Session 2 - Table 7: How Instrument Lifecycle Practices Can Facilitate the Best Technology While Ensuring Quality

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Abstract:

Once limited to therapeutic peptides, monoclonal antibodies and small oligonucleotides, biopharmaceuticals have evolved into ever-more complex entities treating a seemingly limitless breadth of diseases. Multi-specific antibodies, antibody-drug conjugates, viral vectors, and LNP-formulated mRNA medicines are being approved at increasing rates. As these new modalities can be more complex and heterogeneous, suitable analytical procedures are required to ensure therapeutic safety and efficacy, often necessitating an overhaul of existing analytical tools or the development of new ones altogether.

Novel analytical tools, often established through venture funding and industry collaboration, can accelerate drug development timelines, provide novel and critical information to support process development, and may be needed to support analytical control strategy in regulatory filings. Excitement surrounds new analytical instrumentation (e.g. mass photometry, charge detection mass spectrometry, automated liquid handlers, and associated software), often promising faster and higher quality data with less hands-on time. In other instances, it is a necessity when a flagship instrument is deprecated and no longer supported.

As new technologies and software are implemented in the pharmaceutical industry, it is imperative to focus on regulatory compliance and ensuring system and data quality. These activities can take time to gather information to show stakeholders that upgrading instrumentation can be done while ensuring comparable data integrity, but such requirements can also change depending on whether an instrument is used for characterization purposes and not, for example, release testing.

Notes:

- Challenges can be dependent on the instrument. We are in the process of updating Spectromax. Time frame is 5 years, validating through GMP is a difficult task. We are looking at a few different strategies. We do a lot of bioassays for potency. Also our QPCR (fast 7500), which is ten years old, is being upgraded.
- Are you using an analytical target profile? The concept behind that gives more flexibility but it is a very different mindset.
- The proposed strategy is bridging studies.
- Major pharma, not at this table, has protocols written 30 years ago which specify what wavelength/ instrument and its hard for a manufacturer to make a instrument for 30 years because circuit boards change, fluidics can be kept the same but if you specify one brand/ model number and the company changes it or the model number then its no longer the same.
- We agreed to support one assay for one particular reg body for a certain amount of time, but from a vendors perspective they may not be interested in supporting that tech for the time frame we are obligated to keep it from with our products approval.
- For bridging, are you comparing like to like, or like to new

- Things get more refined/ cross talk canceled, wavelengths more defined. There is change so cannot say it is like to like but we are forced to use the new ones.
- As a manufacturer we announce how long we will support an instrument, so our clients evaluate on a like to like basis as the improvements are typically refinements. In our experience only about 5% write SOPs that are instrument specific.
- Is that a change in the industry?
- From an analyst perspective you just write down what you did and that ends up being recorded and can end up in submissions.
- There's big change when it goes commercial.
- If you have multiple sites that adds another layer of complexity as your dealing with different HA dossiers, different requirements, etc.
- It can be seen as not worth the overhead to upgrade.
- One company registered in 117 countries and 25 products using our tech, it creates a tremendous amount of work to change anything in there.
- Being more intentional about method writing in the early stages- focus more on critical method parameters, but not specifying which tech would reduce the amount of paperwork required to upgrade instruments.
- I think that's the idea behind some AQBD work. There was an article a few years ago about analytical QBD. Originally planned on a chromatographic method but found another method that worked better. So the parameters were the same regardless of the method. What do you need to measure, what amounts, level of variation, as opposed to we use X device to get Y data.
- What kind of data do we need to bridge technologies is the question that should be asked.
- That's a method migration kind of thing, I need to do a risk assessment to figure out what will impact the data based on differences in instruments. An example is bringing multiple attribute methods into QC, can you bring a mass spec into QC? As a vendor we make an instrument that is CFR compliant, some companies would rather choose a different detector that can run on the same chromatographic network because there is less of a big change.
- From my time in small molecules, everything on the back end was mass spec and as methods were translated into validation and commercial we got methods from the team to put everything on a phosphate buffer because they wanted to avoid bringing in MS. Are there opportunities then for vendors and companies to streamline the process by providing a suggested set of parameters to evaluate or a skeleton of ‘here's how you could do this efficiently’, they don't like to rely on data that was generated by a vendor.
- We have a lot of experience with this and we did bridging studies but as a vendor that data needed to be created by the company. They had to show equivalence one by one or by a statistical model. Some people would take a stressed MaB and compare it instrument to instrument. They used a combination of alternatives, so we would offer to help but each company would come up with their own way of showing equivalence because they had their own protocols. I visited the FDA and created samples and showed them what the results were and what the specs were and their first question was why is there such wide acceptance criteria. It's because you have to build in a wide tolerance for lot to lot comparisons. The other challenge is that most reviewers have not been behind a bench recently and are not up to date on current tech. They are trying to use old guidelines for new products.
- I remember at this conference years ago they were talking about identifying host cell proteins using mass spec. They asked a question to an FDA panelist and their response was that they only know how to run a 2D gel. An issue with new technology is using an outdated mindset on the regulators' part.
- What happens on the back end between regulators and instrument manufacturers?

