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EXPERT INTERVIEW

Perspectives on Microsampling in Bioanalysis: Opportunities and Challenges in the era of the COVID-19 pandemic- An interview with Dr. Kevin P. Bateman

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Dr. Kevin P. Bateman is a Scientific Associate Vice President at Merck Research Laboratories in the Department of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM). He is the Scientific Lead for Bioanalysis in PPDM where his duties include driving scientific strategies and cross-functional objectives to impact the pipeline independent of modality and stage. As PPDM's senior bioanalytical scientist, he is responsible for driving innovation and capability development for bioanalysis of vaccines, small molecules, peptides, and proteins across the discovery and development pipeline. He also co-founded the Merck Smart Trials initiative that is working to reshape clinical trials using new technologies for dosing and sample collection. He has been with Merck for 24 years and has published over 80 peer-reviewed papers related to mass spectrometry and drug discovery.

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Could you please summarize your experience in bioanalysis and various microsampling techniques?

I have been working at Merck & Co. (also known as MSD) for almost 24 years and much of that time has been focused on both discovery and development stage bioanalysis. Microsampling has been an integral part of my career, including;

1. early work aimed at reducing animal usage through small volume serial liquid blood sampling for mouse PK,
2. one of the first reports on the use of dried blood spots (DBS) for PK studies,
3. two white papers on the implementation of DBS in clinical studies,
4. the use of Volumetric Absorptive Micro Sampling (VAMS) for small molecule and biologics studies, and
5. recent work on patient-centric clinical trials using digital biomarkers and at-home sample collection.

How has COVID-19 changed the need and implementation of microsampling in research?

It's somewhat disheartening that it has required a global pandemic to raise aware-

ness of the value of microsampling, especially in the form of patient-centric sampling. The idea that we can collect samples from patients without the need for them to visit a clinic is incredibly valuable. We need to keep people safe, and that means avoiding travel to high contact areas such as clinics, while also enabling the routine monitoring that is required to ensure safety. We need to develop these approaches and get them implemented, and COVID-19 has created a sense of urgency that did not exist previously. There has been a general upswing in the use of microsampling approaches to monitor serology related to COVID-19, with several studies being conducted and published by a variety of groups and agencies. That's a great start, but there is much more that needs to be done and we need to keep the momentum. The need has created the willingness to adopt new approaches.

Do you think microsampling techniques will become a norm in clinical trials post COVID-19?

I certainly hope so, but I expect we will still have more to do post COVID-19 to get microsampling techniques in clinical trials to be considered "normal". What I do know is that many of the excuses for not using these techniques will no longer exist, so that will be positive. Regulators will be more accustomed to seeing data from microsampling approaches, so that will be a positive outcome. We will have data that shows these approaches do work and can be implemented at scale. Many of the processes required to implement microsampling will be solved. All these are important to the adoption of microsampling more routinely in clinical studies.

What are some pros and cons of the microsampling technique of your choice?

We have implemented several different techniques and I will focus on two that we use in clinical programs. One is the Neoteryx Mitra sampling device that collects a volumetric amount of blood onto a polymer tip. The upside of this approach is the volume control of the sample collection process and the fact that the sampler itself is automation-friendly. The downside is that it requires a finger stick lancet to be used and not all patients are willing or able to use a lancet, especially if frequent sampling is requested. Also, we have seen both under and overfilling of the sampler which makes the samples not suitable for analysis if you are doing a quantitative measurement. The other approach we use is a device from Tasso Inc. called the M20, which is a single-use device that collects blood onto polymer tips held in a cartridge. This device makes it very easy for the patient to collect a sample and it is almost painless when compared to a fingerstick lancet. The challenge is the cartridge is not automation friendly and requires a manual process to remove the tips for sample analysis. Tasso is also a small company and scaling to larger production numbers is required to reduce the cost of the devices and increase overall performance. For both approaches, the analytical work required to develop and validate the method can be time-consuming with extra experiments related to the use of dried blood samples.

What technical hurdles you encountered during the early stages of this technology in your research?

