Introduction and Regulatory Reference Sheet
Circulatory Devices Advisory Panel
December 5-6, 2012

The Panel will discuss and make recommendations regarding three devices at this panel meeting:

- External Counter-Pulsating (ECP) devices – December 5, 2012, Session I
- Intra-Aortic Balloon Pump (IABP) devices – December 5, 2012, Session II
- Nonroller-Type Cardiopulmonary Bypass Blood Pump devices – December 6, 2012

All three device types are pre-Amendment Class III devices, meaning that these device types were marketed prior to the Medical Device Amendments of 1976 and were classified by the original classification panels as Class III but for which FDA never established an effective date for the requirement for premarket approval (PMA). As a result, these devices may proceed to market via the premarket notification [510(k)] process until such time as the classification steps are completed.

On April 9, 2009, the FDA issued an order in the Federal Register (Docket No. FDA-2009-M-0101) requesting safety and effectiveness information for these device types to determine whether the classification for the devices should be revised to require a PMA application or whether the device should be down-classified into Class I (General Controls) or Class II (Special Controls).

At this meeting, the Panel will be asked to discuss the classification of ECP, IABP and nonroller-type cardiopulmonary bypass blood pump devices. For each device type, the panel will discuss the cleared indications, the risks to health, the available safety and effectiveness information and proposed special controls.

After this advisory panel meeting, the FDA will consider all available scientific evidence and the input from panel members in determining whether to require PMA applications for these device types, or whether they should be down-classified into Class II or Class I. The FDA will then publish a proposed Order, which will be open for a public comment period. Then after consideration of all additional comments received, the FDA will intend to proceed with issuance of a final Order to finalize the classification process for these three device types.

What data should be considered when making a classification recommendation?

Initial classification and reclassification decisions are based on existing information for legally marketed devices and their predicates. Although information on future technology or new indications applicable for these devices may be available, this information is not relevant to the deliberations of the panel. The panel must consider only the legally marketed cohort of each device type.

What are the definitions of Class I, Class II and Class III?

Class I, General Controls

A device is Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Examples of general controls are: registration and listing, medical device reporting, labeling and good manufacturing practices (GMPs). Devices may also be considered Class I if the device "is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and does not present a potential unreasonable risk of illness or injury."[1] Most Class I devices are exempt from submitting a 510(k). Examples of Class I devices include general cardiovascular surgical instruments, adhesive bandages, manual stethoscope and crutches.

Class II, Special Controls

A Class II device is "a device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance."[2] Examples of special controls are: performance standards, postmarket surveillance, patient registries and development and dissemination of guidelines. Special controls may also include specific types of performance testing (e.g., biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing) or labeling which FDA may outline in the regulation or a special controls guideline. Most Class II devices require clearance of a 510(k) prior to marketing. Sponsors are required to submit valid scientific evidence in their 510(k) demonstrating that the device is as safe and effective as a predicate device. Companies submitting a 510(k) for a device must demonstrate how any specified special controls have been met in order to receive marketing clearance. Examples of Class II devices include blood pressure cuffs, percutaneous catheters, electronic stethoscopes and vascular graft prostheses.

Class III, Premarket Approval

A Class III device is a device which:

1. "cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device," **and**
2. "cannot be classified as a class II device because insufficient information exists to determine that the special controls…would provide reasonable assurance of its safety and effectiveness," **and**
3. "is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," **or**
4. "presents a potential unreasonable risk of illness or injury."[3]

Class III devices require premarket approval prior to marketing the device and must provide valid scientific evidence to demonstrate that the device has demonstrated a reasonable assurance of safety and effectiveness through the submission of a PMA application. Examples of Class III devices include endovascular grafts, coronary and peripheral stents, percutaneous heart valves, left ventricular assist devices (LVADs), and cardiac occluders.

[1] See Section 513(a)(1)(A) of the Food, Drug and Cosmetic (FD&C) Act.
[2] See Section 513(a)(1)(B) of the FD&C Act.
[3] See Section 513(a)(1)(C) of the FD&C Act.

What will the panel be asked to consider in determining which device class to recommend?

Risks to Health

The FDA will present the risks to health which they have identified to be associated with use of the device type. Some of these risks to health may have been identified by previous classification panels and some may have been identified by FDA and/or the manufacturers in response to the 515 Orders. The panel will be asked to comment on whether they disagree with inclusion of any of the identified risks or whether they believe any other risks should be considered for each device type.

Safety and Effectiveness

The FDA will present available information regarding the safety and effectiveness of each device type as it relates to the cleared indications for use and technology. The panel will be asked to comment on the adequacy of the available scientific evidence with respect to safety and effectiveness for each device type and to determine whether the probable benefits to health from use of the devices for specific indications outweigh the probable risks. If safety and/or effectiveness are not sufficient for each device type, or specific indications or technology of the device type, PMAs should be required and must provide valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness.

