Article

# Early stage analytical method development; balance between de-risking and cost efficiency

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https://www.solvias.com/capabilities/services/biopharmaceutical-analysis/method-development-and-validation.php

## Introduction

In January 2023 Deloitte Centre for Health Solutions published a survey conducted on the 20 biggest pharmaceutical companies (ranked according to their R&D budget). This survey pointed out that the average cost to bring an asset to market increased back to prepandemic heights of $2.284bn in 2022. In contrast the R&D returns declined following the prepandemic downwards trend (here). This study like many others perfectly displays the need of drug developers to be increasingly cost efficient. Although the cost for analytics in general is only a small fraction of drug development budgets, especially in early (pre-)clinical phases the MO for new drug applications at these phases usually and understandably is “fail fast”.
In contrast to that cost efficiency requirements stands the guidance from ICH guidelines Q14 (method development) and Q2(R2) (method validation) which in their last revision (March 2022) strengthened the aspect of de-risking method understanding and robustness at early phases of the molecule development.
In the following it is described what the main decisions to be taken are, how to find the balance between both sides of this coin and what Solvias offers to help drug developers make these decisions.

## (Early phase) method validation

Typically, in very early stages of a molecule development process, it is not meaningful to directly commit to a full validation exercise of the analytical methods. Data on degradation pathways and/or related substances, stability data which might promote process changes and clinical data that confirms the products viability are not sufficiently available to justify cost intensive commitments at early stages. That said, trying to push back costs for validation to late Phase III always bears the risk of discovering inadequacies at a time when redeveloping methods might cause significant delays. At Solvias we apply an early phase appropriate method validation approach (qualification) that tests the whole set of parameters described within ICH Q2(R2) with adaptable complexity (acc. to customer wishes). Solvias usually does not set specifications on the distinct validation parameters during qualification, however the focus is strongly pointed towards the method capability regarding the aspired quality attribute to be tested for. The applied quality standard regarding device qualification, operator training and documentation is identical to a full validation. Applying this strategy, we can guarantee a high-quality method capability and suitability check without the cost burden of a full validation.

## Robustness Testing

While being one of the most important parts of a method validation exercise it is the part with the least guidance given by ICH Q2(R2). That said Q2(R2) as well as Q14 repeatedly state that it is expected that robustness testing is already part of method development and a required data set for method validation submissions.
Depending on the application, method robustness evaluation can be comparably cost extensive leading to a tendency of avoiding it during early method qualification and shifting the exercise into full method validation. This cost saving approach regularly leads to analytical challenges during clinical release activities accompanied by jeopardized timelines within clinical studies which may easily lead to even greater cost constraints.
At Solvias we usually include robustness testing already in method development stages. In case a customer method is provided which needs to be set up and qualified/validated at Solvias we include robustness testing latest in the early phase qualification approaches. Solvias can reduce the efforts for robustness testing as we have standardized processes and protocols paired with technical excellency and expertise on a variety of Biopharmaceuticals and ATMPs. The Solvias approach for robustness testing is designed to balance cost efficiency and de-risking.

## De-risking by applying peak characterization

In an earlier posting Rafael Sande (Solvias) already detailed how Solvias can help de-risking molecule development projects through early phase characterization efforts. The concept of de-risking that is discussed here can also be broken down on the method level. ICH Q14 Annex A speaks of a "clear link between signal and CQA". A common means to obtain this clear link is by checking the pureness of peaks within chromatographic or electrophoretic spectrograms – peak characterization. Solvias offers different approaches for different techniques.

For the quality characteristic "purity by charge" the best way to elucidate the variants behind the peaks is by directly coupling the cIEF profile with a MS readout. Solvias is one of a few contract research organizations that can provide this solution (see also here). Although Solvias also offers peak fractionation experiments, this solution is very cost extensive and therefore not suitable to early phases of molecule development. If Solvias is involved early in a project's method development process, we recommend controlling already the development of the cIEF charge method by MS; in that way the best balance between de-risking and cost efficiency can be reached.

For HPLC applications like SEC, HIC or IEX usually a direct MS coupling is not possible for peak characterization as very often non-MS compatible salts are used within these techniques. In a best-case scenario Solvias develops these methods directly with a later MS coupling in mind, in that way the best cost efficiency is reached. However also for applications which are not directly MS compatible Solvias offers a easy and standardized approach. This technique utilizes a 2D-like LC-MS approach with a "single-heart-cut" trapping of the peak of interests on a RP column for on-line desalting and direct elution into the high-resolution mass spectrometer. This exercise is standardized within the Solvias BioMS team and can also be used in early phases to de-risk key quality control methods within a small budget and with fast turnaround.

## Summary

The high development costs for medicinal products need to be balanced with the requirements stated within the newer versions of ICH chapters Q2 and Q14. We at Solvias strive to offer tailor made solutions to our partners which help bringing the best therapies to the patients faster

## Abbreviations

| | |
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| ICH | International Council for Harmonisation |
| bn | billion |
| MO | modus operandi |
| ATMP | advanced therapy medicinal products |
| CQA | critical quality attribute |
| cIEF | capillary isoelectric focusing |
| (LC)-MS | (liquid chromatography)-mass spectroscopy |
| SEC | size exclusion chromatography |
| HIC | hydrophobic interaction chromatography |
| IEX | Ion exchange chromatography |
| RP | reversed phase |

## Links

Deloitte pharma study: Drop-off in returns on R&D investments – sharp decline in peak sales per asset

https://www2.deloitte.com/ch/en/pages/press-releases/articles/deloitte-pharma-study-drop-off-in-returns-on-r-and-d-investments-sharp-decline-in-peak-sales-per-asset.html

Early phase biologics characterization; a key factor for risks mitigation in biologics product developments

https://www.linkedin.com/posts/solvias-ag_early-phase-biologics-characterization-a-activity-7059441964529664001-CtbT/?utm_source=share&utm_medium=member_desktop

Capillary Isoelectric Focusing with MS detection (cIEF-MS) of protein charge variants

https://www.linkedin.com/posts/solvias-ag_cief-massspectrometry-collaboration-activity-7054385644445282304-PZNo/?utm_source=share&utm_medium=member_desktop

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