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Mitigating Risk of Validated Analytical Procedure Failures When Upgrading or Replacing LC Assets: Harnessing the Power of Quality by Design (QbD) Principles

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EXECUTIVE SUMMARY

THE VALUE OF KEEPING YOUR LC ASSETS CURRENT

In every high-performing lab, innovation drives product quality and efficacy and ultimately commercial success. In order to stay ahead, timely upgrade of existing LC instrumentation is key.

Why some labs fall behind?

- Misconceptions that running a validated analytical procedure on a different model of LC instrument always requires revalidation and regulatory pre-approval
- Reluctance stemming from past experiences where an analytical procedure required revalidation due to inadequate performance on a new instrument
- No time available to invest up-front to compare instrument specifications because the subsequent return on investment (ROI) is not recognized

How do others stay ahead?

By applying Quality by Design (QbD) principles, it is possible to take a proactive approach to help find the answers to two key questions:

- How will this new instrument impact the performance of my validated analytical procedures?
- What can be done to ensure that the new LC instrument will not negatively impact the performance of my validated analytical procedures?

IMPLEMENTING iQbD PRINCIPLES IS KEY

By applying instrument Quality by Design (iQbD) principles, an organization can proactively ensure the performance of their validated analytical procedures while taking advantage of modern technology when older workhorse LC instruments are replaced.

iQbD will help a user:

- Understand more about an existing instrument and what to look for when purchasing/upgrading LC assets
- Focus on the relevant performance/technical aspects of the instrument specifications
- Predict the impact of a new instrument on the analytical procedure
- Proactively prevent issues due to instrument differences by making allowable instrument adjustments to align the differences
- Demonstrate instrument suitability

Ultimately, iQbD helps the lab take advantage of updated technology and improved chromatography without the need to revalidate analytical procedures. Additionally, iQbD helps to minimize uncertainty as to whether the root cause of an issue is due to the instrumentation or the methodology.

INTRODUCTION

Staying innovative in areas like technology, training, as well as hiring and retention, is key to high-performing labs. It's this innovation that drives product quality and efficacy and ultimately commercial success. There are clear benefits to keeping technology like LC systems current, but there is often reluctance to purchase a new instrument or upgrade existing ones.

Some believe, falsely, that running a validated analytical procedure on a different model of LC system requires revalidation of the procedure and that regulatory pre-approval is necessary. The fact is, there is no current regulatory requirement that states this.

For others, the reluctance may stem from past experiences. One such example could be a lab using different LC systems, either in routine use or during a method transfer where there was a failure of the procedure to perform adequately, necessitating revalidation of the procedure. We will explore how this issue can be resolved from an instrument perspective.

Additionally, a reluctance to replace aging technology may stem from the time investment required to review and compare instrument specifications. All too often, vendors provide inconsistent specifications that are not adept at providing the technical information needed to answer the most important question: **"How will this upgrade/ purchase impact the performance of my validated analytical procedure?"**

By applying key Quality by Design principles, this paper proposes a proactive and enhanced approach to help answer this question. Principles like instrument Quality by Design (iQbD) can help one understand the risks of validated analytical procedure performance when older workhorse LC instruments are replaced with newer instruments. The process is independent of analytical procedures and focuses solely on instrument performance. iQbD consolidates key technical information from instrument specifications to identify and control instrument variables independent from other variables that may exist within an analytical procedure. iQbD helps to determine the suitability of new/upgraded instruments prior to purchasing and running validated analytical procedures. It mitigates the risk of problems with analytical procedures due to differences in instrumentation, allows proactive identification, and control of instrument differences, and ultimately, instills confidence that future problems, which may occur with the validated analytical procedure, are not due to switching to a new instrument.

THE iQbD PROCESS

Proactively identifying and mitigating the risk of potential instrument differences will allow for assessment and control of any instrument performance problems, independent of the analytical procedures. Each of the key phases of the process are equally important. iQbD starts prior to the purchase of new technology with a risk assessment of how instrument differences could impact validated procedures, followed by the creation of testing strategies to determine the severity of the potential impact.

The complexity of the iQbD process will depend on the types of differences between instruments and the necessary adjustments or controls required to accommodate them. While the iQbD process may seem long, it is about due diligence – even if in the end the instruments being compared are equivalent and no control strategies are needed, due diligence is done and confidence is gained around the instrument's performance and its potential impact on validated analytical procedures.

