The Journal of Applied Bioanalysis carried out an online survey on the following topic: "Microsampling: Opportunities and Challenges". The survey was created to evaluate the attitudes of scientists from the bioanalysis community toward the application of microsampling technologies in the area of bioanalysis. Microsampling technologies have generated a huge amount of interest and technological developments resulting in the application of these technologies in drug development and (life-sciences) research in recent years. This online survey aimed to acquire a snapshot of attitudes and applications of microsampling technologies in the bioanalysis community and to learn about current opportunities and challenges of microsampling technologies.

INTRODUCTION

Since the introduction of dried blood spots (DBS) in the early 1960s used in newborn inherited metabolic disease screening, various microsampling technologies have been developed and applied. Microsampling technologies like capillary microsampling (CMS) using small heparinized glass capillaries, microneedle for transdermal blood sampling, and volumetric adsorptive microsampling (VAMS) using a polymeric material for hematocrit independent (capillary) blood sampling are currently applied in bioanalysis for the collection of biofluids. Moreover, the development of blood sampling devices such as Tasso-SST device, Capitainer Ab, hemaPEN, and others have paved the path of the patient at home blood sampling for clinical pharmacological and therapeutic drug monitoring studies (TDM).

Online-survey methodology

In the online-survey, nine survey questions targeting two separate survey sections with a specific section related to multiple-choice questions were used. The first survey section dealt with targeted questions concerning the professional status, job title, and background of the respondent. The second survey section contained targeted questions about (conventional) microsampling technologies applications and respondents’ views on microsampling in bioanalysis concerning opportunities and challenges. A total n=53 respondents completed the online survey between October 2022 and December 2022.

Survey section on professional status/job title

The first survey section contained targeted multiple-choice questions concerning respondents’ professional background, job title, and experience with and application of microsampling technologies in the area of employment. This section had four survey questions and respondent statistics are presented.
Q1: "In which research area do you work?"
Academia represented the largest group of respondents (30%) and Pharma was the second largest group of respondents, followed by Research and Development, and clinical research area. Other professional backgrounds indicated by respondents were CRO (3.8%), analytical instrument vendor (7.6%), and medical technology (3.8%), respectively (Figure 1).

![Figure 1. Respondent distribution online survey](image)

Q2: "How long have you been working in this area?"
73.6% of respondents indicated to have more than 5 years of working experience, and 7.5%, 13.2%, and 5.7% of respondents indicated to have <1 year, 1-3 years, or between 3-5 years of working experience, respectively.

Q3: "Which of the following describes your organization?"
Almost one out of three respondents indicated being employed at CRO/CMO and the second largest respondent group was being employed in academia. Other organizations represented by respondents were the medical device industry (3.8%) and academic hospitals (3.8%) (Figure 2).

Q4: "Which of the following describes your job title?"
15.1% of respondents indicated having a professional background as a chemist, 20.8%, 28.3%, 1.9%, and 7.5% indicated having a position as Director/VP/CEO, group leader/manager, laboratory technician, or student. The remaining 26.4% of respondents indicated to have other job titles; pharmacist, research associate, professor, quality professional, post-doc, or marketeer. Survey section on research and microsampling techniques implemented
This survey section contained five targeted multiple-choice questions concerning respondents' experience with microsampling technologies in their current job title. The five targeted survey questions and respondents' statistics are presented below.

Q5: "What type of molecules do you work with?"
One-third of the respondents indicated working with small molecules, followed by biomarkers as the second largest respondent group. Around 5% of the respondents indicated working with other types of molecules such as metabolites, ADC's and oligonucleotides (Figure 3).
Figure 2. Respondent’s organization distribution

Q6: "On what basis do you use microsampling in your research"?
47.2% of respondents indicated using microsampling technologies regularly in bioanalysis, and 26.4%, 7.5%, and 11.3% of the respondents indicated applying microsampling occasionally, only in dedicated assays or aren’t using microsampling at the moment but implementation plans are being made. The remaining 7.5% of the responders are using microsampling for training purposes in clinical investigations.

Q7: "For which studies do you use microsampling"?
Respondents indicated that they mainly use microsampling in discovery and preclinical (non-GLP) studies but also in clinical phases 1-4 is microsampling being used as well as in special studies such as pediatrics, geriatrics, and critically ill patient studies. The remaining 10% of microsampling is being used in bioequivalence studies, newborn screening, therapeutic drug monitoring, DMPK, or in environmental screenings (Figure 4).

Figure 3. Application areas of microsampling technologies
Q8: "What are the major challenges related to the use of microsampling?"
14.5% of respondents indicated that logistics whereunder site training, patient compliance, and time stamp are challenging. Additional 14.5% of the respondents indicated that clinical operations (feasibility) at the clinical site were challenging while 12%, 12%, 36.1%, and 10.8% of the respondents indicated challenging issues with clinical pharmacology (data interpretation, matrix differences peripheral blood versus venous blood), regulatory (lack of clear guidance), bioanalytical sample analysis or that most laboratories are generally not equipped with instrumentation to handle small sample volumes. Mass spectrometry is slowly moving from research labs to non-research labs which may accelerate adaptation. Respondents also indicated challenges arise due to that big inline instrument manufacturers are reluctant to adapt instrumentation to microsampling volumes.

