



FDA ISSUES DRAFT GUIDANCES WITH NEW REGULATORY PATHWAY OPTIONS FOR PMA PRODUCTS

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Purpose and Scope

On April 23, 2014, FDA issued two complementary draft guidance documents related to premarket approval applications: [“Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval \(PMA\)”](#) and [“Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions.”](#) These draft guidance documents reflect the agency’s continued steps towards facilitating a more timely market introduction of PMA products, while still meeting the statutory standard of reasonable safety and effectiveness. This memorandum summarizes the key topics addressed in the guidance documents and the implications of these draft guidances on the medical device industry.

Guidance Summaries

Balancing Pre/Postmarket Data Collection for Devices Subject to Premarket Approval

This guidance describes the role of postmarket data collection in determining “reasonable assurance of safety and effectiveness” during FDA review of PMA applications. FDA understands that premarket studies can add costs and time to marketing approval of a product, and that many controlled clinical trials are not representative of real-world clinical practice. As such, through the “least burdensome” provisions, the agency uses postmarket controls (e.g. compliance with quality systems regulation, postmarket surveillance and/or studies, MDR reporting and labeling requirements) to further ensure products are safe and effective once on the market.

The foundation for evaluation and use of postmarket data collection and studies is the risk- benefit profile of the product (“probable benefits vs. probable risks”). The agency describes seven scenarios when it may be applicable to authorize postmarket studies at the time of PMA approval:

- > Mature technology
- > Confirm mitigation effectiveness for a known risk in a post-approval study
- > Modify warnings, contraindications or precautions in approved labeling
- > Approve for an intended population beyond what was fully evaluated in the pivotal trial, with a confirmatory post-approval study
- > Assess long-term performance in a post-approval study
- > Assess rare adverse events in a post-approval study
- > Confirm bench data with clinical data collected in a post-approval study

The agency encourages sponsors who believe that postmarket data will be required to submit a pre-submission. FDA is intending to implement the use of increased postmarket data collection to evaluate the safety and effectiveness of a medical device as demonstrated in the draft guidance, “Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions.”



Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

This EAP guidance introduces a new voluntary program for sponsors of Class III medical devices, subject to PMA, which “demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions.” This program is influenced by and contains features of FDA’s Innovation Pathway (launched in 2011), including earlier FDA

involvement in the design and development process, and interactive review. It is intended to decrease the product development and PMA review time and cost for products to demonstrate reasonable assurance of safety and effectiveness. FDA intends to try to balance uncertainty at the time of device approval with the potential patient and public health benefits of the device, by allowing earlier access to innovative products, supported by ongoing data evaluation in the postmarket experience.

EAP is a four-step process whereby the sponsor would:

1. Request EAP designation from FDA based on meeting certain criteria
2. Work with FDA to create a Data Development Plan
3. Submit PMA for review and approval
4. Conduct required postmarket studies

In order for FDA to grant the EAP designation, three criteria must be met:

- > The device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition.
- > The device addresses an unmet need as defined by meeting one of the following conditions: a “breakthrough technology” for which no approved alternative treatment exists; the device offers a clinical advantage over existing products; or it provides a benefit to public health.

- > The device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition.
- > The sponsor submits an acceptable draft Data Development Plan, including non-clinical and clinical data to be collected in support of a premarket review and post-approval data collection.

Although a device may meet the three criteria for an EAP designation, the guidance indicates that FDA may still utilize its judgment in granting this designation. Furthermore, once the EAP designation is granted, the agency may revoke it at any time if it becomes aware of evidence to indicate that the device no longer meets the criteria for EAP designation.

Another notable aspect of the guidance is FDA’s willingness to consider alternative clinical evidence strategies to foster improved product development and marketing timeframes for these device types. Examples of these strategies include the use of intermediate and surrogate endpoints to reasonably predict clinical benefit as well as the use of two-phase studies where a pre-market study is employed to evaluate a pre-defined level of success and is paired with postmarket data collection to gather the remaining information. The agency also describes alternative experimental design strategies specific to in vitro diagnostics that include collecting analytical data for a diagnostic that has clinical validity already established in literature, or the use of contrived samples to test diagnostics for rare diseases.

Of note, FDA also indicates that PMAs for EAP devices under specific circumstances may include less manufacturing information. Additionally, quality system inspections (typically performed pre-approval) could be performed within twelve months of PMA approval, or FDA would forego preapproval inspections at certain manufacturing sites.

Finally, the guidance includes conditions of approval for EAP devices and postmarket requirements and actions, including enforcement actions and withdrawal of PMA approval if the conditions of approval are not met or if post-approval study data reveals that the device does not demonstrate “reasonable assurance of safety and effectiveness.”

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Implications of Guidance on Medical Device Industry and FDA

> While purpose of the EAP pathway is to expedite “breakthrough technology” to market, there is concern as to whether this program will truly reduce time to market. It is not clear at this time how many products would be submitted and would qualify for EAP designation. Because of the involvement of senior management and a case manager at FDA in the review process for each of these products, a large number of these requests would likely exacerbate resource constraints within FDA. Furthermore, a greater number of personnel required for review of EAP devices could have a deleterious effect on review time for PMA devices not meeting the criteria for EAP designation. A thorough analysis of the program following implementation would be needed to evaluate its effectiveness. AdvaMed has expressed additional concerns about whether this new framework would be implemented smoothly across the various divisions under ODE and OIR, and whether this framework would have the consequence of increasing requirements for device sponsors.

> The guidance indicates that the EAP designation can be revoked at any time if a device no longer meets the three required criteria. However, the agency does not provide detail as to how this re-evaluation process would work. Additionally, no clarification is provided as to how a device would transition from the EAP program to a traditional PMA review track.

> The guidance indicates that less manufacturing information may be provided in PMAs for some EAP devices and one of the factors in deciding how much information should be presented is whether there are “new, unique manufacturing issues that could adversely impact product quality or performance.” The agency does not specifically indicate the type of information that can be omitted. Additionally, it is not clear how the Agency would evaluate whether a particular manufacturing process is unique unless detailed manufacturing process information is submitted.

> At the FDLI 2014 conference, FDA Commissioner Dr. Margaret Hamburg emphasized that the new pathway for device approval, which offers flexibility to a sponsor, “does not mean [FDA is] abandoning standards or quality.” Instead, FDA is trying to move away from a “rigid one-size approach.”

> Also at the FDLI 2014 conference, Dr. Jeffrey Shuren, Director of CDRH, indicated that the agency will retrospectively evaluate Class III PMA devices to determine whether there are data previously collected in the premarket that would be better done in the postmarket, or perhaps is no longer necessary, and prospectively “bake in” modified requirements for new devices. As it pertains to the manufacturing and quality information in submissions, FDA is also relying on feedback from its “Case for Quality” initiative to better understand what critical factors have the greatest impact on device quality, as based on its technology. FDA does not have plans at this time to apply an EAP model to non-Class III devices.

For More Information

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