Progress on bioanalysis-related ICH activities：S3A and M10 (ICHにおけるバイオアナリシス関連の動向：S3AとM10)

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Background

- Toxicokinetics（TK） evaluation：
  - Need blood sampling of more than 200μL
  - Satellite animals are used for rodents (e.g., mice)
- Accumulation of microsampling studies.
  Low vol. (≤50μL) of blood is enough due to developments of measurement methods with high sensitivity.

– Oct. 2014 Approved concept paper and business plan by ICH
– Dec. 2014 Assigned Implementation Working Group (IWG) members

Histories of IWG activities-2

Date	Task / Activity	Details
17/3/2016	ICH office	➢ Completed Step 1 process
12/5/2016	ICH office	➢ Completed Step 2a process
19/5/2016	ICH office	➢ Completed Step 2b process
19/5/2016	ICH office	➢ Publicized on ICH Web site (Jan 29, 2016 version) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S3A/ICH_S3A_draft_Q_A_Step 1-29Jan2016.pdf)

Outline (Contents)

- PREFACE (Background)
- 1. INTRODUCTION - SCOPE
- 2. BASIC PRINCIPLES ON APPLICATION OF MICROSAMPLING
- 3. EFFECT ON SAFETY EVALUATION
- 4. ISSUES REGARDING THE BIOANALYTICAL METHOD

- 5. ANNEX

Preface (Background)

S3A (Toxicokinetics) guideline:
implemented in 1994

- Recently, analytical method sensitivity (such as that of liquid chromatography / mass spectrometry) has been improved, allowing microsampling techniques (very low volume sampling) to be widely used in toxicokinetic (TK) assessment.

Objective of the Q&A

To describe points to consider before incorporating microsampling method in TK studies, acknowledging

- Its benefits (and limitations) for assessment of TK in main study animals.
- Important contribution to 3Rs benefits (Replacement, Reduction and Refinement) by reducing or eliminating the need for TK satellite animals.

1. INTRODUCTION - SCOPE

1.1 (Q1) What is the definition of microsampling?

A1

A method to collect a very small amount of blood (typically ≤50 µL) to measure TK parameters of the drug and/or its metabolites.

- Matrices: blood and its derived plasma or serum, in liquid or dried form.

  Excluding other matrices (e.g. lung lavage and lymph) those are not yet validated and thus are outside the scope of this Q&A.

- Animal Species: Rodents and non-rodents.

1. INTRODUCTION - SCOPE

1.2 (Q2) What are the benefits/advantages of microsampling?

A2

Minimizing volume of blood collection

- Can minimize pain and distress in animals (improvement of the animal welfare: refinement).
- Can reduce or eliminate the number of required animals in a TK satellite group for rodents (reduction), particularly for mice.
- Can make evaluation of the relationship between safety data and drug exposure in the same animals, when performing on main study group.

2. Basic principle on application of microsampling

2.1 (Q3) For what types of pharmaceuticals and for what types of safety studies can we use microsampling?

A3

Types of pharmaceuticals:

- Applicable to majority of pharmaceuticals and biopharmaceuticals.

  However, consideration should be given on a case-by-case basis as to whether the sensitivity of the measurement method is appropriate with the small sample volumes available.

2. Basic principle on application of microsampling

2.1 (Q3) For what types of pharmaceuticals and for what types of safety studies can we use microsampling?

A3 (continued)

Types of safety studies:

- Can be used in any type of safety study

e.g., single-dose or repeated-dose safety studies, juvenile and reproductive studies, and others.

However, microsampling is not warranted when the lower limit of quantification (LLOQ) of the bioanalytical method is insufficient for the planned sample volume due to low drug exposure levels (e.g., exposure after topical or inhaled administration).

2. Basic principle on application of microsampling

2.2 (Q4) What are the points to consider when applying microsampling to TK studies?

A4

- A bioanalytical method should be developed and qualified (or validated for GLP studies, in accordance with regulatory guideline/guidance in each region) to ensure the reliability of analytical results.
- Analytical characteristics (e.g., LLOQ, matrix effects and the stability of the analyte(s) in the biological matrix for the entire periods) should be carefully assessed.

