Classification and Regulation of Sorbent Hemoperfusion Systems

21 CFR §876.5870

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Division of Reproductive, Gastro-Renal, and Urological Devices

Office of Device Evaluation

Center for Devices and Radiological Health

GU Advisory Panel Meeting

June 27, 2013

Objectives of Panel Meeting

- **Discuss the Risks to Health posed by Sorbent Hemoperfusion Systems in their various clinical uses**

- **Discuss whether there is sufficient evidence of safety and effectiveness to establish special controls for Sorbent Hemoperfusion Systems for their various clinical uses**

Objectives of Panel Meeting (Cont'd)

- **Discuss FDA's proposals for Special Controls for Sorbent Hemoperfusion Systems used for poisoning or drug overdose**

- **Discuss FDA's proposals for the classification of Sorbent Hemoperfusion Systems for their various indications for use**

FDA Presentations

Introduction

Regulatory Background

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Clinical Background

Douglas Silverstein, M.D.

Epidemiology Review

Ozlem Topaloglu, Ph.D.

Summary and FDA Recommendations

Douglas Silverstein, M.D.

Regulatory Definition

21 CFR § 876.5870 Sorbent hemoperfusion system

(a) Identification. A sorbent hemoperfusion system is a device that consists of an extracorporeal blood system similar to that identified in the hemodialysis system and accessories (§ 876.5820) and a container filled with adsorbent material that removes a wide range of substances, both toxic and normal, from blood flowing through it. The adsorbent materials are usually activated-carbon or resins which may be coated or immobilized to prevent fine particles entering the patient's blood. The generic type of device may include lines and filters specifically designed to connect the device to the extracorporeal blood system. The device is used in the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances.

(b) Classification. Class III (premarket approval)

Device Description

- **Extracorporeal system containing filter or cartridge with adsorbent material, typically activated charcoal**
- **May consist of stand-alone filter or cartridge, or a whole, comprehensive system**
- **Adsorber removes wide range of substances, both toxic and normal, from the circulating blood**

Source: http:/http://www.gambro.com/en/ca-en/Products/Hemodialysis/Dialyzers/Adsorba//gardenrain.wordpress.com/2009/04/24/hemoperfusion
http://www.gambro.com/en/global/Therapies/Molecular-Adsorbent-Recirculating Systems

Indications for Use

Per 21 CFR § 876.5870, Sorbent Hemoperfusion Systems are used for the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances

Summary of Sorbent Hemoperfusion Devices Cleared

510(k) Number	Device	Sponsor	Indications for Use	Date of SE
K113313	MARS®	Gambro Renal Products	Hepatic Encephalopathy (HE)	12/14/12
K033262	MARS®	Gambro Renal Products	Drug Overdose	5/27/05
K992196	Biologic-DT	Hemocleanse	Acute HE and Drug Overdose/Poisoning	7/10/99
K984546	Biologic-DT	Hemocleanse	Acute HE and Drug Overdose/Poisoning	8/13/99
K971015	Ahcs Hemoperfusion System	American Health Care System	Detoxification and Drug Removal/Retention	10/22/97
K953751	Biologic-DT	Hemocleanse	Drug Overdose and Hepatic Failure	2/15/96
K885017	Haemosorba CH500, CH350, CH180	Asahi	Drug Intoxication and Hepatic Coma	3/17/89
K873643	Adsorba 150c	Gambro Renal Products	Drug Overdose	12/29/87
K840532	Hemoperfusion System TP-400	Extracorporeal Medical Systems	Drug Overdose	5/30/84
K831029	Hemoperfusion System TP-400	Extracorporeal Medical Systems	Drug Overdose	8/26/83

Revised Indications for Use

- **Hepatic Encephalopathy due to decompensation of chronic liver disease**
- **Acute or chronic hepatic coma**
- **Hepatic failure**

Regulatory History

- **Pre-amendment device – commercialized prior to enactment of Medical Device Amendments in 1976**
- **1978 - Original Classification Panel – recommendation to classify in Class III**
- **1981 - Proposed Rule published in Federal Register proposing classification (Class III)**
- **1983 - Final Rule to finalize classification (Class III) and codify regulation is published**
- **Although classified in Class III, Sorbent Hemoperfusion Systems have been reviewed by FDA as 510(k)s, and there has not been a call for PMAs**

Risks to Health

As identified by original classification panel:

- Platelet loss and thrombocytopenia
- Blood loss
- Depletion of vital nutrients, hormones, or vitamins
- Release of emboli
- Toxic and/or pyrogenic reactions
- Clotting
- Leukopenia
- Hemolysis
- Infection
- Hypotension and
- Metabolic disturbances

Regulatory History (Cont'd)

- **April 9, 2009 – 515(i) order published requiring information on Sorbent Hemoperfusion Systems**
  - **One response received by FDA in support of down-classification of Sorbent Hemoperfusion Devices for drug overdose and poisoning.**
- **February 17, 2012 - Following FDA's review of responses to 515(i), FDA proposed reclassification scheme in Federal Register (Proposed Rule)**
  - **Public comments received until May 17, 2012**
- **July 9, 2012 – Enactment of FDA Safety and Innovation Act (FDASIA) – changes in the reclassification process for medical devices**
- **April 4, 2013 – Re-publishing of FDA's proposals for reclassification of Sorbent Hemoperfusion Systems (Proposed Order)**
  - **Public comments received until May 6, 2013**

