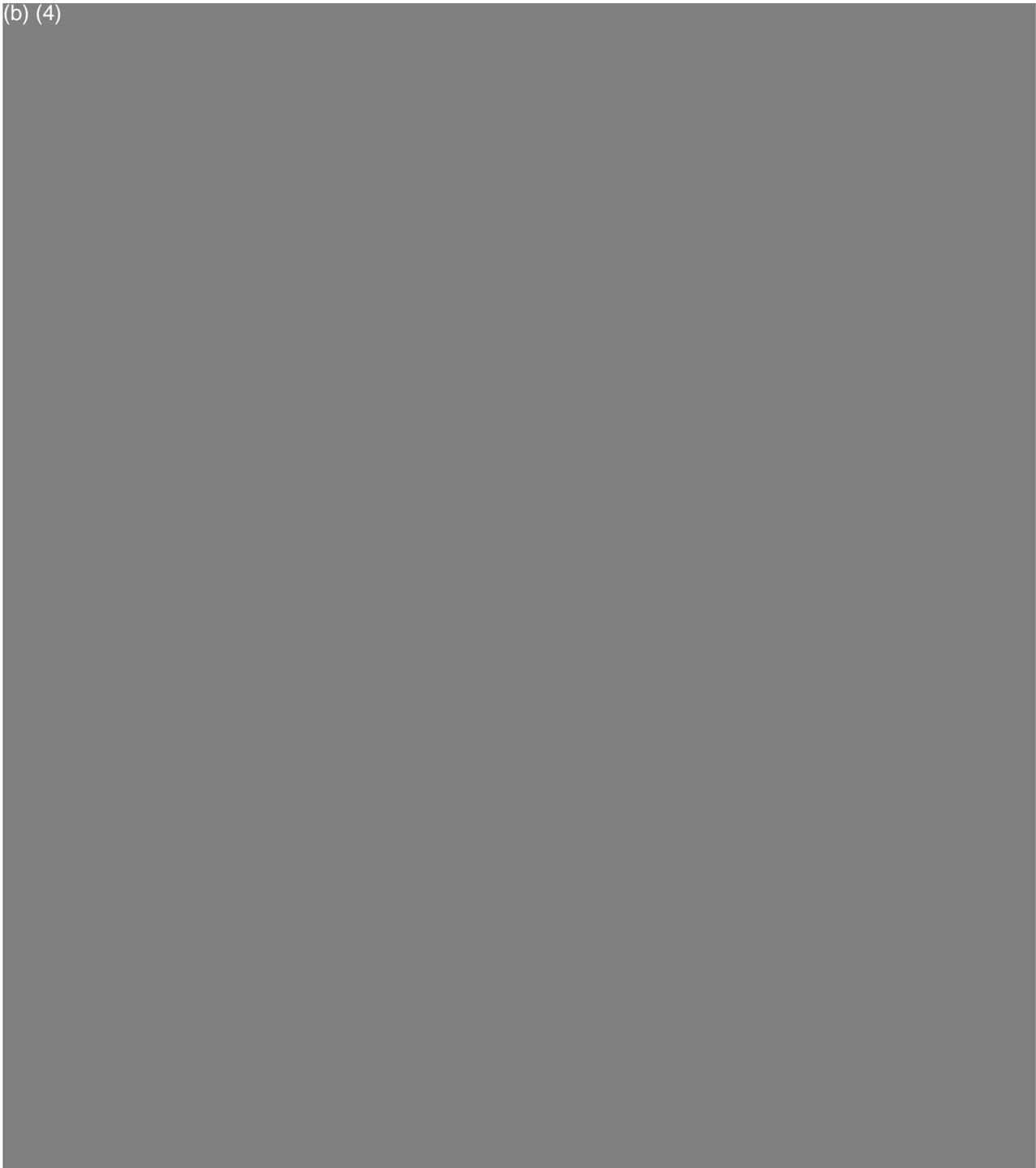


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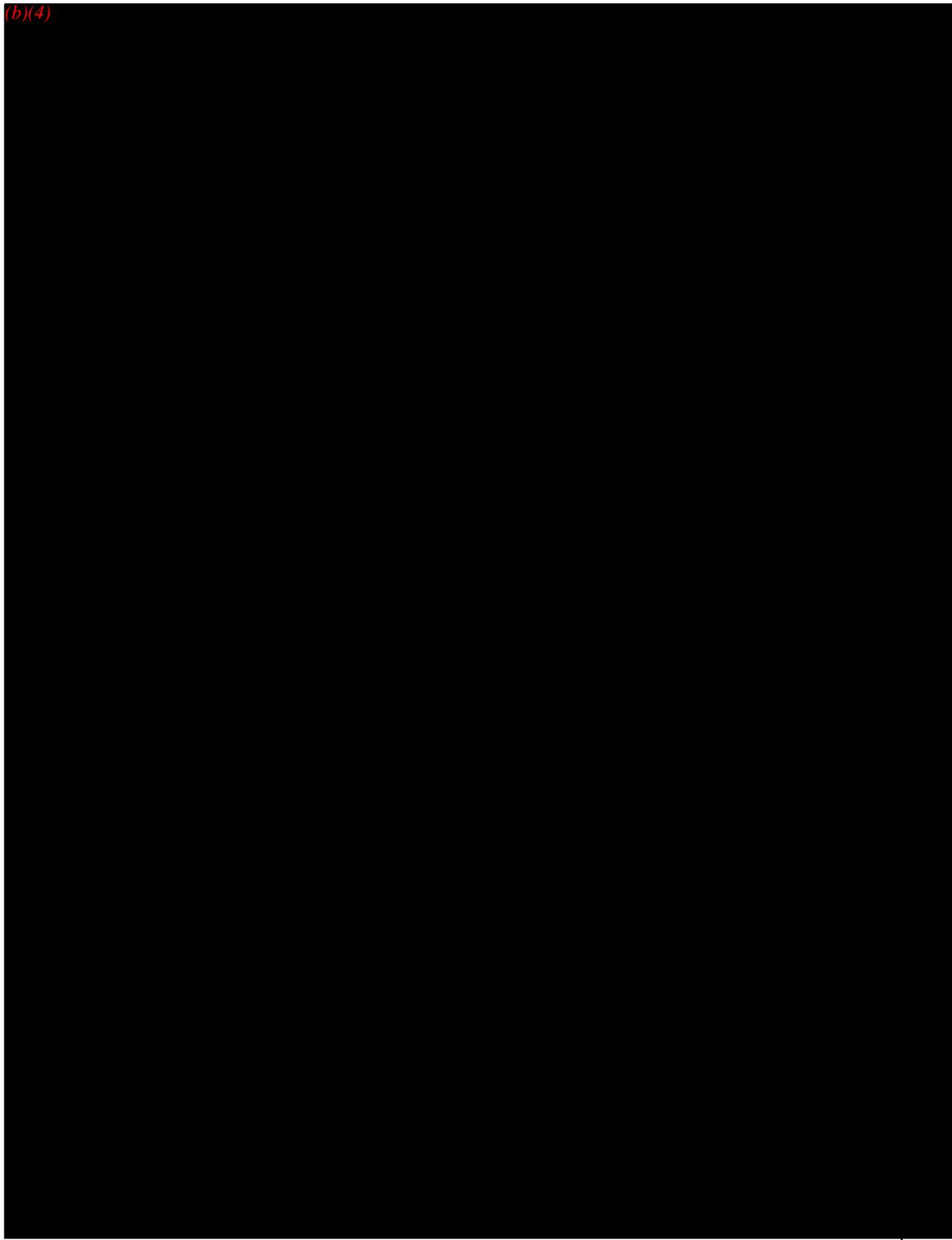
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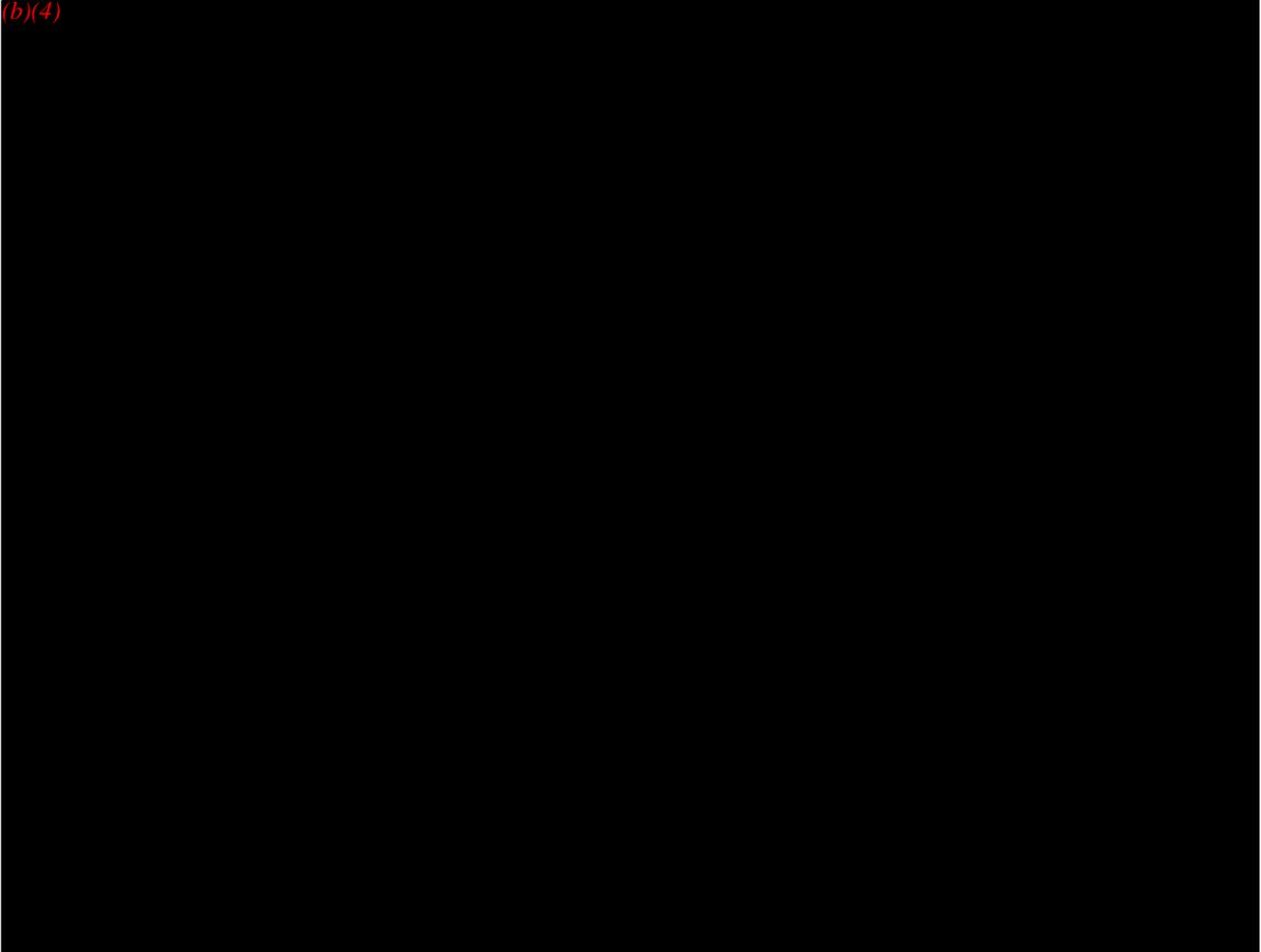
Clinical Data:

(b)(4)



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(b)(4)



### Medline Search

My Medline literature search has revealed numerous other articles which also compare the various organ preservation solutions, including the HTK solution. The sponsor has not provided copies, nor has summarized the data from the following published articles:

- 1) "Comparison of Bretschneider's-HTK and Euro-Collins solution using an in vitro small bowel perfusion model", Burgmann H; Reckendorfer H; Sperlich M; Spieckermann, Transplant Proc 1996 Oct;28(5):2636.
- 2) "Superiority of HTK solution to UW solution for tissue oxygenation in living related liver transplantation", Hatano E; Tanaka A; Shinohara H; Kitai T; Satoh S; Inomoto T; Tanaka K; Yamaoka Y. Transplant Proc 1996 Jun;28(3):1880-1881.
- 3) "Optimal pH of University of Wisconsin solution and rinse solution for rat liver preservation", Sumimoto R; Fukuda Y; Southard JH; Urushihara T; Ohdan Y; Asahara T; Dohi K, Transplant Proc 1996 Jun;28(3):1891-1892.

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- 4) "The HTK solution with nicorandil can improve cardiac function after simple cold storage", Gu K; Kin S; Saitoh Y; Nosaka S; Sasaki T; Yamauchi M; Nakayama K. *Transplant Proc* 1996 Feb;28(1):77-79.
- 5) "Comparison of kidney graft survival in Asian and Caucasian patients transplanted in the United States", Cho YW; Terasaki PI. *Transplant Proc* 1996 Jun;28(3):1571-1573.
- 6) "Comparative analysis of kidney preservation methods. Collaborative Transplant Study". Opelz G; Wujciak T. *Transplant Proc* 1996 Feb;28(1):87-90.
- 7) "Organ specificity of pancreas preservation compared with kidney and heart preservation", Kin S; Gu K; Nagami H; Saitoh Y; Nakayama K; Tamura K; Stephanian E; Sutherland D. *Transplant Proc* 1996 Feb;28(1):335-336.
- 8) "Histidine-tryptophan-ketoglutarate versus Euro-Collins for preservation of kidneys from non-heart-beating donors", Moisiuk Y; Tarabarko N; Vitjazev G; Sharshatkin A; Aroutiounian S; Shumakov V. *Transplant Proc* 1996 Feb;28(1):202.
- 9) "Temperature dependence of proton buffering capacity of HTK, Euro- Collins, and UW solution", Schilling M; Redaelli C; Friess H; Laeuffer J; Buchler M. *Transplant Proc* 1996 Feb;28(1):343-344.
- 10) "Comparison of solutions for preservation of the rabbit liver as tested by isolated perfusion", den Butter G; Saunder A; Marsh DC; Belzer FO; Southard JH. *Transpl Int* 1995;8(6):466-471.
- 11) "Experiences with histidine-tryptophan-ketoglutarate-perfused organs in clinical liver transplantation", Erhard J; Lange R; Scherer R; Eigler FW. *Transplant Proc* 1993 Apr;25(2):1885-1886.
- 12) "Influence of additional warm ischemia on rat hepatic energy metabolism: a comparison of University of Wisconsin and HTK protection", Reckendorfer H; Sperlich M; Burgmann H; Spieckermann PG. *Transplant Proc* 1993 Apr;25(2):1952.
- 13) "Current status of the Eurotransplant randomized multicenter study comparing kidney graft preservation with histidine-tryptophan- ketoglutarate, University of Wisconsin, and Euro-Collins solutions. The HTK Study Group", Groenewoud AF; Thorogood J. *Transplant Proc* 1993 Feb;25(1 Pt 2):1582-1585.
- 14) "An in vitro method for comparing the efficacy of two preservation solutions in one canine liver using the 5'-nucleotidase assay", van Gulik TM; Nio CR; Frederiks WM; Kloppel PJ; van der Heyde MN. *Transpl Int* 1993 Jan;6(1):8-13.

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- 15) "Morphological investigation of the porcine liver directly following preservation with Euro-Collins, University of Wisconsin and Bretschneider's HTK solution", Aminalai A; Kehrer G; Grossmann F; Richter J; Bretschneider HJ. *Langenbecks Arch Chir* 1992;377(2):81-88.
- 16) "Comparison of PBS, HTK, and UW solutions for kidney preservation", Lindell SL; Gandolph D; Southard JH; Belzer FO. *Transplant Proc* 1991 Oct;23(5):2399-2401.
- 17) "Changes in hepatic tissue water content in EC-, UW-, and HTK-preserved livers tested in a pig liver transplant model", Steininger R; Roth E; Holzmuller P; Reckendorfer H; Sperlich M; Grunberg T; Moser E; Muhlbacher F. *Transplant Proc* 1991 Oct;23(5):2414-2415.
- 18) "Hepatic energy metabolism during hypothermic storage and after reperfusion. Evaluation of the University of Wisconsin and the Bretschneider solutions", Reckendorfer H; Burgmann H; Spieckermann PG. *Transplant Proc* 1991 Jun;23(3):1974-1975.
- 19) "[Post-ischemia normal function of living related kidney transplants after preservation with HTK solution]VERNACULAR TITLE: Postischämische Normalfunktion von Verwandtennierentransplantaten nach Protektion mit HTK-Lösung", Vieweg J; Heidecke CD; Beckurts T; Holscher M. *Urologe [A]* 1991 Jul;30(4):256-259.
- 20) "Microcirculatory disturbances and leukocyte adherence in transplanted livers after cold storage in Euro-Collins, UW and HTK solutions", Marzi I; Walcher F; Menger M; Buhren V; Harbauer G; Trentz O. *Transpl Int* 1991 Apr;4(1):45-50.
- 21) "Effects of Euro-Collins, University of Wisconsin, and histidine- tryptophane-ketoglutarate solution on hepatic microcirculation following liver transplantation in the rat", Buhren V; Marzi I; Walcher F; Menger M; Hower R. *Transplant Proc* 1991 Feb;23(1 Pt 1):643-644.
- 22) "Nonrandomized comparative study between University of Wisconsin cold storage and Euro-Collins solution in kidney transplantation", Moukarzel M; Benoit G; Bensadoun H; Hiesse C; Richard C; Bittard H; Depret J; Verdelli G; Charpentier B; Fries D; et al. *Transplant Proc* 1990 Oct;22(5):2289-2290.
- 23) "First results of the multicenter study of HTK protection for kidney transplants", Groenewoud AF; Buchholz B; Gubernatis F; Holscher M; Hoyer J; Isemer F; Niebel W; Wilms H. *Transplant Proc* 1990 Oct;22(5):2212.
- 24) "Preservation of the porcine pancreas with HTK and Euro-Collins solution: studies in a reperfusion system", Leonhardt U; Barthel M; Tytko A; Droge M; Siegel EG; Nebendahl K; Kohler H; Creutzfeldt W. *Eur J Clin Invest* 1990 Oct;20(5):536-539.

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25) "Preservation of the liver with the HTK solution", Lamesch P; Raygrotzki S; Kehrer G; Gubernatis G; Bretschneider HJ; Pichlmayr R. Transplant Proc 1990 Apr;22(2): 518-519.

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27) "Kidney procurement with the HTK solution of Bretschneider", Isemer FE; Ludwig A; Schunck O; Bretschneider HJ; Peiper HJ. Transplant Proc 1988 Oct;20(5):885-886.

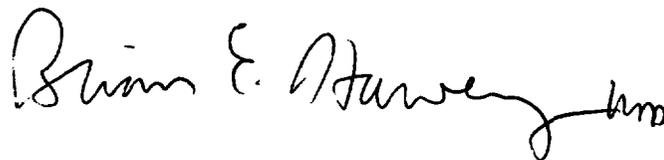
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### Summary

The sponsor must provide the requested information in order for a clinical review to be completed in order to support a substantial equivalence determination. The Cardiology and Microbiological consultations will also impact on the final regulatory decision for this submission.

A handwritten signature in black ink that reads "Brian E. Harvey" followed by a stylized flourish.

Brian E. Harvey, M.D., Ph.D.  
Medical Officer

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**Office of Device Evaluation**

**From:** Brian E. Harvey, M.D., Ph.D.  
Medical Officer  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

**To:** Miriam C. Provost, Ph.D.  
Primary Reviewer  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

**Through:** Carolyn Y. Neuland, Ph.D.  
Branch Chief  
FDA/CDRH/ODE/DRAERD/GRDB  
HFZ-470

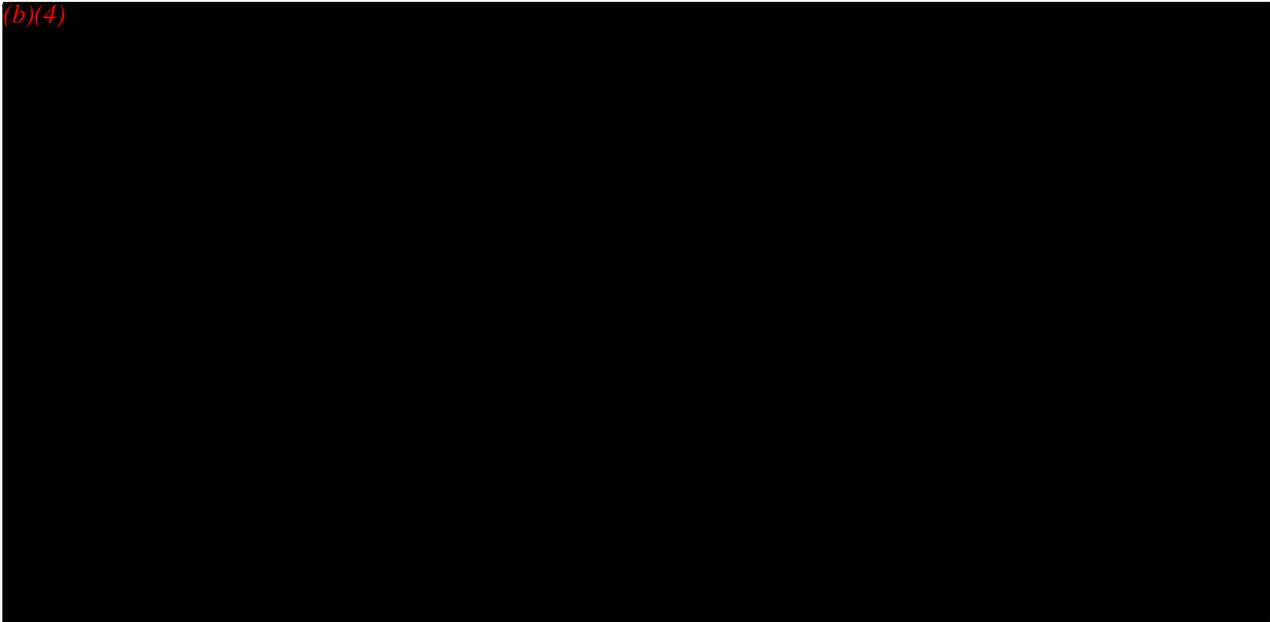
**Subject:** K983103/S1 & S2  
Custodiol® HTK solution  
Dr. F. Kohler Chemie GmbH, Germany

**Date:** April 2, 1999 (Draft)  
April 20, 1999 (Final)

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**Response To Deficiency Letter**

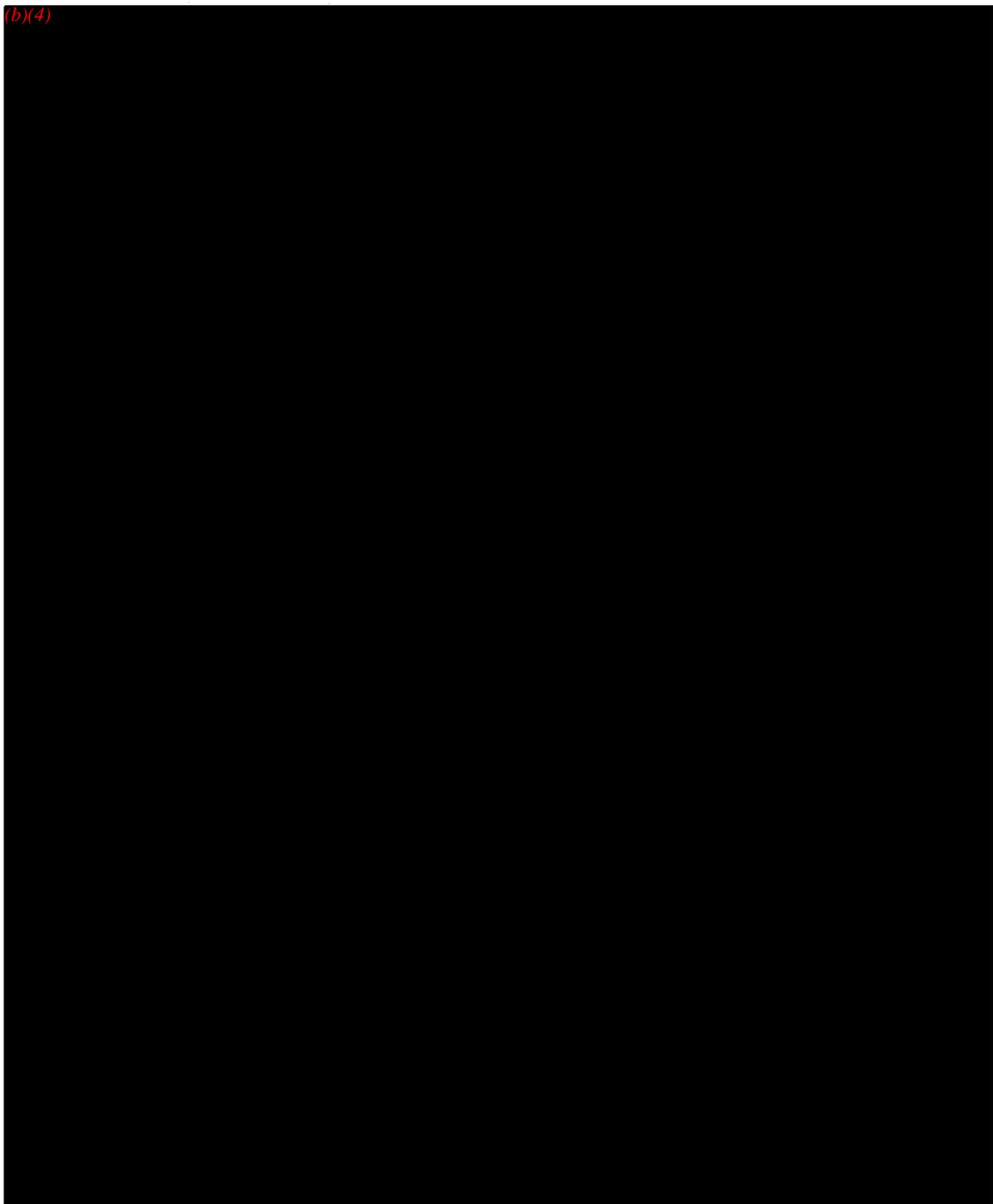
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### Answers To Questions & Comments

(b)(4)



121

(b) (4)



12/2

(b) (4)



123

(b) (4)



### **Summary**

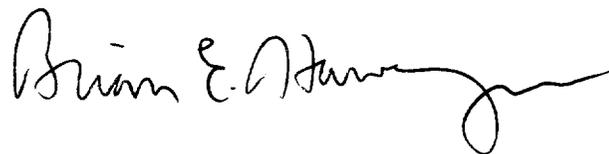
The sponsor has provided adequate clinical data to support the substantial equivalence of their HTK solution for use in kidney transplantation, to the predicate Viaspan Belzer UW Cold Storage Solution (K944866).