- There is not much communication there, that can be good and bad.
- But regulators don't really care about the instruments, they care about the safety and efficacy of the product so the instrument is not the focus.
- Automated liquid handlers are used for bioassays, we have limited supply of vendors that provide this tech. We should increase the use of automated liquid handlers, which would improve the assays, but there's a lot of trouble shooting that goes into using these.
- Have you seen them incorporated into a GMP space?
- One method was but there was lots of difficulty with it.
- Many of our clients use liquid handlers to fill plates, maybe 5% use robotic arms. The reasons for using these are from a safety perspective. From what I've seen it's all in early stage development because the number of samples is highest there.
- We have several assays we have automated, they have not gotten into our QC labs yet. Which is great for us in development but a headache for the QC analysts. Part of the advantage is that certain assays are two day preps/ multi day affairs. If you can automate that it improves many aspects.
- What about some of the lights out initiatives?
- I'm not familiar with that.
- Some people call it the lab of the future, all robotics. No human intervention.
- It's a dream, it will take a long time to get there. To be able to achieve that we should start integrating automated liquid handlers now.
- It's a conflict between lifecycle and new tech.
- With the best tech you get the best results but we are limited by other factors. How are we upgrading it and how are we maintaining the existing instrument.
- A couple of factors for lifecycle- how long is an instrument kept in a lab. I.e. mass spec changes quicker than other tech like HPLC.
- It is limited by how long the company will support the instrument.
- So depreciation does not enter into the picture?
- It probably depends on the company, capital budgets determine that. To build on that, are there ways to facilitate those more rapidly changing tech in-house or do you end up in situations where you are an early adopter and are limited in how you can pivot. Iphones have changed massively from gen 1-5 then the last few were incremental improvements. What are the potential benefits to that incremental upgrading. An example is the Waters Alliance worked well for decades, within that window where people were developing methods using the Alliance there was not a need to think for the future, whereas with more novel tech we are going to plan on using that instrument for 5 years as opposed to 20.
- Genentech 20 years ago talked about how things will change continuously, we will be on the lookout for those changes and implement them. It was built into their psychology. That was a unique philosophy. So part of it is how you anticipate change and how you react to it. Ten years ago Microsoft discontinued support for XP so you had to move to Windows 7, which a lot of instruments did not support. This forced a lot of retirement of instruments.
- As an instrument manufacturer we did think about what would happen if Microsoft did that, but drug makers lacked that foresight.
- When you think about a instruments lifecycle, you want to have a trained professional use and maintain it to get the best of the tech.
- It's also a function of the instrument and ease of use. We had one that months after coming to market interns were operating it because it was easy to use. The retraining is another resource intensive aspect of this conversation.

- There are very sensitive and clunky interfaces that create a high bar for the operator/ training.
- There is a general trend away from expert knowledge to close to a black box/ plug and play.
- It's interesting to me the aspect of software vs. hardware. It seems like many instrument manufacturers outsource the software to third parties.
- The question for lifecycle management is what does it take to update the software and what goes into validating that.
- To just validate an instrument it can take 1-1.5 years to get it to GMP again.
- That's why people qualify in Empower.
- When I started I had no understanding of Empower, it looked like it was built in the 80’s.
- The innovative thing about empower is that it used a relational database, built on Oracle. The reason behind the relational database was that it could do calculations, not compliance. It just happened to be advantageous for compliance.
- We surveyed locally that more people used Empower over Chameleon(?). But there is a certain percentage switching for ease of use.
- That priority is probably different for a start up v. big pharma.
- There are some large companies that use Chameleon in early stage and move to Empower later in development.
- I think next gen will make it all seamless for regulatory filings. If you are digitizing your data capture to generating reports and having everything in the cloud would give a seamless connection between collecting the data and filing.
- So there would be a link to the actual data in the submission itself? So a reviewer would access the raw data.
- Yes
- Is it a good idea to provide a reviewer that may not have deep knowledge on one aspect?
- What's the difference between submitting data now electronically and providing them access in the cloud. For everyday they accelerate getting a product to market there are millions of dollars to be gained for large companies.