THE PRACTICAL IMPACT OF THE FDA DRAFT GUIDANCE ON HUMAN MASS BALANCE STUDIES: A YEAR OF CLIENT DISCUSSIONS

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Purpose

The draft FDA guidance[1] on the clinical pharmacology considerations for human radiolabelled mass balance studies, issued in May 2022, has generated considerable attention within the pharmaceutical industry and in certain aspects has had an immediate impact on expectations for the design and conduct of human mass balance studies.

Conventional human mass balance (ADME) and AMS enabled tracer mass balance (microADME) studies have generally been relatively straightforward in their study design as single dose studies in a small cohort of healthy volunteer which help drug companies generate data to support drug development and registration. The FDA guidance once finalised will confirm the preferred approach. The draft guidance has introduced some differences in approach pending its finalisation.

Summary of Industry Comments submitted to the FDA

A review of the comments submitted to the FDA on the draft guidance[2] indicates a high level of consistency in the overall feedback from both pharmaceutical companies and contract organisations providing services. The key topics are raised are:

- Clarity on the rationale for the increase in evaluable subjects required
- Consideration/ recommendation to reduce the target for recovery of the administered dose in excreta to 80%
- Change to discharge criteria to be 90% recovery or two consecutive days of <1% recovery
- Pooling methods to be maintained as industry best practice
- Further guidance around AMS enabled studies
- Clarity around what is considered the final therapeutic dose, and rewording to include within the linear range for the therapeutic dose

Discussion

Consistent with the comments submitted to the FDA, the most common subjects which have arisen as points of discussion in the planning of human ADME studies between Quotient and our clients since the publication of the draft FDA guidance are summarised in Table 1 together with the general position Quotient have taken to assist clients in reaching a resolution with regard to finalising planned study designs.

These topics are not exclusive but they are the points from which most client questions are drawn and which could have the most immediate impact on the study design or conduct.

Table 1:

Topic	Established Approach	Draft Guidance Approach	Challenges & Implications	Quotient Position
Subject numbers	Six subjects dosed for evaluable data set in four	Evaluable data set in six	Justification for change unclear Increased overall budget	Recruit as usual - drop outs are limited. Remain flexible to change if required upto point study start
Mass balance recovery & discharge criteria	90% recovery OR <1% recovery on two consecutive days	Mixed wording on discharge including 90% Recovery AND <1% recovery on two consecutive days	Uncertainty over correct acceptance criteria, Potential for delayed subject discharge for limited benefit	Established position aligns with Roffey et al[3] Continuing adherence to established position (with client agreement)
Metabolite profiling for AMS enabled studies	Single pooled samples per matrix	No distinction made between conventional and AMS enabled studies – recommends individual subject pools	AMS enabled studies are established as suitable for regulatory submission Increasing requirement to individual pools woud have significant cost implication	Increased data set Impractical to implement given cost and time impact on study delivery - remain at single pools per matrix unless final guidance requires more
Identification of radioactive components observed in excreta	Identification of any single metabolite above 10%.	Ideally more than 80% of recovered radioactivity in excreta should be identified	Potentially very demanding requirement if many metabolites are observed May significantly increase complexity and timelines for metabolite identification in excreta	Consider on a case by case basis at the point of metabolite identification. Can be implemented if practical

Summary

One regular point of concern from our clients is whether they must follow the draft FDA guidance even though it is only in draft form. Consistent in this are observations that other draft guidance's have been followed by industry even though they remain / have remained in draft form for a significant period of time.

Quotient is taking a data driven and pragmatic approach to addressing client concerns with study design taking into account the FDA draft guidance and our experience of running 10-15 ADME studies per year.

- For patient numbers, our advice to clients reflects more the likelihood of subjects dropping out due to an extended residency than the need to ensure a data set of 6 subjects. In general, drop out subjects on short residency studies are rare.
- Our discharge criteria have been consistently applied for many years as >90% mass balance recovery or <1% recovery on two consecutive days (with both urine and faecal samples provided). For conventional studies we remain comfortable that this adequately allows the routes and rates of excretion to be defined and also provides the samples needed for metabolite characterisation to be collected
- With regard to generation of profiles for metabolite investigation, Quotient has an approach we adopt when clients request our advice. For AMS-enabled studies we observe no appetite from clients or from the AMS providers to increase the current approach of single pools per matrix
- Currently for the identification of radioactive components in excreta we have not yet had had to change our usual approach to investigation and will consider on a case by case basis if this becomes necessary.

References

1: Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies, FDA, May 2022

2: Regulations.gov Docket ID: FDA-2022-D-0113

3: Roffey SJ, Obach RS, Gedge JI et al. Drug Metab Rev. 2007; 39(1): 17-43