Current Situation of Microsampling in Japan: Report from the Japan Bioanalysis Forum Discussion Group

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Back ground

Japan Bioanalysis Forum (JBF)

- ✓ The Japan Bioanalysis Forum (JBF) is the first scientific group focused on regulated bioanalysis that was established in 2011 by delegates from the industry, regulatory affairs and academia.
- ✓ The forum's missions are to:
  - ✓ Facilitate discussions regarding regulated bioanalysis in Japan
  - ✓ Interact with Japanese regulators in the field of bioanalysis
  - ✓ Represent Japan in the international bioanalysis community
- ✓ The Discussion Group (DG) was established by JBF to discuss questions/issues raised from daily work, and to obtain some insights for use by bioanalysts.

Discussion Group (DG) for microsampling

The JBF discussion group (DG) for microsampling was established in 2015 to play an active role in promoting microsampling for regulated bioanalysis. Discussions on microsampling have been actively conducted in Japan since the ICH S3A Q&A draft was released in 2016.

Activity of microsampling DG

Year	Discussion Theme	Activity
2015	Survey of status and extraction of issues ➢Current status for each company ➢Issues to be resolved ➢Experimental operation	➢Questionnaire surveys ➢Discussion
2016	Investigation of technical problems ➢Methods and devices used for blood collection ➢Additional items for validation studies ➢Factors effect on analytical accuracy & precision ➢How to increase analytical sensitivity ➢Effects on the PK profile or physiological data	➢Questionnaire surveys after the release of ICH S3A Q&A draft ➢Discussion ➢Presentation in scientific meetings ➢Scientific article research
2017	Suggestions for the study plan ➢What we should consider in dilution, storage, anti-coagulant, device, pipetting	➢Discussion ➢Presentation in scientific meetings ➢Scientific article research

Purpose

- ✓ Report on the following information as representatives of Japanese companies:
  - ✓ How the ICH S3A Q&A draft affected their mind or status
  - ✓ Devices used for collecting blood
  - ✓ Issues related to the application of microsampling to the regulated bioanalysis
- ✓ Obtain further information through discussion

Questionnaire Survey

Target
- ➢ Sep 2016: 31/66 companies (Response rate: 47%) 1 response / 1 company
- ➢ Nov 2016: 48 individuals

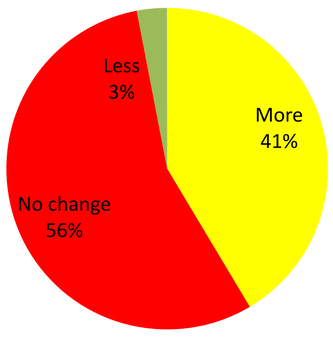
Questionnaire survey was conducted through the website.

* Questionnaire surveys included the questions related to dry samples (e.g. DBS); however, topics in this presentation were limited to liquid samples. In the 2013 survey, 54% (15/28 companies) of Japanese companies had DBS experiences.

Result & Discussion

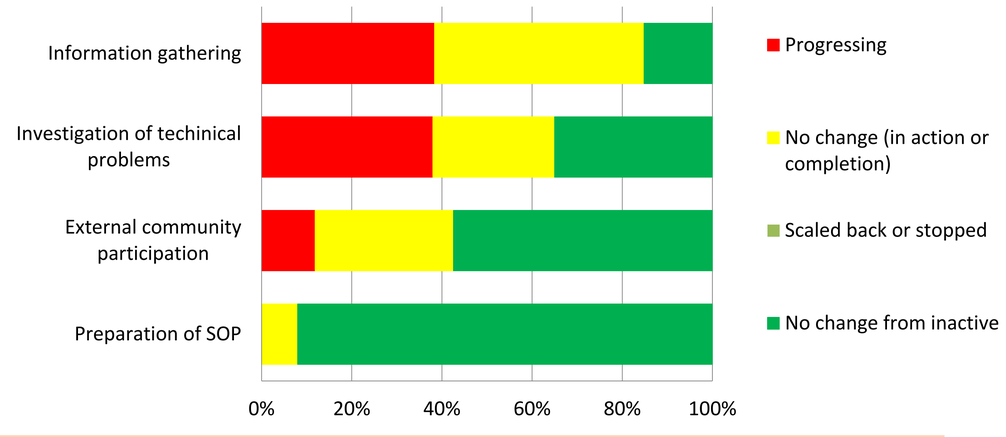
1. Changes after the release of Q&A draft