2. Basic principle on application of microsampling

2.2 (Q4) What are the points to consider when applying microsampling to TK studies?

A4 (continued)

- Bridging from conventional to microsampling methods can be done by assuring comparability of the exposure measurement between microsampling and conventional methods in a separate PK study.
  This separate PK study for comparison may be omitted on a case-by-case basis (for example, when using the same assay conditions in the same matrix to test blood samples drawn from the same site).
- Ideally, the same matrix should be used throughout the TK studies and also in clinical studies.

2. Basic principle on application of microsampling

2.3 (Q5) What types of blood collection and what types of pretreatment methods are used for microsampling?

A5

- Blood can be collected from the tail vein, etc., using capillary tubes or any appropriate miniaturized collection devices and treated either in a liquid or dried form.

<Liquid sample methods>

- In some cases, the sample is diluted with the appropriate solvents or blank matrices prior to storage, shipment and subsequent analysis.

2. Basic principle on application of microsampling

2.3 (Q5) What types of blood collection and what types of pretreatment methods are used for microsampling?

A5 (continued)

<Dried sample methods>

- Sample is usually spotted onto cellulose-based or other types of materials and dried.
- A fixed diameter sub-punch or the whole spot on the card/device can be extracted and measured/analyzed.
- Recent and on-going advancements in microsampling devices have demonstrated the ability to collect precise volumes of blood, such that the entire sample can be used for analysis without additional volumetric measurements.

Newly developed techniques could also be considered with adequate validation.

3. Effect on Safety Evaluation

3.1 (Q6) How to evaluate the effect of blood sampling on the toxicity data and wellbeing of the animal in main study group?

A6

- When blood sampling is done in the main study animals, it is important to consider the effect of blood collection on the physiological condition of animals.

<Main factors to consider for planning protocol>

- Volume and the number of samples taken in a given period
- Properties of the test drug (e.g. effects on red blood cells)
- Test system (e.g. species, age, body weight, total blood volume)
- Site of collection
- Study duration

Sampling protocols should be appropriately established.

3. Effect on Safety Evaluation

3.1 (Q6) How to evaluate the effect of blood sampling on the toxicity data and wellbeing of the animal in main study group?

A6 (Continued)

<Main animal data to record for physiological evaluation>

- Body weight
- Food consumption
- Hematological parameters (e.g. red blood cell count, hemoglobin level, hematocrit value, mean corpuscular volume, electrolytes, total proteins)
- Any effect on the blood collection site (e.g. tissue damage, inflammation)

4. Issues Regarding the Bioanalytical Method

4.1 (Q7) What are important points to consider in bioanalytical method development and validation of treatment of liquid or dried samples?

A7

- Analytical method validation should be stipulated in the bioanalytical guideline/guidance in each regulatory region.
- In addition, the following points should be considered.

<Liquid sample method>

1) Confirmation of the sample homogeneity
2) Small volume handling issues e.g. freezing/drying effects during the storage
3) Potential increase in the LLOQ due to limited sample volume
4) Impact of addition of anticoagulants to small containers/ capillaries, resulting in dilution of the sample

4. Issues Regarding the Bioanalytical Method

4.1 (Q7) What are important points to consider in bioanalytical method development and validation of treatment of liquid or dried samples?

A7 (continued)

<Dried sample method>

Method with best recovery and lowest matrix interference on the drugs should be selected.

- If the sub-punch of the dried spot approach is used, the effect of different hematocrit values should be evaluated. It is important to confirm the uniformity of the spots.
- These issues can be minimized if an accurate volume of blood is collected on the device and the whole sample is subsequently analyzed.

<Incurred sample reanalysis (ISR)>

- ISR should be conducted according to each regional guidance/guideline, if described.

Future plan

1. Public consultation

ICH Website: Finished on Sept. 8, 2016.

Japan: Finished on July 15, 2016.

EU: Finished on Aug. 31, 2016.

USA: Finished on Dec. 7, 2016.

Canada: Finished on Sept. 8, 2016.