Proposed Reclassification Scheme

- **The FDA recommends a split classification for 21 CFR § 876.5870**
- **The FDA recommends the following revision to Section § 876.5870:**

For drug overdose/poisoning:

Class II

- **Although life-supporting or life-sustaining, devices meet definition of a Class II device because special controls can be established**

For hepatic coma and metabolic disturbances:

Class III (call for PMAs)

- **Devices meet definition of Class III devices because they are life-supporting or life-sustaining and special controls cannot be established**

Clinical Evidence

- **Medical Device Reports (MDRs)**
- **Literature Review**
- **Review of Clinical Evidence and Experience**

Medical Device Reports

Methods:

Search of Manufacturer and User Facility Experience (MAUDE) database:

- **MAUDE stores MDRs received by FDA and captures information on the post-market behavior of devices**
- **Report Dates: Jan 1, 1998 to Mar 24, 2013**

Device Issues Focus:

- **Break, leak, dislodge, vascular injury, placement**

Results:

No MDRs found

MDR Reports-Summary

Lack of Reports

- Under-reporting
- Incomplete information
- Manufacturer reporting practices
- Lack of clinical use in the cleared uses
- Few device clearances

Hemoperfusion: Background

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Medical Officer

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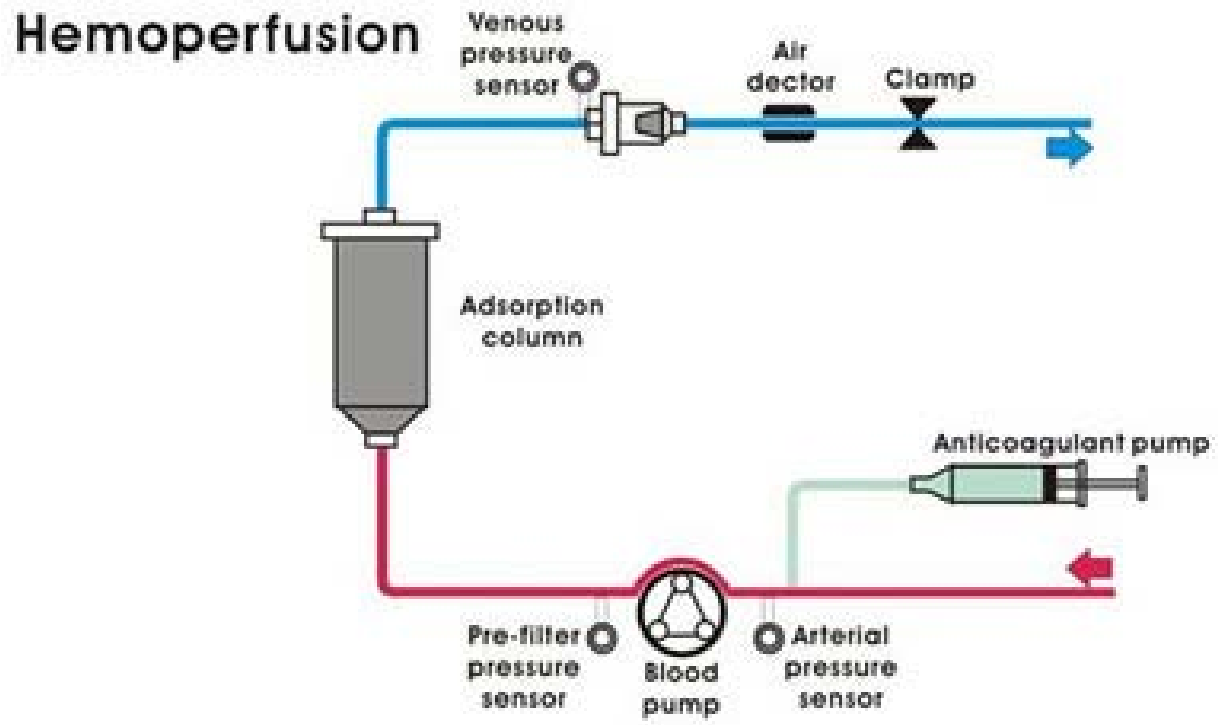
Office of Device Evaluation

June 27, 2013

Indications for Use

Per 21CFR §876.5870:
Sorbent hemoperfusion systems are used in the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances.