1-1 Changes in your companies' conscious mind to microsampling



- ✓ Many companies experienced increased consciousness after the release of Q&A draft
- ✓ No change originated from any legal force nor were there changes in the research of toxicity

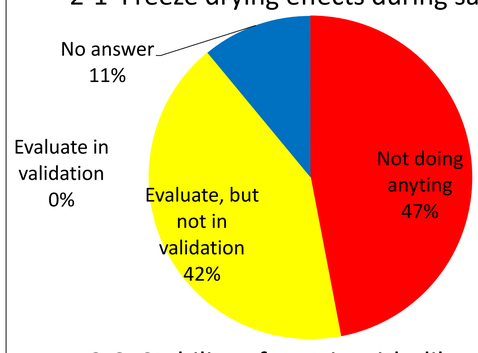
1-2 Changes in operations of microsampling



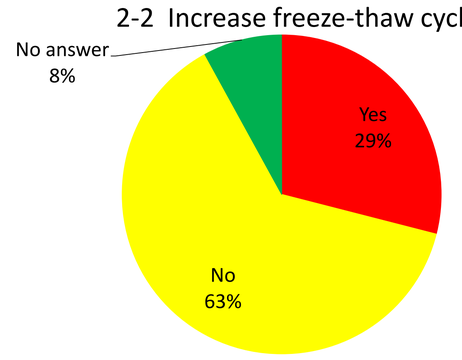
- ✓ Information gathering and investigation of technical problems are on going

2. The necessity of additional validation items

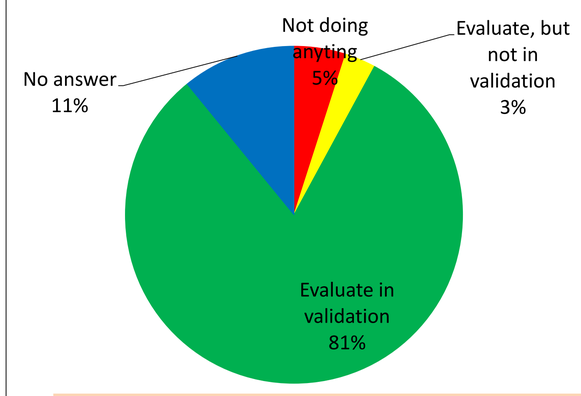
2-1 Freeze drying effects during sample storage



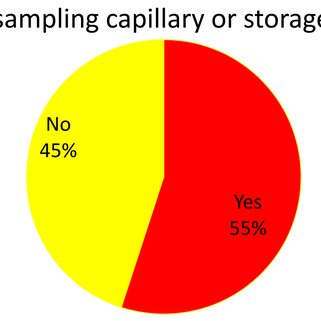
2-2 Increase freeze-thaw cycles?



2-3 Stability of matrix with diluents (except blank matrix)

