Roundtable Session 2 - Table 6 – ICHQ14 and What it Means to CE Method Development

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Abstract

ICHQ14 became effective November 2023. Key throughout the whole document is that all decisions are knowledge driven, that is, scientifically sound. Important concepts in the guideline include the Analytical Target Profile (ATP), Knowledge and Risk Management, and the Analytical Procedure Control Strategy (APCS).

In this discussion, we focus on those aspects that are connected to CE method development.

Discussion Questions:

1. How was ICHQ14 received in your organization, is it actively being implemented as a new approach or is it considered old wine in new bags?
2. Analytical Target Profile: the ATP consists of a description of the intended purpose of the method, relevant product details and relevant performance characteristics with the associated performance criteria.
    a. How well is the intended purpose of the method to be developed documented and understood by the developer?
    b. Is there a clear translation of product attributes into analytical procedure attributes?
    c. Is the ATP really technology-free, or is it still more like: “we need a CE-SDS method”?
    d. Is this description sufficient for your method development, or do you want other details in an ATP as well?
3. Knowledge and Risk Management are important concepts in ICHQ14, and are based on capturing the scientific thinking and justifications (including prior knowledge) throughout the method development and life cycle management process. Knowledge of best practices, state-of-the-art technologies and regulatory expectations contribute to the selection of the most suitable technology for a given purpose. Risk assessment is typically performed early in method development and is updated as more information becomes available. Knowledge related to analytical procedures should be actively managed throughout the product lifecycle.
    a. How are Knowledge and Risk Management organized within your company?
    b. Did you perform risk assessments for CE methods?
        i. What parameters were considered as the highest risks?
        ii. How were these mitigated?

iii. How does your organization deal with proprietary method components or instrumental monopolies?

4. Analytical Procedure Control Strategy: an APCS is to ensure that the analytical procedure is fit for its intended purpose during routine use throughout the life cycle. It should be derived from method and product understanding as well as risk assessments.
    a. How are the SST parameters and criteria set for your CE methods? Are these method and analyte specific, or platform-based?
    b. How do you deal with critical materials, such as commercially provided separation media?
    c. Do you perform a sample suitability assessment?
    d. What kind of factors are part of the ongoing monitoring?

Notes:

Q = Question

A = Answer

C = General Comment

Q: How was ICHQ14 received in your organization, is it actively being implemented as a new approach or is it considered old wine in new bags?

A: A little bit new, must generate analytical target profile is new.

Q: What was done before?

A: They knew it in their head, but writing down and assess risks is new. Generating the document and maintaining documentation. Second on the newness of writing down, but this is a good practice, getting commitment to do this can be difficult so this guidance can help a lot. Makes planning a method easier to understand risk and how to proceed. Sets basic expectations. This documentation will help others understand the why for how methods are set the way they are and eases knowledge transfer.

Q: We work with a lot of kit-based chemistry. How can we develop a good control strategy if we cannot understand the basics of the kit. For example, chemistry of gel?

A: Examine variability of vendor material. Check lot to lot variability, but that does not ensure everything since yet another lot could be different.

Q: How can we do robustness testing when you can't change basic method parameters of what is in the chemistry?

A: In GMP we are following what the vendors provided, system conditions are assigned, and we don't have access that is 'behind the screen'. For parameters we have control of like of analyst can set A and B we access what happens. We can push back on it.

Q: How do we test the core of the method, that is, usually the part that we buy from the vendor?

A: go back to vendor when variability is observed and insist on more consistency.

Q: Is it out of hands because we don't push them? What do we do when they don't' make the kit anymore?

A: Lengthy discussions and we need to ensure continuity, trying to be more aware of to engage up front and ensure we have good vendor relationships to ensure quality product. Lots of engagement and own knowledge of method and how vendor supplies can impact it. Provide feedback to vendor.

A: See gel lot variability. Have an electropherogram in SST then get another lot and it's different. End up screening lots and trying to buy up specific lots.