Schema



Source: http://gardenrain.wordpress.com/2009/04/24/hemoperfusion

General Facts About Hemoperfusion

- First introduced in the 1940s, but active use not observed until 1970s
- 2-3 hours/treatment
- Blood pumped through a column with sorbents that acts as attractants
- Adsorbent materials are usually activated-carbon or resins, which may be coated or immobilized to prevent fine particles entering the patient's blood
- Substances/drugs with molecular weight 100- and 40,000 daltons are removed

Sorbents

- Synthetic resins-remove lipid and protein soluble substances
- Ion exchange resins-remove ionic and organic substances
- Activated carbon
- Charcoal-irreversibly binds drug and chemicals; removes water and protein soluble substances

Benefits of Hemoperfusion

- Clearance of toxic substances
- Treatment of pericarditis, GI symptoms, lethargy, cardiac dysfunction, nerve conduction velocity disorders
- Clearance of organic acids, indoles, myoinositol, amino acids (aromatic-based), other hormones and metabolites
- Low protein loss
- Solute clearance: creatinine, urea, middle molecules

Hemoperfusion for Drug Overdose/Poisoning

- Compared to hemodialysis, hemoperfusion is often superior for poison/drug removal, depending on the type of substance.
- Lipid- and protein-soluble substances of lower (i.e., 113-40,000 daltons) molecular weight are effectively removed, whereas larger substances are mostly retained.
- Efficacy of hemoperfusion for drug overdose and poisoning is dependent on treatment early after exposure.

Hemoperfusion for Drug Overdose/Poisoning

HEMOPERFUSION	HEMODIALYSIS
Phenobarbitol Barbituates Gluthemide Methaqualone Theophylline Digitalis Hypnotics Paraquat Acetaminophen	Salicylates Ethylene glycol Methanol Lithium

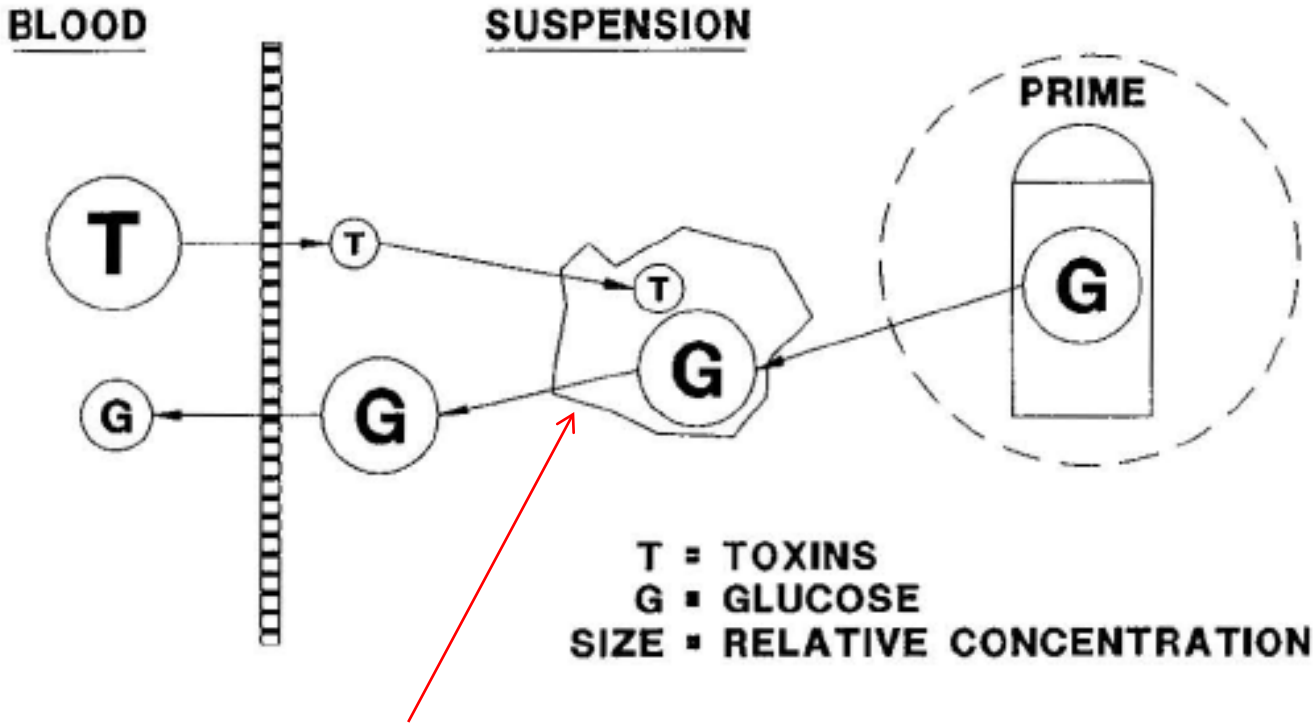
Hepatic Failure/Coma

- Hepatic coma is the final state of hepatic encephalopathy, in which the brain function progressively deteriorates
- Sorbent hemoperfusion systems are used to compensate for liver failure by removing toxins from the blood
- Data (Healthcare Cost and Utilization Project) shows that hepatic coma related hospitalizations are associated with prolonged and costly hospital stays
- In-hospital mortality for hepatic coma is nearly 8 percent

Hemoperfusion for Hepatic Coma: *BioLogic DT*

- **Also called "liver dialysis"**
- **Hemodiabsorption (HD plus HP)**
- **BFR: 200-250 ml/min**
- **Sorbent-based (charcoal) parallel or flat plate dialyzer**
- **Dialyzer contains charcoal, a cation (binds ammonia) exchanger, NaCl, Bicarb, Glucose, Amino acids**
- **Loading of substances on charcoal permits their return to the patient**
- **High drug clearance with low protein binding**