We are constantly learning as we implement new technology for sample collection. Dried blood on a polymer matrix is not the same as liquid plasma in a tube. We need to ensure the method for extraction of the dried blood is robust and works on samples whether they are fresh or aged. We need to understand drying and storage conditions and the impact of the shipping environment. Lot-to-lot variability of volumetric sampling needs to be understood and possibly tracked. Automating the process of getting from the collection device to a sample in a well needs to be addressed to ensure scalability. The number of molecules that have been tested so far is relatively small, so it's almost like starting a new project every time. As we gain more experience and the bioanalysis community shares their experiences, we should be able to define some best practices to overcome technical issues.

Do you have any advice for our readers who may be looking forward to implementing microsampling?
Planning is important, and it's never too early to start. If you want to implement microsampling in the clinic, you will need time to get everything in place. You need the analytical method of course, but implementation requires working with many other groups. You may need to bridge between plasma and dried blood depending on the program, you need your PK scientists on board to build the model to use both plasma and blood. The clinical team needs time to plan and get the protocol written, so you need the proper language to have in the protocol, for the IRB, the training material, etc. The processes are not yet well defined, so start early and talk to everyone about the project so that no surprises pop up when you least expect them.

What are the three biggest challenges that need to be addressed in order to have a wide-spread adoption of microsampling in clinical trials?
Only three? Clinical programs for the most part are on a mission to run very specific clinical trials to get an answer about the drug they are studying with the goal of proving safety and efficacy for patients. Adding anything new to that process is a challenge. There must be a very well-defined reason for including something new like microsampling. A common response to the idea of microsampling in clinical studies has been "That's really interesting, but not on my trial". So, resistance to change is challenge one. Clinical trials, especially Phase III studies can be large, multicenter international studies. Implementing new techniques in a global clinical trial requires that each country has regulatory approval to adopt the new approach and that training material for clinical sites and patients is culturally appropriate. So, scaling operations is challenge two. Ensuring the quality of the data and that it passes regulatory scrutiny is always an important aspect of any clinical trial. Microsampling, especially patient-entric or at-home sampling, adds a layer of complexity to that requirement. No one wants to risk having data rejected by regulators because it was collected using an approach that is new and not traditionally used. So, risk aversion is challenge three.

Could you share some of the most exciting developments that have happened in microsampling techniques in the last 5 years?
I think the fact that we are still talking about microsampling is exciting, especially in a forward-looking manner, given how the bioanalysis community almost crushed the approach before it really got started. The development of volumetric sampling has helped remove some of the concerns for truly quantitative applications. Devices from companies like Tasso and SeventhSense Bio are looking promising to make the collection process much more patient-friendly.
The scope of applications that have been published using microsampling over the past 5 years is also very exciting.

How do you see these techniques evolving in the next 5 years?
With a focus on clinical trials, the use of sampling devices will drive the adoption of patient - centric sampling over the next five years. As these devices gain regulatory approval and other healthcare applications get rolled out, we will see a fundamental shift to using these approaches. Routine patient monitoring of chronic diseases will be a mouse click and a delivery driver away. Longitudinal monitoring, with individuals serving as their own control, will start to become the standard approach, especially as we personalize treatments. At Merck, we are already moving beyond simply measuring drug levels from these samples, we are also measuring pharmacodynamic markers of disease treatment. As we enrich our data sets with these sampling approaches, our understanding of human biology will only improve. Five years from now we will still be in the early days of this journey, but it will be an exciting trip.

Do you see a need of an international consortium to champion and raise awareness for use of patient centric microsampling techniques in future clinical trials?
There are a couple of groups in place that are doing just this. One is the Patient Centric Sampling Interest Group (https://www.pcsig.org/) which is a broad coalition of people with a passion for raising awareness and driving change related to clinical microsampling. The other group is the IQ Consortium (https://iqconsortium.org/) working group on patient-centric sampling. These two groups are a great start, but we need to do more! Most of the work raising awareness has come from a bioanalytical perspective and we need to raise awareness in the clinical space. We need to educate clinicians and others who use our bioanalytical data, on what is possible using patient centric sampling approaches so that they become the champions for this approach. Often bioanalysis is regarded as a commodity that is easily purchased, but the development of patient-centric sampling would never have happened without creative and innovative bioanalytical scientists, so we should make an effort to raise awareness and change clinical trials for the better in the future.