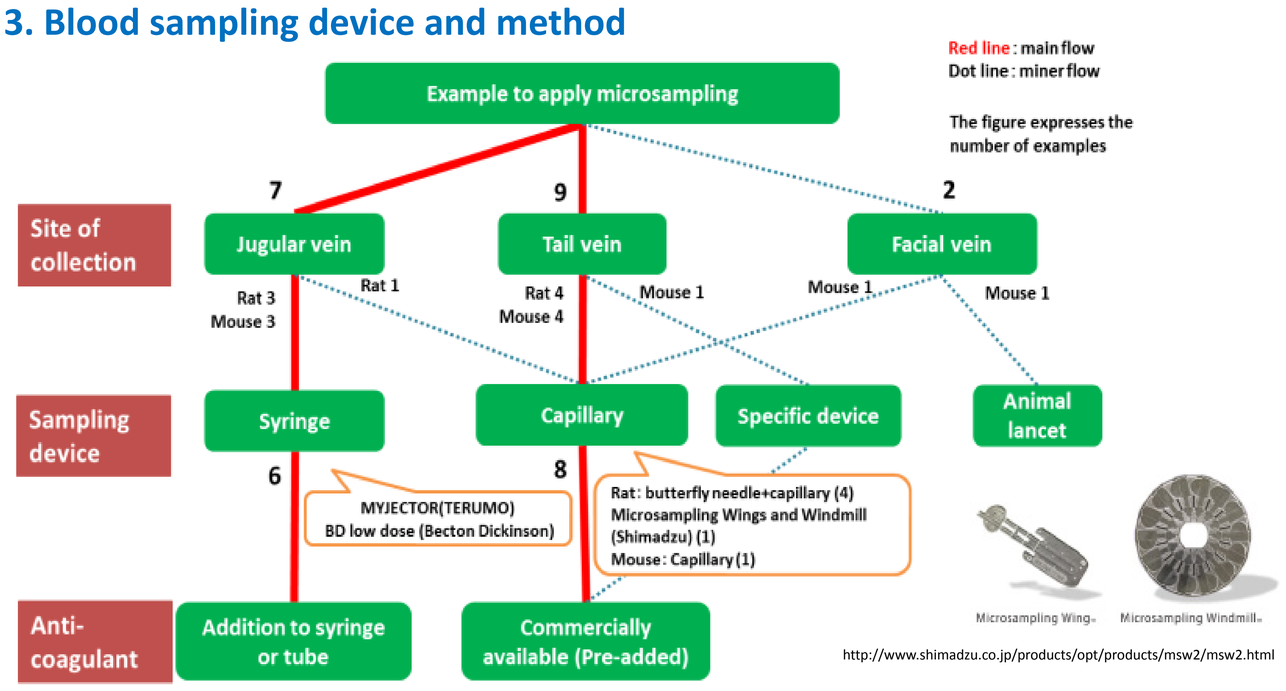


2-4 Consider using correcting factors to calculate concentration due to the effect of anti-coagulant, potentially by adding to the sampling capillary or storage container?



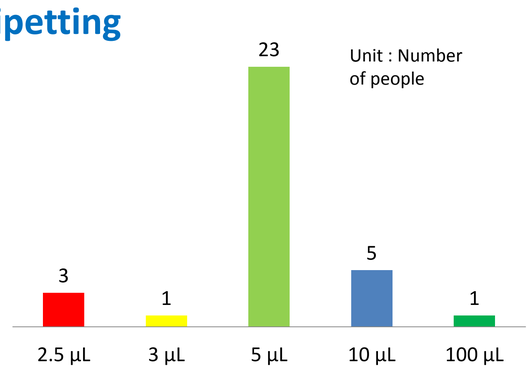
- ✓ It seemed that no special items were considered to be validated, except in the case of diluting samples with diluents to increase total volume for convenience of treatment

3. Blood sampling device and method



Method	From Jugular vein using Syringe	From Tail vein using Capillary
Advantage	➢Sampling time ➢No contamination	➢Operation
Concerns	➢Hemolysis ➢Internal hemorrhage	➢Bleeding ➢IV administration
Resolution	➢Optimization of sampling rate ➢Practice	➢Apply firm pressure ➢Find other blood collecting site

4. Minimum volume of liquid sampling, in which accuracy was confirmed by pipetting



- ✓ 5-µL was the minimum volume possible with manual pipetting

5. Concerns to be discussed or solved

Item	To be discussed	Our proposal
Validation items	➢Q&A draft contains some issues not only for microsampling but common for regular bioanalysis (e.g. the change of blood collection site)	We should test or discuss such points even for regular bioanalysis
ISR	➢How can we obtain samples for ISR? ➢Microsampling is always prior to ISR?	We should do our best to obtain enough samples for ISR prior to microsampling
Device	➢Inaccessibility of some devices for micosampling (e.g. Mitra(R))	Continue to evaluate the feasibility of accessible devices

Conclusion

Since 2015, JBF DG of microsampling revealed the opinions of companies and progress in Japan through surveys. Although there were a few companies that applied microsampling to their regulated bioanalysis, many of them tended to be an positive stance after the release of ICH S3A Q&A draft. Some concerns remain unanswered, and thus they hesitate to use microsampling. JBF DG will continue to discuss microsampling, and we hope that the results would be of help for the drug development of any company.