Impact of DMF First-cycle Approvals on GDUFA Metrics

As industry and FDA recognize, improvements to existing processes are needed to ensure that DMF reviews are as efficient as possible, in order to keep them from unnecessarily delaying or even halting the review and approval of ANDAs. In the GDUFA commitment letter there are several pathways to increase communication and transparency between FDA and the DMF holder. However, based on industry experience, these added tools are either not being utilized effectively, or the information is getting lost or misinterpreted.

To that end, industry provides this overview of two key areas where we request further engagement with FDA. Improvements in these two areas will have a significant impact to improving the current processes and increasing the opportunities for first-cycle approvals, thus reducing multiple-cycle reviews.

FDA Reviews and Guidances

When it comes to FDA review of DMFs under GDUFA, a significant concern is the inconsistent application of standards and requirements as applied by different reviewers. Specifically, some reviewers impose tighter specifications on API products than are required by USP and/or ICH standards, for no known or explained reason related to the product safety or efficacy. Without an understanding of why the request was made, either formulation specific or not meeting the requirements in ICH or USP, there is a missed opportunity to share knowledge between FDA and industry to enable DMF holders to improve the quality of the DMF to meet FDA's expectations.

DMFs have been requested, for example, to prove that improbable impurities are not present in the API leading to costly and time-consuming testing on the part of the DMF holder to prove analytically that the impurity does not exist at any level in the API, even though there is no real basis for the presence of that impurity. This delay may impact the FDA's ability to complete an ANDA review within the timelines required by GDUFA.

Industry feels strongly that the FDA should honor the standards and requirements of USP and ICH, unless there are clear safety or efficacy concerns for the application referencing the DMF. When departures from USP or ICH standards are required, the reason(s) should be clearly described, including the scientific rationale. This serves both to provide consistency in FDA reviews, and educate industry for future DMF applications. For example, when the reason for additional information or changes is formulation based, knowing the reason can promote future pro-active communication between the DMF and ANDA sponsor.

A related concept is around the fact that DMFs are reviewed/re-reviewed each time they are referenced in an ANDA application. An understanding, for example, that tighter specifications for one ANDA that is formulation based, will ensure the DMF is not deemed "inadequate" for other ANDAs that do not have the same formulation.

If DMF holders, ANDA sponsors and FDA reviewers were all in agreement on the expectations around product specifications, it would minimize delays associated with review of DMFs in the context of a wide variety of application reviews. This could, increase the odds that a first-cycle review can be achieved.

The approach that strikes industry as the most efficient and effective way to achieve this outcome is to have DMF technical and process experts from both the industry and FDA work collaboratively on defining

the situations under which reviewers are expected to deviate from the established standards embodied in USP and ICH. We would appreciate the opportunity to engage with the FDA in discussions on this topic.

Communications

The communications between the DMF holder, ANDA sponsor and the FDA must be improved. Many times, the fact that there is a deficiency is not made clear to one of the parties with the result that the cause for delays in approval are not obvious. We recognize that this issue is not solely between industry and the FDA; intra-industry processes also plays a role and our associations are working at improving communications between DMF holders and ANDA sponsors. This said, there are areas where DMF holders, ANDA sponsors and FDA can work together to improve the current process.

A significant area of lost or miscommunication among the DMF holder, ANDA sponsor and FDA is how difficult it may be to access the most up-to-date DMF information. The requirement for electronic submissions will certainly help to keep updates of DMFs easier to access, but it may be difficult to access the paper-submitted DMF information. Industry would like to work with FDA to assure a mechanism to guarantee that all parties have the requisite information to avoid confusion between what is in the DMF and the ANDA.

Industry is also concerned with the timing and delivery of first adequate letters for DMFs. When an amendment, to provide the information for a deficiency request is submitted, there is no other mechanism for communicating back to the DMF holder that the DMF is now adequate. Some member companies have had the ANDA sponsor ask if the DMF is now acceptable, and without a timely first adequate letter, there is no information. The feedback from our association members indicate that DMF holders are not receiving the first adequate letters or receiving them after the approval of the referencing ANDA. Such timing negates the utility of these letters.

Furthermore, the coordination between the DMF holder and ANDA sponsor for amendment submission is another area where communication can be improved. In many instances, one DMF can support many applications that are at various stages of review. Further, the DMF holder may not know the status of the various review cycles of the applications they support. An amendment to a DMF must be well coordinated so as not to adversely affect the review timeline for the various ANDAs supported by that DMF. While FDA has previously stated that this is an industry issue, we recommend that FDA consider allowing ANDA sponsors to submit a post-approval commitment, so that DMF changes do not impact the review timeline for the ANDA. Industry notes that the congressional justification to the FY2020 budget request from the administration includes an FDA request for authority to require NDA, BLA and ANDA sponsors "to submit a post-approval quality update to provide information or implement changes needed to ensure ongoing quality". We believe such authority would help prevent scenarios where a submission of a DMF amendment would not negatively impact various ANDA reviews supported by a single DMF.

In addition, DMF holders are concerned with the allotted time provided by the FDA for a response to an Information Requests (IRs). In most cases, the DMF holder is only given a two- or three-day window to provide a response, despite the 10- to 30-day window often mentioned. Outside-U.S. companies have found that significant response time for IRs can be lost due to the use of U.S. agents in addition to time-zone differences. An industry recommendation that could improve the ability for the DMF holder to provide a timely response is for FDA to send the IR request to both the U.S. agent (if one is named) and the DMF contact listed. We believe this suggestion, if adopted by FDA, would ensure timely and efficient communication to minimize unnecessary delays for DMF holders, ANDA sponsors and FDA.

Lastly, representatives from DMF holders find that their requests for teleconferences (t-cons) are frequently converted into written correspondences. They find this mode less useful than t-cons, especially as these correspondences often simply point to the very guidance that the DMF holder in principle has already addressed, with possibly some misunderstanding. Additional clarification as to where the misunderstanding lies, and how it can be addressed, is much more efficient in a verbal, real-time conversation. Written communication restating the guidance leads the DMF holder to guess as to how to apply the guidance. This adds unnecessary delays to the review timeline in instances where the DMF holder and the FDA can be better served by a t-con.

Conclusion

The industry team is looking forward to having further discussions with FDA about how we can work together to make the preparation and subsequent review of DMFs and approvals of ANDAs more efficient. We know that improvements in this area will translate into resource and cost savings for industry and the FDA, and ultimately more rapid approval of ANDA applications and cost-savings for the American public.

April 8, 2019

aam Association for Accessible Medicines

BPTF Bulk Pharmaceuticals Task Force

efcg EUROPEAN FINE CHEMICALS GROUP

PBOA PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION