

Final Concept Paper
S3A: Q&As on Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure
Focus on Microsampling
dated 21 May 2014

Endorsed by the ICH Steering Committee on 23 October 2014

Type of Harmonisation Action Proposed

Implementation Working Group (IWG) on S3A (Q&A document).

Statement of the Perceived Problem

The ICH S3A Guideline has been successfully implemented for Toxicokinetics (TK) evaluation in the regulatory framework by most authorities around the world. Especially since in recent years these techniques have further evolved, the guideline, however, does not fully address the benefit and use of microsampling techniques (<50 µl) in main study animals ideally as alternatives to the collection of normal (macro) blood samples from satellite animals. Therefore, more supportive text and details in the format of a Q&A document regarding the use of microsampling would encourage and lead to:

1. Directly linking toxicological effects to drug exposure by using the same animals;
2. Contribution to the 3Rs benefits by reducing/eliminating TK satellite animals use and sample volumes.

Thus further facilitation of microsampling techniques by a Q&A to the ICH S3 Guideline should achieve a beneficial result providing higher quality data combined with reduction and better use of animals.

Points to be addressed

The points so far identified and to be addressed by the IWG and, if considered warranted, in the Q&A document on S3A include the following:

1. Comparison of microsampling methods across species and test materials:
E.g. Comparison of benefits/problems in analytical and sample integrity between Dried Dry Blood Spot/Dry Plasma Spot (DBS/DPS) and plasma/serum Capillary MicroSampling (CMS) in several animal species such as rodents and non-rodents including Non Human Primates. Their applicability for biologics as well as low molecular compounds should be also discussed. This comparison may be separated out into different questions addressing on the one hand benefits/problems of wet vs. dry samples and on the other hand benefits/problems of the different matrices e.g. blood vs. plasma vs. serum
2. Good Laboratory Practices (GLP) for validating methods:
E.g. is there any hurdle to improvement of existing bioanalysis techniques?
What type of validation studies are needed for GLP toxicity studies?

3. Expectations for repeat sample analysis:
E.g. Taking only single sample analysis or Incurred Sample Re-analysis (ISR) into account is microsampling acceptable for pivotal regulatory studies, and are there specific recommendations?
4. Impact of repeated sampling on toxicology endpoints:
E.g. Effects of blood volumes on safety assessment using main study animals (non-TK satellite) should be considered and evaluated from the viewpoints of the species difference, and compound class or mechanism of action.

The Q&A document may not necessarily be limited to the above mentioned points, if considered warranted by the IWG other identified points related to the application of microsampling may be added.

Background to the Proposal

The ICH S3A Guideline indicates that TK data should be obtained to provide proof of drug exposure. For this purpose, a blood volume of ≥ 200 μl has been conventionally needed to determine circulating drug concentrations. In rodent studies, relatively large volume of blood could cause anemia or other secondary hematological changes. Therefore, these blood samples are often taken from additional TK satellite animals. This can lead to a large increase in the number of rodents required for typical safety studies. Furthermore, because toxicological effects are assessed in main study animals and drug exposure is determined in TK satellite animals respectively, the TK data from satellite animals do not provide direct correlation between toxicological effects and drug exposure. In some cases, TK samples are also evaluated for metabolites, Anti-Drug Antibodies (ADAs) or Pharmacodynamic (PD) endpoints.

To analyse the TK data with much smaller volume samples, around 25–30 μl , a number of the approaches are currently taken. It is important to share available information and knowledge on microsampling technologies with current practices, regulatory experiences and future direction of microsampling across drug developments.

Type of Implementation Working Group (IWG) and Resources

The IWG will be comprised of two members nominated by EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada and Swissmedic. One member can also be nominated by WHO Observer, each Interested Party as well as RHIs, DRAs/DoH (if requested).

Timing

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| Concept paper approval by the ICH Steering Committee | October 23, 2014 |
| Meetings will be virtual, i.e. by web/teleconference | |
| Adoption of <i>Step 2a/b</i> document | 1Q 2015 |
| Adoption of <i>Step 4</i> document | 4Q 2015 |