BENEFITS OF iQbD

Performance of the LC instrument is the foundation of any analytical procedure, which is why it is so important to have confidence that any instrument will perform as required when running an analytical procedure and at the same time, benefit from improvements in technology.

iQbD will help a user:

- Understand more about an existing instrument and what to look for when purchasing/upgrading LC assets
- Focus on the relevant performance/technical aspects of the instrument specifications
- Predict the impact of a new instrument on the analytical procedure
- Proactively prevent issues due to instrument differences by making allowable instrument adjustments to align the differences characteristics to allow differences
- Demonstrate instrument suitability

When moving an analytical procedure over to a new system, iQbD is incredibly important to ensure success. iQbD will help prevent data quality erosion (changes in retention times and resolution, increases in peak tailing, etc.). It will also help eliminate confusion around whether root causes of issues were due to the instrument or the analytical procedure. The iQbD process may appear complex, but it is about ensuring the new instrument is fit-for-purpose and preventing unforeseen complications needed to be addressed after the fact. The time spent up-front will ultimately minimize risks and save time in the long run.

QUALITY BY DESIGN (QbD)

Application of QbD principles in the pharmaceutical industry became popular with the publication of three key documents.

1. ICHQ8[1] for scientific approaches and quality risk management to the development of a product and its manufacturing process
2. ICHQ9[2] that offers a systematic approach to quality risk management
3. ICHQ10[3] that describes a comprehensive model for an effective pharmaceutical quality system for the pharmaceutical industry

ICH Q8, Q9, and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process and the control strategy of pharmaceutical products.

It was recognized that analytical procedures could benefit from a similar approach, hence Analytical Quality by Design (AQbD) was conceptualized around 2007. With many publications,[4, 5, 6, 7] AQbD is now the subject of two key guidance documents pending publication in 2021: USP chapter <1220> and ICH Q14.[8, 9]

Very few references are made to instruments in AQbD approaches. If mentioned, it is usually in the context of a prerequisite to AQbD in that instruments are properly calibrated and qualified prior to proceeding with the validation of an analytical procedure. This is also a requirement of Good Manufacturing Practices and industry guidance documents.[10, 11] Burgess and McDowall describe an adaptation of the Analytical Life Cycle Approach to Instruments and Systems,[12, 13] which is a step in the right direction, but it does not address the impact that changing different models/vendors of instruments will have on the performance of the validated analytical procedure. Analytical procedure issues that are traced to instrument differences show that simple calibration, qualification, and maintenance procedures are not enough to ensure acceptable, comparable performance between instruments throughout the life-cycle of the analytical procedure.

INSTRUMENT QUALITY BY DESIGN (iQbD) AND INSTRUMENT LIFECYCLE MANAGEMENT

Instrument lifecycle management follows a four (4) stage process. The process helps clarify the impact any differences between an existing and a new/upgraded instrument may have on validated analytical procedures and what controls can be put in place to compensate for any physical instrument differences. The process is based on a single instrument-to-instrument comparison.

PREREQUISITES

- Define an Instrument Suitability Target (IST). An IST is a prospective summary of the performance characteristics describing the required performance criteria of both instruments to demonstrate suitability.

STAGE 1: INSTRUMENT UNDERSTANDING

Instrument understanding has a similar structure to Stage 1 of AQbD/lifecycle for analytical procedures and is completed prior to any instrument changes, purchases, or upgrades.

Knowledge gathering

This step involves finding the differences and similarities of capabilities between the existing and the new/upgraded instrument. It is used to uncover differences between the LC instruments that could contribute to inconsistent performance of the analytical procedure.

i. Risk assessment

Risk assessment is used to identify and evaluate specific instrument differences that could cause variability in performance, which would impact the performance of the analytical procedure. Risk levels are assigned against a risk statement in order to identify which differences need to be controlled so both instruments meet the requirements of the IST.

ii. Creation and application of a control/ adjustment strategy

A control/adjustment strategy is the outcome of the knowledge gathering and risk assessment exercises. Application of a control or adjustment strategy minimizes the impact any differences, identified as high or medium risk, may have on the new instrument's ability to meet the IST. Integration of the identified controls or adjustments are made during the installation of the upgraded or new instrument. In an ideal environment, they would be shared with the instrument vendor for successful implementation and would also be included in the User Requirement Specification (URS).

