Roundtable Session 2 – Table 14 –
Allowable Excess Volume and Gross Content Requirements for Injectable Drug Products Filled in Vials or Ampules

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Abstract:

This roundtable will discuss complications with defining analytical specifications for 'allowable excess volume' or 'gross content' for injectable drug products filled in vials or ampules. Some requirements and expectations are not consistent across all regions which hinders global harmonization of specifications.

Discussion Questions:

Topics to be addressed include:

1) Understanding the concepts of net container content, gross content, appropriate excess content

2) What are appropriate excess volumes or gross content limits for finished drug products ?

3) What are established practices to control the net content in 'real-time' during manufacturing, and how does this relate to setting a gross content release specification ?

Notes:

Industry was requested to include gross content in drug product specifications by the FDA since 2022, often using information requests during review and via pre-BLA meetings. The request initially included a reference to MAPP 5019.1, available on the FDA website:

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

The scope of the roundtable includes the intended commercial presentation as well as clinical stage development, both liquid and lyophilized presentations. The MAPP 5019.1 is an FDA-internal guidance document which has no public commenting process. A training was provided by the FDA:

MAPP 5019.1 Allowable Excess Volume/Content in Injectable Drug and Biological Products

Industry has raised concerns that some expectations defined in MAPP 5019.1 should be refined, a platform to debate such perspectives does not exist.

- Excessive overfill in a vial might motivate for pooling residual drug product amounts to deliver extra doses

- It is unclear, why the control of the fill weight during filling control is not sufficient, and why FDA requests a release test.
- Clinical stage risk of dosing errors from taking multiple doses from a vial; focused to avoid potential dosing errors
- A fixed commercial dose always needs to meet the minimum dose / label claim

Participants shared their perspectives:

- USP has an excess volume compendium, not clear why this is insufficient for a given vial size.
- Some companies reported that FDA insisted to see a reported value for container fill volume on the CoA.
- Alternative way to ensure product quality is defining upper and lower limits during filling process and define pass/fail criteria in an SOP or manufacturing instructions.
- Manufacturing control is usually based on weight of the filled solution. When reporting of the filled volume, the monitored weight must be divided by the density of the solution.

For liquid presentations, use IPC data in combination with release data, that's effectively a real-time release approach. Fill weight checks, plus volume in container/deliverable volume on release, plus validated hold up volume studies, with upper and lower limits. The manufacturing process is better controlled versus having gross content on the specs.

Roundtable aligned that it is best to utilize risk-based approach

- Issues were reported when the overfill is too small, so that 'Closed System Transfer Devices (CSTDs) with increased hold up volume might not be used anymore. Companies might recommend specific CSTDs to be used, but hospitals might have to use alternative devices for a variety of reasons. Complex devices may require a greater overfill in the drug product vial.

Most companies specify the protein concentration with +-10% around the target value. This encounters for both process and analytical variability.

For lyophilized presentations there are additional complications:
Solid dosage form needs to have at least 100% of label claim (cited in the CFR); FDA interpretation is that the lower end of the fill range must be at least 100% protein amount. Would require a separate SKU for the US market compared to product made in other regions. For industry this means targeting the label claim plus a certain percentage to ensure that always at least 100% protein is filled per vial. That's not aligned with the intention to manufacture a drug product with an average label claim.

The clinical impact will depend also on the modality, e.g. ADCs can be weight-based dose rather than fixed dose.