The sponsor has also provided some supporting published data, and the initial data from one of the four centers participating in a European trial on HTK solution for transplant liver perfusion. If the finalized data from the other 3 centers in the European trial on HTK solution for transplant liver perfusion is consistent with this initial data presented by the sponsor, then at that time, the HTK solution could be cleared for liver transplantation.

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The data in support of the HTK solution for the pancreatic tissue indication for use as presented by the sponsor, appears to be limited, as well as incomplete.

The data supporting the cardiac transplantation indication for use is currently being reviewed by the cardiology consultant.

A handwritten signature in black ink, reading "Brian E. Harvey". The signature is written in a cursive style with a long, sweeping tail that loops back under the name.

Brian E. Harvey, M.D., Ph.D.  
Medical Officer

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Public Health Service

Food and Drug Administration  
 Center for Devices and  
 Radiological Health  
 Office of Device Evaluation  
 Document Mail Center (HFZ-401)  
 9200 Corporate Blvd.  
 Rockville, Maryland 20850

July 01, 1999

DR. FRANZ KOHLER CHEMIE GMBH  
 C/O C.L. MCINTOSH & ASSOCIATES  
 12300 TWINBROOK PARKWAY  
 SUITE 625  
 ROCKVILLE, MD 20852  
 ATTN: T. WHIT ATHEY

510(k) Number: K992209  
 Received: 30-JUN-1999  
 Product: CUSTODIOL

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. **YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.**

On January 1, 1996, FDA began requiring that all 510(k) submitters provide on a separate page and clearly marked "Indication For Use" the indication for use of their device. If you have not included this information on a separate page in your submission, please complete the attached and amend your 510(k) as soon as possible. Also if you have not included your 510(k) Summary or 510(k) Statement, or your Truthful and Accurate Statement, please do so as soon as possible. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers Assistance (DSMA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission **MUST** be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the Document Mail Center will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations, we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official. Any telefaxed material must be followed by a hard copy to the Document Mail Center (HFZ-401).

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address <http://www.fda.gov/cdrh/dsmamain.html> or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman  
 Consumer Safety Officer  
 Premarket Notification Staff

K9 92209

**C.L. McIntosh**

**& ASSOCIATES, INC.**

*Medical & Regulatory Affairs Services*

12300 Twinbrook Parkway, Suite 625  
Rockville, Maryland 20852

Tel.: (301) 770-9590  
Fax: (301) 770-9584

June 29, 1999

Center for Devices and Radiological Health  
Food and Drug Administration  
Document Mail Center  
9200 Corporate Blvd  
Rockville, MD 20850

ATTN: Gastroenterology and Renal Devices Branch, HFZ-470  
Division of Reproductive, Abdominal, ENT, and Radiology Devices

Re: 510(k) Premarket Notification  
Custodiol® HTK Solution

Dear Sir or Madam:

We are submitting this document on behalf of our client, Dr. F. Kohler Chemie GmbH, in order to demonstrate that the product, **Custodiol® HTK Solution**, is substantially equivalent to similar devices presently cleared for marketing.

The enclosed information meets all the Food and Drug Administration's requirements for a premarket notification. To assist you in coming to the same conclusion, we have provided a completed "Premarket Notification 510(k) Checklist for Acceptance Decision" and a "Premarket Submission Cover Sheet" which follow this cover letter.

All of this 510(k)'s administrative information is provided in this cover letter, namely information on the device's trade or proprietary name, the common or usual name, the classification name, registration information, discussion on the applicable classification regulation, product code, panel, manufacturing site, name of consultant, name of contact, name of owner, information on previous submissions, any information on integrity issues, tier designation, and any applicable FDA device specific guidelines.

In addition, the cover letter describes the location of other information, specifically the information that FDA asks to be provided in separate sections of the 510(k), all of which are contained herein as Exhibits.

For your convenience, **Section I** of this premarket notification contains an Overview or Executive Summary of the submission. We recommend that the reviewer read this section first in order to become familiar with the organization and content of this submission.

REC'D  
JUN 30 4 12 PM '99  
FDA/CDRH/OCE/DHO

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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 2

## ADMINISTRATIVE INFORMATION

Following are some of the required elements of a 510(k).

### Proprietary, Common, and Classification Names

The **proprietary name** of the device is **Custodiol®**. The classification name of the device that Dr. F. Kohler Chemie GmbH intends to introduce is Isolated Kidney Perfusion and Transport System and Accessories. The common name for this device is organ perfusion and preservation solution.

### Establishment Registration

The Establishment Registration number for Dr. F. Kohler Chemie GmbH has not yet been assigned. Registration will be completed prior to marketing of the device.

### Classification, Regulation, Product Code, and Panel

Classification: 21 CFR 876.5880, Class II

Procode: KDL

Panel: Gastroenterology Devices Panel

### Manufacturing Site

The manufacturing site is Dr. F. Kohler Chemie GmbH, Neue Bergstrasse 3-7, Alsbach-Hahnlein 64665, Germany.

### Name of Consultant

The staff of C. L. McIntosh & Associates are providing consulting services on this 510(k) to Dr. F. Kohler Chemie GmbH.

### Name of Submission Correspondent

The contact person for all questions regarding this document is the undersigned, T. Whit Athey.

Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 3

Owner of the 510(k) Submission

The owner of the 510(k) submission is Dr. F. Kohler Chemie GmbH.

Information on Previous Submissions

A 510(k) for Custodiol Solution was submitted on September 3, 1998 and received the file number, K983103. This 510(k) covered the indications for several organs for which the product is marketed in the EU and most other countries in the world. The present 510(k), resubmitted at the request of FDA, is for the kidney indication only. There is no new information in the present submission beyond that contained in K983103, other than that specifically requested in the FDA letter of April 29, 1999.

Integrity Issues

The applicant has not been the subject of an integrity investigation.

Tier Designation

Tier II

Guidance Documents

The applicant is unaware of any draft FDA guidance for this type of device.

OTHER INFORMATION

510(k) Summary

In response to the requirements addressed by the SMDA of 1990, we have enclosed a summary of the safety and effectiveness information upon which the substantial equivalence<sup>1</sup> determination is based. This 510(k) Summary contains the information described in 21 CFR 807.92, and is provided in **Exhibit 1**.

Premarket Notification Truthful and Accurate Statement

We have also enclosed the Premarket Notification Truthful and Accurate

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<sup>1</sup> The terms "substantial equivalence" and "substantially equivalent" are used in this letter and the enclosed 510(k) as they are defined in the Federal Food, Drug, and Cosmetic Act.

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Dr. F. Kohler Chemie GmbH  
510(k) Notification  
Page 4

Statement Certification as required by 21 CFR 807.87(j) in **Exhibit 2**.

Statement of Indications for Use

In response to the requirement that a 510(k) contain a statement of indications for use on a separate labeled page, we have included such a statement as **Exhibit 3**.

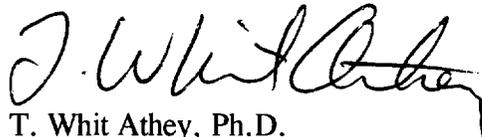
**CONFIDENTIALITY**

We request, in accordance with 21 CFR 807.95(b), that FDA hold confidential the information in this premarket notification as it relates to our intention to market this product in the U.S. Further, some of the information in this application may be trade secret or commercial/financial information that is privileged or confidential. This confidential information is nondisclosable under the Freedom of Information Act, even after the existence of the application becomes public. We ask that you consult with us, as provided for in 21 CFR 20.45, should you have any question whether requested information is confidential. Each page or section of this document containing "Confidential" information has been clearly identified.

This 510(k) will demonstrate that the **Custodiol® HTK Solution** is substantially equivalent to presently marketed devices. Based on the information submitted herein, Dr. F. Kohler Chemie GmbH requests clearance to market this product as soon as possible.

Thank you for your consideration of this matter. If you require any additional information or clarification, please call the undersigned at 301-770-9590.

Sincerely yours,



T. Whit Athey, Ph.D.  
Senior Consultant

Enclosures: 510(k) Cover Sheet  
510(k) Checklist  
510(k) Premarket Notification

**CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
Premarket Submission Cover Sheet**

Date of Submission:

FDA Document Number:

**Section A Type of Submission**

- |   |   |  |   |
|---|---|--|---|
| <input checked="" type="checkbox"/> 510(k)        | <input type="checkbox"/> IDE            | <input type="checkbox"/> PMA           | <input type="checkbox"/> PMA Supplement - Regular     |
| <input type="checkbox"/> 510(k) Add'l information | <input type="checkbox"/> IDE Amendment  | <input type="checkbox"/> PMA Amendment | <input type="checkbox"/> PMA Supplement - Special     |
|   | <input type="checkbox"/> IDE Supplement | <input type="checkbox"/> PMA Report    | <input type="checkbox"/> PMA Supplement - 30 day      |
|   | <input type="checkbox"/> IDE Report     |  | <input type="checkbox"/> PMA Supplement - Panel Track |

**Section B1 Reason for Submission - 510(k)s Only**

- |  |   |  |
|--|---|--|
| <input checked="" type="checkbox"/> New device   | <input type="checkbox"/> Additional or expanded indications | <input type="checkbox"/> Change in technology, design, materials, or manufacturing process |
| <input type="checkbox"/> Other reason (specify): |   |  |

**Section B2 Reason for Submission - PMAs Only**

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> New device                         | <input type="checkbox"/> Change in design, component, or specification: | <input type="checkbox"/> Location change:    |
| <input type="checkbox"/> Withdrawal                         | <input type="checkbox"/> Software                                       | <input type="checkbox"/> Manufacturer        |
| <input type="checkbox"/> Additional or expanded indications | <input type="checkbox"/> Color Additive                                 | <input type="checkbox"/> Sterilizer          |
| <input type="checkbox"/> Licensing agreement                | <input type="checkbox"/> Other (specify below)                          | <input type="checkbox"/> Packager            |
| <input type="checkbox"/> Labeling change:                   | <input type="checkbox"/> Process change:                                | <input type="checkbox"/> Report submission:  |
| <input type="checkbox"/> Indications                        | <input type="checkbox"/> Manufacturer                                   | <input type="checkbox"/> Annual or periodic  |
| <input type="checkbox"/> Instructions                       | <input type="checkbox"/> Sterilizer                                     | <input type="checkbox"/> Post-approval study |
| <input type="checkbox"/> Performance Characteristics        | <input type="checkbox"/> Packager                                       | <input type="checkbox"/> Adverse reaction    |
| <input type="checkbox"/> Shelf life                         |   | <input type="checkbox"/> Device defect       |
| <input type="checkbox"/> Trade name                         | <input type="checkbox"/> Response to FDA correspondence (specify below) | <input type="checkbox"/> Amendment           |
| <input type="checkbox"/> Other (specify below)              | <input type="checkbox"/> Request for applicant hold                     |  |
| <input type="checkbox"/> Change in ownership                | <input type="checkbox"/> Request for removal of applicant hold          |  |
| <input type="checkbox"/> Change in correspondent            | <input type="checkbox"/> Request for extension                          |  |
| <input type="checkbox"/> Other reason (specify):            | <input type="checkbox"/> Request to remove or add manufacturing site    |  |

**Section B3 Reason for Submission - IDEs Only**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> New device                    | <input type="checkbox"/> Change in:                | <input type="checkbox"/> Response to FDA letter concerning:          |
| <input type="checkbox"/> Addition of institution       | <input type="checkbox"/> Correspondent             | <input type="checkbox"/> Conditional approval                        |
| <input type="checkbox"/> Expansion/extension of study  | <input type="checkbox"/> Design                    | <input type="checkbox"/> Deemed approved                             |
| <input type="checkbox"/> IRB certification             | <input type="checkbox"/> Informed consent          | <input type="checkbox"/> Deficient final report                      |
| <input type="checkbox"/> Request hearing               | <input type="checkbox"/> Manufacturer              | <input type="checkbox"/> Deficient progress report                   |
| <input type="checkbox"/> Request waiver                | <input type="checkbox"/> Protocol - feasibility    | <input type="checkbox"/> Deficient investigator report               |
| <input type="checkbox"/> Termination of study          | <input type="checkbox"/> Protocol - other          | <input type="checkbox"/> Disapproval                                 |
| <input type="checkbox"/> Withdrawal of application     | <input type="checkbox"/> Sponsor                   | <input type="checkbox"/> Request extension of time to respond to FDA |
| <input type="checkbox"/> Emergency use:                | <input type="checkbox"/> Report submission:        | <input type="checkbox"/> Request meeting                             |
| <input type="checkbox"/> Notification of emergency use | <input type="checkbox"/> Current investigator      | <input type="checkbox"/> IOL submissions only:                       |
| <input type="checkbox"/> Additional information        | <input type="checkbox"/> Annual progress           | <input type="checkbox"/> Change in IOL style                         |
| <input type="checkbox"/> Other reason (specify):       | <input type="checkbox"/> Site waiver limit reached | <input type="checkbox"/> Request for protocol waiver                 |
|  | <input type="checkbox"/> Final                     |  |

	FDA Document Number:
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<b>Section C</b>	<b>Product Classification</b>
------------------	-------------------------------

Product code: <b>KDL</b>	CFR Section: <b>21 CFR 876.5880</b>	Device class:
Classification panel: <b>Gastroenterology/Urology Panel</b>		<input type="checkbox"/> Class I <input checked="" type="checkbox"/> Class II <input type="checkbox"/> Class III <input type="checkbox"/> Unclassified

<b>Section D</b>	<b>Information on 510(k) Submissions</b>
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Product codes of devices to which substantial equivalence is claimed:	Summary of, or statement concerning, safety and effectiveness data: <input checked="" type="checkbox"/> 510(k) summary attached <input type="checkbox"/> 510(k) statement								
<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:25%;">1 <b>KDL</b></td> <td style="width:25%;">2</td> <td style="width:25%;">3</td> <td style="width:25%;">4</td> </tr> <tr> <td>5</td> <td>6</td> <td>7</td> <td>8</td> </tr> </table>		1 <b>KDL</b>	2	3	4	5	6	7	8
1 <b>KDL</b>		2	3	4					
5	6	7	8						
Information on devices to which substantial equivalence is claimed:									

510(k) Number	Trade or proprietary or model name	Manufacturer
1 <b>K944866</b>	1 <b>ViaSpan Belzer UW Cold Storage Solution</b>	1 <b>DuPont Pharmaceuticals</b>
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6

<b>Section E</b>	<b>Product Information - Applicable to All Applications</b>
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Common or usual name or classification name: **Cold storage solution or transplant solution. Considered to fall under the classification name, Kidney Perfusion and Transport System and Accessories.**

Trade or proprietary or model name	Model number
1	1
2	2
3	3
4	4
5	5
6	6

FDA document numbers of all prior related submissions (regardless of outcome):					
1 <b>K983103</b>	2	3	4	5	6
7	8	9	10	11	12

Data included in submission:       Laboratory testing       Animal trials       Human trials

Indications (from labeling): **Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.**

		FDA Document Number:	
<b>Section F Manufacturing / Packaging / Sterilization Sites</b>			
<input checked="" type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA establishment registration number: (In process)	<input checked="" type="checkbox"/> Manufacturer <input type="checkbox"/> Contract sterilizer <input type="checkbox"/> Contract manufacturer <input type="checkbox"/> Repackager / relabeler	
Company / Institution name: <b>Dr. Franz Köhler Chemie GmbH</b>			
Division name (if applicable):		Phone number (include area code): <b>+49-62-575090</b>	
Street address: <b>Neue Bergstrasse 3-7</b>		FAX number (include area code): <b>+49-62-5750946</b>	
City: <b>Alsbach-Hähnlein</b>	State / Province:	Country: <b>Germany</b>	ZIP / Postal Code: <b>64665</b>
Contact name: <b>Dr. E. Schaffner</b>			
Contact title: <b>Clinical Director</b>			
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA establishment registration number: (In process)	<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract sterilizer <input type="checkbox"/> Contract manufacturer <input type="checkbox"/> Repackager / relabeler	
Company / Institution name:			
Division name (if applicable):		Phone number (include area code):	
Street address:		FAX number (include area code):	
City:	State / Province:	Country:	ZIP / Postal Code:
Contact name:			
Contact title:			

			FDA Document Number:
<b>Section G Applicant or Sponsor</b>			
Company / Institution name: <b>Dr. Franz Köhler Chemie GmbH</b>			FDA establishment registration number:
Division name (if applicable):			Phone number (include area code): <b>+ 49-62-575090</b>
Street address: <b>Neue Bergstrasse 3-7</b>			FAX number (include area code): <b>+ 49-62-5750946</b>
City: <b>Alsbach-Hähnlein</b>	State/Province:	Country: <b>Germany</b>	ZIP / Postal Code: <b>64665</b>
Signature:			
Name:			
Title:			
<b>Section II Submission correspondent (if different from above)</b>			
Company / Institution name: <b>C. L. McIntosh &amp; Associates</b>			
Division name (if applicable):			Phone number (include area code): <b>301-770-9590</b>
Street address: <b>12300 Twinbrook Parkway, Suite 625</b>			FAX number (include area code): <b>301-770-9584</b>
City: <b>Rockville</b>	State / Province: <b>MD</b>	Country:	ZIP / Postal Code: <b>20852</b>
Contact name: <b>T. Whit Athey</b>			
Contact title: <b>Senior Consultant</b>			

Your voluntary completion of this Premarket Submission Cover Sheet will not affect any FDA decision concerning your submission, but will help FDA's Center for Devices and Radiological Health process your submission more efficiently. The information you provide should apply *only* to a single accompanying submission. Please do not send cover sheets for any previous submissions. See the instructions for additional information on completing the cover sheet. If you have a question concerning completion of the cover sheet, please contact the Division of Small Manufacturers Assistance at (800) 638-2041 or (301) 443-6597.

DRAERD Premarket Notification 510(k)  
Reviewer's Screening Checklist

Device Name: Custodiol® HTK Solution

510(k) Number \_\_\_\_\_

ITEM	PRESENT/NEEDED?
1. General Information	All of the required administrative information is contained in the cover letter.
2. Proposed Labeling	The proposed labeling is summarized in Section V of the 510(k). There, reference may be found to the location of all of the individual items.
3. Comparison of similarities and differences to predicate devices.	Section III.D has a comparison table.
Predicate device labeling	Predicate labeling is included in Exhibit 20.
4. List of all patient contacting materials in new device	The components of HTK solution are listed in Section II.
5. Biocompatibility information for patient contacting materials OR certification of same material as predicate device.	All of the components of HTK Solution are natural substances occurring normally in the body.
6. Performance data: Bench Data Animal Data Clinical Data	See Section II Not included See Section IV
7. Sterilization information	The solution is provided in sterile form. Section II.G discusses sterilization.

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- |     |   |   |
|-----|---|---|
| 8.  | Software Documentation  | N/A   |
| 9.  | 510(k) Summary or Statement   | A 510(k) Summary is included as Exhibit 1.                              |
| 10. | Class III Certification   | The device is not a Class III device.                                   |
| 11. | If kit, kit certification   | The device is not a kit.  |
| S1. | Is the product a device   | Kidney perfusion systems and accessories are considered devices by FDA. |
| S2. | Is the device exempt from 510(k) requirements                                   | No, the device is not exempt.   |
| S3. | Has the device been the subject of a previous NSE decision                      | No, the device has not been the subject of a previous NSE decision.     |
| S4. | Are you aware of the submitter being the subject of an integrity investigation? | The submitter has not been the subject of an integrity investigation.   |
| S5. | Is there a specific guidance document for this device or device issue.          | No.   |
| S6. | Address of manufacturing facility   | The address of the manufacturing facility is given in the cover letter. |

# 510(k) Premarket Notification

## Custodiol HTK Solution

### Applicant

Dr. Franz Kohler Chemie GmbH  
Neue Bergstrasse 3-7  
64665 Alsbach-Hahnlein  
Germany

ATTN: E. Schaffner, M.D., D.G.P.M.

Tel: +49-62-575090  
FAX: +49-62-575946

### Submission Correspondent

C. L. McIntosh & Associates  
12300 Twinbrook Parkway, Suite 625  
Rockville, MD 20852

ATTN: T. Whit Athey, Ph.D.

Tel: (301) 770-9590  
FAX: (301) 770-9584

June 29, 1999

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## SECTION I

### 510(k) OVERVIEW

#### A. REASON FOR SUBMISSION

The Dr. F. Kohler Chemie GmbH wishes to introduce into commerce a product called **Custodiol HTK Solution** as a preservative/protective and storage medium for organs for transplant. The product is presently registered for use for this intended use in various countries in Europe, Latin America, and throughout the rest of the world and has been used extensively during the last several years.

#### B. PREDICATE DEVICE

The **Custodiol HTK Solution** is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996.

#### C. DEVICE DESCRIPTION OVERVIEW

**Section II** of this submission contains a detailed description of the **Custodiol HTK Solution**. This section is intended as a brief introduction.

The HTK solution is based on the principle of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intensive buffering of the extracellular space by means of histidine/histidine HCl, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen supply. Only a small portion of the osmolality of the HTK solution is due to the sodium and potassium. The composition of HTK is similar to that of extracellular fluid. All of the components of the HTK solution occur naturally in the body.

The HTK solution is relatively low in potassium concentration so that residual solution in the transplanted organ poses no danger to the recipient. This is particularly important in organs that take up relatively large amounts of the perfusate, which may find its way into the recipient's circulation.

The HTK solution has a low viscosity, even at low temperatures. This characteristic assures rapid flow rates during initial perfusion, allowing the organ to be quickly cooled.

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The HTK solution is relatively low in potassium concentration so that residual solution in the transplanted organ poses no danger to the recipient. This is particularly important in organs that take up relatively large amounts of the perfusate, which may find its way into the recipient's circulation.

The HTK solution has a low viscosity, even at low temperatures. This characteristic assures rapid flow rates during initial perfusion, allowing the organ to be quickly cooled.

**TABLE 1**

510(k) Review Issues	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device implanted (short-term or <u>long-term</u> )?		X	
Does the device use software?		X	
Is the device shipped sterile?	X		
Is the device single use?			X
Is the device home use?		X	
Is the device for prescription only?	X		
Does the device contain a drug or biological product as a component?		X*	
Is this device a kit?		X	
Is the device subject to Postmarket Surveillance		X	
Is the device subject to the Radiation Control Act		X	

\* The components of the solution are all naturally occurring substances in the human body and under some uses or interpretations, some components might be considered to be "drugs." For the present intended use, none of the components are intended to affect the bodily function of the recipient of the transplant, though the solution is intended to affect the explanted organ prior to implant in the recipient.

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## D. REGULATORY HISTORY

The present 510(k) is the second submission from Dr. F. Kohler Chemie GmbH to the Center for Devices and Radiological Health (CDRH) for the product. The company submitted a 510(k), K983103, listing indications for several organs, but CDRH, after two 90-day review cycles, has requested that the indications for kidney be separated from the others in a new 510(k).

The company has previously received an IND (No. 40,491) for the product for a somewhat different intended use, cardioplegia, from the Center for Drug Evaluation and Research. The intended use as proposed in the present 510(k) falls under the jurisdiction of CDRH, as did the clearance process for the predicate device.

## E. SUBSTANTIAL EQUIVALENCE SUMMARY

### 1. Predicate Devices

The **Custodiol HTK Solution** is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996.

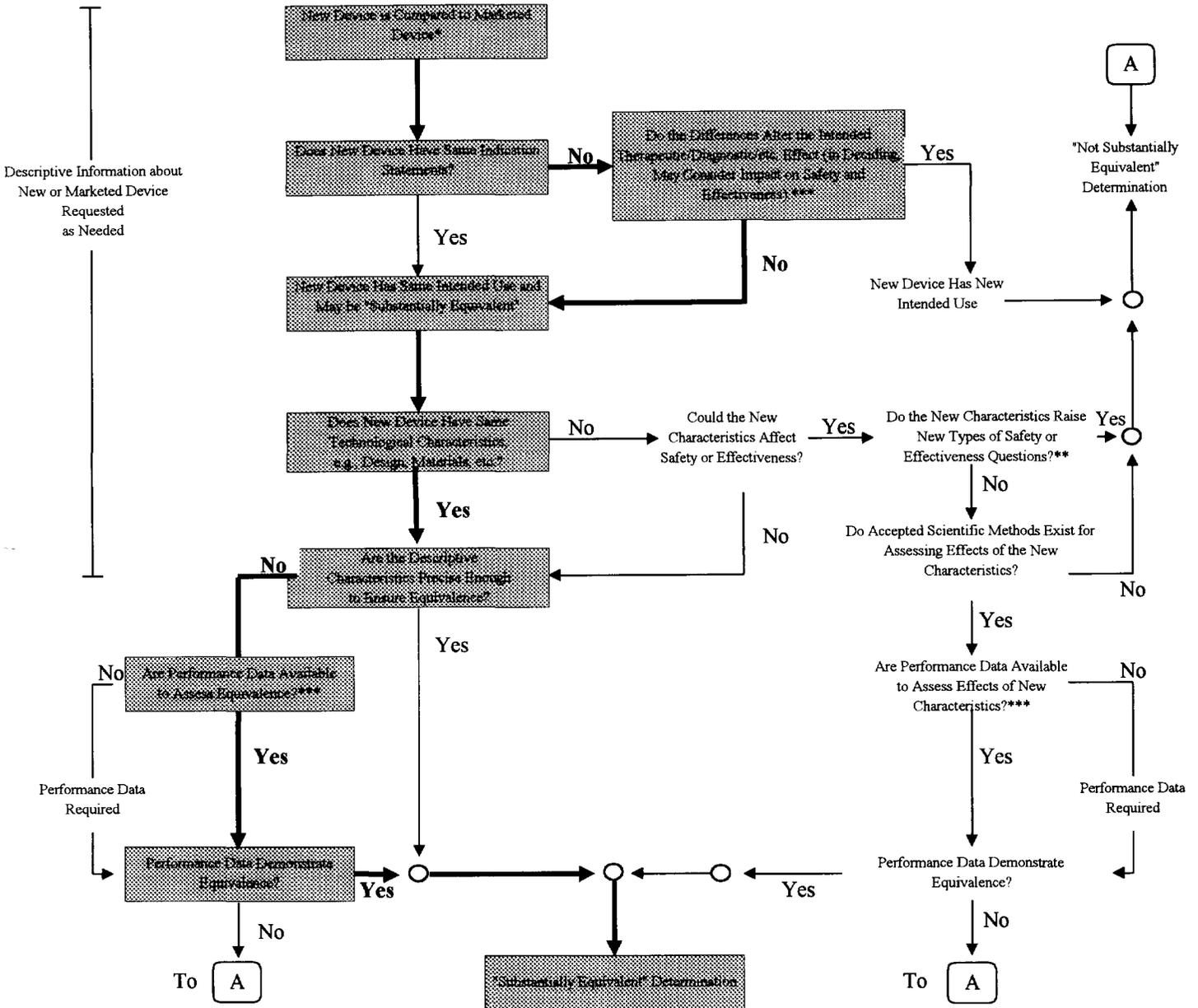
### 2. Substantial Equivalence Algorithm

**Figure 1.1** illustrates the flow chart for a decision of substantial equivalence for the **Custodiol HTK Solution**. This 510(k) will provide information that documents the path to substantial equivalence that is highlighted, and a brief explanation for the decision points follows. The detailed substantial equivalence argument will be presented in **Section III**.