STAGE 2: DEMONSTRATION OF INSTRUMENT SUITABILITY

This is performed post-purchase of a new/upgraded instrument. It includes running independent prepared test solutions like Waters Quality Control Reference Materials (QCRMs) that are ideal for instrument performance monitoring. The same LC method and QCRM are run on both existing and new instruments. It is recommended that this is performed as part of the lab's specific Performance Qualification in accordance with a protocol. The results are then documented in a report that details the comparison between the two instruments and to the instrument suitability target (IST). If the data between the two systems is comparable per the IST, then the control strategies used to address any impactful differences between the systems to ensure instrument suitability performance were successfully carried out – meaning both systems are suitable to run the validated analytical procedures. If the instruments gave different answers and the new instrument did not meet the IST, then there could be other instrument differences that were not identified, addressed, and controlled for.

STAGE 3: ONGOING MONITORING

Monitoring the ongoing performance of new instruments is performed as part of the company's in-house calibration and maintenance program. The use of independent prepared test solutions like QCRMs[14] is ideal for instrument performance monitoring. Stage 3 is outside the scope of this paper.

STAGE 4: RETIREMENT/REPLACEMENT OF SYSTEM

When a system is due for retirement and or replacement, instrumentation should be decontaminated in accordance with health and safety requirements prior to removal and disposal. Instrument vendors should offer services for decommissioning instrumentation and disposal/recycling in line with local regulations and sustainability guidelines.

** Please ask your local Waters representative for details of local services and specific deals when trading in old equipment for new.*

EXECUTING THE PROCESS

INSTRUMENT SUITABILITY TARGET (IST)

The output from each instrument is compared and should meet the predetermined IST based on the Waters QCRMs.

General example of an IST

- Retention time comparability
- Injector volume precision
- Resolution between the critical pair is comparable on each system
- Low level analyte is observed on each system with a comparable signal to noise ratio

Acceptance criteria for the above are determined prior to running the instrument suitability test solution.

STAGE 1: INSTRUMENT UNDERSTANDING (LC)

Knowledge gathering

The four most common approaches to knowledge gathering are:

1. Mapping and observing where in the sample analysis process can the instrument potentially impact results based on its performance.
2. Using historical data to identify changes (if any) that were done with the existing instrument that impacted or did not impact instrument performance.
3. Enlisting instrument experts and experiences to help understand how instrument features impact performance.
4. Performing experiments to observe the severity of impact on performance when instrument features are changed.

a. Map the process

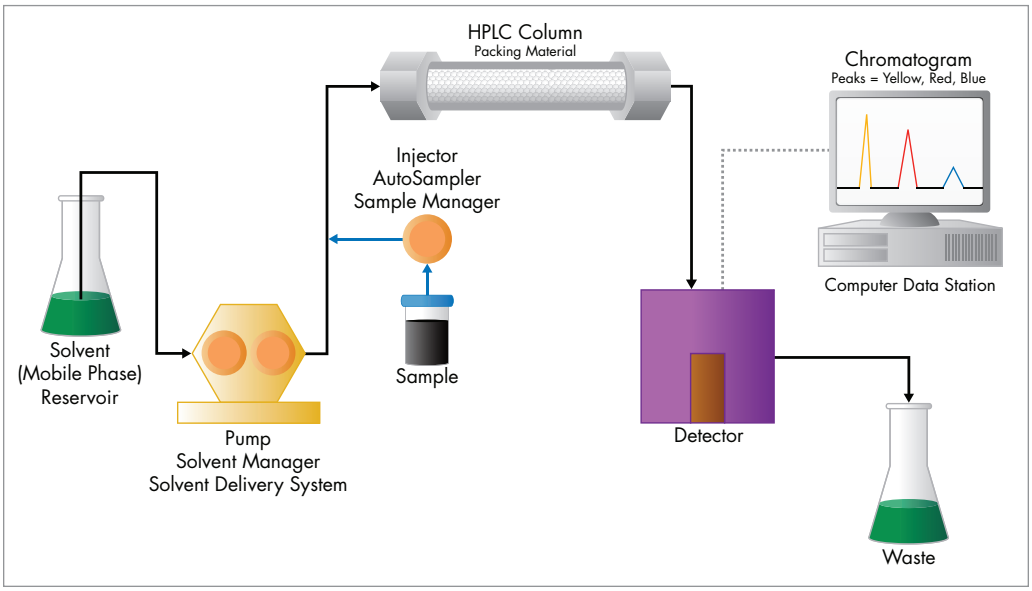

Figure 1. The path of a sample through an LC instrument.

b. Prepare a risk statement

As with all risk management exercises, we must pose a risk question or statement that defines our needs: "Identify instrument features which (if different) could potentially impact the performance of the instrument to the extent that the requirements of the IST would not be met."

c. Prepare an Ishikawa diagram (fishbone)

This step allows the user to document all instrument variables that could impact instrument performance.