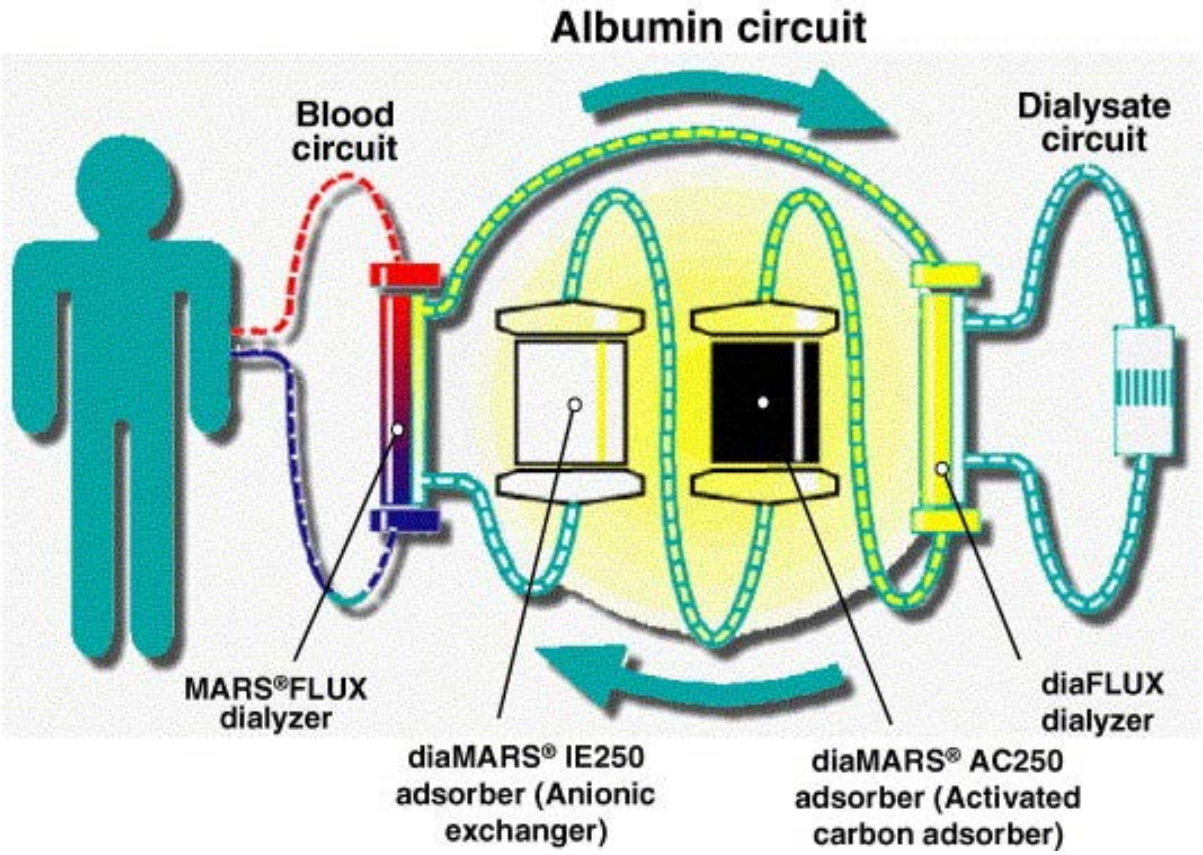
Hemoperfusion for Hepatic Coma: *BioLogic DT*



Charcoal

Source: Ash SR: ASAIO J 40: 80-82, 1994

Hemoperfusion for Hepatic Coma:
Molecular Adsorbent Recirculating System (MARS, ECAD)



Source: Stegmayr BG: A survey of blood purification techniques. Transf Apher Sci 32:209-220, 2005

Hemoperfusion for Metabolic Disturbance

- **Defines disorders characterized by loss of metabolic balance, featuring liver and kidney failure**
- **Examples:**
  - **Inborn errors of metabolism (e.g., PKU)**
  - **Type I diabetes**
  - **Gaucher disease**
  - **Thyroid disease**
- **Symptoms: Respiratory difficulty, altered mental status, seizures, organ failure**
- ***Shi and Chang, Int J Artif Organs, 1984***
  - **Showed that HP significantly reduced various amino acids in rats**
- ***Horky et al, Czech Med, 1981:***
  - **Showed that HP effectively removed various substances (phenols, urate) in 7/9 patients with metabolic disorders with minimal adverse events**

Systematic Literature Review of Sorbent Hemoperfusion Systems

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June 27, 2013

Outline

- Objective
- Methods
- Results on safety and effectiveness
- Strengths and Limitations
- Summary

Objective

To summarize the safety and effectiveness of the use of sorbent hemoperfusion (HP) systems in the treatment of poisoning, drug overdose, hepatic failure/coma and metabolic disturbance

