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FDA releases final guidance document on PMA manufacturing site change supplements

20 December 2018

On 17 December 2018 the U.S. Food and Drug Administration (FDA) issued a final guidance document intended to help manufacturers determine the appropriate premarket approval (PMA) application supplement reporting pathway for implementing changes in the manufacturing sites used for a PMA approved device. The guidance also includes the required contents of a PMA site change supplement and the general factors that FDA intends to consider when determining whether to conduct an inspection prior to approval of a site change supplement. The final guidance document, "Manufacturing Site Change Supplements: Content and Submission," replaces a 2015 draft guidance document of the same name. The 2015 draft was intended to distinguish when a change to a manufacturing site for an approved PMA requires submission of a 180-day site change supplement versus submission of a 30-day notice for a modification to manufacturing procedures or methods of manufacture. The 2015 draft was written in a Q&A format and provided a table that identified various site change scenarios and FDA's position as to whether such a change required a 180-day site change supplement or a 30-day notice submission. The 2015 draft also provided a table outlining the agency's thinking with respect to when a site change supplement also triggered the need for a preapproval inspection.

The final guidance document adopts much of the 2015 draft guidance, including the use of a user-friendly Q&A format, illustrative examples, and tables. There are several points that industry should be aware of:

- *General principle for when a manufacturing site change should be submitted as a 180-day site change supplement versus a 30-day notice:*
    - A 180-day site change supplement should be submitted in the following situations:
        1) where the site was not approved as part of the original PMA or a PMA supplement; or
        2) where the site(s) was/were approved as part of the original PMA or PMA supplement, but only for the performance of different manufacturing activities.

FDA explains that the different site would have no experience with either the process or the technology, or a similar process or technology, for manufacturing the same or a similar device, and FDA would not have had the opportunity to evaluate the change due to it not being a part of the PMA application.

- A 30-day notice should be submitted if the site is among the sites already approved in the PMA and if the change is for performance of the same or similar manufacturing activities and for the same or similar device as those at the PMA approved site. FDA explains that if the previously approved site and its personnel use and have experience with similar technology and processes for manufacturing a similar device, then the new manufacturing site would not be considered "different," which would otherwise trigger the need for a 180-day site change supplement.

- *Criteria for preapproval inspection*: The final guidance states that FDA generally determines whether to conduct an inspection of a new site associated with a site change supplement based upon the following factors:

  - the dates of the last inspection(s) of the current site and the new site;
  - the classification(s) of the last inspection(s) of the current site and the new site;
  - the relevance of the last Quality System regulation inspection to the moved manufacturing, processing, or packaging activities (e.g., whether similar products or processes were inspected);
  - a review of relevant recalls and adverse events associated with manufacturing processes for devices manufactured, processed, or packaged at this site (note that this criteria was not included in the draft guidance document); and
  - the risk to the safety or effectiveness of the device associated with the manufacturing activities performed at the new site.

  FDA intends to consider the above factors in determining the need for an inspection at the time of review. The guidance provides as an example that, when the new site has not been inspected or the last inspection of either the current or the new site was classified as Official Action Indicated, then FDA intends to conduct a preapproval inspection. The applicant may contact FDA to discuss whether a preapproval inspection may be required and notes that the presubmission process may be utilized for such interactions, if appropriate.

- *Availability of process validation data*: The final guidance document indicates that:

  - For site change supplements for which it would be likely that FDA would conduct a preapproval inspection, the agency recommends the applicant provide the process validation or revalidation protocols for the processes requiring validation or revalidation. If a determination has been made that only a subset of process validation activities needs to completed, then the rationale and supporting data for that decision should be supplied. When available, applicants should provide a copy of any completed validation reports. All validation activities should be completed before the scheduling of an inspection. Thus, the guidance states that the applicant should provide a date when its validation activities will be complete and the site will be ready for an inspection. In addition, in our view, it is important to ensure

that the applicant understands FDA's expectations as to when validation and revalidation protocols and reports will be available, which ones are required to be included in the applicant's supplement, and how the availability and/or submission of such information affects the inspection readiness date.

- The guidance further states that if FDA decides not to conduct a preapproval inspection, the agency will likely recommend the applicant provide the process validation or revalidation protocols and completed reports for all of the processes that require validation.

We encourage manufacturers of products subject to PMA site change supplements to review their future manufacturing plans to assess whether the final guidance impacts future submissions and business planning.

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