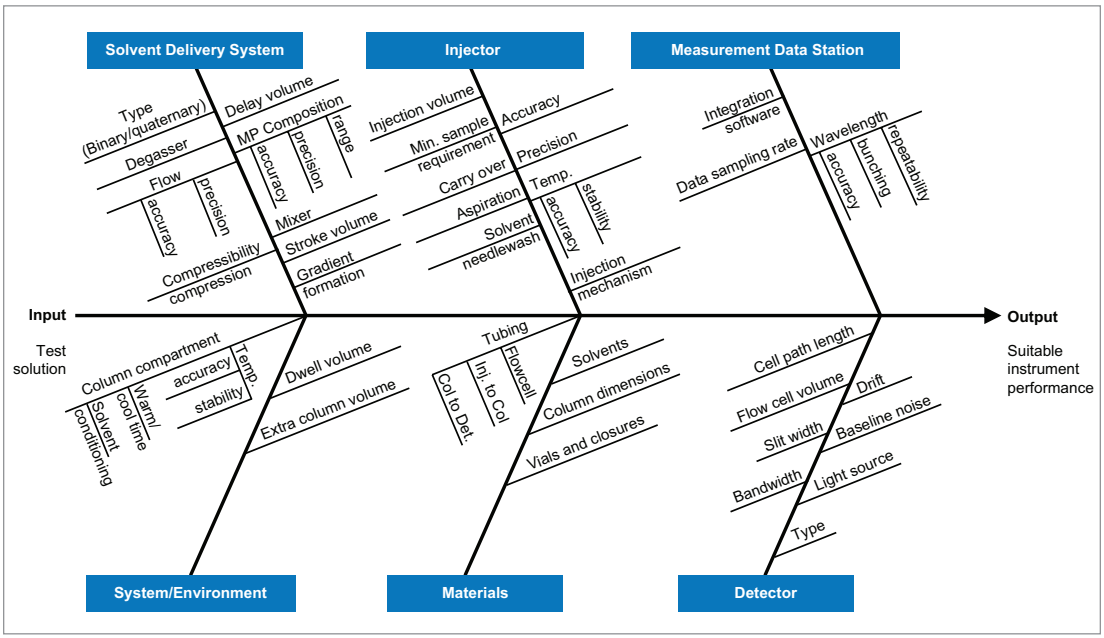

Figure 2. Ishikawa diagram (fishbone) to identify instrument features (variables) of any LC system that could potentially impact instrument performance.

d. Experiment (existing instrument)

System dispersion

System effects such as tubing internal diameter (I.D.) and length, connections, and detector flow cell volumes can impact system dispersion that, in turn, can impact chromatographic separations due to differences in peak shape. It follows that differences in system dispersion could potentially have a negative impact on the performance of the validated analytical procedure on a new/ upgraded instrument.

It is important, therefore, that differences in extra-column volume and dwell volume between the existing and new/upgraded instruments are understood. (Refer to Figure 3). If any differences are identified as high risk with regards to negatively impacting procedure performance to the extent the IST will not be met, they are corrected prior to running the instrument suitability test solution in Stage 2.

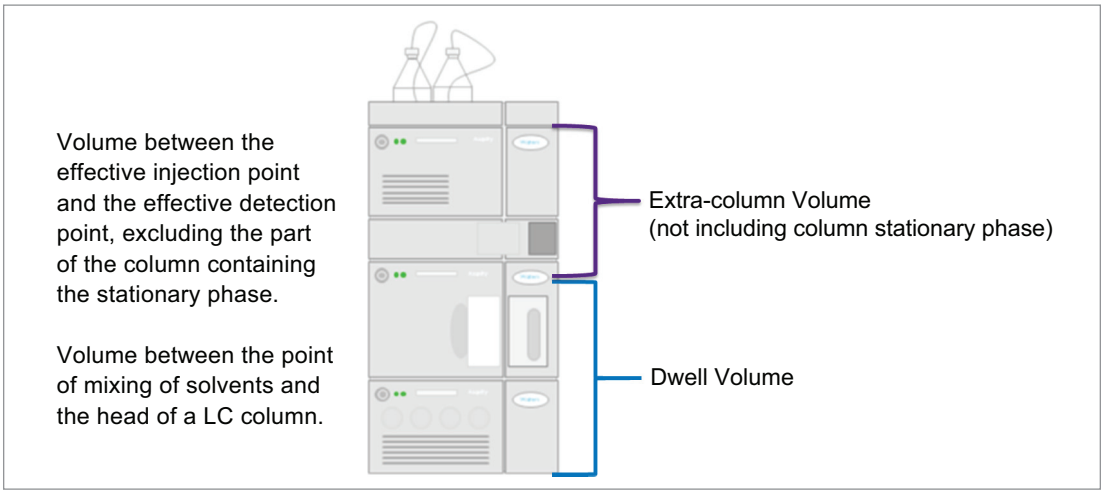

Figure 3. Different system volumes to consider between instruments.[16]

