Table 2: Implementing the Analytical Method Lifecycle Approach (ICH Q14/revision of ICH Q2)

SCOPE:
The ICH is working on guideline Q14 Analytical Procedure Development. The new guideline is proposed to harmonise the scientific approaches of Analytical Procedure Development, and to provide the principles relating to the description of Analytical Procedure Development process.

Analytical procedures are necessary to develop products and manufacturing process, to measure critical quality attributes and to ensure the quality of final products. These analytics would be modified or improved throughout the product lifecycle because of continual improvement activities.
Some of main technical and scientific elements include:

- Submission of Analytical Procedure Development and related information in CTD format
- The concept and strategy of enhanced approaches for Analytical Procedures
- Performance criteria of Analytical Procedures
- In line with ICH Q8 and ICH Q11, greater understanding of Analytical Procedure can create the basis for more efficient, sound science and risked-based change management (e.g., using analytical Quality by Design principles).

We are beginning to understand what the guideline will encompass (see e.g. https://www.casss.org/page/NLab1219 , https://www.casss.org/resource/resmgr/at_europe_speaker_slides/2019_barry_slides.pdf).
In addition, there are many high-level papers on AQbD and MLCM. How do we translate these high-level thought and strategies practically and pragmatically to our (company's) way of working and how do we implement these? Often, many aspects are already present in an organization, but not connected.

QUESTIONS FOR DISCUSSION:

1. How do we translate the high-level thought and strategies practically and pragmatically to our (company's) way of working and how do we implement these?
2. How do we connect different aspects of AQbD/MLCM that are already present in the organization and align them with ICH Q14?
3. How does one design an efficient and effective control strategy?
4. What is AQbD and life cycle management/method maintenance and how do we implement this?

DISCUSSION NOTES:

What is AQbD:
The proposed questions for discussion were about the implantation of ICHQ14 and the revision of ICHQ2 within the organization. It became clear that the terms and principles are not always well understood by people that have to apply analytical quality by design (AQbD) or by clients or management that have to approve of this way of developing methods.
What do the terms AQbD and analytical target profile (ATP) for example exactly mean? How do you write an ATP, how detailed should it be, and how do you develop methods according to

AQbD principles? Some are sensing a feeling that the purpose or gain of using AQbD is not really clear. People might ask what is new about AQbD, what is so different from what is already being done. Is it not the same with just more work in writing it down? More paperwork, generating presentations and files. One could wonder if AQbD is not just piling on top of all the traditions that are already in place in an organization and therefore, becoming just another tick box exercise.

In answer to these questions that people often hear, our response was that AQbD is a tool to make method development easier, not just bureaucracy for more paperwork. We should not forget that we already do a lot of the parts of AQbD. AQbD can help us making the process easier. For instance, at the moment, do we really know what a method is going to be used for, is the intended purpose always clear (range, required precision and accuracy)? Or are we only looking at that during validation, when we are thinking about setting the validation requirements. Often, we use defaults, which is not per se wrong, these defaults have been thought through and encompass prior knowledge and experience. But are these defaults really applicable for what you want to do now, or for what you want to do next? If you start method development, do you really know what you need to develop? AQbD is a tool to help focus on these questions.

You almost never start method development from scratch, you always use the knowledge that you gained from previous methods. Often, the same method is just implemented for different molecules. That might work, or you can run into problems later. Using an ATP and AQbD does not state that you have to start from scratch, it only helps to document decisions and show where a gap might be. Using an ATP can show you if a method that is around can work or if it might need optimalisation. It can also help identify the need for implementing new technology. Over the course of a project lifetime, the requirements of the method will change. They will become more stringent or specific. The ATP shows what a method is developed for, including the precision, accuracy, and selectivity. With new knowledge, the specifications might change. The ATP shows the gap and could support when asking for resources to do development. If you develop a method for a formulated product, the method may fall through as soon as you have to apply it on process development samples in dirty matrices, or low concentrations. When using an ATP, which states that the method is developed for a certain compound, at a certain concentration, in a certain matrix, it is directly clear that there is a gap when going to a different matrix. Often, verifying if the method will work with a different matrix will be sufficient. When that does not work, it is clear that the method needs optimization. Having an ATP helps with this decision process and documenting this. When making and ATP and working according to the principles of AQbD, you can take a step back and think about which method you actually need. This could prevent running into problems later on.

Using an ATP could even help you think before the analytics. Think about the molecule and what properties are important. If a molecule works in a way that glycan structures do not matter at all, do you need glycan profiling? You can rethink why you need specific methods.

ICH Q14 might provide evidence to convince clients or management to invest time in method development. When not investing the time during method development, often problems emerge during routine testing, and the time not invested during method development should be spent on trouble shooting and reanalysis, usually when it is least convenient to do so.

What could be misunderstood, is that working with the principles of AQbD is not more time consuming than developing methods without using these principles, often quite the opposite. All information required for an ATP need to be gathered anyway. And if you invest more time in developing a fit-for-purpose, robust method, the risk of needing to do reanalysis for batch release is greatly reduced.

Robustness testing:

It is often experienced that people do not want to do robustness testing and it is only done in phase 3. Robustness is not something you should test for at the end, you should build in robustness from the start. Robustness is a part of method development, therefore, it is removed from ICH Q2 and implemented in ICH Q14. Unfortunately, robustness testing during method development is often seen as additional/not required time spent on the development. If you do good method development in a coordinated way, you already collect a lot of information about the robustness.

Design of Experiments:

Using Design of Experiments (DoE) is a very powerful. It is a tool; you still have to think about the science. If you use wrong parameters or ranges, the DoE does not work. You should not skip feasibility experiments to check if the design has physical chemical meaning. DoE can be used for method development and robustness testing. If DoE experiments for method development show that a certain parameter does not have any influence on the results, this is very useful information about the robustness of the method.

Implementing AQbD:

In some companies, implementing AQbD is hot topic, for some companies it is just being implemented because that is requested. There it feels like a formality, and it is not clear why, how, or what for to implement it.

The implementation of AQbD is different for every company. It is very dependent on how an organization works and how the people in that organization work and deal with their knowledge. What the new guidelines are stating, should have already been a logical part of our work. We should use these guidelines as a framework for easier, more logically, and better documenting of the things we already do. It will help us keep the focus on the science and the purpose of the method. It should not matter which technique you use, as long as it provides reliable measurements. Implanting AQbD could really help keeping the focus on developing an applicable method.

Opinions on the term "platform method":

During the discussion, the term platform method came up. The term platform method is being interpreted in different ways. It is seen as a starting point for method development, or as a method which is validated for several molecules. Unfortunately, quite some people have the misunderstanding that the term platform method implies that the method is finished and can be applied for any molecule.

The terminology of these kind of platform methods has changed over time. It started out with calling it method development strategies, then it changed to method development starting conditions, later generic methods, and now platform methods. They all stand for having a plan, looking at the physical chemical properties, looking at which techniques to use, and knowing what you are going to develop. It is a misunderstanding that a platform method is directly ready. A unique molecule that is going to cure a disease, with unique physical chemical properties, cannot perform the same as all the other unique molecules in a physical chemical system which is called an analytical method.

A platform method could be used to provide some preliminary answers, however, when you know which molecule to proceed with, you should further develop the method for that specific molecule.

You could also talk about platform molecules, for example certain oligonucleotides with the same modification. A platform method could be used for these platform molecules.