Table 7 and Table 25: Developing the Right Drug Product Strength – Challenges with MaPP 5019.1 and 5019.2

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Key Words:

labeled strength, excess volume, drug product design

Scope:

This roundtable will discuss challenges with two new MaPP's for CDER reviewers, MaPP 5019.1 and 5019.2, which went into effect in 2022. These MaPP's relate to aspects of volume in container for vialed sterile drug products, with emphasis on the "Goldilocks" principle of not too little and not too much. Justification is based on risk of microbial contamination during dose preparation and handling (either from need to pool too many vials or from excess leftover in vial and perceived motivation to combine). In the context of acceleration of product development, where pivotal clinical data may be from Phase 2 studies, matching dose to vial strength for commercialization is at best difficult to do and developing multiple strengths can add cost and time. Further, 5019.1 indicates a requirement for a gross content specification including an upper content limit which is redundant with in-process fill weight control. We will discuss concerns and strategies for development without delaying time to market.

Questions for Discussion:

1. What strategies can firms adopt in designing intended-commercial drug product with the "right" strength when the final commercial dose or dosing is not yet known? Does MaPP 5019.2 imply that the strength proposed for commercial marketing must be known already by end of Phase 2, and if so, is that even feasible?

2. How does the challenge differ for a liquid versus a lyophilized drug product? How does this impact development strategy?

3. What kinds of adaptations are needed in foundational development, such as drug product strength of primary batches enrolled in stability studies for establishment of commercial shelf-life? (MaPP 5019.2 "..to ensure the sponsor has sufficient time to generate adequate stability data…")

4. Are in-process fill weight measurements justifiably a better control strategy for gross content than a test performed during release testing? If so, why? (counter MaPP 5019.1)

References:

Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, JUNE 2015:

https://www.fda.gov/media/88138/download

MaPP 5019.1: https://www.fda.gov/media/155066/download

MaPP 5019.2: https://www.fda.gov/media/159219/download

Discussion Notes:

- MAPP 5019.1, which went into effect Jan 2022, is a companion document to MAPP5019.2, which went into effect June 2022. MAPP 5019.1 includes language directing the FDA assessor to ensure that for products in a vial, that a gross content per vial acceptance criteria exists that includes both an upper and lower acceptance criterion for fill volume.
- While minimum withdrawable volume has long been a standard requirement for a vial, a requirement for an upper limit specification criterion for fill volume has not. The roundtable members understood the rationale for controlling the upper fill volume, and the FDAs concern that it could otherwise lead to excessive residual volume and potential misuse and associated microbial challenges. However, during both sessions, it was unanimously considered that requiring a new specification is unnecessary to achieve this control, and therefore adds unnecessary burden. Instead, controlling the upper fill volume to avoid excessive overfill is accomplished through IPC fill weight control during DP manufacturing, where in process weight checks are performed throughout the fill, and fill weight/volumes exceeding a certain limit are discarded. These checks are done throughout the fill and this actually provides a better degree of control than a random vial(s) tested on release. Ppk analysis for fill weight/volume could also be leveraged for this rationale.
- One general concern noted with this MAPP is that it has specific detailed requirements that are not present in the industry guidance. Further, unlike industry guidance, industry does not have a chance to review and comment on draft MAPPs.
- Two companies have been requested to add gross content specifications on recent commercial filings for a vial. These companies are negotiating or have negotiated not to include gross content on the specifications, since upper fill volume limit is well controlled using fill-weight IPCs.
- Another topic discussed was the expectation in MAPP 5019.2 to avoid pooling of multiple vials, and also to avoid excess overfill in a vial. These two concepts can contradict each other when it comes to weight-based dosing, where pooling of vials and some residual volume left in the vial is unavoidable for some patients, unless an unreasonable number of different drug product configurations were made by the sponsor. This may be further complicated when the final commercial dose is not known until late in development (e.g., sometimes not until completion of pivotal trials).
- In summary, some flexibility of the principles in the MAPP guidance are considered essential for industry.
- Early dialogue with the FDA, prior to starting pivotal studies, was recommended to ensure alignment and agreement with rationale that a sponsor has regarding fill volume and strength per vial. This will provide an opportunity to explain to the agency aspects that may conflict with the MAPP principles (e.g., dose and vial configuration may not be optimized at start of pivotal study, and for some accelerated products it may mean optimization of fill volume and strength is a post-commercial commitment, etc.).
- It was noted that one appropriate place to express opinions regarding MAPP 5019 (e.g., disagreement with gross content specification requirements) is through the inbox of OPPQ (Office of Policy for Pharmaceutical Quality). Individual companies can express their opinion in this manner.

- Another suggestion with respect to feedback on the gross content requirement, was to consider providing a higher level of feedback under an industry umbrella (e.g., potentially authoring of a white paper by multiple companies through AAPS, IQ, BPOG, PDA, etc.). Offline discussions will occur to follow-up on this idea.