The **Custodiol HTK Solution** is a medical device, and it has a similar indications for use as the legally marketed predicate device. While the indications for use statement is not identical to that of the predicate device, the intended use is clearly the same.

The **Custodiol HTK Solution** has the same technological characteristics as the predicate devices. However, the characteristics may not be sufficiently precise to assure equivalence through a point by point comparison. Therefore, extensive clinical data has been collected by the sponsor and others. The performance data clearly demonstrates equivalence.

## A3 - 510(k) "Substantial Equivalence" Decision-Making Process (Detailed)



\* 510(k) submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" devices is unclear.

\*\* This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

\*\*\* Data may be in the 510(k)s, the Center's classification files, or the literature.

Figur 1.1

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### **3. Summary**

This pre-market submission will demonstrate Substantial Equivalence as defined and understood in the Federal Food Drug and Cosmetic Act and various guidance documents issued by the Center for Devices and Radiological Health.

## **F. LABELING OVERVIEW**

### **1. Claims**

Dr. F. Kohler Chemie GmbH makes no specific claims for the device beyond those expressed or implied by the statement of indications for use.

### **2. Product Literature**

Product labeling: Instructions for use (package insert), package labeling, and promotional literature, are contained in **Section V** of this submission. A comparison of this labeling with that of the predicate devices is contained in **Section III**.

## **G. REQUIRED INFORMATION**

In accordance with 21 CFR 807.87(h), Dr. F. Kohler Chemie GmbH has prepared a 510(k) Summary which is included as **Exhibit 1**. Also required by 21 CFR 807.87(j)) is a statement certifying that the information contained in a 510(k) notification is truthful and accurate. This statement is included as **Exhibit 2**. The statement of Indications for Use is included as **Exhibit 3**, using FDA's optional format.

## **H. GUIDE TO NEW MATERIAL**

Since nearly all of the present submission has already been reviewed by FDA as a part of K983103, a considerable savings of FDA review resources may be realized if the reviewer concentrates on the parts of the present submission that are new or different. This section is intended as a guide to the reviewer in that regard.

Much of the original Section II, Device Description has been rewritten to incorporate the responses the sponsor submitted in its first major amendment dated 29 January 1999. These additions address the requests for additional information in FDA's letter of 02 Dec 1998 and also in FDA's letter of 29 April 1999. However, only the responses to the letter of 29 April 1999 are new. These new responses address the

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following requests for additional information:

- (1) A comparison of the specifications of USP and EP (response to item 3 of 29 April 1999 letter, addressed in Section II-B of the present submission),
- (2) the justification for the safety of the IAC impurity (response to item 5 of the letter, addressed in Section II-D),
- (3) F. Kohler Chemie's particulate specification (response to item 4 of the letter, addressed in Section II-E), and
- (4) the materials of the five-liter container (response to item 2 of the letter, addressed in Section II-F).

Section III of the present submission is substantially the same as the original, with only minor changes necessitated by the revision of the indications.

Section IV of the present submission has the additional information that was submitted as a part of the amendment of 29 January 1999. The studies that address other indications have been removed. No additional information was requested by FDA concerning the clinical studies of kidney transplants and none is provided in the present submission. Therefore, all of the present Section IV and the Exhibits to which it refers have been previously reviewed.

Section V on labeling has been completely revised to address the comments of FDA and to remove the references to indications other than kidney preservation.

The 510(k) Summary has been revised to reflect the restriction to the kidney indication.

Nearly all of the Exhibits for the present submission were included either in the original submission or in the amendment of 19 January 1999. Exhibit 1 contains the revised 510(k) Summary and Exhibit 3 contains the revised Indications for Use Statement. Exhibits 16, 17, and 19 provide additional information to address concerns in the FDA letter of April 29, 1999, but the remaining exhibits are not new. Following is a cross-reference for the exhibits of the present submission:

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Present Exhibit	Original 510(k) Location
Exhibit 4	Amendment Attachment I
Exhibit 5	K983103, Exhibit 4
Exhibit 6	K983103, Exhibit 5
Exhibit 7	K983103, Exhibit 6
Exhibit 8	Amendment Attachment N
Exhibit 9	Amendment Attachment L
Exhibit 10	Amendment Attachment K
Exhibit 11	K983103, Exhibit 13
Exhibit 12	Amendment Attachment A
Exhibit 13	Amendment Attachment B
Exhibit 14	Amendment Attachment D
Exhibit 15	K983103, Exhibit 7
Exhibit 16	New
Exhibit 17	New
Exhibit 18	Amendment Attachment J
Exhibit 19	New
Exhibit 20	K983103, Exhibit 14

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## SECTION II

### DEVICE DESCRIPTION

#### A. INTRODUCTION

The **Custodiol® HTK Solution** is a solution intended for use in protecting and cooling human kidneys for transplant. "HTK" refers to three of its constituents, histidine, tryptophane, and ketoglutarate.

#### B. COMPOSITION

The composition of the **Custodiol® HTK Solution** follows the formula of Bretschneider:

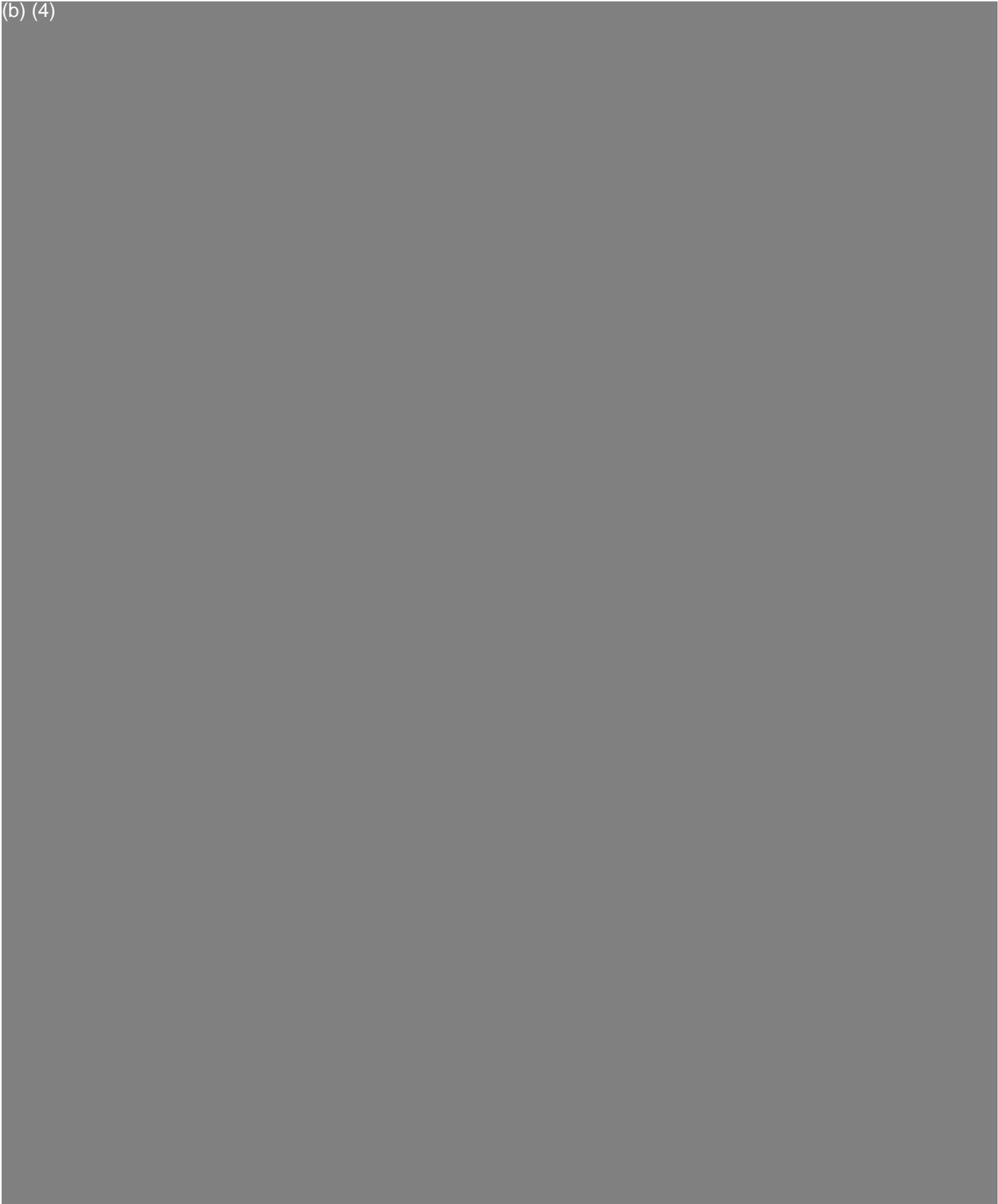
Each liter of aqueous sterile solution contains the following:

0.8766 g	Sodium chloride (15.0 mmol)
0.6710 g	Potassium chloride (9.0 mmol)
0.1842 g	Potassium hydrogen 2-ketoglutarate (1.0 mmol)
0.8132 g	Magnesium chloride • 6H <sub>2</sub> O (4.0 mmol)
3.7733 g	Histidine • HCl H <sub>2</sub> O (18.0 mmol)
27.9289 g	Histidine (180.0 mmol)
0.4085 g	Tryptophan (2.0 mmol)
5.4651 g	Mannitol (30.0 mmol)
0.0022 g	Calcium chloride (0.015 mmol)

All components are USP or EP (European Pharmacopoeia) grade, except for the 2-ketoglutarate. A USP or EP specification for 2-ketoglutarate does not exist, but the company purity specification chosen for this substance is very similar to those of other USP specifications for amino acids as shown in the following table:

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(b) (4)



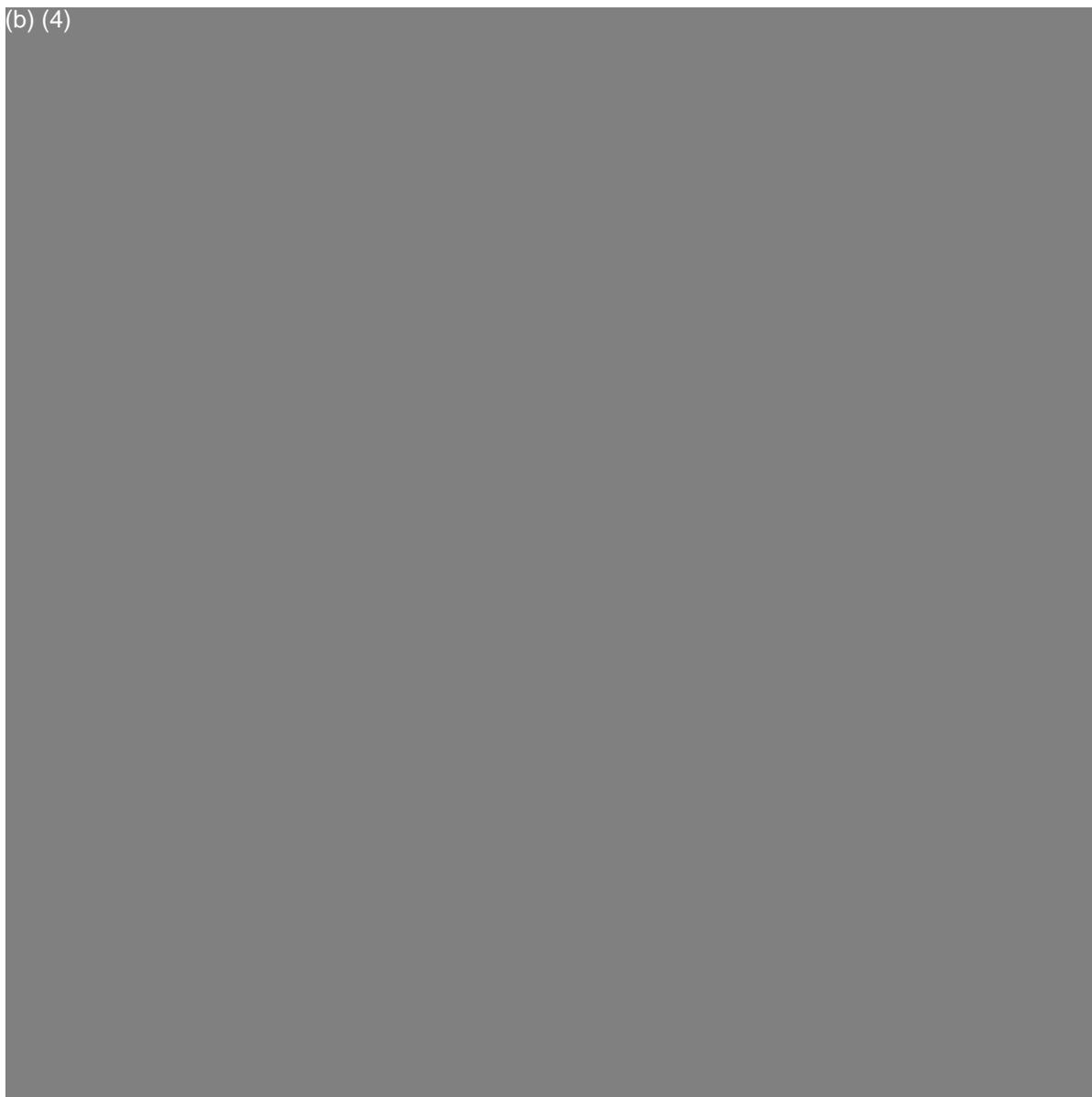
**C. PROPERTIES**

(b) (4)



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(b) (4)



**D. STABILITY AND IMPURITIES**

**Custodiol** is labeled for a one-year expiration date. Information on stability that supports this expiration date is included in **Exhibit 7**,

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(b) (4)



**E. PRODUCT RELEASE TESTING**

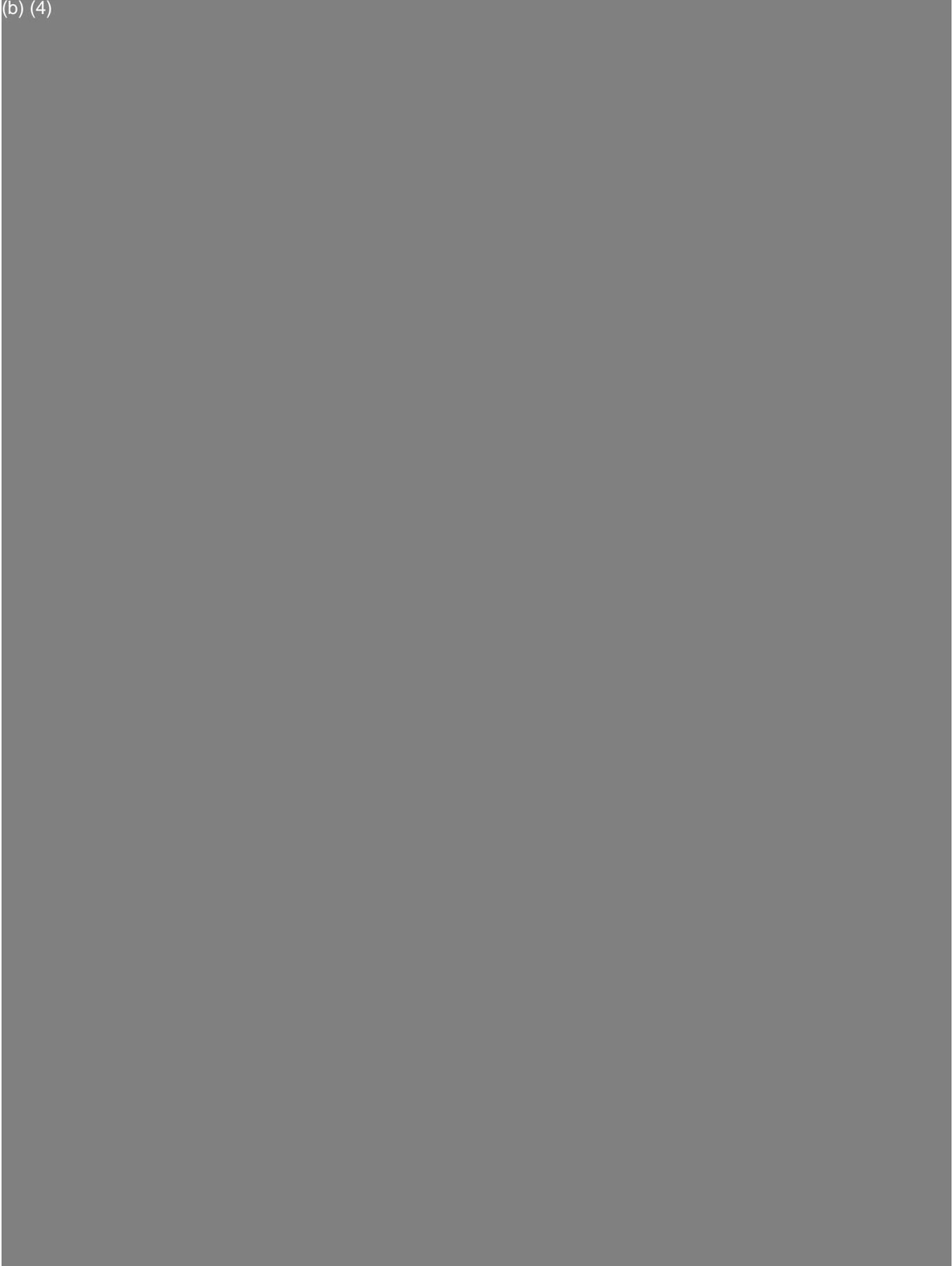
(b) (4)



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(b) (4)



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(b) (4)



#### F. CONTAINERS

The **HTK Solution** is available in one-liter bottles, described in Section 7.2.4.3 of **Exhibit 5**, and in five-liter plastic containers, described in **Exhibit 10**. The larger size is made from polypropylene (Vestolen P 6500) which complies with EP VI.1.2.2.3, "Propylene for containers (used) for filling with parenteral preparations," (equivalent to USP XXII). The polypropylene material also complies with 21 CFR 177.1520 (olefin polymers) and 178.2010.

**HTK Solution** is also available in Europe and elsewhere in 100 ml bottles for other indications that require only small volumes, but these small bottles will not be marketed in the U.S. for the kidney indication.

The elastomeric stopper WI902 meets the requirements of ISO887/A1 (see **Exhibit 18** for Amendment 1 to ISO887). Furthermore, the stopper

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WI902 meets the requirements of USP XXII for "Systemic Injection Test" and "Intracutaneous Test." **Exhibit 19** has additional information on the WI902 stopper which is used for both one-liter and five-liter containers.

**G. STERILIZATION**

The storage bottles are not sterilized prior to filling with HTK. The procedure used by F. Köhler Chemie for cleaning and filling the bottles is outlined in **Exhibit 5** (section 7.2.4.3). Sterilization of the filling equipment and filling and sterilization of the filled bottles is described in section 7.2.4.4 of **Exhibit 5**. The assured SAL is  $10^{-6}$ . The quality assurance procedure requires that the lot testing show no growth of the indicator, so the actual sterility level is more favorable in practice. The D value suggested by the details of the lot testing is about 10 D.

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## SECTION III

### SUBSTANTIAL EQUIVALENCE

#### A. INTRODUCTION

The **Custodiol HTK Solution** is within a type of device called kidney perfusion systems and are considered by FDA to be Isolated Kidney Perfusion and Transport System and Accessories, devices which are described in a regulation, 21 CFR 876.5880, and are classified as Class II devices under the responsibility of the Gastroenterology Devices Panel.

#### B. PREDICATE DEVICE

The **Custodiol HTK Solution** is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996.

#### C. SUBSTANTIAL EQUIVALENCE

The Substantial Equivalence Algorithm was included in **Section I** this submission as **Figure 1.1**.

##### 1. Does the New Device Have the Same Indications Statement?

No. The **Custodiol HTK Solution** has a slightly different indications for use statement from the legally marketed predicate device. The predicate device 510(k) is indicated for use as "a general solution for most organs, both for initial cooling during in situ donor organ flushing and for subsequent cold storage," while the **Custodiol** solution is indicated for "perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor." Note, however, that the **Custodiol HTK Solution** indications statement is essentially contained within the predicate indications statement, and only slightly reworded.

##### 2. Do the Differences Alter the Intended Effect?

No. The differences do not alter the intended effect. Both solutions are used to preserve and cool organs for transplant. That is, they have the same intended use.

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**3. Does the New Device Have the Same Technological Characteristics?**

Yes. The **Custodiol HTK Solution** has the "same technological characteristics" as the predicate devices. Both are composed of electrolytes and other naturally occurring substances in aqueous solution designed to provide ischemic tolerance.

**4. Are the Descriptive Characteristics Precise Enough to Ensure Equivalence?**

No. The descriptive characteristics may not be sufficiently precise to assure substantial equivalence since the composition is somewhat different from that of the predicate device. However, a side-by-side comparison of the descriptive characteristics of the **Custodiol HTK Solution** and the predicate device is presented anyway in Table 3.1 below.

**5. Are Performance Data Available to Assess Equivalence?**

Yes. **Section IV** summarizes the performance data for the HTK solution.

**6. Do the Performance Data Demonstrate Equivalence?**

Yes. As discussed in more detail in **Section IV**, the performance data demonstrate that the performance of the HTK solution is equal to or better than that of the predicate solution for the intended use.

The primary evidence for performance comes from two large prospective randomized clinical trials carried out in Europe that compare the performance of three solutions for kidney preservation. The three solutions are the HTK solution, the Belzer UW solution (the predicate device), and the Euro-Collins solution (which served as a predicate device for the Belzer UW premarket notification). The primary conclusion of this study was that the HTK and UW solutions "provided a significantly lower incidence of delayed graft function compared to Euro-Collins solution." Furthermore, delayed graft function (DGF)

*requiring two or more dialysis treatments in the 1<sup>st</sup> postoperative week was 20% (107/544) in the HTK [group], 25% (66/266) in the UW [group], and 32% (85/268) in the EC group ( $p = 0.001$ ). For all risk factors, DGF was lower in the HTK and UW groups*

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*than in the EC group. Postoperative serum creatine values in functioning grafts decreased more rapidly in HTK- and UW-preserved kidneys than in the EC-preserved kidneys. The median creatinine clearance on day 14 was 58 ml/min in HTK kidneys, 49 ml/min in UW kidneys and 38 ml/min in EC kidneys.*

Data supporting the other indications are also included in **Section IV**.

**6. Substantial Equivalence**

The decision algorithm brings us to a determination of Substantial Equivalence, as defined in the Federal Food, Drug, and Cosmetic Act.

**D. COMPARISON OF DESCRIPTIVE CHARACTERISTICS**

Table 3.1, the Side-by-Side Comparison Table, provides a comparison of the characteristics of the **Custodiol HTK Solution** with the predicate device.

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**TABLE 3.1**  
**Product Comparison Table**

Items	Custodiol HTK Solution	Belzer UW Solution
Intended Use	Custodiol HTK Solution is indicated for perfusion and flushing donor kidney prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.	This solution is intended for flushing and cold storage of organs including kidney, liver and pancreas at the time of their removal from the donor in preparation for storage, transportation and eventual transplantation into a recipient.
Constituents in Common		
Sodium	29 mmol/L	15 mmol/L
Potassium	10 mmol/L	125 mmol/L
Magnesium	4 mmol/L	5 mmol/L
Other Constituents		
Chloride	50 mmol/L	
Calcium	0.015 mmol/L	
Histidine	180 mmol/L	
Histidine HCl	18 mmol/L	
Mannitol	30 mmol/L	
Tryptophan	2 mmol/L	
Ketoglutarate	1 mmol/L	
Phosphate		25 mmol/L
Lactobionate		100 mmol/L
Raffinose		30 mmol/L
Glutathionate		3 mmol/L
Hydroxyethyl starch		50 g/L
Adenosine		5 mmol/L
Insulin		100U/L
Decatron		8 mg/L
Penicillin		133 mg/L
Allopurinol		1 mmol/L
pH	7.1 at 25 °C, 7.4 at 4 °C	7.4
Osmolality	310 milliosmal/kg	373 milliosmal/kg

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**E. COMPARISON OF LABELING**

The intended use statement from the package insert of ViaSpan Belzer UW Solution is:

This solution is intended for flushing and cold storage of organs including kidney, liver and pancreas at the time of their removal from the donor in preparation for storage, transportation and eventual transplantation into a recipient.

The indications for use statement for the Custodiol HTK Solution is:

*Custodiol HTK Solution is indicated for perfusion and flushing of donor kidney prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.*

The Custodiol indications for use statement is very similar to that for ViaSpan, except that only the kidney indication is included for Custodiol. Section IV summarizes the evidence for safety and effectiveness for the kidney application.