Special Controls

The FDA will present proposed special controls for those indications or technologies which they believe have established a reasonable assurance of safety and effectiveness. The panel will be asked to comment on the adequacy of these proposed special controls in providing a reasonable assurance of safety and effectiveness in light of the available scientific evidence. The panel will also comment on whether any additional special controls should be proposed. If there is sufficient safety and effectiveness information and special controls can mitigate the identified risks to health, it would be appropriate to recommend down-classification of the device types to Class II, special controls.

What is a "reasonable assurance of safety"?

As defined in 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 used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

What is a "reasonable assurance of effectiveness"?

As defined in 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."

What are the practical implications of maintaining these three device types in Class III?

If FDA issues a final rule classifying ECP, IABP and/or nonroller-type cardiopulmonary bypass blood pump devices, or portions of these device types, into Class III, companies wishing to continue to market existing devices of these types must file a premarket approval (PMA) application within the specified timeframe that is designated in the final classification order. To support approval, the information in the PMA (including clinical data) would have to demonstrate a reasonable assurance of safety and effectiveness. New devices or changes to existing devices would require approval of a PMA or PMA supplement. If a company does not file a PMA within the specified timeframe or otherwise does not receive an approval order for their product, the products are considered to be misbranded and should be removed from the market.

What happens if FDA decides to down-classify these three device types into Class II?

If ECP, IABP and/or nonroller-type cardiopulmonary bypass blood pump devices, or portions of these device types, are down-classified, these devices would continue to be subject to the premarket notification [510(k)] requirements and any special controls specified in the final classification order. Companies with existing legally marketed devices would be subject to the special controls, and must ensure that their existing products meet all specified requirements. New devices and changes to existing devices that require a new submission to FDA would require a 510(k), demonstration that the special controls have been met, and a substantial equivalence determination.

What happens if FDA decides to split the classification for these three device types?

In some situations, FDA may find it appropriate to split the classification of a device type by indications for use and/or device technologies. For example, FDA may determine that some indications for which the device is used are not supported by sufficient safety and effectiveness information and/or special controls cannot be established to mitigate the risks to health from use of the device type for those indications. As a result, FDA may choose to split a classification regulation and maintain the Class III classification (call for PMAs) for certain indications and down-classify to Class II (special controls) other indications.

What are the practical differences between PMA (Class III) and 510(k) (Class II) requirements?

A PMA application must provide evidence to independently demonstrate a reasonable assurance of safety and effectiveness of the device. PMAs typically involve data from clinical trials of the specific device that support both safety and effectiveness, as well as detailed manufacturing information for the device. Conversely, a 510(k) submission leverages existing information on predicate devices, including applicable clinical data, to support marketing clearance. For devices subject to 510(k), the premarket submission need only provide evidence that the device has indications and technological characteristics consistent with existing legally marketed predicate devices and meets any required special controls. The current body of evidence considered as

part of the panel meeting will be leveraged to support future substantially equivalent determinations through the 510(k) program.

Once a PMA is approved, the PMA holder must report all design, manufacturing, and labeling changes made to the approved device to FDA via PMA supplements[4] and PMA annual reports[5]. PMA holders are also typically subject to ongoing postmarket requirements. 510(k) holders are not subject to as stringent postmarket oversight. For example, for 510(k) devices, companies do not need to submit many types of minor changes to a device or its labeling to FDA for review nor do they need to submit manufacturing changes or annual reports.

Regardless of the classification of these device types, FDA does not regulate the practice of medicine, specifically, which devices clinicians can use and how they use them.

Why are these three device types in the most stringently regulated Class III classification, but are currently reviewed by FDA via the premarket clearance (510(k)) process?

When FDA's medical device regulation program began in the late 1970s, FDA regulated over 170 Class III device types through the 510(k) program. The intent was that FDA's regulation would be temporary and that, over time, FDA would decide to reclassify those device types (or regulations) into Class I or II, or to sustain the classification in Class III and call for PMA applications. Over the years, FDA has made progress in this original list; however, as of 2009, 26 medical device classification regulations, including the classification regulations for ECP, IABP and nonroller-type cardiopulmonary bypass blood pump devices, remained in this transitional state awaiting final classification. This panel meeting is the result of FDA's ongoing 515 Program Initiative to facilitate the final adjudication of these remaining Class III device types. Based on recent legislative changes made to the Federal Food, Drug and Cosmetic Act through the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, FDA is now required to hold a meeting of a device classification panel prior to finalizing the reclassification of a device type. FDA is seeking panel input on ECP, IABP and nonroller-type cardiopulmonary bypass blood pump devices to inform FDA's recommendation which will be published in a proposed order for these device types.

[4] Refer to FDA's Guidance for Industry and FDA Staff: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080192.htm).

[5] Refer to FDA's Draft Guidance for Annual Reports for Approved Premarket Approval Applications (PMA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089381.htm .