i. To identify the level of risk due to differences in volumes, the following information should be gathered and documented for the existing system:

- Dimensions and material of the tubing that connects
  - the injector to the column
  - the column to the detector
- Connections
- Flow cell volume

ii. In addition, an experiment should be performed to calculate the extra column volume and dwell volume (if gradient analytical procedures will be used) for the existing instrument. This is particularly important if the tubing is not the original tubing and if respective flow cell volumes are different.

Note: Dwell volume, if different, is known to impact instrument performance and can be responsible for failure of the analytical procedures to perform as required for gradient methods on a new system. System tubing and volume and pump type all contribute to dwell volume. Therefore, it is important that the dwell volume on the existing instrument is measured experimentally to compare with the dwell volume on the new instrument and address if needed.[15]

e. Review the specifications

Specifications can be overwhelming and despite containing many values and descriptions, they are often hard to compare across instruments. Instrument experts at Waters summarized the specifications for the instruments[16, 17] used in the example in Table 1. Using this information, a list of the differences in the LC instruments that could potentially impact performance was compiled for the risk assessment.

RISK ASSESSMENT

Understanding the similarities and differences between LC instruments is key to assessing the relative risk to the performance of validated analytical procedures. It is also important to have a good knowledge of the validated procedures to be moved and what instrument parameters they are sensitive to. The risk assessment helps determine the potential variables (differences between instruments) that are acceptable, those that need to be controlled, and those that require further investigation (more experimentation to determine the severity of impact). A heat map is a risk tool which lends itself to a simple 3 level assessment. The risk assessment is performed with the risk statement in mind using predefined risk assessment criteria.

Risk Statement: *"Identify instrument features that (if different) could potentially impact the performance of the instrument to the extent that the requirements of the IST would not be met."*

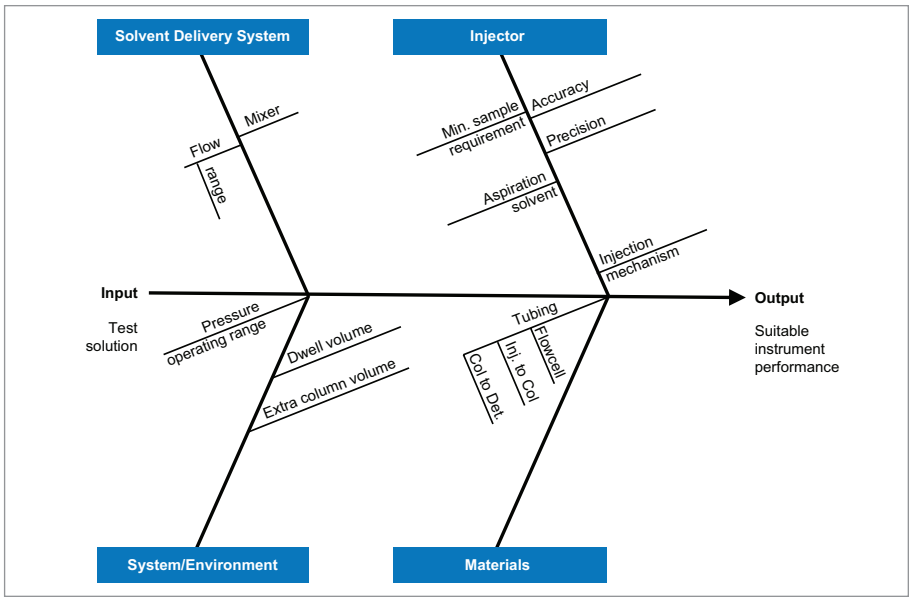

Figure 4. Simplified fishbone diagram showing which variables will be included in the risk assessment.

Predefined risk assessment criteria

High risk (RED): Indicates that further knowledge or experimentation **is** required as it **will** impact the IST.

Medium risk (YELLOW): Indicates that further knowledge or experimentation **may** be required as it **may** impact the IST.