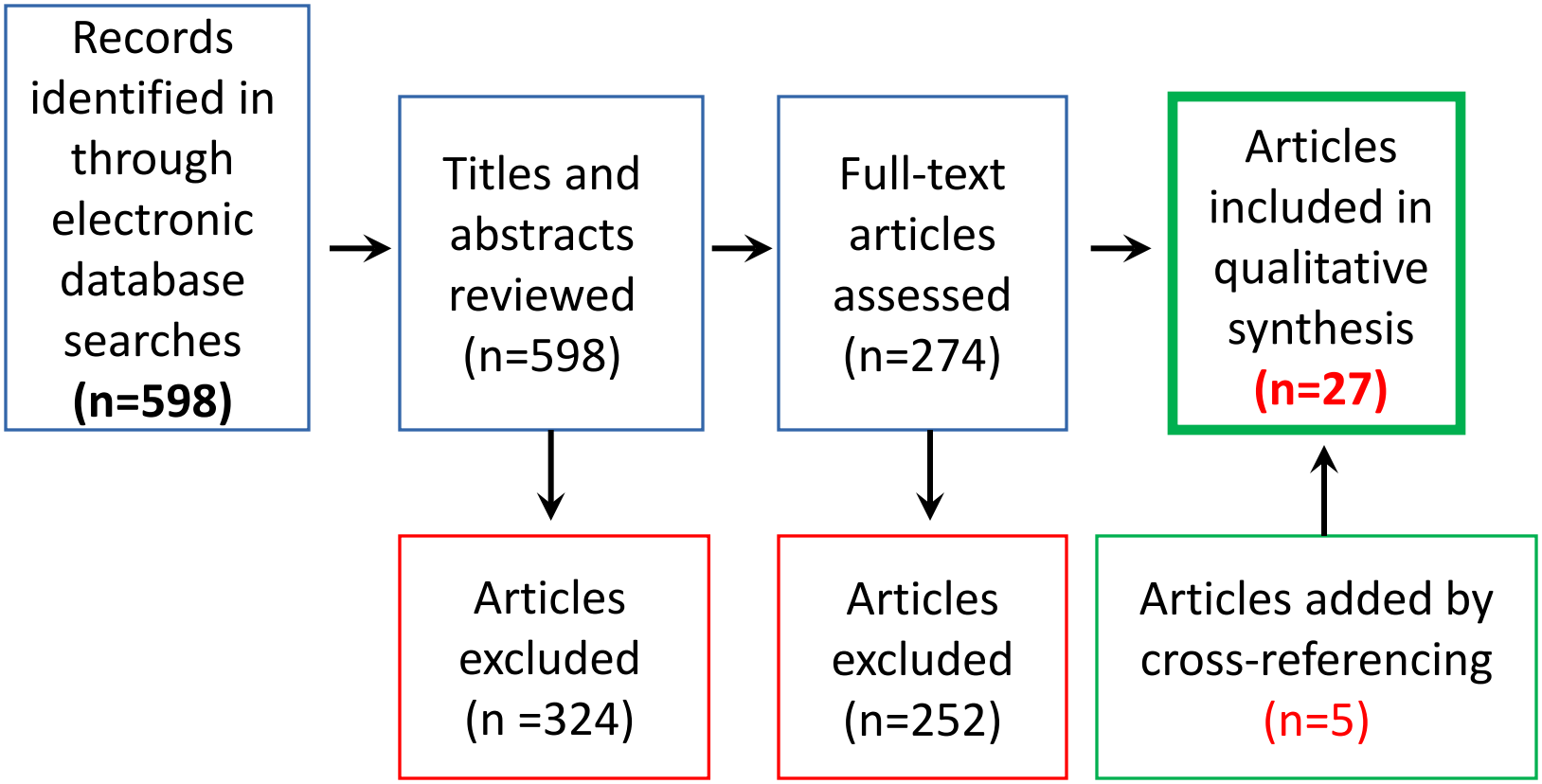
Methods

- **A search of PubMed database and Cochrane Library was conducted on May 3, 2013**
- **Search terms:**

  "charcoal hemoperfusion" or "charcoal haemoperfusion"
  "sorbent hemoperfusion system" or "sorbent haemoperfusion system"
  "therapeutic sorbent hemoperfusion" or "therapeutic sorbent haemoperfusion"
  "sorbent hemoperfusion" or "sorbent haemoperfusion"
  "sorbent hemofiltration" or "sorbent haemofiltration"
  "liver dialysis unit" or "liver dialysis plasmafilter unit"
  "BioLogic-DTPF system" or "biologic dtpf"
  "BioLogic-DT system" or "biologic dt"
  "albumin dialysis" or "albumin circulating technology"

- **All articles were limited to Human, English, RCTs and observational studies with more than 50 patients and systematic reviews/meta analysis**

Article Retrieval and Selection



Results

- **A total of 27 studies included**
  - **RCTs (n=15)**
  - **Observational studies (n=8)**
  - **Systematic reviews/Meta-analyses (n=4)**
- **Per indication**
  - **Poisoning (n=3)**
  - **Drug overdose (n=4)**
  - **Hepatic failure and coma (n=20)**
  - **Metabolic disturbance (n=0)**

