Table 8 and Table 26: Regulator Review Preferences and Recent Review Trends: Questions and Key Issues

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Key Words:

Regulatory Filing, Regulatory Review, Regulatory Approval

Scope:

This roundtable discusses experiences with recent regulatory review trends and questions. Upon completion of the clinical development program, the regulatory approval process is the first step in making the medicine widely available to patients. Therefore, it is in the best interests of patients for the regulatory review process to proceed smoothly and rapidly. To optimize when to start the regulatory review process, Industry must find a balance with regulators on the right level of information to include in the registered dossier. To avoid unnecessarily extending the duration of the review process, Industry must understand regulatory requirements and themes that are not always clearly elucidated in the available published guidance documents. Furthermore, understanding these themes facilitates streamlined post-approval change management.

This roundtable discussion seeks to gain insight into current regulatory review preferences and the recent review trends, for both common approaches and those that push the boundaries.

Overall Trends in Review Questions

There is still a large trend of responses with regards to setting of specifications, and how to support the acceptance range. Many sponsors are using a 95/99 Tolerance interval approach to setting specifications, and some are being questioned on this approach and asked to tighten the resultant specification range, even if the sponsor believes the wider range is justified from clinical experience. So there still seems to be a strong push from health authorities (HA) for consistency-based specifications versus an approach of clinical relevance. Sponsors are also seeing more requests for analysis of excipients during stability studies, for example confirmation of quantity of PS-80 included in drug product formulation at end of shelf life.

Several sponsors noted concern regarding a recent FDA issuance of MAPP 5019.1, which placed new requirements for dose verification specifications on the filled drug product containers. The industry interpretation is the revised procedure creates a new required specification, but the concern is that unlike guidance for industry documents, in the case of a MAPP industry does not have opportunity to review drafts or provide comments before finalization.

With regards to validation of analytical methods, sponsors are being asked for more verification testing of compendial methods, beyond just verification studies for microbial methods. Sponsors are also being asked for method validation information earlier during the development stages, and they are starting to see requests as early as phase II development filings. It was noted that this might be more of a check on progress, rather than an absolute requirement to complete validation at this stage.

During application review, sponsors are trying hard not to update the living or established condition sections of dossiers with the information requests, and so they provide responses in module 1 documents. However, this approach is not always accepted by HA's, so frequent module 3 updates are needed, including updating of supportive information or development sections.

A final trend sponsors are seeing is a request for more GMP information as part of application review, and this increased during the pandemic. This includes items specific to the pharmaceutical quality system (PQS) and how it operates. Sponsors are trying to adapt to this by creating templates for their application submissions but still struggle with where to place this information within the dossier.

Industry perspective on HA Meetings

Industry acknowledges that during the years of the pandemic, that HA meetings were conducted via telecon, or more commonly a requested meeting was not held but written responses were provided instead. Industry notes that in the earlier months of the pandemic, the live meetings were very bumpy as regulators were adapting to remote work, but that this improved over time and is no longer an issue. Industry also noted that the written responses, while valuable, do not provide opportunity for dialogue which is most helpful in explaining complex subjects or in ensuring HA feedback is understood correctly. However, it was also noted that HA's are now putting more context into written responses, so this is improving.

With regards to new meeting types described in US FDA's PDUFA VII commitment letter, only one sponsor had experience with the new meeting types (specifically a Type D meeting), and they found the meeting to be useful. One sponsor also indicated that they had engaged FDA with an applicant orientation meeting after submission of their BLA, and that this meeting was very helpful in preventing common information requests as to the location of information in the dossier. Most sponsors point out that email correspondence with FDA continues to be an avenue for resolving quick review questions and receiving information requests.

Trends on combination product and Device related information

Sponsors noted a common concern that there is not clear guidance on where to place device related information in a dossier, and therefore each sponsor may resolve this differently. Sponsors noted that they are seeing more frequent requests for stability of the drug product in the final assembled integrated device combination products. In the case of implanted devices, sponsors are seeing more frequent requests for end of shelf life data of the drug-implant combination product, and also requests for more non-clinical toxicity data on the drug-implant.

Trends for use of new regulatory tools from ICH Q12

Of those participating in the round table, many sponsors indicated they are starting to think about established conditions and how to use the product life cycle management document. However, no participants have pursued this yet, with exception of one sponsor that had presented on this topic in a plenary session at CASSS WCBP. Sponsors indicated that it is usually the regulatory team that is leading these discussions within the companies. It was discussed that with the upcoming revisions to the Common Technical Document defined in ICH M4Q, that use of established conditions terminology will take on more importance, and so that is likely why adoption of terminology is being driven by the regulatory teams.

With regards to use of the PACMP tool (i.e. comparability protocols in US FDA terminology), it was noted that some sponsors are using this tool for component dual sourcing initiatives, whether this was for final drug product container closure components, or for in process components like filters. Sponsors see more success in US than outside of the US with the PACMP approach, however it was also noted that some of this is merely resistance to the PACMP term itself and not the underlying scientific rationale. Several sponsors found that if they called the submission a protocol, it could be accepted by a health authority, but it would not be accepted if it was called a PACMP. At least one sponsor reported success using a PACMP style submission for site changes in EMA, but they noted that they did not get reduced reporting category due to requirement for site inspection. Finally, it was mentioned that new FDA guidance for industry issued in October 2022 for use of PACMP clarified situations when reduction in reporting category might be more likely.

Overall, it appears Industry is still in the early stages of advocating/adopting ICH Q12 approaches for regulatory flexibility when considering regulators beyond the US FDA.