A: Trying to avoid in house screening so pushing back on vendor to ensure there are proper controls. Ask a lot of questions about their process and understand where they are and get it written in to CoA. Actively proposing additional CoA parameters when it impacts quality so it's not just something that goes though.

Q: Has a vendor updated the CoA based on your request?

A: Yes, leachable profile shift from bottle change.

A: We need to understand where our strength and weaknesses are, but we are always responsible for the quality of our drugs and need to be responsible for results. First CE-SDS kit was from BioRad and that has since disappeared.

Q: What do you do if a kit disappears?

A: We must consider kits as a sole supplier.

A: There is always a risk that a company goes out of business, so there is always risk here.

Q: How do you handle that risk when you don't know what the product is made of. If you don't know the chemistry, how do you replace it, how can you assure your product's quality and assure patient safety?

A: If we are responsible for the method and there for what leads into it, we need to push vendors for clarity.

A: In QC the needs in this area are sometimes ignored.

A: Carrier ampholytes that are proprietary makes me very uncomfortable

Q: Have you had success setting up supply agreements?

A: Yes, this has worked, and some are actively engaged. Although some companies experienced push-backs and less willing vendors

Q: Is ICHQ14 enough to push our companies and vendors to do this?

A: It helps.
A: Helps to have the guidance but still need to generate buy-in. Vendor and industry should be more partners in assuring patient safety, not just commercial client and sales.

C: Recently asked a few different people if there was a new vendor with kits and if they were clear and open about the composition, would they switch? Many said yes, people would buy more not less if they knew.

Q: **During method dev should you run two parallel methods to have options?**

A: For iCIEF there are some options with AES and PS, we go forward with only PS, but do experiment to show equivalency.

A: Have done work to try to find secondar service.

Q: How do you deal with vendors doing pass through, buying from another and rebadging?

A: Can be difficult to know.

Q: Do you screen your ampholytes?

A: Yes, we have to screen every batch, and this is a large burden on our team.

Q: Do you use risk assessments in your company when making methods?

A: Not formally, but in our heads.

Q: Do you apply risk assessment tools for all method parameters?

A: No.

A: We use a fishbone structure to characterize as part of AQbD guidelines to guide though entire development process. One part is analytical process control strategy.

C: Implementing AQbD we work very early to capture risk assessments. Capture in short sentences the reason why method changes are made and identify key paraments. Capture in early development and build a comprehensive risk assessment table throughout the process. At the beginning there is a threshold to get over to get this implemented.

C: In early stages haven't focused on it as much, but interesting to consider doing this earlier in development.

Q: **What are you doing for risk assessment.**

A: Thinking about how to implement more.

Q: **What about the case of transferring method to 3rd party?**

A: Document what key parameters are and provide needed training. There's a method that QC lab outsources and differences in steps totally changed outcome and made it not work. Need to be very specific in SOP.

Q: Do you have an ATP?

A: Yes, we do this, but find challenge in getting people to sign the paperwork, so email and say if there's no reply it's consent.

Q: Who writes the ATP?

A: We state the values in AD.

A: Well yes for fragments it's always CGE. Owner of method defines the specifics. If we don't have ATP, we will not touch development at all. This is a handshake between AD and project team.

Q: How do you deal with SS, and you go to a team and they offer a generic number for precision or accuracy and they throw out 1%? How do you deal with this?

A: Use what we know and set the upper limit. Based on analytical capability (this is a popular answer).

Q: Do you work from CQA specification? How do you translate to your ATP?

A: If we have a CQA we must find a method then we need to write the ATP.

Q: If they spec is +/-10% how do you deal with it?

A: It depends on CQA we don't have it before hand, and you have to go figure out the method. For CE methods we generally don't have pre-existing specs.

C: In early development it's more 'what can the method do'. As you get ready to launch you have clinical data and manufacturing. You can pull this information in to coalesce on the spec.

Q: How does product requirement pair with analytical capability?

A: Your analytical capability needs to be better than the product requirement.