Poisoning & Drug Overdose

- **Seven studies identified; RCT (n=1) and observational studies (n=6)**
- **A total of 609 patients included from UK (n=89), USA (n=303), Taiwan (n=54), China (n=108) and Czechoslovakia (n=55)**
- **Acetaminophen, theophylline, phenobarbitol, paraquat, dichlorvous, various other drugs and substances**

Poisoning

Author	Substance	No. of patients*	Comparison group	Study results
Talbot 1989	Paraquat	54	None	Almost 100% removal at 15 min
Peng 2004	Dichlorvous	67	SMT¶	- Significantly lower mortality rate in HP (7.5% vs 34%)
Mydlik 1983	Multiple	55	None	- Mortality rate: 22% - No concerns about platelet counts, no AEs

* No. of patients treated with HP; ¶: Standard of Medical Therapy

Drug Overdose

Author	Drug	No. of patients*	Comparison group	Study results
Gazzard 1974	Acetaminophen	16	SMT¶	- No survival benefit
Higgins 1996	Acetaminophen	51	None	- Decrease in plasma drug level (HP group) - Lower peak prothrombin time, bilirubin, and creatine (admitted in first 42 hours)
Koffler 1978	Multiple drugs	54	None	- Phenobarbitol intoxication improved most - Discharge 3-25 days after admission
Shannon 1993	Theophylline	38	None	- Prophylactic HP reduced the incidence of major toxicity from 71% to 5%

* No. of patients treated with HP; ¶: Standard of Medical Therapy

Poisoning & Drug Overdose

Safety

- **No serious hypotensive or anaphylactic reactions**
- **Platelet counts decreased below normal range (100,000/mm^3) during HP**
- **No serious bleeding observed**

Hepatic Failure and Coma

- **Charcoal Hemoperfusion**
  - **RCTs (n=2)**
  - **Observational Study (n=1)**
- **BioLogic-DT**
  - **RCTs (n=4)**
- **Molecular Adsorbent Recirculating System (MARS)**
  - **RCTs (n=9)**
  - **Observational study (n=1)**
- **Systematic Reviews and meta-analyses (n=4)**

Charcoal Hemoperfusion

Author	Patient Population	No. of patients	Treatment groups	Survival
O'Grady 1988	RCT	62	10h vs SMT	34.5% vs 39.3% (HP vs control)
O'Grady 1988	RCT	75	5h vs 10h HP	51.3% vs 50.0% (HP vs control)
O'Grady 1986	Observational Study¶	620	HP only	21.7%-46.9%* 15.4%-60.0%δ 10.0%-15.0%ϕ

¶ Survival rate over time period from 1973 to 1985
*Acetaminophen-induced liver failure
δviral hepatitis
ϕNon-A and non-B FH and halothane and drug induced
HP: Hemoperfusion

BioLogic-DT

- **Four small RCTs identified**

Author	Sample size	Survival
Ellis 1999*	10	- No survivors in either group
Hughes 1994	10	- 1 out 5 patients (Biologic-DT); - 3 out of 5 (control)
Kramer 2000	20	NR
Wilkinson 1998	11	- 3 out 6 patients (Biologic-DT); - 0 out of 4¶ (control)

*Survival was chosen as a study endpoint
NR: Not reported; ¶: One patient retransplanted before trial

BioLogic-DT

Safety

- **Two studies reported that there were no AEs observed**
- **One study reported that major complication observed was disseminated intravascular coagulation**
- **One study reported clotting in the circuit due to poor blood flow (<80 ml/min) (n=1)**
- **Inconsistent reporting on decrease in platelet counts**
  - **Two studies reported that excessive platelet consumption was not observed**
  - **Two studies reported that a large decrease in platelet counts observed**

MARS®

- Nine RCTs were identified
- 249 patients treated with MARS® and 235 patients with Standard of Medical Therapy (SMT)
- Seven RCTs compared MARS® to SMT
- Two RCTs compared MARS® to plasma exchange and Prometheus Adsorbent Recirculation System
- The cause and type of liver failure varied
  - 7 RCTs included patients with ACLF
  - 2 RCTs included patients with chronic liver failure
- MARS® treatment varied from 3 to 10 sessions, with variable treatment duration/session
- Duration of follow-up varied from 7 - 180 days

Study results on survival and HE

Author	No. of Patients	Comparison group	Survival (MARS vs Control)	Hepatic Encephalopathy (HE) (MARS vs Control)
Banares 2013	189	SMT	At 28 days*: 61% vs 59% At 90 days*: 46% vs 42% *: transplant-free survival	Reduction in the HE grade (from grade II-IV to grade 0-I): 63% vs 38%
Hassanein 2007	70	SMT	At 180 days: 36% vs 29%	Improvement proportion during 5 days: 34% vs 19%
Heemann 2002	24	SMT	At 30 days: 92% vs 50% At 6 months: 50% vs 50%	At any visit after MARS treatment: A significantly lower HE degree of HE in MARS vs control
Huang 2012	120	Plasma Exchange+ MARS	At 30 days: 90% vs 82%	Consciousness at 3 days: 90% vs 88%
Mitzner 2000	13	SMT+hemodia-filtration	At 7 days: 38% vs 0%, At 30 days: 25% (MARS)	Not reported
Sen 2004	18	SMT	At discharge: 44% vs 44% (all alive at 3 months)	Improvement in HE (reduction by ≥ 1 grade) at day 7: 100% vs 67%