The precaution for ViaSpan that is necessary because of its relatively high potassium concentration, namely that the donor organ must be flushed free of ViaSpan before reperfusion is established in the recipient, is not necessary for Custodiol because its potassium concentration is much lower, 10 mmol versus 125 mmol.

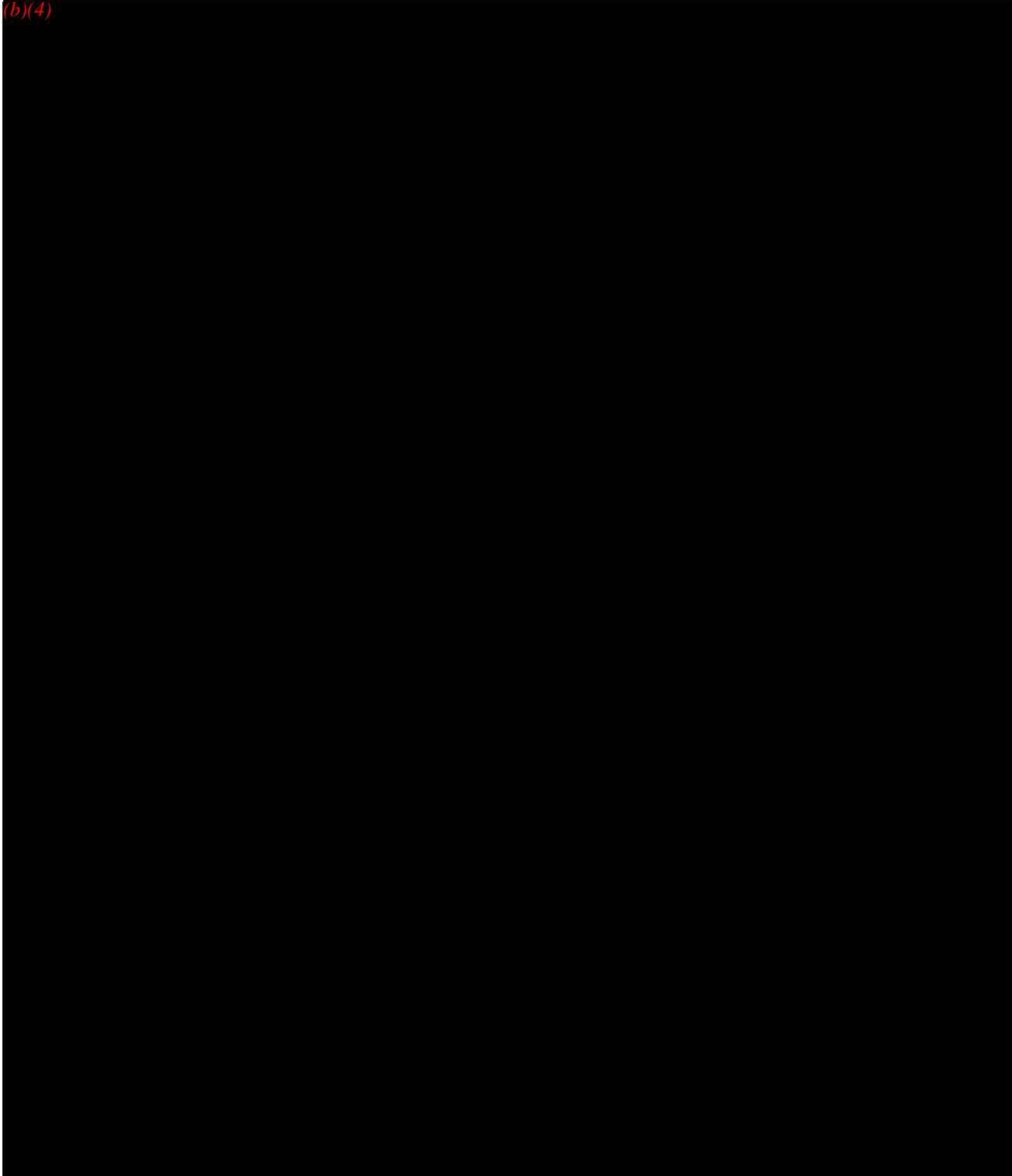
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## SECTION IV

### CLINICAL AND OTHER PERFORMANCE DATA

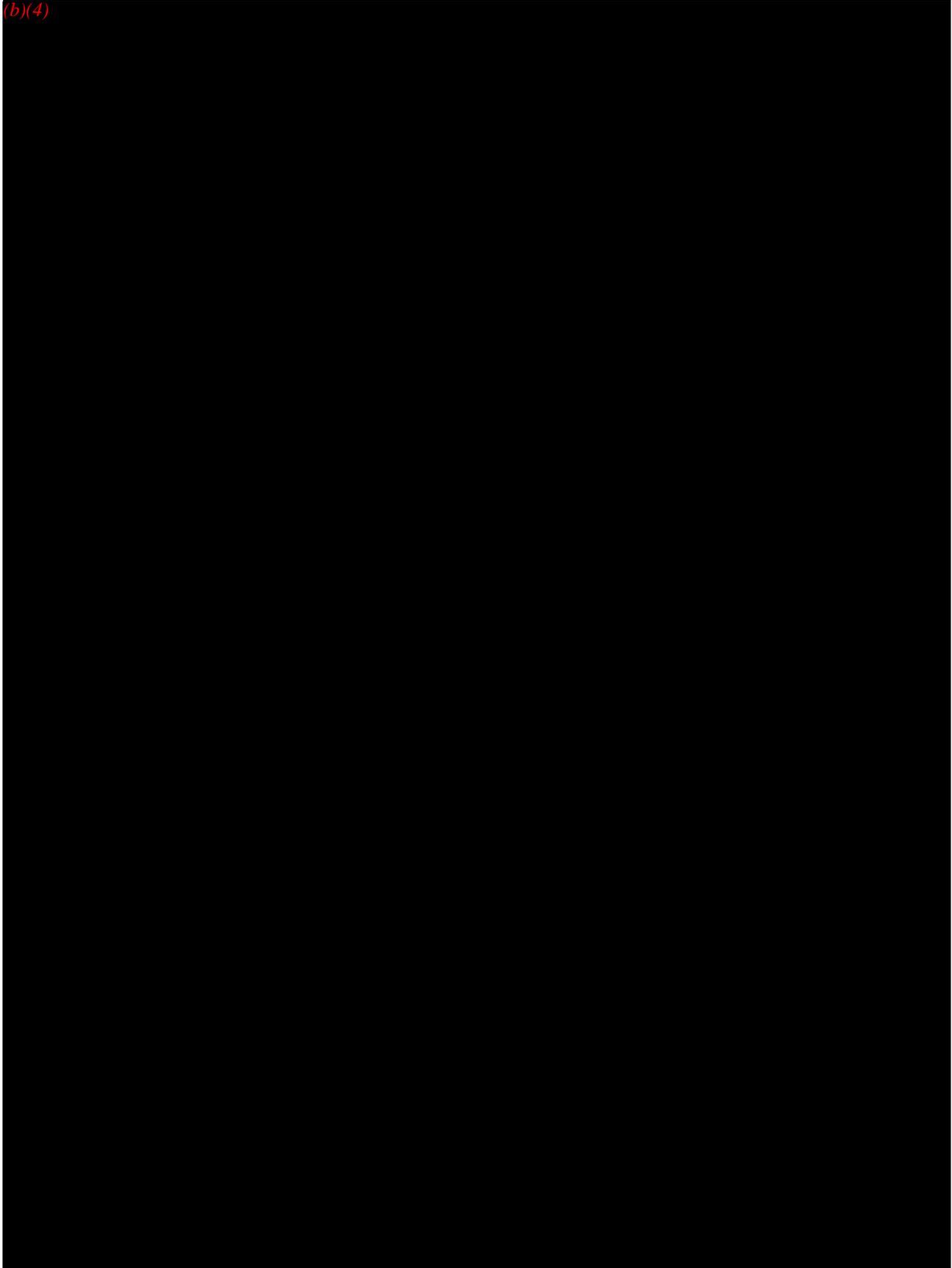
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## SECTION V

### LABELING

This section contains the product labeling: claims, instructions for use, and promotional literature.

#### A. CLAIMS

See the Statement of Indications for Use (see **Exhibit 3**).

#### B. INSTRUCTIONS FOR USE

The Package Insert for the product is included at the end of this section.

#### C. PACKAGE LABELING

The label affixed to the product package is illustrated on the following page. The label includes all of the required information: Company identification, address, telephone number, device name, prescription statement, formula, and lot number. In addition, the statement regarding storage at proper temperature (requested by FDA) has been added.

#### D. PROMOTIONAL MATERIALS

Draft promotional literature to be used with the device follows the package labeling in this section.

#### E. PREDICATE LABELING

Copies of the predicate labeling, including selected pages from the Package Insert, may be found in **Exhibit 20**.

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(Package Label)

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Labeling

*fluted*

1000 ml perfusion solution

Custodiol®  
Bretschneider HTK solution  
For kidney preservation

1000 ml perfusion solution contains

0,8766 g sodium chloride	=	15,0 mmol/l
0,6710 g potassium chloride	=	9,0 mmol/l
0,1842 g potassium hydrogen 2-ketoglutarate	=	1,0 mmol/l
0,8132 g magnesium chloride x 6 H <sub>2</sub> O	=	4,0 mmol/l
3,7733 g histidine x HCl H <sub>2</sub> O	=	18,0 mmol/l
27,9289 g histidine	=	180,0 mmol/l
0,4085 g tryptophan	=	2,0 mmol/l
5,4651 g mannitol	=	30,0 mmol/l
0,0022 g calcium chloride	=	0,015 mmol/l

in water for injections

Osmolality: 310 mosmol/kg

Anion: Cl 50 mEq

Solution for perfusion in connection with kidney transplantation.

Do not use the solution if it is not clear or if the container is damaged!

**Custodiol solution must be stored at the recommended temperature (8 °C – 15 °C)**      Protect from light  
Sterile and pyrogen-free

Batch number:                      /expiry date:

Caution. Federal law restricts this device to sale by or on the order of a physician.

Dr. F. Köhler Chemie GmbH  
P.O. Box 1117, D-64659 Alsbach-Hähnlein  
Germany

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## EXHIBIT 1

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## 510(k) Summary

### Custodiol® HTK Solution

Common/Classification Name: Isolated Kidney Perfusion and Transport System and Accessories, 21 CFR 876.5880

Dr. Franz Kohler Chemie GmbH  
Postfach 1117  
D-64659 Alsbach-Hahnlein  
Germany

Contact: E. Schaffner, M.D. Prepared: June 16, 1999

#### A. LEGALLY MARKETED PREDICATE DEVICES

The **Custodiol HTK Solution** is substantially equivalent to the Viaspan Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996.

#### B. DEVICE DESCRIPTION

The HTK solution is intended for perfusion and flushing donor kidneys prior to removal from the donor and for preserving the kidney during hypothermic storage and transport to the recipient. HTK solution is based on the principle of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intensive buffering of the extracellular space by means of histidine/histidine HCl, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen supply. Only a small portion of the osmolality of the HTK solution is due to the sodium and potassium. The composition of HTK is similar to that of extracellular fluid. All of the components of the HTK solution occur naturally in the body.

The HTK solution is relatively low in potassium concentration so that residual solution in the transplanted organ poses no danger to the recipient. This is particularly important in organs that take up relatively large amounts of the perfusate, which may find its way into the recipient's circulation.

The HTK solution has a low viscosity, even at low temperatures. This characteristic assures rapid flow rates during initial perfusion, allowing the organ to be quickly cooled.

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**C. INDICATIONS FOR USE**

Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

**D. SUBSTANTIAL EQUIVALENCE SUMMARY**

The **Custodiol HTK Solution** is a medical device, and it has a similar indications for use as the legally marketed predicate device. While the indications for use statement is not identical to that of the predicate device, the intended use is clearly the same.

The **Custodiol HTK Solution** has the same technological characteristics as the predicate devices. However, the characteristics may not be sufficiently precise to assure equivalence through a point by point comparison. Therefore, extensive clinical data has been collected by the sponsor and others. The performance data clearly demonstrates equivalence.

**E. TECHNOLOGICAL CHARACTERISTICS**

Both the Custodiol HTK Solution and the predicate device are solutions containing electrolytes, buffering agents, and other materials occurring naturally in the body. Both solutions are intended to reduce metabolism and preserve physiological conditions of explanted organs and tissue during cold storage.

**F. TESTING**

Several clinical studies have been reported that compared the performance of Custodiol HTK Solution with the Viaspan Belzer UW Solution. These studies have compared survival rates and other outcome measures. The primary evidence for the equivalence of Custodiol and UW solutions has come from the 47-center randomized clinical study carried out under the guidance of the Eurotransplant organization of Leiden, The Netherlands. Over a thousand kidneys were included in the study.

This study showed that the HTK solution performs as well as the UW solution and significantly better than EC solution for kidney transplants. The overall kidney survival rates from the 47-center study for HTK versus UW at four time points were:

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	<u>HTK</u>	<u>UW</u>
1 Month	91%	91%
12 Months	83%	82%
24 Months	77%	74%
36 months	74%	68%

**G. CONCLUSIONS**

The clinical and other performance data amply demonstrate that Custodiol performs as well as the predicate device. This pre-market submission demonstrates Substantial Equivalence as defined and understood in the Federal Food Drug and Cosmetic Act and various guidance documents issued by the Center for Devices and Radiological Health.

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## EXHIBIT 2

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DR. F. KÖHLER CHEMIE

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**PREMARKET NOTIFICATION**

**TRUTHFUL AND ACCURATE STATEMENT**

(As Required by 21 CFR 807.87 (j) )

I certify that, in my capacity as president, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

Dr. Franz Köhler Chemie GmbH



Dr. Gernot Köhler (President)

11. May 1999

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## EXHIBIT 3

STATEMENT OF INDICATIONS FOR USE

510(k) Number (if known): \_\_\_\_\_

Device Name: Custodiol HTK Solution

Indications For Use:

Custodiol HTK Solution is indicated for perfusion and flushing donor kidneys prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

\_\_\_\_\_  
Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use \_\_\_\_\_  
(Per 21 CFR 801.109)

OR

Over-The-Counter Use \_\_\_\_\_

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## EXHIBIT 4

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**EXHIBIT 5**

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725 SPECIFICATIONS AND ANALYTICAL METHODS

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## EXHIBIT 6

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Expert opinion

on the pharmacology and toxicology

of a cardioplegic and organ-protecting solution based on the principle of inactivating organ function by withdrawal of extracellular sodium and calcium together with intensive buffering of the extracellular space by means of histidine/histidine hydrochloride, so as to prolong the period for which the heart and kidneys will tolerate interruption of blood and oxygen supply (prolongation of ischaemia tolerance time).

from the

Centre for Physiology and Pathophysiology,  
University of Göttingen

by

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A. Fundamentals

A.I. Requirements of open heart surgery and conditions for the technique of extracorporeal circulation (ECC) (heart-lung machine)

New surgical procedures for the reconstruction of major congenital cardiac malformations, improvements in heart valve prostheses and advances in coronary artery surgery have opened up new possibilities for the complete recovery of very ill patients. An essential prerequisite for these generally lengthy operations on the open heart was to improve heart-lung machines so as to minimize trauma to the corpuscular elements of the blood, and to bring smaller priming volumes and more reliable handling. Heart-lung machine technique is nowadays no longer a limiting factor for complex cardiac operations, although it is certainly capable of further improvement. In many cases the limiting factor is in fact is the ischaemia tolerance of the heart.

If blood and oxygen supply via the coronary arteries is completely cut off, the heart, previously working normally as a circulatory pump, will very soon - after only 10 beats - begin to show signs of breakdown of energy metabolism and performance. For this reason 321

some cardiac surgeons prefer to maintain a separate 000175

more or less continuous supply of blood to the coronary arteries by means of special pumps and cannulas. However, this coronary perfusion technique has grave disadvantages: it is not always possible to cannulate all the main branches of the coronary system; the coronary perfusion catheters obstruct the surgical field; aspiration of coronary venous blood damages blood cells; as the heart is still perfused, blood tends to obscure the operation field, and the beating or fibrillating movement of the heart makes it impossible to use an operating microscope for microsurgical techniques. Lastly, there are now increasing numbers of reports of acute cardiac failure in the postoperative period.

These disadvantages of coronary perfusion quickly led to the alternative approach, namely operating on the nonbeating heart cut off from its blood and oxygen supply. The simplest method of artificial cardiac arrest, still in use today for brief operations, is complete interruption of blood supply to the heart previously relieved of its circulatory work; this is "ischaemic cardiac arrest". The heart stops within a short time and will survive - depending on temperature and pre-existing injury - for 10 - 30 minutes.

Thereafter, however, the far reaching exhaustion of energy reserves necessitates a lengthy recovery period

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with continuing relief of the heart by means of a heart-lung machine. Another drawback is the increased risk during the early postoperative days after prolonged ischaemic cardiac arrest. Furthermore, the surgeon is under great pressure when using simple ischaemic cardiac arrest for more difficult and complex operations, since the very limited ischaemia tolerance time must not be exceeded whatever the circumstances.

The time constraints on surgery under purely ischaemic cardiac arrest prompted numerous initiatives in the fifties and sixties aimed at improving artificial cardiac arrest or enhancing "myocardial protection". Among the substances used to induce cardiac arrest were acetylcholine, potassium citrate, potassium chloride, magnesium salts and Novocaine (procaine), all of which have now been discarded (2, 7, 20, 21, 34, 60).

The techniques developed for inducing cardiac arrest, otherwise known as cardioplegia, can be divided into two categories:

1. Cardioplegic solutions of extracellular type.

These solutions are similar to extracellular fluid though their ionic composition has been modified.

The main difference is that their potassium and magnesium concentrations have been raised so as to

induce cardiac arrest. One example of this type **000177**

of cardioplegic solution is the St. Thomas's solution developed by Hearse. Many of these solutions are buffered with bicarbonate.

2. Cardioplegic solutions of intracellular type. These solutions are closer to intracellular fluid. Cardiac arrest is brought about by withdrawal of extracellular calcium and exchange of extracellular fluid for a calcium-free, low sodium solution. The buffer substance employed is histidine.

The latter type is similar to the calcium-free, low sodium "cardioplegic solution" described by the author in 1964. This original solution offered - given the same heart temperature - an ischaemia tolerance time about three times longer than that permissible under simple ischaemic cardiac arrest. However, advances in surgical technique in the last decade suggested that further prolongation of ischaemia tolerance time would be desirable. Yet the necessary recovery time had to be kept as short as possible - no more than 10 minutes - in order to keep the total duration of ECC within reasonable limits. This objective was not attainable with existing techniques. The idea thus arose of combining a technique that minimizes energy requirements with a procedure that provides intensive buffering of the myocardial extracellular compartment.

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with the aim of improving anaerobic energy provision. This "organ-protective" combination ultimately allowed a further doubling of ischaemia tolerance time to about 240 minutes at 25°C, thus giving a total time gain six times greater than that given by purely ischaemic cardiac arrest at the same temperature (5, 6, 8, 23, 29, 33, 35, 64, 65, 69, 70, 71, 73, 74, 89, 90).

A.II            Physiology and biochemistry of aerobic and anaerobic energy supply to the heart

The energy requirement of the heart working under resting conditions - expressed in oxygen equivalents - is about 7 ml O<sub>2</sub> per minute per 100 g. Under maximal load energy turnover can increase temporarily to ten times this value. The energy requirement of the beating heart can be broken down into the following "consumers":

- (a) The contractile system, in the strict sense.
- (b) The outer muscle cell membrane which provides the electrophysiological stimulus.
- (c) The intracellular membranes of the sarcoplasmic reticulum, which inactivates the contractile system by reabsorbing calcium ions.
- (d) The maintenance metabolism of the remaining structures.

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After artificial arrest, the energy requirement of the heart will therefore be reduced, and the reduction will depend on the degree to which the contractile system is inactivated and relaxed and the extent to which the loads on the ion pumps of the external cell membrane and internal membrane structures are relieved. However, when considering measures to cut down energy requirement with the purpose of prolonging ischaemia tolerance time it is essential to remember that they must be rapidly reversible and must not reduce energy input to a level below that necessary for structural maintenance metabolism. Given optimal inactivation of the heart, the energy requirement at 35°C is 0.8 ml O<sub>2</sub>/min x 100 g and at 5°C 0.1 ml O<sub>2</sub>/min x 100 g.

The very high energy turnover of the beating heart can be met only via the aerobic pathway, i.e., by "burning" substrates - essentially glucose, lactic acid and fatty acids - to CO<sub>2</sub> and H<sub>2</sub>O with the aid of oxygen. Without oxygen the substrates can be only partially broken down along the anaerobic pathway and can hence yield only a fraction - roughly 1/13 - of the energy stored in them. The anaerobic energy supply of the heart is based essentially on breakdown of the stored glycogen to form lactic acid. In addition, the stored energy of phosphocreatine and part of that of adenosine

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triphosphate (ATP) can be used. However, ATP depletion exceeding 30% of normal will considerably prolong recovery time, and an ATP level of about 50% of normal is the lower limit for restarting the heart under clinical conditions (1, 3, 4, 9, 11, 12, 14, 24, 25, 27, 36).

Anaerobic energy supply to the heart by glycogenolysis, i.e. by the breakdown of glycogen to lactic acid, is fundamentally limited by three factors:

1. Glycogen reserves are limited, and there is no way of increasing them.
2. The increasing self-inhibition of glycolysis due to the acidification of myocardial cells caused by the end product, lactic acid.
3. The obviously unavoidable decrease in the total ATP content of the cells (despite partial resynthesis of ATP) which occurs during anaerobiosis, and which must not drop below a certain minimum level if glycolysis is to continue.

The reasons why anaerobic glycolysis in the myocardium is inadequate for ATP regeneration are not fully clear, but they may perhaps affect only specific parts or compartments of the cell. Analysis of lactic acid and

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glycogen concentrations in hearts which have come to the end of their potential for recovery has shown that the level of glycogen reserves does not usually limit survival time. Rigor mortis sets in even when substantial glycogen reserves are still present, provided that the initial levels were not abnormally low. This finding suggests that the capacity for glycolysis could be enhanced by eliminating the self-inhibition caused by lactic acidosis. This could be done by intensive buffering, which would also utilize the relatively large extracellular space of the heart: this amounts to about 50% of the intracellular distribution volume.

A.III The heterogeneity of the parts of the heart

Endeavours directed towards optimizing artificial arrest (cardioplegia) and the related need to provide optimal protection against any interruption of blood flow (ischaemia) must take into account the fact that the heart is composed of a variety of tissues with special requirements which have to be met by a single protective solution. This solution must therefore be formulated on physiological principles applicable to all the tissues which make up the heart. The following kinds of cardiac tissue must be taken into account:

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1. The working myocardium, composed of myocytes.
2. The stimulus generating and conducting system, which consists of muscle tissue having a special structure.
3. Special endocrine cells and receptor cells.
4. The parts of the autonomic nervous system situated within the heart.
5. The "smooth muscle cells" of the coronary vessels.
6. The coronary endothelium and the endothelial structures of the valves and endocardium.

For rapid and reliable induction of artificial cardiac arrest it is essential that the cardioplegic solution should maximally dilate the coronary arteries. Any coronary constriction would delay or prevent homogeneous equilibration of the myocardium, especially of its inner layers. The changeover or equilibration to the ionic composition of the cardioplegic solution must comprise the interstitial compartment as well as the intravascular compartment, and should if possible be completed within a few minutes.

A.IV            The concept of an organ-protective cardioplegic solution consisting solely of substances naturally present in the body

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namely enhancement of the capacity for and the efficiency of anaerobic energy production from glycolysis by means of intensive buffering, can be achieved in practice only if the "osmotic margin" - the high concentration of buffer substance of about 200 mmol/l necessary for the purpose - is provided in advance in the composition of the solution, i.e., if the other constituents of the solution do not create an osmolarity higher than about 100 mosmol/l, so that the total osmolarity of the cardioplegic solution does not significantly exceed the normal osmolarity of the plasma and the intracellular fluid of about 300 mosmol/l. Furthermore, the buffer must have the following properties:

1. Minimal adverse biological reactions, even in high concentration.
2. Adequate solubility in water to provide the required concentration.
3. Favourable pK value even at low temperatures.
4. Good powers of permeation through the capillary endothelium to ensure equilibration of the interstitial space.
5. Minimal powers of permeation through cell membranes to ensure osmotic equilibrium.
6. As compared with its binding capacity for H<sup>+</sup> ions, it must have weak binding capacity for bivalent ions such as calcium and magnesium.

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In the present state of knowledge, these requirements appear to be best met by histidine buffer (58,92).

These requisites for effective buffering of the extracellular space can only be fulfilled if the buffer concept is combined with the concept of a cardioplegic solution acting by withdrawal of extracellular sodium and calcium. Extensive experimental studies have shown that a decrease in sodium concentration to about 1/10 of the normal value (to 15 mmol/l) and a decrease in ionized calcium to about 1/100 of the normal value (to 15  $\mu$ mol/l) are optimal. The most favourable potassium concentration for use at these sodium and calcium concentrations is 10 mmol/l, and the best magnesium concentration is 4 mmol/l. The histidine/histidine hydrochloride concentration can thus be brought to 180/18 mmol/l. For the purpose of special membrane protection tryptophan is added at 2 mmol/l. Ketoglutarate at 1 mmol/l serves as a substrate for aerobic energy production during induction of cardioplegia. The remainder of the osmotic margin is made up by mannitol at 30 mmol/l, a substance which also offers beneficial properties as a "free radical scavenger". The total osmolarity of the solution is therefore 310 mosmol/l.

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Consisting as it does entirely of substances naturally present in the body, and having a relatively low potassium concentration, the solution offers the advantage of a wide therapeutic safety margin.

B. Pharmacological action on the heart

B. I Pharmacodynamics

The mechanisms of action of this cardioplegic solution are

1. Overall suspension of activation processes in all membrane structures capable of excitation, whether of muscular, neural or endocrine nature.
  2. Enhancement of glycolytic energy production by intensive buffering of the entire extracellular compartment.
  3. A consequent delay in the onset of critical intracellular acidosis and,
  4. on the basis of (2) and (3), postponement of critical intracellular oedema consequent on breakdown of osmotic regulation of the cell.
- The effects noted under (2) and (4) are especially pronounced, because energy requirements are minimized by the mechanism noted under (1).