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![Figure 4. Application areas of microsampling technologies](image)

![Figure 5. Microsampling technologies applied by respondents](image)
Q9*: What type of microsampling do you use in your research?*
23.9% of respondents indicated (still) using traditional DBS, but also microsampling technologies such as capillary microsampling, volumetric absorptive microsampling (VAMS), and dried matrix microsampling (excl. blood) are being applied by respondents. The remaining 10.1% are microsampling techniques such as respectively whereunder SPME, biopsies, SPE, Capitainer, Tasso M20, or DLLME (Figure 5).

Online-survey summary
Conclusions that can be drawn from this online survey on microsampling technologies in Bioanalysis:

Survey section on professional status/job title
1. The majority (75.5%) of microsampling technology implementations in bioanalysis are still in the fields of pharma, academia, and in research and development. Other areas applying microsampling are clinical settings (9.4%) although assays using microsampling can be found with CROs (1.9%), medical technology companies (1.9%), and vendors/manufacturer of analytical instrumentation (3.8%).
2. Almost three out of four respondents indicated to have more than 5 years of working experience in Bioanalysis.
3. The largest participation in this online survey came from respondents working in CRO/CMO and academia. Both organizations counted in the total for 58.5% of all respondents, while the second largest organization was clinical diagnostics (11.3%) followed by large pharma and biotech companies representing 9.4% of the respondents.

Survey section on research and microsampling technologies implemented
1. One out of three respondents indicated using microsampling for small molecules (34.1%) followed by 20.9% applying microsampling for biomarker analysis/discovery and microsampling for protein analysis good for 14.7% of all respondents.
2. Almost 1 out of two respondents (47.2%) indicated using microsampling regularly in research, 26.4% use microsampling occasionally and 11.3% of the respondents are currently not using microsampling but are considering the implementation.
3. The survey shows that microsampling is mainly applied in early clinical phases like discovery studies (22.1%) and pre-clinical phase studies (22.1%). In the pre-clinical phase, microsampling is used in a non-GLP environment while 12.4% of the respondents use microsampling in a GLP environment. Nevertheless, 17.7% of the respondents indicated that they use microsampling also in clinical phase studies 1-4.
4. The biggest challenge of microsampling application in bioanalysis according to respondents is with bioanalytical sample analysis of prepared microsamples. One out of three (36.1%) of the survey respondents indicated that this part of microsampling in bioanalysis is the most challenging of all. Other bioanalytical challenges, but less frequently challenging are logistics (14.5%), clinical operations when using microsampling (14.5%), and regulatory implications (12%) due to the lack of clear regulatory guidance, but also the pharmacological data interpretation (12%) when using different biofluid matrices, such as peripheral blood versus venous blood.
5. Respondents indicated that the most frequently used microsampling technology is dried blood spots (23.9%), followed by volumetric absorptive microsampling (19.3), dried matrix sampling of other biofluids (urine, plasma, saliva, etc) by 19.3% of the respondents, and capillary microsampling is being applied by 18.3% of the respondents.

CONCLUSIONS
In conclusion, various microsampling technologies are being used across different areas of bioanalysis in academia, the pharmaceutical industry, and clinical research. Microsampling technologies have found their way into industrial partners such as CROs, Medtech companies,
and analytical instrument manufacturers/vendors.
The results from this online survey indicate that microsampling technologies are still mostly being implemented in the analysis of small molecules. Biomarker research (discovery/analysis) and proteins are the areas where microsampling technologies after small molecules are used the second most frequently.

Microsampling has become a sampling technique being applied by scientists from academia and industry regularly in bioanalysis or with a special reason occasionally in dedicated bioassays for example. Microsampling has been industry and academia-wide implemented not yet to the fullest as can be concluded from this online survey results. Respondents (11.3%) indicated that the implementation of microsampling technologies is planned for the future.

Microsampling technologies are implemented throughout pharmaceutical development and different clinical phase studies but are also being applied in dedicated research areas such as pediatrics, geriatric and clinical studies for critically ill patients. Other research areas although with lower microsampling implementation rates are within bioequivalence studies, TDM, DMPK, and environmental monitoring studies.

The biggest current major challenge on microsampling technologies in bioanalysis is microsample analysis followed by logistics of microsampling such as site training, and patient compliance) and clinical operations for the clinical site as being still other challenges. Respondents indicated that minor challenges are regulatory and pharmacological related concerning regulatory guidance and the interpretation of pharmacological data when using different types of biofluids.

The most used microsampling technology indicated by survey respondents is dried blood spots (DBS), but also other microsampling techniques are being used and are catching up with the DBS. After DBS, VAMS is the second most applied microsampling technology probably based on the claim of eliminating the hematocrit effect. A good third is capillary microsampling followed by dried matrix microsampling of a plethora of biofluids such as saliva, urine, plasma, and others.

The use of microsampling technologies has become since the start of the use of the dried blood spots microsampling technique (DBS) today about 60 years ago, a widespread multifunctional microsampling being applied in multiple areas of pharmaceutical, clinical, and life science research. Microsampling technologies are nowadays being applied for sample collection in a plethora of analytical and bioanalytical assays and applications. New microsampling technologies devices are still being developed, improved- and tested for purposes in many different research areas. Microsampling technologies are exciting biofluid sampling technologies that can provide many advantages compared to the classical collection of large sample volumes by venous blood sampling techniques but they are also technologies that still have some major challenges to be solved before eventually microsampling technologies will be fully implemented in pharmaceutical, clinical, life sciences but also other research disciplines where implementation of microsampling technologies are under consideration or hopefully will be considered.

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