MARS® - Observational Study

- Patients with ACLF (n=149) (Hessel 2010)
- MARS® (n=67) vs SMT (n=82)
- Duration of follow-up: 3 years
- Mean survival rates at 3 years (MARS® vs SMT): 33% vs 15%

MARS®

Safety

- **No significant differences in AEs between groups**
- **Mild thrombocytopenia, fever/sepsis due to catheter, and hemodynamic instability**

Systematic Literature Reviews/Meta-Analyses

- **Four systematic literature reviews/meta-analyses identified**
- **Two were on artificial and bioartificial systems**

Liu 2004

- **No significant effect on mortality**
- **Beneficial effect on HE**
- **Reduced mortality in AoCLF, not in ALF**

Stutchfield 2010

- **Survival benefit in ALF**
- **No survival benefit in AoCLF**

- **Two were on MARS® (Vaid, Khuroo)**
  - **No survival benefit**
- **Safety and AEs were not collected systematically or not at all**

Strengths and Limitations of this Systematic Literature Review

- RCTs and large observational studies included
- No limitation on the publication date
- Observational studies (sample size <50) and case reports/series excluded
- Search conducted in only MEDLINE/PubMed and Cochrane Library

Summary

Poisoning and drug overdose

- **One small RCT and six relatively large observational studies were identified**
- **Although the evidence is limited, these studies suggest that hemoperfusion may be a safe and effective method for treating multiple types of poisoning and drug overdose**

Summary

Hepatic failure and coma

- **One RCT with charcoal hemoperfusion, which did not show overall survival benefit, but suggested that survival might be related with the etiology of the hepatic failure**
- **Four RCTs with BioLogic-DT, which did not show significant survival benefit. However, due to the very small sample size, it is difficult to draw conclusions.**
- **Nine RCTs with MARS, mortality was not consistently shown to be improved. Some studies demonstrated improvement in liver function and HE scores.**
- **Safety data was not provided in all studies. Adverse events included thrombocytopenia and bleeding**

Summary

Metabolic disturbance

- **No studies were identified with the criteria for this literature review**
- **Therefore, for this indication, there is insufficient evidence that sorbent hemoperfusion systems are safe and effective**

Hemoperfusion: FDA Summary and Recommendations

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Medical Officer

Division of Reproductive, Gastro-Renal and Urological Devices

Office of Device Evaluation

June 27, 2013

Poisoning and Drug Overdose

Summary: Hemoperfusion for Drug Overdose/Poisoning

- **There are often no alternative therapies to hemoperfusion for the removal of certain substances (e.g., paraquat).**
- **Studies show well-understood risks for hemoperfusion for these indications.**
- **FDA believes that medical evidence strongly displays benefit over risk, and that there is sufficient evidence to establish special controls for drug overdose and poisoning.**

The panel will be asked whether the identified risks to health can be appropriately mitigated with the proposed special controls and whether any additional or different special controls are recommended for the use of hemoperfusion for the treatment of drug overdose and poisoning.

FDA Assessment of Risks With Hemoperfusion

Risks Identified by Original Panel

- **Platelet loss and thrombocytopenia**
- **Blood loss**
- **Depletion of vital nutrients, hormones, or vitamins**
- **Release of emboli (adsorbent gel)**
- **Toxic and/or pyrogenic reactions**
- **Clotting**
- **Leukopenia**
- **Hemolysis**
- **Infection**
- **Hypotension**
- **Metabolic disturbances**

Newly Identified Risks

- **Extracorporeal leaks**
- **Lack of effectiveness**
- **Lack of sterility**
- **Depletion of drugs**
- **Lack of biocompatibility**
- **Treatment interruptions or discontinuations**
- **Electrical shock due to lack of electrical safety**
- **Electromagnetic interference, which may lead to adverse interactions with other patient systems**

The panel will specifically be requested to comment on the Risks to Health and whether there are additional risks that should be considered for these devices.

Risks and Mitigations: Establishment of Special Controls for Drug Overdose/Poisoning

RISK	MITIGATION
Platelet Loss/Thrombocytopenia	Labeling
Blood loss	Device design ;Mechanical integrity testing
Depletion of nutrients/substances	Labeling; Bench studies
Leak of adsorbent/emboli	Device design; Bench/elution testing
Toxic reaction	Device design; Biocompatible materials; Clean manufacturing techniques; Proper sterilization and packaging
Clotting	Labeling
Leukopenia	Labeling
Hemolysis	Bench studies
Sterility break/Infection	Device design; Sterility assurance testing
Hypotension	Labeling
Metabolic disturbance	Bench studies; Labeling
Reduced biocompatibility	Bench testing
Lack of efficacy	Device design; Bench studies
Treatment disruption	Device design; Labeling
Electrical complications	Device design; Bench studies

Proposed Special Controls for Drug Overdose/Poisoning

- The device must be demonstrated to be biocompatible
- Performance data is necessary to demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength)
- Performance data is available to demonstrate device sterility and shelf life
- Bench performance data is available to demonstrate device functionality and extent of substance removal according to the device labeling, and validated by the device's safeguards
- A summary of clinical experience with the device (safety and performance, including adverse events) is available

