

## FDA Draft Questions

June 27, 2013 Meeting of the Gastroenterology and Urology Devices Panel of Medical Devices Advisory Committee  
Sorberent Hemoperfusion Systems 876.5870)

Please refer to the Regulatory Reference Sheet for additional information regarding classification procedures and definitions.

1. FDA has identified the following risks to health for hemoperfusion devices for various indications based on the input of the original classification panel, review of industry responses to the 2009 515(i) order, the 2012 proposed rule, and the 2013 proposed order, and FDA's literature review:
  - Extracorporeal Leaks (blood loss);
  - Platelet loss and thrombocytopenia;
  - Leukopenia;
  - Hemolysis;
  - Leak of adsorbent agent into fluid path (release of emboli);
  - Lack of sterility;
  - Toxic and/or pyrogenic reactions;
  - Infection;
  - Hypotension;
  - Lack of biocompatibility in materials or solutions contacting blood;
  - Clotting (blood loss);
  - Removal or depletion of vital nutrients, hormones, vitamins, substances and drugs (e.g., adsorption of glucose, unspecific removal characteristics, drop in patients' hematocrit), due to device's lack of specificity;
  - Metabolic disturbances;
  - Lack of effectiveness – failure to remove drugs in drug overdose, or bring on clinical improvement in hepatic encephalopathy/failure, inadequate adsorption;
  - Treatment interruptions or discontinuations;
  - Electrical shock due to lack of electrical safety;
  - Electromagnetic interference, which may lead to adverse interactions with other patient systems.
- a) Please comment on whether this is a complete and accurate list of the risks to health presented by sorberent hemoperfusion devices.
- b) Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of sorberent hemoperfusion devices, specifically for the treatment of drug overdose, poisoning.

- c) Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of sorbent hemoperfusion devices, specifically for the treatment of hepatic coma or metabolic disturbances.
2. According to 21 CFR 860.7(d)(1), “there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence use to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury association with the use of the device for its intended uses and conditions of use.” In addition, according to 21 CFR 860.7(e)(1), “there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

FDA believes that the available scientific evidence supports a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when used for the treatment of drug overdose or poisoning.

- a) Please discuss whether you believe the available scientific evidence is adequate to demonstrate the safety and effectiveness of sorbent hemoperfusion systems for these indications for use.
- b) Please comment on whether the probable benefits to health from use of sorbent hemoperfusion systems for these indications for use outweigh the probable risks to health.
3. FDA believes that the following Special Controls can adequately mitigate the risks to health for sorbent hemoperfusion devices when used for the treatment of drug overdose or poisoning, and can provide sufficient evidence of safety and effectiveness:

Proposed Special Controls

- The device should be demonstrated to be biocompatible;
- Performance data to demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength), including testing for the possibility of leaks, ruptures, release of particles and/or disconnections;
- Performance data to demonstrate device sterility and shelf life;

- Bench performance data to demonstrate device functionality in terms of substances, toxins, and drugs removed by the device, and the extent that these are removed when the device is used according to its labeling;
- Summary of clinical experience with the device that discusses and analyzes device safety and performance, including a list of adverse events observed during the testing;
- Labeling controls, including appropriate warnings, precautions, cautions, and contraindications statements to alert and inform users of proper device use and potential clinical adverse effects, including blood loss, platelet loss, leukopenia, hemolysis, hypotension, clotting, metabolic disturbances, and loss of vital nutrients and substances. Labeling recommendations must be consistent with the performance data obtained for the device, and must include a list of the drugs the device has been demonstrated to remove, and the extent of removal/depletion; and
- For those devices that incorporate electrical components, appropriate analysis and testing to validate electrical safety and electromagnetic compatibility.

- a) Please discuss whether you agree that the proposed special controls are adequate to mitigate the risks to health for hemoperfusion devices when used for the treatment of drug overdose and poisonings, and to provide reasonable assurance of safety and effectiveness.
- b) Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

4. FDA believes that the safety and effectiveness of sorbent hemoperfusion devices when used in the treatment of hepatic coma or metabolic disturbances is not well established. This is based on the lack of valid, scientific evidence in those uses, including the limited number of devices cleared by FDA for those uses, the inconclusive evidence from the published scientific literature regarding the benefit/risk ratio of these devices when used for those indications, and on the general risk we believe they pose to their target patient population.

- a) Please comment on whether you agree that the available valid scientific evidence is not adequate to support the safety and effectiveness of sorbent hemoperfusion devices when used in the treatment of hepatic coma or metabolic disturbances.
- b) If you do not agree, please explain by identifying and discussing the following:
  - i) the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of sorbent hemoperfusion

systems when used in the treatment of hepatic coma or metabolic disturbances; and

- ii) special controls that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when used in the treatment of hepatic coma or metabolic disturbances.

5. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

I: Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, and

II: If, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Regarding requirement I above, please discuss the following:

- a) Whether you believe that the application of general controls, required for all medical devices, are insufficient to provide a reasonable assurance of safety and effectiveness for sorbent hemoperfusion systems.
- b) Whether you agree or disagree with FDA's view that the application of general controls, and the special controls proposed in Question 3 above, are sufficient to provide reasonable assurance of safety and effectiveness for sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning.
- c) Whether you agree or disagree with FDA's view (in Question 4) that there is insufficient information to determine whether special controls can be established to provide a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when intended for the treatment of hepatic coma or metabolic disturbances.

Regarding requirement II above, please discuss the following:

- d) Whether you believe that sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

- e) Whether you believe sorbent hemoperfusion systems when intended for the treatment of hepatic coma or metabolic disturbances are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

Please note that the question above refers to Class III eligibility only; the next questions will ask for a final recommendation for device classification.

6. Based upon the available scientific evidence and special controls proposed in Question 3, do you recommend Class II or Class III for sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning. Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 5 above.
7. Based upon the available scientific evidence discussed in Question 4 (if any), do you recommend Class II or Class III for sorbent hemoperfusion devices when intended for use in the treatment of hepatic coma or metabolic disturbances. Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 5 above.