This minimization of energy turnover is effective

0°C, and, in keeping with the RGT rule (van't Hoff's law governing the relation between reaction rate and temperature) it is most pronounced at low temperatures.

Cardiac arrest can be induced whatever the conditions, irrespective of any supplementary pharmacological drive and of any electrical or mechanical stimulation. The residual energy requirement of the inactivated heart is, however, not governed by temperature alone; it is also to some extent dependent on thyroid hormone and catecholamine effects and on appropriate blocking drugs.

Used as recommended with an initial perfusion pressure of 100 mmHg (for adults), the cardioplegic solution induces cardiac arrest 10 - 30 seconds after starting perfusion. Temperature equilibrium is reached after 2-4 minutes of continued perfusion, and after 7-12 minutes' perfusion oxygen consumption falls to a minimum corresponding to the temperature level reached. The recommended refrigerator temperature of about 5°C for the cardioplegic solution produces a heart temperature of about 10°C after a few minutes' perfusion; under these conditions the O<sub>2</sub> consumption of the arrested heart is 0.15 ml/min x 100 g before the onset of anaerobiosis. This small O<sub>2</sub> requirement is met (with a wide safety margin) by the O<sub>2</sub> content of the cardioplegic solution; in equilibrium with air at 5°C

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the latter contains about 0.6vols % O<sub>2</sub>. The partial pressure of oxygen in the venous efflux of cardioplegic solution is generally above 100 mmHg after as little as 2 minutes' perfusion time.

The fundamental pharmacodynamic and pharmacokinetic research work was carried out mainly from 1960-1980 in numerous experiments chiefly in dogs. Once any possibility of acute harm to human beings had been completely excluded, this work opened the way for pioneering use in patients. The task of drafting this report more than two decades after the solution was first used in patients has presented certain difficulties in that the procedures employed in those days, notably during clinical use, obviously did not conform to all the formal regulations in force today (e.g., GCP). This report is accordingly based on numerous findings published in the international literature in recent decades, some by the author himself and some by other workers. Attention is drawn to the exhaustive collection of references at the end of this report.

## B. II Pharmacokinetics

The induction of cardioplegia and myocardial protection, like their reversal and the reactivation or restarting of the heart, do not coincide in time with

the "influx" of cardioplegic solution into the intravascular space and the "washing out" phase, but they do coincide with equilibration of the interstitial space with the new ionic medium. Whereas exchange within the intravascular space is completed within the first minute, exchange in the interstitial space takes two or three minutes. Minor shifts in the extracellular milieu may necessitate even longer times, as a completely new steady state of aerobic metabolism is not reached until perfusion with the protective solution has been in progress for at least 7 minutes.

To ensure prompt discontinuation of cardioplegia and restarting of the heart it is essential not to use any drugs that have prolonged effects. Once the heart has been reconnected to the circulation, it will begin to beat again about one minute after resumption of blood flow through the coronary vessels. Provided it is within the tolerance limits of energy status, intracellular acidosis and intracellular oedema, the heart will resume its normal rhythm within a few minutes; if reperfusion and rewarming are uneven cardiac activity may begin with fibrillation, but this can generally be corrected with a single electric shock after waiting for about 3 minutes.

As already mentioned, the action of HTK solution depends solely on ion exchange in the myocardium at  
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cellular level. In pharmacodynamic terms, therefore, the solution cannot produce any unwanted effects unless large amounts enter the systemic circulation. For technical reasons this means that during cardiac surgery - unless the perfusate is aspirated - there may be systemic uptake of up to the total amount of solution perfused, i.e. up to 3000 ml. The consequences of systemic uptake of cardioplegic solution are theoretically as follows:

1. Water balance (haemodilution). A haemodiluting effect from systemic uptake of a crystalloid solution during the course of coronary perfusion can be expected, though the measurable effects are not as great as those of the primary dilution resulting from the priming volume of the heart-lung machine. Some minor uptake of water, probably distributed within the interstitial compartment for the first 24 hours, must be expected, though it will be completely eliminated within 48 hours. Beneficial effects are likely from the improvement in blood rheology, which may be reflected both in improved intraoperative cerebral blood flow and in a lower perioperative infarct rate.

2. Electrolytes and trace elements

Sodium:

After the cardioplegic solution has been

completely taken up, the serum sodium level drops

briefly below the normal range. Total osmolarity is unaffected and serum levels return to normal within two hours. The fall in serum sodium level during the reperfusion phase may conceivably have beneficial effects.

Potassium: The raised potassium concentration in the cardioplegic solution has practically no measurable effects on serum level. At most, any previous slight fall in serum potassium level will be made good. Postoperatively, after total uptake of the cardioplegic solution, patients require noticeably less potassium replacement.

Magnesium: The cardioplegic solution contains magnesium and its uptake raises serum magnesium level above normal for a short time. Because many patients have increased magnesium requirements in the perioperative phase, this might help to reduce any perioperative magnesium replacement which would otherwise be necessary.

Zinc: There is an initial fall in serum zinc level caused by haemodilution from the use of the heart-lung machine. Even if the cardioplegic solution is completely absorbed, this is not enough to make good any systemic zinc depletion.

3. Aminoacid uptake

Histidine: Full uptake of the histidine-containing solution can have excessive

repercussions on other amino acids as well. During the first 24 hours short-chain amino acids rise above the normal range. Double-chain amino acids react with a distinctly smaller decline; the significance of these amino acids for postischaemic cardiac metabolism is well known. The ketoglutarate added to the cardioplegic solution may be of value in maintaining normal serum levels of glutamic acid, as it is the precursor of the latter. It occupies a key position on the pathway leading to the intermediates of the citric acid cycle and can therefore raise intracellular oxidative energy production.

Uptake of the solution with the amino acids which it contains can thus moderate some of the typical changes of postoperative metabolism. Amino acids which occupy important positions in the intracellular mechanisms of energy production and detoxication can therefore have beneficial effects on postoperative rehabilitation.

Biochemical breakdown of additives:

Potassium hydrogen 2-ketoglutarate: Degradation takes place via the citric acid cycle. Outside the citric acid cycle, acceptance of an  $\text{NH}_3$  group and reaction with

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each L-amino acid leads to glutamine. Glutamic acid can also be formed.

Tryptophan: The volume of solution employed entails uptake of more than 4mmol or about 1 g of tryptophan. Rises in serum level to a maximum of 130  $\mu\text{mol/ml}$  have been found during haemodilution. When given by mouth for therapeutic purposes, serum levels of up to 350  $\mu\text{mol/ml}$  are not unusual. Tryptophan is broken down within a few hours. Biochemical degradation normally takes place by the intervention of ketoglutarate as ammonia acceptor and formation of glutamic acid via indol pyruvate to kinorenin, which is then broken down once more via numerous intermediate stages to oxaloacetate and ketoglutarate with the formation of other glutamic acids. The brevity of the serum peak which follows a single dose, as compared with the sustained change in serum level during continuous medication, proves that there is no danger of systemic toxicity. The dose of 1 g is equivalent to the average quantity of tryptophan in commercial amino acid solutions for parenteral nutrition, for which the recommended daily dose is 1.8 to 2 g. The amount taken up from the cardioplegic solution is considerably less.

Histidine: In the present state of knowledge any harmful effect from uptake of the cardioplegic solution

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with its short duration of action can be ruled out. The total dose of about 70 g amino acids, though approximately equivalent to the resting requirement of a patient on total parenteral nutrition (0.7 g amino acids/kg body weight/day), is not sufficient completely to meet amino acid requirements (1 to 2 g/kg body weight/day) in the postoperative metabolic phase after major surgery such as a cardiac operation. Rapid elimination of histidine from the circulating blood is effected by several available metabolic pathways such as acetylation to N-acetylhistidine, methylation to 3-methylhistidine or formation of carnosine. The typical degradation pathway in the human body is transamination followed by oxidative deamination. The end products are excreted via the kidney and through the skin in the sweat (16,18).

#### B.III. Local side effects

Complete immobility renders the myocardium vulnerable to overstretching. When inducing cardioplegia - especially when carrying out perfusion via the root of the aorta - care must therefore be taken to ensure reliable venting of the left ventricle. Any overdistension - especially of children's and infants' hearts, which have thin walls and relatively little connective tissue - can also induce an unduly high coronary artery perfusion pressure. Small vulnerable

hearts should accordingly be perfused at a maximum pressure not exceeding about 50 mmHg.

The very low concentration of calcium in the solution (50  $\mu\text{mol/l}$ ) reinforces and sustains the suspension of blood coagulation necessary in every open heart operation - any clotting would represent a special risk to the coronary system.

The very low viscosity of the solution is attributable to the omission of colloidal and corpuscular elements and is of special value in patients with coronary artery disease. It ensures rapid and complete equilibration and inactivation, even of poststenotic areas.

The local tolerance of HTK solution is incontestable and there is no question of local side effects on the isolated heart. HTK solution consists exclusively of substances naturally present in the body, and as they are present in reduced concentrations, their effect, i.e. electromechanical decoupling and hence induction of cardiac arrest, also constitutes the sole "desired" side effect on the heart. Other solutions, however, because of their high potassium concentration, are known to be liable to produce serious local side effects postoperatively (postoperative sinus

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arrhythmias), and may even have systemic side effects (hypertension with a raised incidence of strokes).

#### B.IV. Safety

The volume of cardioplegic solution normally used for medium sized human hearts weighing 300 to 400 g is 2 to 4 litres. Dyskiéwicz reported experiments in which dog hearts were perfused for 24 hours, yet were fully capable of resuscitation at the end of that time (19). In our own studies dog hearts weighing about 200 g were continuously perfused for 1 hour, during which up to 30l of the solution was perfused through the coronary system. Taking into account the smaller heart weight, this volume is equivalent to roughly 20 times the amount normally used in cardiac surgery. All four of the (isolated) dog hearts stressed in this way proved to be readily capable of resuscitation and were restarted without delay or complications after subsequent change over to perfusion with Tyrode solution. These experimental findings are in keeping with clinical experience in patients having a well developed non-coronary collateral circulation for the heart, most notably patients with coronary artery disease: in such cases the cardioplegic solution is relatively quickly washed out - in some circumstances

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in as little as 15 minutes - although the ascending aorta is completely clamped and may have been opened as well. Cardioplegic perfusion must then be repeated at shorter intervals. If the normal mode of administering the cardioplegic agent is impracticable because of the need for surgical access to the root of the aorta or because of pathological lesions, retrograde perfusion - via the coronary sinus - is another possibility, though this route usually fails to reach the right ventricle in its entirety. As regards the total volume of cardioplegic solution employed - and irrespective of the mode of perfusion (orthograde or retrograde) - there are no limitations on the therapeutic safety margin; this statement applies to all forms of congenital and acquired cardiac defects and to diseases of the aorta.

C. Pharmacology in the isolated systemic circulation, maintained by the heart/lung machine

All the effects of the solution in the general circulation are quantitatively dependent on the amount of cardioplegic solution which finds its way from the coronary venous system via the right side of the heart into the general circulation, either directly or via a suction system. Depending on the nature of the cardiac defect requiring surgery, the chosen technique, the duration of the operation and the patient's body size,

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the necessary volume of cardioplegic solution varies between 0.1 and 2.0 litres (16,17).

C.I. Flow resistance

The low viscosity, the enhanced magnesium concentration and the greatly reduced concentrations of sodium and calcium in the solution induce a decrease in peripheral flow resistance. This effect is normally desirable because patients not infrequently display "acute hypertension" during extracorporeal circulation (ECC), an abnormality due to vasoconstrictor reactions of unknown origin.

C.II. Renal function

Urine output is augmented by inflow of the solution into the general circulation, although - because of hypothermia during ECC - the kidney usually displays an antidiuretic tendency. This diuresis partially compensates for any excessive diluting effect from the ECC priming volume while the patient is still connected to the heart-lung machine. Forced diuresis during ECC also offers some protection against acute renal failure, formerly a frequent accompaniment of cardiac surgery. Furthermore, the cardioplegic agent possesses direct renal protective effects, as will be apparent

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from the two publications cited at the end of the reference list.

### C.III. Systemic side effects

The general effects and consequences of extracorporeal concentration are sufficiently well known. Despite continuous technical improvement, a perfusion syndrome can arise from contact of air with foreign surfaces or from interference with temperature regulation.

Depending on the time which has elapsed, a wide range of possible mechanisms has been suggested. Deficient lymph drainage, microembolization by air, fat or particles, protein denaturation, intravascular protein aggregations, and endotoxin liberation are known causes. To be distinguished from these are the side effects which might possibly arise from inflow of large amounts of cardioplegic solution into the general circulation.

In principle, any inflow of large amounts of cardioplegic solution into the general circulation will raise potassium and magnesium concentrations in the ECC and lower sodium and calcium concentrations. To arrive at a quantitative estimate of the relevant changes the patient's total extracellular space plus the priming volume for ECC must be taken as the baseline, and not solely the intravascular space. A patient weighing 80

kg has an extracellular space of about 18 litres; together with 2 litres of ECC capacity this makes a total of about 20 litres. An inflow of 2 litres of cardiac solution - which would be the upper limit - would represent only 1/10 or 10% of this. Any resulting increases in potassium and magnesium concentrations in the extracellular space would be negligible, especially as there is usually some fall in potassium level during ECC unless extra potassium is given.

The effect of any substantial inflow of cardioplegic solution on sodium and calcium concentrations in the extracellular compartment is more pronounced, since the concentrations of these electrolytes in the solution differ substantially from their normal extracellular values. The differences are as follows: for sodium  $145-15 = 130\text{mmol/l}$ , for calcium  $2.5 - 0.015 = 2.5\text{mmol/l}$ . Replacement of sodium and calcium, guided by appropriate assays, is therefore necessary during ECC if more than 1 litre of cardioplegic solution has entered the general circulation.

There is no evidence of any side effects due to histamine, though this substance might conceivably arise from histidine; in such circumstances any traces of histamine would be antagonized by the surplus of histidine at the receptors.

Pronounced but short-lasting rises in histidine concentration in the ECC - in adults up to about 20 mmol/l from inflow of 2 litres of cardioplegic solution - are tolerated without adverse clinical signs and are almost completely corrected by intense diuresis within 24 hours. In this connection it should be emphasized that incorporation of about 20% of the solution will result in uptake of 80-90 mmol histidine. This quantity could conceivably rectify or moderate the drop in serum levels affecting short-chain and sulphur-containing amino acids, and also aspartic acid/asparagine/glutamine and proline. Administration of the cardioplegic solution results in the uptake of more than 4 mmol of tryptophan, equivalent to roughly 1 g. Tryptophan is known to have direct pharmacological effects. Measurements carried out by our research group have revealed a rise in serum concentration to a maximum of 130  $\mu$ mol/ml during haemodilution, but also show that the serum level is considerably lower than that known to be produced by oral administration in conventional daily doses. Pharmacokinetic findings in the patients studied confirm that tryptophan is swiftly broken down within a few hours, as stated in the literature. Because the serum peak after a single dose is so brief as compared with the sustained changes in serum level during long-term medication, there is no likelihood of systemic toxicity. A single input of 1 g

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is well below the daily dose of 1.8 to 2 g recommended for parenteral nutrition.

The oxygen content of the cardioplegic solution is 0.6 vols %. This is indeed ample to cover the oxygen requirement of the non-beating heart under hypothermia during selective perfusion, but it is not enough for O<sub>2</sub> transport function during ECC priming. Haemodilution to 70% or temporarily to about 50% of normal offers clear cut advantages during the heart-lung machine phase as compared with whole body perfusion with undiluted blood, but deeper haemodilution entails some danger of oxygen deficiency, especially in the brain. The volume of cardioplegic solution tolerated in the ECC is therefore dependent on the previously set level of haemodilution.

Other evidence, in particular Doetsch's investigations, rules out any risk of acute harm and any probability of late sequelae from systemic uptake of HTK cardioplegic solution (16,18).

#### C.IV. Safety (therapeutic margin)

In the setting of cardiac surgery, the solution is not intended for use in the intact circulation. It is in fact employed for selective perfusion of the coronary

arrest, but not until the pump function of the heart has been taken over by a heart-lung machine. The statements made under C.III. are applicable under these conditions.

If the cardioplegic solution were inadvertently given intravenously, an infusion of 500 ml in 30 minutes would be tolerated by adults without any unusual symptoms or signs. This conclusion is derived from the quantitative estimate set out under C.III. and has also been substantiated by appropriate experiments in dogs.

When using the protective solution in the kidney in situ, a few hundred millilitres might escape into the circulation during the first minute of perfusion via the renal artery, until venous outflow from the kidney is cut off; the resulting short lived increase in dilution effect is well tolerated by the circulation.

#### D. Toxicity

##### D.I. Acute toxic effects on the heart

As stated under B. - and particularly under B.IV. - the therapeutic safety margin in the heart is so wide that under clinical conditions in adults a potentially toxic range will never be reached even with a perfusion volume totalling more than 60 litres.

Nevertheless, if the three fundamental premises are disregarded there is some possibility of "toxic action in the wider sense":

1. If the inactivated, relaxed myocardium is overstretched because of defective ventricular venting or unduly high coronary perfusion pressure.
2. If perfusion flow rates, volumes or pressures are not adjusted in keeping with the physiological conditions in children's or infants' hearts.
3. If the cardioplegic solution infused or pumped into the coronary system is not cooled to a temperature between 5°C and 10°C - as directed.

If the cardioplegic solution is perfused at a temperature of around 37°C the so-called calcium paradox will be initiated after a few minutes. This takes the form of reactivation of the heart with destruction of myocardial cells. Provided the solution is cooled to 10°C or below any possibility of calcium paradox can be excluded even under extreme experimental conditions. The calcium concentration of the nominally calcium-free solution is approximately 15  $\mu\text{mol/l}$ . This level has two consequences: first, at low temperatures any calcium paradox can be excluded, and

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secondly, there will not be any calcium-dependent stimulation of energy consumption with associated curtailment of tolerated ischaemia time. Even a slight increase to a level of only 50  $\mu\text{mol/l}$  calcium is definitely detrimental in this respect (22, 26, 67, 68, 79).

The methods available for assessing myocardial function or determining the reversibility of damage inflicted on the heart by ischaemia include electron microscopic changes, haemodynamic parameters and reproducible measurements of the electrical impedance of the heart. Numerous studies in experimental animals have shown the clear superiority of myocardial protection given by HTK solution with regard to the contractile status of the heart damaged by ischaemia (15, 19, 28, 30, 32, 56, 57, 75, 81, 82, 83, 84, 85, 86, 87, 88, 96).

The acid test for judging the effectiveness of myocardial protection is and remains rapid post-ischaemic recovery, i.e., immediate resumption of function after reconnection to the body's circulation (72, 76, 80).

D.II. Acute toxicity in the general systemic circulation

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C.IV. - there is no question of toxicity in the general circulation, because

1. In the context of cardiac surgery, the cardioplegic solution is not primarily intended for use in the general systemic circulation,
2. In the event of any influx into the ECC the solution will be well tolerated in the volumes likely to be involved.
3. Any further haemodilution is impermissible because of the fact that there is a lower limit to the oxygen transport capacity of the blood; any drop below this limit will not be tolerated, and it must not be transgressed.

D.III. Chronic toxicity and embryotoxicity

After complicated cardiac operations, e.g., insertion of an aortic valve, the blame for postoperative mortality as such cannot be laid upon the cardioplegic solution. Immediate resumption of normal cardiac function must be regarded as the crucial criterion of the efficacy of the solution. It should be emphasised yet again that not one fatality following administration of HTK solution has hitherto been

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well over 100,000 operations in which the solution has been used (various references, in particular the clinical reports by Renner and Kübler) (59,78).

Second and subsequent cardiac operations on the same patient with cardioplegia and heart-lung machine technique are still unusual, though becoming increasingly frequent. Among possible reasons are: a second operation on a congenital defect for the purpose of complete reconstruction after an initial operation directed towards relief of symptoms; replacement of a prosthetic heart valve which has become defective; a second or subsequent coronary bypass operation; revision of previous surgery following a complication (re-operation).

A second or third operation after a shorter or longer interval can hardly be simulated by studies in experimental animals - if only because of antivivisection legislation - and no relevant experimental work has in fact been published. However, extensive clinical experience in recent years shows that the cardioplegic solution is and remains well tolerated even in repeated operations on the same patient.

The calculations set out under C.III. show that the electrolyte concentration changes in the extracellular

compartment of a pregnant woman can be kept so small as to be unquestionably harmless to the embryo. As regards histidine, this statement should not be accepted without further consideration: in the placenta there may conceivably be special transport systems for amino acids, similar to those in the proximal tubules of the kidney; on the other hand, bearing in mind the rapidly falling histidine level in the maternal circulation, it may be expected that retrograde transport - in keeping with the reversed gradient - will soon commence. For reasons of safety, however, if an emergency operation is necessary during pregnancy the cardioplegic solution should be aspirated from the right side of the heart, as was the general practice in the first few years when the cardioplegia method was on trial. No cases of embryotoxicity from the solution are known.

#### D.IV. Carcinogenicity

The composition of the solution, consisting as it does exclusively of substances naturally present in the body, the short time for which the constituents remain within the circulation, the fact that in substantial concentration they are confined exclusively to the isolated heart, and the restriction on the use of the solution to a single, or in extremely rare cases to

considerations exclude any possibility of carcinogenicity.

**D.V. Acute and chronic toxic effects on the vein wall**

HTK solution has proved of value for short term storage of vein grafts, usually taken from the great saphenous vein, as successfully used for many years for bypassing narrowed segments of the coronary arteries. By analogy with the considerations set out above, and bearing in mind that the solution consists exclusively of substances naturally present in the body, no cytotoxic effect is to be expected when the solution is used for protection of venous endothelium and no such effect has ever been described in the literature (31,66,95).

**E. Statement of problem and fundamentals of renal protection**

**E.1. Requirements for operations on the ischaemic kidney**

The amazingly rapid development of modern surgical techniques and materials, in particular suture materials and microsurgical instruments, together with progress in invasive and noninvasive investigative techniques, besides broadening the potentialities of

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surgery in other organs such as the kidney. For example, a renal transplant, besides offering life expectancy comparable with that of the general population, is economically advantageous in that it offers considerable cost savings. There are currently two indications where organ protection of the kidney is necessary:

1. Operations of long duration which have to be performed with the kidney under ischaemia.
2. Kidney transplants where long ischaemia times are inevitable while the donor kidney is being transported to the recipient. In principle - as in myocardial protection - the aim is to achieve the longest possible ischaemia tolerance time and at the same time to ensure rapid and complete restoration of function after reconnection to the general circulation.

E.II.                   Physiology and biochemistry of aerobic and anaerobic energy supply to the kidney

The pathophysiological phenomena taking place in the various cells of the kidney during ischaemia are fundamentally the same as in the cells of the heart

referred to Section A.II.

E.III. Principles governing the use of the  
organ-protective solution

The effects utilised for renal protection are fundamentally the same as those employed for myocardial protection. The fact that the sodium concentration of the solution is lowered to approximately intracellular levels relieves the ion pumps of the burden of tubular sodium reabsorption and thus helps to reduce the energy consumption of the kidney. As the solution is practically calcium-free, any calcium influx into the cell is cut down. This reduces anaerobic energy turnover and delays the emergence of lactic acidosis. The elevated magnesium content of the solution likewise helps to lessen energy turnover, by its calcium-antagonistic effect on the cell membrane. The minimal amount of added potassium also reduces anaerobic glycolysis in the renal cell, and by its buffering action the added histidine-HCl prevents any tendency to tissue acidosis. Added tryptophan has inhibitory effects on amino acid transport, and mannitol retards the osmotically-induced formation of cellular oedema in the renal cell. At 10°C the physically dissolved oxygen amounts to 0.6 volumes percent at a partial pressure of 150 mmHg. Because of the reduced energy requirement, this is sufficient to maintain aerobic

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metabolism during the perfusion phase.

## F. Pharmacology in the kidney

### F.1. Pharmacodynamics

In principle, the statements made under B.I. apply also to the kidney, i.e., the mechanisms of action of the organ-protective solution are the same as for the heart.

Protection of the kidney can be divided into the following phases:

1. Aerobic blood flow with pretreatment under general anaesthesia.
2. Aerobic perfusion in situ with the protective solution.
3. Subsequent complete ischaemia, during which ischaemic stress is governed, as in the heart, by time and temperature.
4. The phase of aerobic reperfusion divided into early recovery (during the first 1-3 hours postoperatively) and subsequent recovery over 1-2 weeks.

Studies in experimental animals prove that, as in myocardial protection, homogeneous equilibration of the

extracellular space of the kidney and an adequate level

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of urine output during selective perfusion are of importance. During perfusion with HTK solution an outflow of "artificial urine" at a rate of about 13 ml/minute/100g wet weight was recorded in dogs during perfusion of 6 minutes' duration. More or less complete equilibration in the vascular system and even in the renal tubular system was reached at 6 minutes. Renal oxygen consumption fell to 0.2 ml/minute x 100 g wet weight after 6 minutes. After 6 minutes' protective perfusion with HTK solution the ATP concentration in the kidneys took 60 minutes at 35°C to drop from the initial level of 10 µmol/g dry weight to 1 µmol/g. The corresponding time in control kidneys was only 30 minutes. Neither at 35°C nor at 25°C did intrarenal pH fall below 6.7 at any point in the entire ischaemia period. At 25°C an ATP concentration of 1 µmol/g dry weight was not reached until 120 minutes. Given previous HTK protection, renal oxygen consumption after 120 minutes' ischaemia was 5 ml/minute x 100 g wet weight at 30°C as compared with 5-6 ml/minute x 100 g wet weight in control kidneys. After this ischaemic stress endogenous creatinine clearance was 20-25 ml/minute/100 g wet weight (41, 42, 43, 44, 45).

F.II. Pharmacokinetics

whether intended for use in the heart or the kidney, does not contain any drugs that remain for long in the body. After reconnecting the kidney to the general circulation reperfusion commences immediately, though function is not fully resumed at first. In experimental animals, after ischaemia of 120 minutes duration at 32-34°C under HTK protection, there was a transient rise in plasma creatinine level, maximum readings on the first or second post-operative day amounting to 2.6 mg%. After 7 days there were no detectable differences, either in terms of functional efficiency or in biochemical or morphological findings, between these kidneys and those from untreated controls. This is not true of other protection methods; they are known to entail some danger of anuria after as little as 60 minutes' ischaemia and necessitate elaborate haemodialysis procedures after the operation. The limiting factor governing ischaemia tolerance in kidneys protected by the use of HTK solution is in the last analysis the critical energy status of the kidney or of the renal cell. This limitation comes into operation much later than after the use of other protective methods (38, 39, 40).