Proposed Special Controls (Cont'd)

- **Labeling controls (e.g., warnings, precautions, cautions, and contraindications, including potential clinical adverse effects) and recommendations must be consistent with the performance data and must include a list of the drugs and/or poisons the device has been demonstrated to remove, and the extent for removal/depletion**

- **For devices that incorporate electrical components, validation testing of electrical safety and electromagnetic compatibility is available**

Hepatic Coma and Metabolic Disturbances

Charcoal Columns for Hepatic Coma

- 2 RCT and 1 observational study
- O'Grady et al, Gastroenterol, 1988: Showed that the Haemocol 100 charcoal column did not improve survival in 137 patients with hepatic failure, regardless of duration of HP, although etiology of HF impacted response to HP
- O'Grady et al, Schweiz Med Wochenschur, 1986: Showed that charcoal HP did not improve outcome in 620 patients with grade 3-4 hepatic encephalopathy
- Safety not adequately reported

Hemoperfusion for Hepatic Coma: *BioLogic DT*

BENEFITS	RISKS
1) Combines HD + HP–electrolyte balance 2) Improvement of hepatic function (variable) 3) Reduced lactate levels (not consistent) 4) Improved physiologic stability 5) Enhanced glucose control 6) Proven biocompatibility	1) Few reports of studies in humans 2) Catheter complications 3) Thrombocytopenia 4) Decrease in fibrinogen (DIC) 5) Inconsistent removal of metabolites 6) Unreliable decrease in serum ammonia 7) Transient but significant decrease in hemoglobin and WBC 8) Increases in pro-inflammatory cytokines (activation of WBC)

References: Ellis AJ et al, IJAO, 1999; Hughes et al, IJAO, 1994; Ash ASAIO J, 1993

Hemoperfusion for Hepatic Coma: Molecular Adsorbent Recirculating System (MARS®)

BENEFITS	RISKS
1) Removal of protein bound and water soluble toxins 2) Mimics the biological detoxification process of hepatocytes 3) Management of fluid, electrolyte, and acid/base balance 4) Control of glucose and lactate level 5) Recycling of toxin binding proteins 6) Proven biocompatibility, high selectivity, cell-free operation 7) Used in conjunction with CRRT	1) Catheter complications 2) Bleeding 3) Thrombocytopenia 4) Decrease in fibrinogen (DIC) 5) Hypotension 6) Fever

References include: Vaid, ASAIO J, 2012; Heeman, Hep, 2002; Khuroo, Liv Trans, 2004; Banares, Hep, 2013; Laleman, Crit Care, 2006; Hassenein, AJG, 2009; Mitzner, Liv Trans, 2000

Summary: Hemoperfusion for Hepatic Coma

- **FDA believes that the human clinical evidence shows insufficient evidence showing the benefit for hemoperfusion for hepatic coma**
- **Inadequate information about the substances being removed by all devices**
- **There are significant risks for hemoperfusion in patients with hepatic coma, including bleeding and thrombocytopenia, for which adequate safety provisions (special controls) are not yet established**

The panel will be asked to comment on whether they agree that special controls cannot be established to mitigate the risks to health posed by sorbent hemoperfusion devices for the treatment of hepatic coma, and thus that these devices should remain in Class III.

Summary: Hemoperfusion for Metabolic Disturbances

- **Limited medical literature and insufficient evidence and variable efficacy showing the benefit for hemoperfusion in metabolic disturbances**
- **Risks are not adequately studied**
- **Special controls cannot be properly established due to lack of information**

The panel will be asked to comment on whether they agree that special controls cannot be established to mitigate the risks to health posed by sorbent hemoperfusion devices for the treatment of metabolic disturbances, and thus that these devices should remain in Class III.

Summary Rationale for FDA Recommendations

PARAMETER	DRUG OVERDOSE/POISONING	HEPATIC COMA/METABOLIC DISTURBANCE
Adequate knowledge of offending substances	**Yes**	**Not always**
Bench data available on substances being removed	**Yes**	**Not always**
Bench testing available to assess safety	**Yes**	**Yes**
Treatments required	**Usually one**	**Often multiple**
Alternative therapies available with similar benefit/risk	**Not commonly**	**Possible**
Acceptable safety profile with mitigated risks	**Yes**	**Not always**
Special controls well defined	**Yes**	**No**
Benefit outweighs risk	**Usually**	**Not clear**

FDA Recommendations

- **The FDA recommends a split classification and the following revision to Section §876.5870:**

  <u>For drug overdose/poisoning:</u>

  Class II

  <u>For hepatic coma and metabolic disturbances:</u>

  Class III (premarket approval)

- **FDA believes that special controls can be established to permit reclassification of hemoperfusion for the treatment of drug overdose/poisoning to Class II.**

- **FDA believes that adequate special controls cannot be established to permit reclassification of hemoperfusion for the treatment of hepatic coma and metabolic disturbances, and that these devices meet the criteria for Class III devices for these indications.**