2. Finalization of the Q&A

Based on the received comments, IWG will discuss and (if necessary) change the draft Q&A document, and finalize it.

M10 Bioanalytical Method Validation

Current reginal Bioanalytical Method Validation guidelines/guidances

EMA
Guideline on Bioanalytical Method Validation (2011)

FDA
Guidance for Industry Bioanalytical Methods Validation (2001)
→ revision DRAFT (2013)

MHLW
Guideline on Bioanalytical Method Validation
Chromatography(2013)
LBA (2014)

Establishment of M10 guideline will result in the harmonisation of current regional guidelines/guidances and support streamlined global drug development.

Progress on M10 Informal WG and EWG

- Jun. 2016 Adopted as a new topic at ICH Lisbon meeting

  M10 Bioanalytical Method Validation

  (Proposed by Japan MHLW/PMDA)

- Jul. 2016 Set up M10 Informal WG
- Oct. 2016 Approved and released concept paper and business plan by ICH
- Oct. 2016 Set up M10 Expert WG
- Nov. 2016 1st face to face EWG meeting at Osaka

M10's mission

To provide recommendations on Bioanalytical Method Validation and Study sample Analyses to obtain the reliable drug/metabolite concentration data in biological matrices, which will be used for regulatory submission.

M10 EWG 1st face-to-face meeting in Osaka, Nov. 7-10, 2016

Purpose

Gap analysis on controversial issues in current regional guidelines/guidances and scientific discussion towards harmonisation

Goal

Establish the outline of 1st draft of M10 guideline

Discussion on 1st M10 EWG meeting at Osaka

Agenda

1. Presentations and discussion on differences in current regional guidelines/guidances
2. Discussion on outline of M10 draft guideline
   - ✓ Scope
   - ✓ Method validation
   - ✓ Analytical run
   - ✓ Other issues
3. Tentative table of contents for 1st draft guideline

(1) Comparison on MHLW / EMA / FDA BMV guidelines (Scope)

MHLW 2013&2014	EMA 2011	FDA draft 2013
Methods LC or GC with or without mass spectrometry Ligand-binding assay	Chromatographic methods Ligand-binding assay	LC or GC with or without mass spectrometry Ligand-binding assay, Immunological and microbiological procedures
Phases Clinical studies (Inc. BE studies) Non-clinical TK studies	Clinical studies (Inc. BE studies) Non-clinical TK studies	Clinical studies (Inc. BE studies) Non-clinical TK studies Non-clinical PK studies
Analytes Drugs, Metabolites (Inc. biologics with same amino acid sequence by LBA) (Exc. endogenous compounds)	Drugs, Metabolites	Drugs, Metabolites Endogenous compounds (Conceptual) Biomarkers (Conceptual)
Biological matrices Not specified (e.g., serum, plasma, urine)	Not specified (e.g., blood, serum, plasma, urine and saliva)	Not specified (e.g., blood, serum, plasma, urine, tissue, skin)

Key issues discussed in Osaka: (2) Validation

- Regarding Chromatographic assay and Ligand binding assay, validation characteristics needed for method validation, as well as evaluation methods and acceptance criteria for each validation characteristics were discussed.

- ✓ Selectivity
- ✓ Specificity
- ✓ Calibration curve
- ✓ Accuracy and precision
- ✓ Carry-over
- ✓ Parallelism
- ✓ Matrix effect
- ✓ Stability

- ✓ MRD
- ✓ Recovery
- ✓ Reproducibility

Key issues discussed in Osaka:
(3) Study sample analysis

- ✓ Calibration curve
- ✓ QC samples (accuracy and precision)
- ✓ Re-analysis

(4) Other important issues

- ✓ Partial validation
- ✓ Cross validation
- ✓ Reference Standard
- ✓ Critical reagents
- ✓ Incurred sample reanalysis

Future plan

- M10 1st draft (～Feb., 2017)
- Discussion via e-mail and telephone on M10 1st draft (Mar. ～ May, 2017)
- Probable face to face meeting at next ICH conference in Montreal (May, 2017)
- Reaching step 2 (June, 2018)
- Reaching step 4 (June, 2019)

Thank You for your attention!