F.III. Local side effects in the kidney

Experimental investigations in the dog kidney have

shown that recovery of renal function may take up to 1

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days and is sometimes accompanied by a temporary rise in creatinine. Histologically, there is evidence of damage to the ultrastructure of the renal cell in the shape of cellular swelling and single cell necrosis; as the duration of renal ischaemia lengthens, the latter lesions coalesce to form necrotic patches. However, after perfusion with HTK solution at 5°C, structural lesions do not occur until 48 hours' ischaemia have elapsed, whereas after pure ischaemia without protection or with other protective techniques such lesions become apparent very much earlier. Four weeks later, histological examination of dog kidneys which had been protected with HTK solution showed normal appearances in the parenchyma. No other structural lesions were observed (37, 49, 51, 53, 54, 55).

#### F.IV. Safety

The volume generally used for protection of one kidney is 2-3 litres. Given a healthy kidney, this is enough to ensure protection for 48 hours at 0-5°C. In terms of therapeutic safety margin, there are no limitations on the total volume of organ-protective solution which can be used.

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G. Toxicity

G.I. Acute toxic effects on the kidney

As in the heart (see above, especially B.IV and D.I) the therapeutic safety margin in the kidney, despite its totally different cell structures, is very wide. In dogs, long-term perfusion even of several days' duration does not lead to irreversible structural damage or to loss of renal function. At worst, unduly high perfusion pressures may conceivably cause local damage to the renal parenchyma in the acute phase of perfusion (61).

G.II. Chronic toxic effects on the kidney

Without protective perfusion, adequate protection of the structures of the kidney during deep hypothermia cannot be guaranteed beyond a maximum of 12 hours' ischaemia. Perfusion with HTK solution under deep hypothermia guarantees good structural protection of all segments of the nephron and of the renal vessels

cell swelling and necroses become apparent, and AMP concentration drops below 5  $\mu\text{mol/dry weight}$ . This unavoidable fall in energy-rich phosphates is the ultimate factor limiting protection. After complicated operations on the kidney such as partial nephrectomy for cancer or implantation of a donor kidney into a recipient after prolonged ischaemia, any postoperative delay in resumption of renal function cannot be blamed upon HTK solution. Rejection of the graft - a frequent complication in the early days of renal transplantation though now less common since the introduction of cyclosporin for immunosuppressive therapy - can likewise not be laid at the door of HTK solution. The ultimate criterion of renal protection is and remains healthy postoperative function of the kidney, this functional health being reflected in good preservation of the ultrastructure. Up to the present there have been no reports of fatalities or complications associated with the use of HTK solution for renal protection (78).

#### H. Possible prophylactic value

The possibility of prophylactic value might at most be discussed in terms of a beneficial influence on postoperative metabolism. At present there is no concrete evidence of any such effect, and the same is

true of possible benefits in the perioperative period

due to changes in blood electrolyte composition, e.g.

temporary lowering of sodium or elevation of magnesium.

Here again, there are no substantiated results.

#### I. Interactions with other drugs

Premedication - and also long-term medication - with digitalis glycosides, diuretics, nitrites, antihypertensives, betareceptor blockers and calcium antagonists in therapeutic doses do not interfere with the action of the cardioplegic and organ-protective solution. Routine medication therefore need not be discontinued - or at most just before the day of operation. During extracorporeal circulation with the heart-lung machine, drugs are not infrequently needed to control hypertensive reactions; but as the heart is cut off from the general circulation these reach it only in minimal amounts through a non-coronary collateral circulation (see Section B.IV). Over the many years in which cardioplegia has been practised, a large range of drugs has been used simultaneously. During the perioperative phase these include antiarrhythmic agents (e.g., digitalis glycosides, betablockers, calcium antagonists), diuretics, corticosteroids, antithrombotics, fibrinolytics, analgesics, sedatives, anaesthetics and muscle relaxants, antihypertensives and anti-inflammatory

drugs. There are no reports of any interactions with other drugs in any of the numerous clinical studies reviewed.

Addition of drugs to the cardioplegic solution itself is in principle inadvisable, until such time as relevant experimental studies have proved their usefulness and harmlessness beyond all doubt. This warning is based on extensive experimental studies in the author's laboratory. Their negative results can be summarised as follows;

1. The electrolyte composition of the cardioplegic solution differs greatly from that of plasma; in nearly all cases this causes a marked change in pharmacodynamics and a shift in the dose-effect relationship.
2. The intracellular and extracellular acidosis which becomes increasingly marked during anaerobiosis causes further and unpredictable modification of the spectrum of action of any drugs added to the cardioplegic solution.
3. The fluctuating temperatures to which the myocardium is exposed during cardioplegia cause further alterations in specific pharmacological effects.

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## J. Contraindications

Nearly 30 years have now passed during which well over 100,000 operations have been performed on the arrested heart, yet no contraindications have ever been reported.

This applies both to infants with grave cardiac defects, many of whom would formerly have died a few days or weeks after birth, and desperately ill cardiac patients who would have been classified as inoperable before the introduction of cardioplegia. There are no known concurrent diseases which would preclude use of the cardioplegic agent in a cardiac operation (see Section D.III). In this connection the reader is again referred to the extensive list of references from clinical sources on which the two expert clinical reports are based.

## K. Summary

The therapeutic concept of the cardioplegic organ-protective solution - as outlined in Section A and in particular in A.IV - is fully in accordance with experimental findings and with clinical experience.

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The physiological principles on which it is based are applicable to the majority of organs and tissues. The composition of the solution, consisting exclusively of substances naturally present in the body, is derived from these principles. The wide ranging scope of indications for its use and the generous safety margin are further corollaries. In terms of the prolongation of ischaemia tolerance time attainable over the entire temperature range down to 0°C - as compared with the unprotected state - the solution is superior to any of the techniques for cardioplegia and myocardial protection previously introduced, and in addition it is highly suitable for preserving the heart. One reservation is necessary (Section D.I.), namely that the solution must not be used at body temperature but only at reduced temperature. As stated in the directive, it is most effective when infused into the coronary system at a temperature between 5°C and 10°C.

#### L. Conclusion

The concept of cardioplegia pioneered by Melrose in 1955 is now an everyday reality, implemented with maximum efficiency and safety by the use of HTK solution. The solution is now - like modern surgical instruments - an indispensable necessity for a wide range of operations. Delicate and intricate operations

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now offer infants and young children the chance of living practically normal lives - an outcome that would have been inconceivable before the introduction of cardioplegia. The underlying principle of HTK solution is not confined to the heart. Over the last 15 years it has proved of great value in other organs such as the kidney and also for the short-term preservation of vein grafts (62, 63, 77, 91, 93, 94).

Prof.(em.) Dr. med. Dr.med.h.c.H.J.Bretschneider

Göttingen (date)

Appendices:

- (M) Reference list
- (N) Curriculum vitae

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Curriculum vitae

Prof Dr.med.Hans Jürgen Bretschneider

born 30th July 1922 in Neubrandenburg (Mecklenburg)

1939-1946	Service in the German Navy
1947-1952	Studied medicine in the University of Göttingen
1952	Awarded degree of Dr.med. in Göttingen
1952-1953	Assistant in the Physiological Institute, Göttingen, and the Max-Planck Institute for Experimental Medicine, Heidelberg
1953-1960	Assistant in the Department of Medicine University of Göttingen
1958	Recognition as University teacher in the subject of "Pathophysiology"
1960	Specialist in internal (general) medicine
1960-68	Head of Department of Experimental Surgery, University of Cologne
1964	Appointed to the Chair of Experimental Surgery, University of Cologne
1968	Accepted call to the Chair of Physiology I, University of Göttingen

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From 1972 Member of the Academy of Sciences,  
Göttingen

1975, 76, 77 Dean of Medical Faculty, University of  
Göttingen

1971-1986 Spokesman for the Special Research Unit,  
Cardiology, Göttingen (SFB 89)

1981 Declined a call to the University of  
Düsseldorf

1986 Honorary membership of the German  
Society for Anaesthesiology and  
Intensive Care

1986-87 President of the German Society for  
Cardiovascular Research

1987 Honorary membership of the German  
Society for Thoracic, Cardiac and  
Vascular Surgery

from 1987 Spokesman for the Special Research Unit  
Organ Protection (SFB 330), Göttingen

1990 Award of Emeritus Status, University of  
Göttingen

1992 Honorary membership of the German  
Society for Cardiovascular Research

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## EXHIBIT 7





Records processed under FOIA Request 2014-5611; Released 10/29/14









## EXHIBIT 8

**Stability Data after 12 months of Storage (8°C)**

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**Stability Data after 12 Months of Storage (25°C)**

000242

Records processed under FOIA Request 2014-5611; Released 10/29/14

## EXHIBIT 9

# COULTER CALIBRATION STANDARD

## Assay Sheet

**INTENDED USE:**

Polymer latex particles intended for the calibration of COULTER COUNTER\* instruments, other than those to be used for red and white blood cell sizing or counting.

NUMBER MODE (Figure A)	21.6 $\mu\text{m}$ DIAMETER 5277 $\mu\text{l}$ VOLUME
(MULTISIZER and CHANNELYZER* instruments).	
SIZE DISTRIBUTION (ZMCHANNELYZER 256).	see overleaf

Other parameters:

SINGLET NUMBER MEDIAN DIAMETER (Non-multichannel instruments; Figure B).	22.7 $\mu\text{m}$ DIAMETER
WEIGHT PEAK SPLIT (Models TA/TA II; Figure C).	23.6 $\mu\text{m}$ DIAMETER
1:2 WEIGHT PEAK SPLIT (Models TA/TA II; Figure D).	22.5 $\mu\text{m}$ DIAMETER
NUMBER PEAK SPLIT (Models TA IV/PCA (PCA 1); Figure E).	23.0 $\mu\text{m}$ DIAMETER
<b>TYPICAL USAGE RATE:</b> 200 $\mu\text{m}$ Aperture, 1-2 drops per 100ml 280 $\mu\text{m}$ Aperture, 1 drop per 100ml	

**CALIBRATION TRACEABILITY - QUALITY ASSURANCE:**

ASSAY VALUES have been determined using COULTER COUNTER\* models MULTISIZER, TA IV/PCA, ZM and CHANNELYZER\* 256 which are verified for performance and calibrated and checked with primary reference standard particles from the National Institute of Standards and Technology, N.I.S.T., (formerly National Bureau of Standards, N.B.S.), and the Community Bureau of Reference, B.C.R. (\*).

Properly documented records of the calibrations performed with this Coulter Calibration Standard, when used as recommended in the relevant instrument Instruction Manual, will allow traceability of those calibrations to the N.I.S.T., (N.B.S.) and B.C.R. particle size Reference Materials, as required by some National authorities, such as BS 5750 and NAMAS in the United Kingdom.

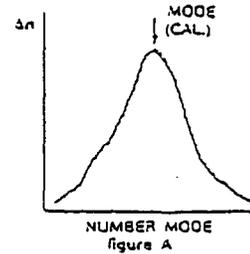
**CALIBRATION STANDARD SUSPENSION:**

The suggested concentration for both accuracy and speed of calibration is at a concentration giving around 5% coincidence loss. Particles are suspended at a concentration in aqueous dispersant plus preservative such that the typical usage rate gives approximately 5% coincidence for calibration of an aperture ten times the latex's nominal diameter. Poly(styrene divinyl benzene) (P.D.V.B.) latices are durable and will not change size upon immersion in most electrolyte solutions used with COULTER COUNTER\* instruments. Latices may swell or dissolve in some organic liquids, e.g. ketones, chlorinated hydrocarbons and some higher alcohols. With constant current COULTER COUNTER\* models, calibration may be performed in an electrolyte solution different from that used for sample analysis. There is no evidence of instability with time of Coulter Calibration Standards, as packed, but for maximum security it is recommended that the product is discarded at the expiry date given above.

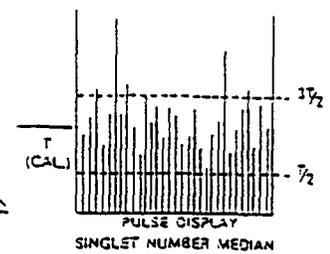
**SIZE CALIBRATION:**

COULTER COUNTER\* instruments can be self calibrated by measuring a suspension of a narrow size range of the material under investigation at a known concentration. From the immersed relative density (g/ml) of the material, and

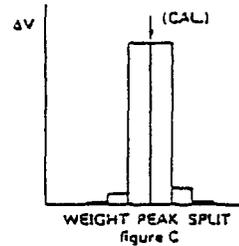
BATCH	F.31
MATERIAL	P.D.V.B. LATEX
DO NOT USE AFTER	31st DECEMBER 1996



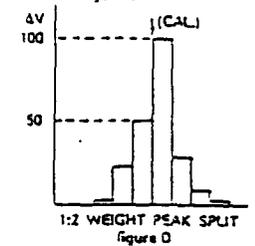
NUMBER MODE  
figure A



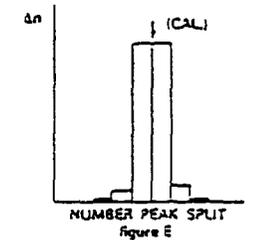
SINGLET NUMBER MEDIAN  
figure B



WEIGHT PEAK SPLIT  
figure C



1:2 WEIGHT PEAK SPLIT  
figure D



NUMBER PEAK SPLIT  
figure E

from the total volume measured, the calibration factor can be calculated for the COULTER COUNTER\* instrument and sensing aperture in use (\*). This procedure will remove any doubt concerning accurate calibration with very irregularly shaped or conducting particles.

In practice, it is more convenient to calibrate using narrow range particles which have already been sized by other techniques. The most common method is to calibrate with spherical polymer latex particles; the Secondary Calibration procedure of BS 3406: Part 3: 1983 (\*).

Using a series of sensing apertures and latex particles, Harfield, Wharton and Lines (\*) verified that the response of a COULTER COUNTER Model ZM was linear with particle volume to some 80% of the aperture diameter. By using a series of apertures and verified COULTER COUNTER\* models, each calibrated to the mode of the size distribution of the relevant N.I.S.T. (N.B.S.) Standard or B.C.R. Certified latex reference materials (\*), this Coulter Calibration Standard has been assigned the values given above.

Instruments of high definition size distribution (e.g. MULTISIZER, CHANNELYZER\* models) are most conveniently calibrated using the number mode size (diameter or volume), see Figure A above.

Single or double threshold instruments (e.g. Models A, B, O Industrial, ZS, and ZM without CHANNELYZER accessory) are more conveniently calibrated using the singlet number median diameter, see Figure B above.

The 'weight peak split' method (Figure C) is intended for calibration of TA and TAIL Models without a Population Count Accessory, whereby the calibration point is the junction of two consecutive channels containing equal weight (volume).

Earlier calibration methods for the TA or TAIL used the '1:2 weight peak split' method (Figure D) whereby the calibration point is the junction of two consecutive channels containing twice the weight (volume) in the right hand channel as in the left.

The 'number peak split' method (Figure E) is intended for the Model TAIL with PCA or PCA 1 population count accessory.

## EXHIBIT 10

**5000 ml Plastic container**

**000245**

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## EXHIBIT 11

# Current Status of the HTK Solution of Bretschneider in Organ Preservation

M. Hölscher and A.F. Groenewoud

THE clinical introduction of University of Wisconsin (UW) and Histidine-Tryptophane-Ketoglutarate (HTK) solutions for single- and multiple-organ donation have stimulated scientific discussions about organ preservation methods in the field of transplantation, as in the 1970s.

Basically organ-protective methods during anaerobiosis have to be strongly differentiated from those that allow aerobic metabolism in hypothermia. During anaerobiosis, energy resources for maintenance of the structural protection are limited. Therefore, all protective procedures adapted to anaerobiosis are focusing on preservation of all individual organ functions (protection of functions), on protection of the energy resources (protection of energy status), and on protection of the morphological structures (protection of structure).

The aim of preservation is to develop flush, or so-called, equilibration solutions, using general biological principles of preservation to protect different organs with all their morphological and biochemical heterogeneity. The effect of hypothermia has to be differentiated from the specific protective effect of protective solutions. The general principles of organ protection in total ischemia can be summarized as inhibition of unavoidable acidosis (intra- and extracellular) and prevention from critical pH values; maintenance of volume regulation of all cells, especially of endothelial cells; optimal use of anaerobic energy resources; reversible inhibition of unuseful working processes; and maintenance of structure, which will keep ready organ function. In judgment on different protective procedures, the criterion of immediate restitution of all organ functions seems to be more important than the criterion of life support after a certain recovery time from ischemia.

## HISTORICAL DEVELOPMENT OF HTK SOLUTION

About 30 years ago, Prof. Bretschneider was looking for an electrolyte composition as basis for a cardioplegic solution. In the early 1970s, a biologically compatible, administrable buffer system with a high buffer capacity was found using the amino acid histidine. Starting experimental work in 1961, he clinically introduced his solution.<sup>1,2</sup> German heart surgeons, who were in favour of this solution, have been using HTK (Dr. Franz Köhler Chemie GmbH, FRG) in heart transplantation as well since 1985. In 1978, experimental work was set up for renal protection,<sup>3-8</sup> resulting in the first human kidney transplants protected with HTK solution.<sup>4</sup> Because this solution has a protective ability even in warm ischemia, the solution has

Table 1. Historical Development of HTK Solution (Custodiol®) by Bretschneider

	Begin Exp. Work*	Clinical Use
Cardioplegia	1961	
Open heart surgery		1979
Transplantation		1985/86
Kidney protection	1978	
Related and unrelated transplantation		1987
In-situ surgery		1987
Liver protection	1987	
Transplantation		1988
Ex-vivo surgery		1988
Pancreas protection	1989	
Transplantation		1989

\*The experimental work was mainly done by Prof. Bretschneider and coworkers, supported by SFB of the Deutsche Forschungsgemeinschaft.

been thought to be ideal for in situ and ex vivo surgery of kidneys.<sup>10,11</sup> The protection of the liver with the HTK solution is experimentally and clinically under evaluation.<sup>12</sup> The first ex situ operations protecting the liver by HTK solution have been performed by Pichlmayr.<sup>13</sup> The latest field of research is the protection of the pancreas, as well as the heart and lungs, with HTK against total ischemia.

Of course, the originally discovered and designed solution for cardioplegia has been slightly changed over the years. Since the solution fulfills the above-mentioned general criteria for organ protection, indications for application will expand in future.

## PRINCIPLES OF ORGAN PROTECTION WITH HTK SOLUTION

### Equilibration

In a wide sense, the HTK solution is a flush solution like Euro-Collins (EC) or UW solution, but it is important to stay within the limits of equilibration. To get optimal protective effects, the vascular, extracellular, and tubular space (kidney) have to be equilibrated with the fluid. The equilibration of the different compartments of the kidney is nearly accomplished after 10 to 12 minutes of perfusion

From the Department of Surgery, Technical University of Munich, München 80, Germany.

Address reprint requests to M. Hölscher, MD, Department of Surgery, Technical University of Munich, Ismaninger Str. 22, 8000 München 80, Germany.

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## CURRENT STATUS OF HTK SOLUTION

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Table 2. Current Status of Clinical Use of HTK Solution (Custodiol<sup>®</sup>) by Bretschneider\*

	Numbers in Clinical Use (Estimated 1991)	Location of Clinical Use (Mainly)	Studies
<b>Cardioplegia</b>			
Open heart surgery	>100,000	40 centers FRG + EC countries	Routinely used retrospective studies
Transplantation	350-400	FRG	Single center study
<b>Kidney Protection</b>			
In-situ surgery	30	FRG	Single case study
Related transplantation	14	FRG	Single center study
Unrelated transplantation	800	Eurotransplant	Multicenter pilot study Random HTK-EC + HTK-UW studies
<b>Liver protection</b>			
Transplantation	60	FRG	Single center study
Ex-vivo surgery	30	FRG	Single center study
<b>Pancreas transplantation</b>	5	FRG	Single case study

\*All clinical work done in cooperation with Prof. Bretschneider.

with a hydrostatic pressure of 120 cm H<sub>2</sub>O. The perfusion volume should be sufficient, and the kidney requires at least a ten-fold of the organ weight, according to measurements of fluid substrates of the venous and tubular outflow.<sup>14</sup>

Different amounts of fluid are needed for the equilibration of the compartments of other organs; eg, the heart needs two to three times the organ weight, and the liver six times the organ weight.

**Buffering**

Buffering of the compartments of an organ is as important as the fact that H<sup>+</sup> ions and lactate are able to pass the cell membrane in anaerobiosis, a process that is pH dependent. Since anaerobic glycolysis is the only energy resource in anaerobiosis, this process is important for the metabolism of structural integrity. Interstitial pH measurements at the corticomedullary border of incubated canine kidneys demonstrate the temperature and buffer-capacity-dependent pH values. Experimental data and clinical studies show that a pH of 6.2 at 35°C or 6.6 at 5°C is marginally tolerated. Intrarenal acidosis beyond these values seems to be the first limiting factor for graft function in kidneys.<sup>6,9,15</sup> Because of differently existing quantitative anaerobic glycolysis, buffering is necessary in organ-specific ways.

**Cellular Swelling**

As we now understand, cellular swelling is caused by insufficient ion pumps due to ischemia and excessive charge of the lactate transport system which is pH dependent. Low extracellular sodium, buffering, and a low glycolysis rate are important to prevent cellular swelling, which is even possible with an iso-osmolar fluid like HTK solution.<sup>16,17</sup>

**Energy Status**

Energy turnover, caused mainly by anaerobic glycolysis, influences the degradation process of energy-rich phos-

phates which deliver energy for metabolism of structural integrity. On the other hand, it is important to have a certain amount of energy to maintain the possibility of resuscitation in anaerobiosis.<sup>18</sup> However, the interpretation of energy status is quite difficult in comparing different flush solutions, because the energy status is not correlated to structural protection.<sup>16,19,20</sup>

**Structural Protection**

Structural protection, metabolism, energy resources, and functional readiness are closely related,<sup>16,18,19</sup> and it is difficult to reveal the limiting factor, especially when comparing the use of different solutions with different organs.

**CURRENT STATUS OF CLINICAL HTK ORGAN PROTECTION**

Cardioplegia for open heart surgery has been the first aim of this preservation solution. At the end of 1990, approximately 120,000 to 150,000 operations have routinely been performed in more than 40 centers. German and some other European centers have used the solution in cardiac transplantation in approximately 350 to 400 cases since 1985. Cold ischemia time of 4 to 8 hours (the longest time was 18 hours) did not play a major role in posttransplant pathology. Therefore, the surgeons did not respond to this subject with trials until now.<sup>21</sup> The procedure of cardioplegia seems to be safe for 4 to 8 hours of cold ischemia.

Human kidney preservation with HTK solution started in 1987.<sup>9</sup> Since a protective ability of the solution was described in 1982<sup>6</sup> at all temperature ranges, especially in warm ischemia, in situ surgery also started 1987.<sup>11</sup> A Eurotransplant pilot study in kidney transplantation was set up in 1988 and completed in 1990.<sup>22</sup> Until now, 800 unrelated transplants have been performed. A two-arm, randomized trial has been set up by Eurotransplant in 1990, comparing HTK vs EC solution and HTK vs UW solution. The set-up of this study is comparable with the

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European study UW vs EC solution, which has also been completed recently.<sup>23</sup>

Liver protection with HTK solution is mainly used in two German centers, Essen and Hannover. Single center studies are "on their way," but have not practiced randomized trials.<sup>12</sup> Because of the protective ability, even in warm ischemia, ex-vivo surgery on the liver has been made justifiable.<sup>13</sup>

Clinical pancreas transplantation has successfully been done in single cases using HTK solution, on the basis of experimental data.<sup>24</sup> There is clinical evidence that HTK solution can be used for several organs, however, the limits of protection have not been worked out precisely regarding the liver and pancreas.

COMPARISON OF THE PROTECTIVE ABILITY OF EC, UW, AND HTK SOLUTION IN KIDNEY TRANSPLANTATION

Whereas experiments in small animals are not very helpful, because ischemia and anaerobiosis are not complete, ideal experimental conditions can be set up in larger animals. These ideal conditions, however, cannot be transferred to the clinical situation in humans. They do, at least, give us a hint of what to expect.

Harvested organs very often do not have normal and, by no means, optimal functions. Several factors, such as donor age, aging of an organ, possible underlying not clinically evident diseases, and acquired functional organ injuries by the disease leading to brain death are influencing the outcome of transplantation and organ protection. Before organ donation, we only have rough parameters to reveal structural integrity and to quantify organ function (at least we rely on clinical judgment). Comparing the results of clinical studies, those factors have to be taken into account. What is the demand on organ protection? We are able to define the limits of a protective procedure as immediate, quick restitution of all organ functions at the "good end," and functions which give life support after a certain time of recovery at the "bad end." But an organ in which ischemic tolerance is not exceeded, should be offered nowadays.

Since the randomized HTK trials are not complete, we compared the European randomized study, UW vs EC solution,<sup>23</sup> with the Eurotransplant pilot study using HTK solution alone in kidney transplantation.<sup>22</sup> Those studies were conducted in the same period (1988-89), and were evaluated by the same criteria. Only the most important donor and grafting criteria are shown (Table 3). These data, in heart-beating donors, demonstrate minor differences between the groups only. Graft loss, graft loss for ischemic injury, delayed graft function (two or more dialysis the first week), and recipient death is significantly higher using the EC solution (Table 4).

The historical comparison of HTK and UW data (different studies) are demonstrating no difference. However, the data of all groups demonstrate clearly that ischemic injury

Table 3. Comparison of Donor and Grafting Criteria in Kidney Transplantation With Different Protective Solutions

Heart-Beating Donors	HTK* (n = 205)	UW† (n = 352)	EC† (n = 343)
Donor age (years)	41.0	41.2	42.5
Donor diagnosis			
Trauma capitis	40%	42%	47%
Intracranial bleeding	42%	38%	40%
Others	18%	20%	13%
Cardiac arrest	19%	16%	17%
Severe hypotensive periods	39%	29%	33%
Oliguria last 24 hours	30%	31%	48%
Cold ischemia period (hours)	23	24	24
Anastomosis time (minutes)	31	30	32
Vascular problems	9%	7%	10%

\*Eurotransplant pilot study (Groenewold).

†European randomized study (Ploeg).

is responsible for 3.5% to 6.5% of graft loss and 20% to 35% of impaired functions.

Median serum creatinine decline of all kidneys (permanent nonfunctioning kidneys excluded) demonstrates an advantage for UW and HTK protection (Fig 1). In analyzing the HTK group according to the parameter of complete immediate recovery of organ function, 38% of the transplants do have normal function after 24 hours of ischemia (serum creatinine and clearance). They have the same function after operation as the remaining kidneys in living related donors, and as transplants within 4 hours of cold ischemia and HTK protection.<sup>9</sup> Twenty-nine percent of kidneys had nearly normal function (values not with standard deviation of normal function).

From the clinical point of view, 11% still had a good function, but were significantly impaired up to 10 days posttransplant. Delayed graft function (DGF) due to ischemic injury was only observed in 11%, whereas, in another 11%, DGF was additionally caused by other reasons, ie, rejection, etc (Fig 2).

LIMITS OF ORGAN PROTECTION

In animal experiments, ideal conditions for organ preservation exist. We are able to define limits of ischemic tolerance of animal organs and of the protective procedures; ie, limits of protection of functions, energy status, and structure. However, the results are usually not com-

Table 4. Comparison of Kidney Transplant Function

No. of Recipients	EC (n = 343)	UW (n = 352)	HTK (n = 205)
Graft loss (3-month)	12%	8.2%	9.2%
Caused by ischemia	6.4%	3.7%	3.4%
Delayed graft function	33%	23%	22%
Function	67%	77%	78%
Recipient death (3-month)	1%	0.5%	0.5%

European randomized study: UW-EW solution; Eurotransplant pilot study: HTK solution.

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CURRENT STATUS OF HTK SOLUTION

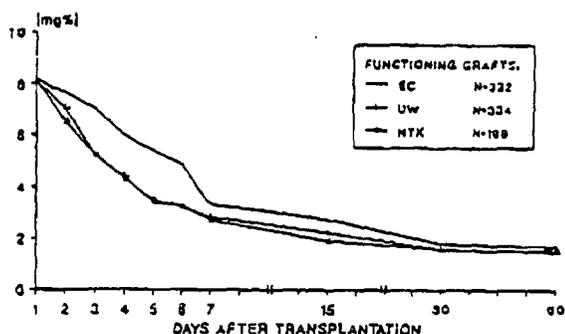


Fig 1. Comparison of mean serum creatinine decline (European randomized [UW-EC solution] and Eurotransplant pilot study [HTK solution]).

parable with the clinical situation. Donor and recipient criteria currently being utilized demonstrate that we have rough criteria for the functional status of organs only, and that there lacks good correlation with the posttransplant function of the graft. Even hypotension, cardiac arrest, and oliguria are not correlating with the qualitative function of kidney allografts, which could be shown by the above-mentioned studies. But recipients of grafts from donors with a combination of hypotension, cardiac arrest, and oliguria, so-called "bad donors," do not have a DGF after 24 hours of cold ischemia in 63% using EC, 78% using UW, and 85% using HTK solution. Therefore, we conclude that most donor criteria existing for kidney transplants are not suitable to predict posttransplant graft function.

In most clinical situations, ischemic stress is tolerable using the above-mentioned protective procedures, but not all organs tolerate the amount of ischemic stress in addition to their preexisting injury. This leads to ischemic graft

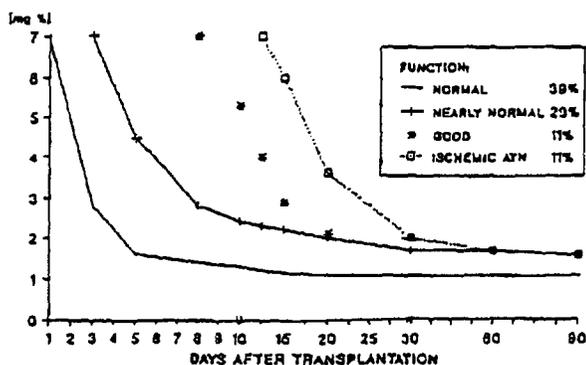


Fig 2. Mean serum creatinine decline of different groups of HTK-protected kidney transplants (Eurotransplant pilot study).

loss of 3% to 7% and 20% to 40% of delayed graft function in kidney transplants. Therefore, it seems logical to focus on organ function in donors to define the risk group which will tolerate less ischemic stress.

Bretschneider's HTK solution uses general principles of organ protection that have been successfully used in the protection of hearts and kidneys. Initial clinical results demonstrate that it can be used in human liver and pancreas as well. In the near future we may have two competitive solutions for multiple organ donation.

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Stand: 06.01.1998

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## EXHIBIT 12

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## EXHIBIT 13

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*Printed*

**Labeling**

1000 ml perfusion solution

**Custodiol®**

**Bretschneider HTK solution**

For organ preservation (heart, kidney, liver and multiorgan protection)

1000 ml perfusion solution contains

0,8766 g sodium chloride	=	15,0 mmol/l
0,6710 g potassium chloride	=	9,0 mmol/l
0,1842 g potassium hydrogen 2-ketoglutarate	=	1,0 mmol/l
0,8132 g magnesium chloride x 6 H <sub>2</sub> O	=	4,0 mmol/l
3,7733 g histidine x HCl H <sub>2</sub> O	=	18,0 mmol/l
27,9289 g histidine	=	180,0 mmol/l
0,4085 g tryptophan	=	2,0 mmol/l
5,4651 g mannitol	=	30,0 mmol/l
0,0022 g calcium chloride	=	0,015 mmol/l

in water for injections

Osmolality: 310 mosmol/kg

Anion: Cl 50 mEq

Solution for organ perfusion in connection with „in-situ-operations“ and organ transplantation, and for organ preservation and arterial and venous graft storage.

Do not use the solution if it is not clear or if the container is damaged!

Store at 8° - 15°C

Protect from light

~~Prescription only medicine~~

Sterile and pyrogen-free

Batch number:

/expiry date:

*Caution. Federal law restricts this device to sale by or on the order of a physician.*

Dr. F. Köhler Chemie GmbH  
P.O. Box 1117, D-64659 Alsbach-Hähnlein  
Germany

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**Eurotransplant Telefax**  
**\*\* 31 71 5 79 00 57**

For the urgent attention of :  
**Dr. Schaffner**  
**Köhler Chemie**

**FAX 00 49 62 57 50 946**

Leiden, January 8, 1989

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Dear Dr. Schaffner,

Enclosed you will find an overview of the number of kidney and liver donor organs, perfused with HTK and used in a transplant (carried out in the Eurotransplant area).

With best regards,  
Yours sincerely,

Dr. Johan De Meester  
Head Medical Affairs



**EXHIBIT 14**

471



## EXHIBIT 15

473

A.F. Groenewoud  
J. de Boer  
for the HTK study group

# A report of the eurotransplant randomized multicenter study comparing kidney graft preservation with HTK, UW and EC solutions

A.F. Groenewoud (✉) · J. de Boer  
Department of Surgery and  
Transplantation,  
Technical University Hospital  
Rechts der Isar,  
Ismaningerstrasse 22,  
D-81675 Munich, Germany

**Abstract** Special attention has been focused in this randomized study on the primary function of renal allografts preserved with different solutions. Histidine-Tryptophane-Ketoglutarate (HTK) and University of Wisconsin (UW) solutions provided a significantly lower incidence of delayed graft function compared to Euro-Collins solution.

Improved renal function after transplantation was observed in the HTK and UW groups compared to the EC group.

**Key words** Renal transplantation  
Delayed graft function  
Randomized study  
Preservation with HTK, UW, and EC

## Introduction

The aim of preservation is to maintain kidneys in optimal condition from the time of explantation until transplantation. Delayed graft function (DGF) is a serious complication. A multifactorial pathogenicity has been attributed to the aetiology of DGF that may include donor management, age, ischemic periods, use of cyclosporin-A (CyA) and preservation quality. The aim of this study was to test the efficacy of the Histidine-Tryptophane-Ketoglutarate (HTK) preservation solution compared to the University of Wisconsin (UW) and Euro-Collins (EC) solutions by means of two prospective randomized clinical trials.

## Materials and methods

Forty-seven centers have participated and followed a strict protocol for organ preservation. Randomized assignment of the preservation solution and data collection were coordinated by a central office. The follow-up questionnaires of 1078 consecutive kidney transplantations were available for this analysis.

## Results

The characteristics of donor and recipient that could influence the graft function were comparable between all groups. The median cold ischemic period in HTK- and UW-preserved kidneys was 26 h, and in EC-preserved it was 27 h. Initial nonfunction with graft failure within the 1st postoperative week was 5% in all groups. DGF requiring two or more dialysis treatments in the 1st postoperative week was 20% (107/544) in the HTK, 25% (66/266) in the UW, and 32% (85/268) in the EC group ( $P = 0.001$ ). For all risk factors, DGF was lower in the HTK and UW groups than in the EC group. Postoperative serum creatinine values in functioning grafts decreased more rapidly in HTK- and UW-preserved kidneys than in the EC-preserved kidneys. The median creatinine clearance on day 14 was 58 ml/min in HTK kidneys, 49 ml/min in UW kidneys and 38 ml/min in EC kidneys.

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**Conclusions**

An important finding in this study was that the incidence of DGF was 5% lower in the HTK group than in the UW group and 12% lower in the HTK group than in the EC

group. Improved renal allograft function was indicated by a rapid decrease in serum creatinine levels and higher creatinine values in the HTK and UW groups compared to the EC group.

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## EXHIBIT 16

**COMPARISON OF USP AND EP SPECIFICATIONS  
FOR HISTIDINE HYDROCHLORIDE MONOHYDRATE**

Testing Parameter	USP Specification (the Histidine monograph of USP 23 is used)	EP Specification (for Histidine Hydrochloride Monohydrate)	Comments
1. Identification			
1.1 Infrared Absorption	The test specimen is compared to a reference standard	Examine by infrared spectrophotometry (V.6.18). The absorption maxima in the spectrum obtained with the substance to be examined must correspond in position and relative intensity to those in Histidine HCl•H <sub>2</sub> O CRS	EP is equivalent to USP
1.2 Specific Rotation	Between +12.6° and 14.0°	Between +9.2° and 10.6°	The specifications 1.2-1.4 are not comparable on a quantitative basis because USP is for Histidine and EP is for Histidine HCl•H <sub>2</sub> O. However, they are specifications for the same characteristics.
1.3 pH	Between 7.0 and 8.5, in a solution 1:50	Between 3.0 and 5.0	
1.4 Loss on Drying	n.m.t. 0.2% of its weight	Between 7.0% and 10.0%	
2. Impurities			
2.1 Chloride	n.m.t. 0.050%	N/A	
2.2 Sulfate	n.m.t. 0.030%	n.m.t. 0.030%	EP is equivalent to USP
2.3 Arsenic	n.m.t. 1.5 ppm	Not listed	
2.4 Iron	n.m.t. 0.003%	n.m.t. 0.001%	EP is better than USP
2.5 Heavy metals	n.m.t. 0.0015%	n.m.t. 0.001%	EP is better than USP
3 Assay	Potentiometric titration (98.5 – 101.5%)	Potentiometric titration (98.5 – 101.0%)	EP is equivalent to USP

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Records processed under FOIA Request 2014-5611; Released 10/29/14

Records processed under FOIA Request 2014-5611; Released 10/29/14









## EXHIBIT 17

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## EXHIBIT 18

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## EXHIBIT 19

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## EXHIBIT 20

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# ViaSpan<sup>®</sup>

(BELZER UW)  
COLD STORAGE SOLUTION \*\*

**DIRECTIONS FOR PREPARATION AND USE**

**NOT FOR DIRECT INJECTION OR INTRAVENOUS INFUSION.**

**DESCRIPTION**

ViaSpan<sup>®</sup> (Belzer UW) can be used for hypothermic flushing and storage of organs including kidney, liver, and pancreas in preparation for transportation prior to transplantation.

The solution composition is:

Pentafraction*	50	g/L
Lactobionic Acid (as Lactone)	35.83	g/L
Potassium Phosphate monobasic	3.4	g/L
Magnesium Sulfate heptahydrate	1.23	g/L
Raffinose pentahydrate	17.83	g/L
Adenosine	1.34	g/L
Allopurinol	0.136	g/L
Total Glutathione	0.922	g/L
Potassium Hydroxide	q.s.	
Sodium Hydroxide	adjust to pH 7.4	
Water for Injection	q.s.	

ViaSpan<sup>®</sup> (Belzer UW) is a clear to light yellow, sterile, non-pyrogenic solution for hypothermic flushing and storage of organs. The solution has an approximate calculated osmolality of 320 mOsm, a sodium concentration of 29 mEq/L, a potassium concentration of 125 mEq/L, and a pH of about 7.4 at room temperature.

**ACTIONS**

After precooling the solution to about 2-6°C (35.6-43°F) in ice, the cold solution is used to flush the isolated organ immediately before removal from the donor and/or immediately after removal from the donor. The solution is then left in the organ vasculature during hypothermic storage and transportation. This solution is to be used for cold storage of the organ and not for continuous machine perfusion. Administration of the solution at the recommended temperatures will effectively cool the organ and should reduce its metabolic requirements.

**INTENDED USE**

This solution is intended for flushing and cold storage of organs including kidney, liver and pancreas at the time of their removal from the donor in preparation for storage, transportation and eventual transplantation into a recipient.

**CONTRAINDICATIONS**

There are no known contraindications when used as directed.

**WARNINGS**

**NOT FOR DIRECT INJECTION OR INTRAVENOUS INFUSION.**

**PRECAUTIONS**

ViaSpan<sup>®</sup> (Belzer UW) includes drug constituents which individually have caused hypersensitivity reactions in patients (allopurinol, penicillin, insulin, dexamethasone, and pentafraction). Physicians should consult drug labeling individually and be alert to treat possible reactions. Before reperfusion is established in the recipient, the donor organ must be flushed free of the cold storage solution using a physiological solution to prevent occurrence in the recipient of potential serious cardiovascular complications such as hyperkalemic cardiac arrest or bradyarrhythmia. Because of the high concentration of potassium in the solution, precautions must be taken during donor organ retrieval to avoid cardiac arrest.

**ADVERSE REACTIONS**

No adverse reactions thought to be attributable to the solution have been observed when the solution is used as described. However, cardiovascular complications such as bradyarrhythmia have been reported cases where the organ has been reflushed with fresh solution within a short period (1-3 hours) prior to release of vascular anastomosis clamps in the recipient, or when inadequate flush out of the solution has occurred.

**PREPARATION AND ADMINISTRATION**

Remove overwrap prior to use. Cool the solution to 2-6°C in ice. Remove twist-off plug from port designated "delivery set port". Insert spike from the administration set into port with twisting motion. Prior to connection to the organ, the solution container should be suspended from a sufficient height to allow for a steady stream of solution and to produce flow rates of at least 30 mL/min during flushing. Flushing should be continued until the organ is uniformly pale and the effluent is relatively clear.

Immediately prior to use, to formulate the final solution, aseptically add the following additives:

1. Penicillin G 200,000 units
2. Regular Insulin 40 units
3. Dexamethasone 16 mg

**Suggested Minimum Volumes**

*In vivo* aortic flush:

- adults, 2-4 L
- infants, 50 mL/kg

*Ex vivo* infusion:

- liver (via portal vein and biliary tree)
  - adults, 1200 mL
  - infants, 50 mL/kg
- pancreas or kidney
  - adults, 300-500 mL
  - infants, 150-250 mL

Additional solution should be dispensed into the container holding the organ. Seal the container aseptically. The organ storage container should be maintained within a well-insulated transport container. Ice should be used to surround the organ storage container, but should not be used within the container, where the ice could come into direct contact with the organ. Do not use solution if particulate matter, precipitates, or contamination is evident in the solution. Check bag for leaks by squeezing container firmly. If leaks are found, discard solution containers. In order to minimize residues of the solution in the liver, just prior to anastomosis, flush one liter of lactated Ringer's through the hepatic portal vein.

**HOW SUPPLIED**

Code = 10C0-46-06

1000 mL ViaSpan<sup>®</sup> (Belzer UW), Cold Storage Solution in one liter bags, shall carton of 10. Store product at refrigerated temperatures 2-8°C (35.6-48°F) until use. Avoid excessive heat. Do not freeze the solution. Do not use if discolored or particulates are present.

**CAUTION:** Federal (USA) law restricts this device to sale by or on the order of a physician.

Manufactured by:  
NPBI B.V.  
The Netherlands

Distributed by  
**Du Pont Pharmaceuticals**  
The Du Pont Merck Pharmaceutical Co.  
Wilmington, Delaware 19880

6204-4/Rev. Oct., 1992

- \* Patent 4,798,824
- \*\* Patent 4,879,283



ViaSpan<sup>®</sup> is a registered trademark of The Du Pont Merck Pharmaceutical Co.

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Von: DR. F. KOHLER CHEMIE

10:15

17-08-98

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# ViaSpan<sup>®</sup>

(BELZER UW)  
COLD STORAGE SOLUTION \*\*

## DIRECTIONS FOR PREPARATION AND USE

NOT FOR DIRECT INJECTION OR INTRAVENOUS INFUSION.

## DESCRIPTION

ViaSpan<sup>®</sup> (Belzer UW) can be used for hypothermic flushing and storage of organs including kidney, liver, and pancreas in preparation for transportation prior to transplantation.

The solution composition is:

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Potassium Phosphate monobasic	3.4	g/L
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Raffinose pentahydrate	17.83	g/L
Adenosine	1.34	g/L
Allopurinol	0.136	g/L
Total Glutathione	0.922	g/L
Potassium Hydroxide	q.s.	
Sodium Hydroxide	adjust to pH 7.4	
Water for Injection	q.s.	

ViaSpan<sup>®</sup> (Belzer UW) is a clear to light yellow, sterile, non-pyrogenic solution for hypothermic flushing and storage of organs. The solution has an approximate calculated osmolarity of 320 mOsM, a sodium concentration of 29 mEq/L, a potassium concentration of 125 mEq/L, and a pH of about 7.4 at room temperature.

## ACTIONS

After precooling the solution to about 2-6°C (35.6-43°F) in ice, the cold solution is used to flush the isolated organ immediately before removal from the donor and/or immediately after removal from the donor. The solution is then left in the organ vasculature during hypothermic storage and transportation. This solution is to be used for cold storage of the organ and not for continuous machine perfusion. Administration of the solution at the recommended temperatures will effectively cool the organ and should reduce its metabolic requirements.

## INTENDED USE

This solution is intended for flushing and cold storage of organs including kidney, liver and pancreas at the time of their removal from the donor in preparation for storage, transportation and eventual transplantation into a recipient.

## CONTRAINDICATIONS

There are no known contraindications when used as directed.

## WARNINGS

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## PRECAUTIONS

ViaSpan<sup>®</sup> (Belzer UW) includes drug constituents which individually have caused hypersensitivity reactions in patients (allopurinol, penicillin, insulin, dexamethasone, and pentafraction). Physicians should consult drug labeling individually and be alert to treat possible reactions. Before reperfusion is established in the recipient, the donor organ must be flushed free of the cold storage solution using a physiological solution to prevent occurrence in the recipient of potentially serious cardiovascular complications such as hyperkalemic cardiac arrest or bradyarrhythmia. Because of the high concentration of potassium in the solution, precautions must be taken during donor organ retrieval to avoid cardiac arrest.

## ADVERSE REACTIONS

No adverse reactions thought to be attributable to the solution have been observed when the solution is used as described. However, cardiovascular complications such as bradyarrhythmia have been reported in which the organ has been reflushed with fresh solution within a short period (1-3 hours) prior to cardiovascular anastomosis clamps in the recipient, or when inadequate flush out of the solution has

**PREPARATION AND ADMINISTRATION**

Remove overwrap prior to use. Cool the solution to 2-6°C in ice. Remove twist-off plug from port designated "delivery set port". Insert spike from the administration set into port with twisting motion. Prior to connection to the organ, the solution container should be suspended from a sufficient height to allow for a steady stream of solution and to produce flow rates of at least 30 mL/min during flushing. Flushing should be continued until the organ is uniformly pale and the effluent is relatively clear.

Immediately prior to use, to formulate the final solution, aseptically add the following additives:

1. Penicillin G 200,000 units
2. Regular Insulin 40 units
3. Dexamethasone 16 mg

**Suggested Minimum Volumes**

*In vivo* aortic flush:

- adults, 2-4 L
- infants, 50 mL/kg

*Ex vivo* infusion:

- liver (via portal vein and biliary tree)
  - adults, 1200 mL
  - infants, 50 mL/kg
- pancreas or kidney
  - adults, 300-500 mL
  - infants, 150-250 mL

Additional solution should be dispensed into the container holding the organ. Seal the container aseptically. The organ storage container should be maintained within a well-insulated transport container. Ice should be used to surround the organ storage container, but should not be used within the container, where the ice could come into direct contact with the organ.

Do not use solution if particulate matter, precipitates, or contamination is evident in the solution. Check bag for leaks by squeezing container firmly. If leaks are found, discard solution containers.

In order to minimize residues of the solution in the liver, just prior to anastomosis, flush one liter of lactated Ringer's through the hepatic portal vein.

**HOW SUPPLIED**

Code = 1000-46-06

1000 mL ViaSpan® (Belzer UW), Cold Storage Solution in one liter bags, shelf carton of 10. Store product at refrigerated temperatures 2-8°C (35.6-46°F) until use. Avoid excessive heat. Do not freeze the solution. Do not use if discolored or particulates are present.

**CAUTION:** Federal (USA) law restricts this device to sale by or on the order of a physician.

Manufactured by:

NPBI B.V.  
The Netherlands

Distributed by:

**Du Pont Pharmaceuticals**

The Du Pont Merck Pharmaceutical Co.  
Wilmington, Delaware 19880



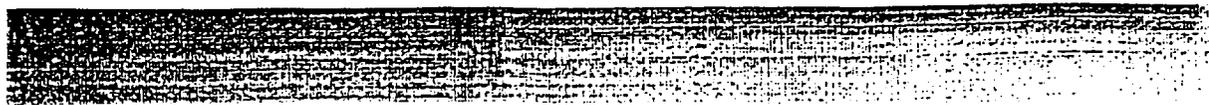
6204-4/Rev. Oct., 1992

Patent 4,798,824

Patent 4,879,283

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**Belzer UW Cold Storage Solution**  
*available for clinical use...*  
*only from Du Pont Pharmaceuticals*

**New**

TM

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Belzer UW Cold Storage Solution

*Better things for better living*



**Pharmaceuticals**

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H-16733 8/89

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Questions? Contact FDA/CDRH/OCE/DID at [CDRH-FOISTATUS@fda.hhs.gov](mailto:CDRH-FOISTATUS@fda.hhs.gov) or 301-796-8118

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## Introduction

Since the first living-related kidney transplant was performed at Brigham Hospital, Boston, in 1954, transplantation surgery has advanced at a startling pace. Nineteen eighty-nine will be remembered as the year of a particularly significant breakthrough in organ preservation and transplantation because of the introduction of ViaSpan™ (Belzer UW Cold Storage Solution).

Although you've probably heard of ViaSpan™, read about it, or may have even used it in clinical trials, you may want to know more about this remarkable cold storage solution. With this in mind, Du Pont Pharmaceuticals has developed this brochure to answer some of the most commonly asked questions about ViaSpan™. We are confident you will agree that ViaSpan™ is the name to remember for superior organ preservation.

ViaSpan™ was designed and developed through the efforts of Folkert Belzer, M.D., a transplant surgeon, and James Southard, Ph.D., a biochemist, both from the University of Wisconsin, in collaboration with Du Pont Pharmaceuticals. This cold storage solution marks the first in a new Du Pont family of important transplantation products. As the leader in synthetic colloids, Du Pont Pharmaceuticals continues to be fully committed to ongoing research and development of innovative high-quality products for the advancement of transplantation surgery.

For more clinical information about ViaSpan™, please call Du Pont Pharmaceuticals, Medical Affairs, at 1-800-441-9861. To place an order, please phone Customer Service at 1-800-543-8693.

**QUESTION**

**ANSWER**

**What is ViaSpan™ (Belzer UW Cold Storage Solution)?**

ViaSpan™ is a sterile, nonpyrogenic solution that safely preserves the human kidney, liver, or pancreas prior to transplantation. It can be used for *in vivo* aortic flush, *ex vivo* infusion, and subsequent cold storage.<sup>1,2</sup>

**What important advantages does ViaSpan™ offer?**

ViaSpan™ dramatically prolongs the *ex vivo* viability of these organs, which will increase the number of organs available for transplantation. The time available between donation of a liver or pancreas and its transplantation into a recipient can be up to tripled with the solution. Previously, these organs had to be transplanted within eight hours. ViaSpan™ also matches current kidney preservation times up to 40 hours. Preliminary findings from one study demonstrated that kidneys preserved in ViaSpan™ required less postoperative dialysis than those preserved in Euro-Collins solution.<sup>2,3</sup>

**In view of these advantages, how can ViaSpan™ improve transplantation surgery?**

Increased *ex vivo* organ viability with ViaSpan™ opens up a number of important opportunities: Organs can be removed and preserved prior to the recipient's arrival; livers can be obtained even before there is a recipient, thus increasing organ availability and reducing waste; organs can be transported from greater distances; and there is more time for analysis of donor organ and recipient tissues. Overall, transplantation surgery can now be scheduled in advance rather than as an emergency procedure.<sup>2</sup>

**How does ViaSpan™ confer these benefits?**

Because of its unique formulation, ViaSpan™ fulfills the criteria essential for safe, effective, and extended preservation of the donor kidney, liver, or pancreas prior to transplantation:

- Contains Pentafraction™; a unique low-molecular weight colloid, for superior oncotic support to prevent expansion of the interstitial space
- Contains lactobionate, an impermeant anion with a large relative molecular mass, and raffinose, a saccharide with a large relative molecular mass, to prevent hypothermic-induced cell swelling
- Contains glutathione\* which is depleted during ischemia and considered essential for the reduction of cytotoxic agents, such as hydrogen peroxide, lipid peroxides, disulfides, ascorbate, and free radicals
- Contains allopurinol\* to inhibit xanthine oxidase, which, in turn, prevents injury from oxygen-free radicals especially during reperfusion
- Contains adenosine\* to stimulate adenosine triphosphate (ATP) synthesis after perfusion, necessary for energy metabolism
- Contains no glucose to stimulate lactic acid or hydrogen ion production and thus prevents intracellular acidosis, which is particularly important for effective liver and pancreas preservation\*

\*Included for theoretical reasons; the role of this ingredient in organ preservation is not clear.

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**Why is the colloid Pentafraction™ such an important ingredient of ViaSpan™?**

Pentafraction™ is a unique low-molecular weight colloid that is a modification of Du Pont Pharmaceuticals' widely used plasma volume expander Hespan™ (6% hetastarch). By providing superior oncotic support, Pentafraction™ helps to maintain an open vascular network and prevents the expansion of extracellular space for improved organ preservation.<sup>2,4</sup>

**What other ingredients does ViaSpan™ contain?**

In addition to the aforementioned ingredients, ViaSpan™ contains potassium phosphate monobasic, magnesium sulfate heptahydrate, potassium hydroxide, sodium hydroxide, and water for injection. Immediately before use, the following should be added aseptically to formulate the final solution: 200,000 units of penicillin G; 40 units of regular insulin; and 16 mg of dexamethasone.<sup>1</sup>

**Should any specific precautions be taken when preserving organs in ViaSpan™?**

Because ViaSpan™ has a high potassium concentration, the donor organ, particularly the liver, must be flushed just prior to anastomosis with one liter of lactated Ringer's solution to wash out the cold storage solution before reperfusion. This is extremely important in order to prevent hyperkalemic cardiac arrest in the recipient. The kidney and pancreas should be allowed to drain completely prior to anastomosis.<sup>1</sup>

**Why should ViaSpan™ be used at the onset of *in vivo* aortic flushing and for *ex vivo* infusion and cold storage?**

There are important reasons to use ViaSpan™ from the beginning of *in situ* flushing, as well as for subsequent *ex vivo* infusion and cold storage. Using ViaSpan™ achieves rapid cooling and maximal saturation of the organ's vasculature. In this way, you can avoid cell swelling that can occur once the organ has been clamped off. *Ex vivo* infusion allows for continued flushing of blood and effluent to yield a uniformly pale and relatively clear effluent.

**How does ViaSpan™ differ from Euro-Collins solution?**

Unlike ViaSpan™, which contains the impermeants lactobionate and raffinose, Euro-Collins solution utilizes glucose as the main impermeant. Because glucose can pass into the liver and pancreas, it does not effectively prevent cell swelling and can cause acidosis in these organs. In view of this, Euro-Collins solution is not effective for extended preservation of these organs. Moreover, ViaSpan™ contains Pentafraction™ to help maintain an open vascular network and prevent the expansion of extracellular space, while Euro-Collins does not contain a colloid to exert oncotic support.<sup>4</sup>

**Does ViaSpan™ have advantages over other currently available preservation solutions in kidney transplantation?**

According to preliminary results reported by Dr. Rutger Ploeg of the University Hospital Leiden, The Netherlands, and colleagues, at the American Society of Transplant Surgeons meeting in June 1989, ViaSpan™ is superior to Euro-Collins solution for the preservation of kidneys. Of the 108 kidney transplants analyzed in the prospective, randomized phase of this multicenter European clinical trial, patients with kidneys preserved in ViaSpan™ showed a 50% decrease in postoperative serum creatinine levels within five days compared to 14 days for those with Euro-Collins-preserved kidneys.

Furthermore, patients with kidneys preserved in ViaSpan™ required less postoperative dialysis:

- 16.6% lower dialysis rate (8 of 54 patients for the ViaSpan™ group vs. 17 of 54 patients for Euro-Collins solution)
- 63% fewer procedures
- The total number of dialyses required until day 14 was 29 with ViaSpan™-preserved kidneys and 78 with Euro-Collins-preserved kidneys<sup>3</sup>

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Considering the demonstrated superior quality of the kidneys preserved in ViaSpan™ and the reduced need for dialysis, this *in vivo* aortic flushing and cold storage solution greatly increases the potential for more successful and cost-effective kidney transplantations.

**How does ViaSpan™ compare with other currently available preservation solutions in extending liver preservation time?**

Liver graft preservation time *ex vivo* was significantly longer with ViaSpan™ than with Euro-Collins solution, according to a study conducted by Drs. Satoru Todo and Thomas Starzl and colleagues.

	ViaSpan™ (N = 185)	Euro-Collins solution (N = 180)
Mean cold ischemia time (hours)	10.1 ± 5.0*	5.9 ± 1.4
Range (hours)	4-24	3-9.5

\*Statistically significantly longer at the p<.001 level.

Moreover, these investigators from the University Health Center of Pittsburgh observed higher rates of graft survival and graft function with ViaSpan™. Also, there was a significant reduction of hepatic artery thrombosis (p<.05), possibly due to inhibition of cell swelling by ViaSpan™. Very importantly, fewer retransplantations were required in the ViaSpan™ group. According to this study published in *JAMA*, "The remarkable effectiveness of the UW solution [ViaSpan™] has revolutionized liver transplantation at almost every level."<sup>5</sup>

**How does ViaSpan™ compare with other currently available preservation solutions in regard to degree of hepatic preservation injury?**

Liver allografts sustained far less preservation injury when preserved in ViaSpan™ as opposed to Euro-Collins solution, according to a retrospective analysis of 215 liver transplants. Using initial transaminase levels (24 hours postoperative), Drs. Todd Howard and Goran Klintmalm and colleagues at the Baylor University Medical Center, Dallas, classified 70 livers as severely injured (SGOT>2000) and 35 as minimally injured (SGOT<600). Severe injury occurred more often than minimal injury in grafts preserved in Euro-Collins solution; in contrast, minimal injury was more prevalent than severe injury in livers preserved in ViaSpan™.

Rejection during the first 35 postoperative days was significantly greater in severely injured livers than in those with minimal injury (71% vs. 37%, p<.002). Also, there was more graft loss (17% vs. 3%) and delayed recovery of graft function when preservation injury was severe. Rejection severity and the frequency of recurrent or chronic rejection were comparable in the two groups. In light of these results, the investigators recommend measures be taken to reduce hepatic preservation injury in order to reduce rejection and increase graft survival.<sup>6</sup>

**Can ViaSpan™ be used to preserve other organs?**

Du Pont Pharmaceuticals is now investigating ViaSpan™ and modifications of the cold storage solution for use in transplantation of other organs.

**How is ViaSpan™ supplied?**

ViaSpan™ is packaged in convenient one-liter plastic bags, with 10 bags per shelf carton. The minimum order is one carton. The solution is available in the U.S., Canada, and Europe.

**Are there any special storage requirements for ViaSpan™?**

ViaSpan™ should be stored at refrigerated temperatures of 2-8° C (35.6-46° F).

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**What is the shelf-life of ViaSpan™?**

The shelf-life of ViaSpan™ from the date of manufacture is 12 months; on receipt at your hospital, the shelf-life will probably be six to nine months.

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**Why does ViaSpan™ cost more?**

ViaSpan™ contains several ingredients that have to be specially formulated, and the solution requires constant refrigeration prior to use, both of which are costly. Although ViaSpan™ may seem expensive, its far-reaching benefits in transplantation surgery should result in more cost-effective hospitalization.

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**Is ViaSpan™ readily available?**

ViaSpan™ is normally shipped only on Mondays, Tuesdays, and Wednesdays to ensure that personnel are available to receive and refrigerate the solution upon arrival and prior to the weekend. To ensure prompt and efficient delivery, Du Pont Customer Service should be notified of your receiving hours.

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**Is ViaSpan™ available on an emergency basis?**

Should a supply of ViaSpan™ be required for an emergency procedure, it can be delivered the same day or overnight. To place an order, please phone Du Pont Pharmaceuticals, Customer Service at 1-800-543-8693.

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**How can I obtain more clinical information about ViaSpan™?**

For more clinical information about ViaSpan™, please call Du Pont Pharmaceuticals, Medical Affairs at 1-800-441-9861.

**References:**

1. ViaSpan™ Package Insert.
2. Data on file, Du Pont Pharmaceuticals.
3. Ploeg RJ for the European Multicenter Trial sponsored by FO Belzer, MD: Kidney preservation with the UW and Euro-Collins solutions: A preliminary clinical comparison. Presented at the 15th Annual Scientific Meeting of the American Society of Transplant Surgeons, Chicago, Illinois, May 31-June 2, 1989.
4. Belzer FO, Southard JH: Principles of solid-organ preservation by cold storage. *Transplantation* 1988; 45:673-676.
5. Todo S, Nery J, Yanaga K, et al: Extended preservation of human liver grafts with UW solution. *JAMA* 1989; 261:711-714.
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PHARMA

NORTH AMERICAN REGION

P.O. Box 80025  
Wilmington, Delaware 19880-0025

July 15, 1994

Colin Kendell, M.D.  
267 Cherry Valley Road  
Princeton, NJ 08540

Dear Dr. Kendell:

Thank you for your inquiry regarding information about VIASPAN® (Belzer UW-CSS).

VIASPAN® (Belzer UW-CSS)

COLD STORAGE SOLUTION

BACKGROUND

VIASPAN is intended for use as an *in situ* hypothermic flushing agent and cold storage solution for organs including the kidney, liver, and pancreas in preparation for storage, transportation, and eventual transplantation. After the solution is precooled, it is infused into the isolated organ either immediately before or after its removal from the donor. The solution is then left in the organ vasculature during hypothermic storage and transportation. VIASPAN is to be used only for cold storage of the organ and not for continuous machine perfusion.

VIASPAN was developed by Folkert O. Belzer, M.D., and James H. Southard, Ph.D., both of the University of Wisconsin at Madison.<sup>1</sup> Its composition was designed to meet specific requirements that these investigators believe are necessary for an effective cold storage solution. It contains lactobionate and raffinose as osmotically active, nonmetabolized impermeants to suppress cellular swelling induced by hypothermia; potassium phosphate for effective buffering to prevent intracellular acidosis; pentafraction\* (a modified pentastarch), to provide sufficient colloidal osmotic pressure to prevent expansion of the interstitial space during the flush-out period; glutathione and allopurinol to prevent cytotoxic injury from oxygen free radicals; and adenosine for regeneration of high-energy phosphate compounds during reperfusion. Finally, the solution contains magnesium, an impermeable anion, to prevent cellular swelling and a high concentration of potassium to facilitate the maintenance of normal intracellular osmolality. VIASPAN has an approximate calculated osmolality of 373 mOsm, a sodium concentration of

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29 mEq/L, a potassium concentration of 125 mEq/L, and a pH of 7.4 at room temperature.

The following is a brief summary of currently available data on the use of VIASPAN in the preservation and cold storage of human liver, pancreas, and kidney.

\*Du Pont Patent

#### LIVER

Kalayoglu *et al*<sup>2</sup> have published the results of 17 consecutive successful orthotopic liver transplants using VIASPAN (*in situ* flush and cold storage). The patients, ranging in age from 6 months to 60 years, were all suffering from end-stage liver disease. The mean total preservation time was 10.5 hours (range, 6-20 hr); in nine cases, the preservation time exceeded 10 hours (range, 11-20 hr). In all patients, intra- and postoperative bile production was excellent and there was primary graft function; intraoperative liver biopsies revealed normal liver histology. Serum aspartate aminotransferase (AST) levels were found to be similar in patients with livers preserved for 6 to 10 hours or 11 to 20 hours (all values returned towards normal by the fifth postoperative day). The duration of graft preservation did not affect serum total bilirubin, prothrombin time, or partial thromboplastin time. All patients left the hospital with normal liver function and enzyme values.

In a clinical study conducted by Todo *et al*,<sup>3</sup> VIASPAN and Euro-Collins solution were compared by following the outcome of liver transplantation for 3 months in VIASPAN patients and 5 months in Euro-Collins patients. Data on VIASPAN-stored livers preserved for 4 to 24 hours were collected prospectively; retrospective data on livers stored for 3.0 to 9.5 hours in Euro-Collins solution were used for comparison.

Of the 316 recipients studied, 164 patients received 185 livers preserved with VIASPAN while 152 patients received 180 livers stored in Euro-Collins solution.<sup>3</sup> More than twice as many primary transplant patients in the Euro-Collins group required retransplantation as compared to the VIASPAN group (29 of 144 vs. 17 of 151; 20% and 11%, respectively). In addition, the VIASPAN group had a statistically significant ( $p < 0.05$ ) decrease in hepatic artery thrombosis. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly increased ( $p < 0.05$ ) and prothrombin time was prolonged in livers stored in Euro-Collins solution for more than 5 hours. A correlation between preservation time up to 24 hours and liver abnormalities was not observed in the VIASPAN group. Despite the longer preservation time for the VIASPAN-stored grafts, hepatic function tests (ALT, AST, and prothrombin time) were comparable to the livers preserved in Euro-Collins solution during the first postoperative week.

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PANCREAS

In a clinical trial (unpublished data,<sup>4</sup> May 25, 1986, to February 7, 1988) conducted by Dr. Belzer, Euro-Collins solution and VIASPAN were compared for their effectiveness as a cold storage solution for preservation of human pancreas grafts. Prospective data from nine grafts preserved with VIASPAN were compared with retrospective data on six Euro-Collins-preserved pancreas grafts. Graft function after transplantation was assessed by examining serum and urinary amylase results, as well as blood glucose levels, measured daily for 1 week and at 1 month following surgery.

The mean preservation time for grafts stored in VIASPAN (8.7 hr; range, 4.0-16.0 hr) was significantly longer ( $p=0.01$ ) than for Euro-Collins-stored grafts (3.7 hr; range, 3.0-5.0 hr).<sup>4</sup> Statistically significant differences were not observed between the two groups in serum amylase, urinary amylase, or blood glucose levels even with longer storage times. However, mean serum amylase levels were considerably higher (561 vs. 287 U/L) in the Euro-Collins group on the first day after transplantation. The blood glucose values tended to increase at the end of the 7-day postoperative period in Euro-Collins patients, but decreased in VIASPAN patients. These data suggest that pancreas grafts preserved with VIASPAN and Euro-Collins solution have comparable post-transplant function despite longer storage times with VIASPAN.

KIDNEY

A worldwide multicenter trial (unpublished data,<sup>4</sup> August 1986 to October 1988) was conducted to compare the effectiveness of VIASPAN and Euro-Collins solution for flushing and cold storage of kidneys for transplantation. Data for VIASPAN were collected prospectively, while Euro-Collins data were gathered retrospectively. One hundred fifty-eight (158) patients, ranging in age from one to 66 years, suffering mainly from diabetes mellitus, glomerulonephritis, hypertension, and polycystic kidney disease, received 161 kidney transplants. Of these, 69 kidneys were stored in VIASPAN and 92 were stored in Euro-Collins solution.

An interim analysis of data showed no statistically significant differences between the two groups in mean preservation times or in graft function during the first postoperative week as assessed by serum creatinine and blood urea nitrogen (BUN).<sup>4</sup> Only 14 of 69 patients (20%) who received VIASPAN-stored kidneys required 1 or more days of dialysis within the first postoperative week as compared to 26 of 92 patients (28%) in the Euro-Collins group. These data suggest that VIASPAN is substantially equivalent to Euro-Collins solution as a cold storage solution for donor kidneys awaiting transplant, although post transplant kidney function appears to be better in those kidneys stored in VIASPAN.

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A European multicenter trial began in July 1988 to compare the efficacy of **VIASPAN** versus Euro-Collins solution in the cold storage preservation of the liver, kidney, and pancreas for transplantation.<sup>5</sup> To date, 37 transplant centers are participating in this ongoing study. Data on procedures for organ procurement as well as pre- and postoperative procedures on kidney recipients are being collected. Following surgery, kidney function is measured daily for 14 days and at 1, 3, and 12 months. Preliminary kidney results on the prospectively randomized portion of the study are presented below.

Currently 450 kidney transplants have been performed (240 nonrandomized, 220 randomized).<sup>5</sup> Interim data analysis on kidney preservation from the prospectively randomized portion of the study was performed on 115 kidneys (57 preserved with **VIASPAN** and 58 preserved with Euro-Collins solution). There were no differences in patient demography between the two groups. The median cold storage preservation time was 25 hours (range, 6-45 hr) for kidneys stored in **VIASPAN** and 24 hours (range, 13-38 hr) for those stored in Euro-Collins solution. There have been seven graft failures (three in **VIASPAN** and four in Euro-Collins solution) and one death in the Euro-Collins group. None of these occurrences were transplantation or preservation related. In the first 14 days following transplantation, serum creatinine values decreased much faster in the 54 functioning kidneys preserved with **VIASPAN** than in the 54 functioning kidneys preserved with Euro-Collins solution. Within 5 days after surgery, the mean postoperative serum creatinine levels decreased 49% from preoperative levels in the **VIASPAN**-stored kidneys (from 801 to 407  $\mu\text{mol/L}$ ), whereas 14 days was required for kidneys stored in Euro-Collins solution to achieve the same percent reduction (from 799 to 380  $\mu\text{mol/L}$ ; 52%). Approximately twice as many patients in the Euro-Collins group required postoperative dialysis (17 of 54; 31%) as compared to the **VIASPAN** patients (8 of 54; 15%). These preliminary data suggest that kidneys stored in **VIASPAN** maintain their quality better than those stored in Euro-Collins solution.

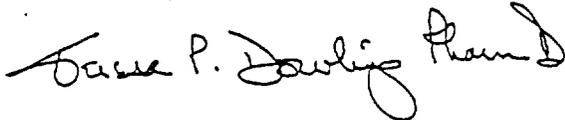
#### SUMMARY

In summary, clinical trial results thus far indicate that **VIASPAN** safely preserves the kidney, liver, and pancreas prior to transplantation. Additionally, it extends the preservation time for these organs compared with the duration of organ preservation currently used with Euro-Collins solution. It has the potential to increase the supply of needed and valuable donor organs by reducing organ wastage, improving organ function after transplantation, providing additional time for tissue matching between donor and recipient, and making liver and pancreas transplantation "semi-elective" operations. For patients with end-stage liver disease, **VIASPAN** can be potentially life saving by providing more organs for transplantation and reducing morbidity afterward. It can also yield cost savings by reducing the requirements for postoperative care.

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If you need further information or assistance, please do not hesitate to contact us at 1-800-4-PHARMA (1-800-474-2762). We welcome the opportunity to assist you and appreciate your interest in our products.

Sincerely,



Teresa P. Dowling, Pharm.D.  
Associate Director  
Professional Services

TPD:JAH

Enclosure: VIASPAN Package Insert

#### REFERENCES

1. Belzer FO, Southard JH. Principles of solid-organ preservation by cold storage. *Transplantation* 1988; 45(4):673-676.
2. Kalayoglu M, Stratta RJ, Hoffmann RM, Sollinger HW, D'Alessandro AM, Pirsch JD, Belzer FO. Extended preservation of the liver for clinical transplantation. *Lancet* 1988;1:617-619.
3. Todo S, Nery J, Yanaga K, Podesta L, Gordon RD, Starzl TE. Extended preservation of human liver grafts with UW solution. *JAMA* 1989;261(5):711-714.
4. Data on file, Du Pont Pharmaceuticals.
5. Ploeg RJ. Kidney preservation with the UW and Euro-Collins solutions: a preliminary clinical comparison. Rutger J. Ploeg, M.D. for the European Multicenter Trial sponsored by F.O. Belzer, M.D. Presented at the American Society of Transplant Surgeons; May 31-June 2, 1989; Chicago.

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**SUMMARY OF SAFETY AND EFFICACY SUBMITTED IN 1988 TO SUPPORT  
ORIGINAL 510(k) FILING**

**Introduction**

The Belzer UW Cold Storage Solution preserves organs, by cold storage, just as well as currently marketed media, such as Collins' solution. Belzer UW Cold Storage Solution, hereafter known as BELZER UW-CSS, can be used for cold storage of the liver, pancreas, and kidney. BELZER UW-CSS has the potential to be used as a general solution for most organs, both for initial cooling during in situ donor organ flushing and for subsequent cold storage. Use of BELZER UW-CSS could transform liver and pancreas transplantation from emergency operations to semi-elective procedures.

**Preclinical Data****Kidney**

Currently, kidneys are preserved by cold storage in Collins' or EuroCollins' solution (ECS) for cold storage transportation for clinical transplantation. Preservation in these solutions is limited to 48 hours. A comparison of EuroCollins' solution to BELZER UW-CSS in a dog transplant model gave 80% survival of dogs receiving kidneys stored for 48 hours in EuroCollins', but no dog survived after organ storage for 72 hours in this solution. In contrast, all dogs transplanted with kidneys preserved in BELZER UW-CSS for 48 to 72 hours survived. Initial post transplant renal function was better in kidneys stored in BELZER UW-CSS, as indicated by serum creatinine values immediately post-transplant and the rapid return of renal function to normal. Thus, storage in BELZER UW-CSS produces less damage to the kidney than storage in ECS. The results of this study indicate the equivalency, and suggest superiority of the BELZER UW-CSS to ECS for kidney preservation.

**Clinical Data****Liver**

A clinical study compared EuroCollins' Solution (ECS) and the BELZER UW-CSS as preservation and cold storage media for livers harvested for orthotopic transplant. Data for ECS were collected retrospectively, while BELZER UW-CSS data were gathered prospectively. The sample consisted of 126 livers preserved in ECS and 122 livers preserved in BELZER UW-CSS.

Once a donor became available, the liver was isolated and flushed in situ with lactated Ringer's solution and/or ECS solution. The final ex-vivo flush utilized either ECS or BELZER UW-CSS with subsequent storage in the same medium. The preservation time for each liver was recorded. After transplantation, graft function was assessed by the following selected clinical laboratory variables (SGOT, SGPT, alkaline phosphatase, total bilirubin, prothrombin time and partial thromboplastin time) for seven days after surgery and at one month post transplant. Post transplant patient follow up included monitoring for indication of graft dysfunction or rejection, which might indicate the need for a retransplantation. Donor and recipient selection followed the requirements established by the respective institutions sponsoring the transplant procedure.

Two hundred forty-eight liver transplants (126 in ECS group and 122 in the BELZER UW-CSS group) were done in 219 patients. Mean liver preservation times were significantly different for the two treatment groups, with BELZER UW-CSS livers preserved 88% longer than ECS livers (see Table 1).

Table I

	ECS (n=126)	BELZER UW-CSS (n=122)	
Mean Preservation Time (hours)	5.53±0.14	10.39±0.47	(p<0.01)
Range (hours)	0.75-10.0	0.5-28.7	

The principle differences among the various laboratory values examined between the two treatment groups occurred in SGOT, SGPT, total bilirubin and alkaline phosphatase. Mean levels of SGOT and SGPT in BELZER UW-CSS patients were significantly lower than ECS patients on the first day after surgery.

The differences between the ECS and BELZER UW-CSS groups in total bilirubin and alkaline phosphatase became apparent in the seven-day follow-up period. At the end of seven days, alkaline phosphatase levels in the BELZER UW-CSS patients were significantly lower than those in the ECS patients whereas total bilirubin levels were slightly higher in BELZER UW-CSS patients, than in ECS patients.

The need for retransplantation was higher in the ECS group, compared to the BELZER UW-CSS group (19 vs. 10). There were 23 deaths over 21.5 months for ECS patients compared to seven deaths over four months in the BELZER UW-CSS group. The incidence of hepatic artery thrombosis was greater for ECS patients (7 vs. 3), as well. It should be noted, the observation period for patients in the retrospective (ECS) sample was longer than that for BELZER UW-CSS patients (21.5 vs. 4 months).

In conclusion, BELZER UW-CSS was found to compare favorably with the present preservation cold storage solution, ECS. These data show that the use of BELZER UW-CSS for liver preservation prior to transplant can safely extend storage times. In addition, livers preserved in BELZER UW-CSS solution showed better post transplant function, as evidenced by lower enzyme levels (SGOT, SGPT), when compared to livers preserved with ECS.

A safety concern with the use of both Collins' solution or BELZER UW-CSS relates to the high potassium concentration. Both of these solutions must be flushed from the vascular space of the preserved liver prior to transplantation to prevent a systemic overload of potassium. Therefore, no contraindications to use of this solution are anticipated particularly since this solution is not given to the patient but is flushed from the donor organ prior to transplantation.

#### Pancreas

A clinical study was performed to compare the effectiveness of ECS and the BELZER UW-CSS as preservation media for cold storage of human pancreas grafts intended for transplant.

ECS data (six grafts) were collected retrospectively while BELZER UW-CSS data (nine grafts) were obtained prospectively. Graft function post transplant was assessed by examining serum and urinary amylase values, as well as blood glucose levels, for seven days following surgery and at one month.

The mean preservation time for pancreas grafts stored in BELZER UW-CSS was significantly longer than for those stored in ECS (Table 2).

Table 2

	<u>ECS</u> n=6	<u>BELZER UW-CSS</u> n=9
Mean Preservation Time (hours)	3.7±0.3	8.7±1.4
Range (hours)	3.0-5.0	4.0-16.0

There were no statistically significant differences in mean Day 1 serum amylase, urinary amylase or blood glucose levels between the two treatment groups, although Day 1 serum amylase values were higher in ECS versus BELZER UW-CSS patients.

Over the seven day postoperative period, serum and urinary amylase levels were not significantly different in the ECS and BELZER UW-CSS groups. However, blood glucose values tended to increase at the end of the week in ECS patients, but decreased in BELZER UW-CSS patients.

In conclusion, these data show that pancreas grafts preserved with BELZER UW-CSS or EC are substantially equivalent when compared by post transplant function.

#### Summary

Results from clinical trials demonstrate the ability of this solution to safely preserve kidney, liver, and pancreas prior to transplantation. Furthermore, this solution extends the preservation time for all of these organs compared with the duration of organ preservation deemed safe and effective with Collins' solution. This should increase the supply of much needed and valuable donor organs by reducing organ wastage.

Thus, this solution is both safe and substantially equivalent to Collins' and EuroCollins solutions.