Low risk (GREEN): Indicates that further knowledge or experimentation **is not** required as it **will not** impact the IST.

Assumptions

- The same column, solvents and vials will be used for the instrument suitability test. These may be removed from the fishbone diagram for this example.

Review of the respective instrument specifications will allow the user to simplify the fishbone diagram, such as when specifications are the same on both instruments (Figure 4). The remaining variables are then entered into the risk assessment heat map to determine the risk level (Table 1).

It is important to also include operational differences, such as minimum sample requirements and operating ranges, in the risk assessment. In some cases, these may suggest the new instrument is or is not suitable for its intended purpose when compared to the existing instrument. The risk assessment in Table 1 is an example based on a scenario of a customer considering the purchase of an Arc™ HPLC System to replace an Alliance™ IEEE. The future intended use of the new instrument is to run existing validated procedures. Please note that assignment of risk levels may vary when applied to a different scenario.

Table 1. Risk assessment outcome for the movement of a method from an Alliance IEEE to an Arc HPLC for gradient methods

Potential variables	Potential to impact				
	Retention time	Precision	Resolution	Sensitivity	Tailing
Dimensions and material of the tubing					
Injector to column					
Column to detector					
Flow cell tubing					
Extra column volume @ 4 σ					
Flow operating range	No impact to chromatography as long as flow rate is kept to 5mL/min or below; however, Arc HPLC is not suitable for analytical procedures requiring a flow rate greater than 5 mL/min. Typical use will be between 0.1 mL/min and 3.0 mL/min which is within the operating range of both instruments. The Arc HPLC offers lower flow capability which is a positive risk.				
Mixer					
Minimum sample requirement	Could impact precision and sensitivity, however the analytical procedures that will be run on the Arc HPLC system scenario do not typically require low sample volumes.				
Injection accuracy	Both instruments report values within the normal operating range required by the analytical procedures for which it will be used. The Arc HPLC offers improved precision and accuracy, therefore difference is considered a positive risk.				
Injection precision	Typically, HPLC analytical procedures have injection volumes between 10 and 50 µL. The Arc HPLC offers improved precision over this range by using a 100 µL syringe, therefore considered a positive risk.				
Injection mechanism	Carryover may impact precision and sensitivity. A separate line/purge solvent reduces potential for carryover. This is an improved performance feature of the Arc HPLC. Difference considered a positive risk.				
Aspiration solvent					
Maximum operating range (pressure)	No impact to chromatography; improved performance feature of the Arc HPLC, difference is considered a positive risk.				

Risk Level	Color Indication
High – the difference will impact results	
Medium – the difference may impact results	
Low – the difference will not impact results	

Mitigation of high and medium risks between the Alliance IEEE and Arc HPLC

This can be achieved by gathering more knowledge or further experimentation to justify risk mitigation or address the risk in the control/adjustment strategy. Some potential risks have already been mitigated in the table by justifying that the differences between the Alliance IEEE and Arc HPLC will not impact the typical use of the intended instrument and validated analytical procedures.

Identified high risks

1. In the example in Table 1, the tubing from the injector to column on the existing instrument had been modified, including the diameter and length.
   Risk decision: Add to control/adjustment strategy.
2. Mixing mechanisms, if different, are known to impact instrument performance such as retention time, precision, resolution, and tailing.
   Risk decision: Further knowledge is required. Further experiments may also need to be performed.

Identified medium risks

1. Differences were noted in both the dwell volume and the extra-column volume values. Further consideration of each value and the impact on chromatography lead to the following conclusions and actions:
   - Although different, the dwell volumes were similar and would not impact retention time
   - Differences in tubing were noted. These values which typically contribute to differences in extra column volumes are the same post column
   - The instrument suitability test will use an identical column for both instruments

   Risk decision: The tubing has already been assigned to the control strategy and by applying that control at the time of installation, it should resolve any impact the extra column volume would have on the IST.

CONTROL/ADJUSTMENT STRATEGY

- Ensure the analytical methods intended to be moved to the Arc HPLC System have flow rates and injection volumes within the operating ranges of both instruments and do not require low injection volumes.
- Accommodate any differences in tubing at time of instrument installation.
- Accommodate any minor physical adjustments required for mixing inconsistencies at time of installation.

Conclusion

As long as the analytical procedures targeted to be moved to the Arc HPLC System comply with the justifications above and the control/adjustment strategy is followed, results between the two systems should be comparable. Upon purchase, the justifications and control strategy are shared, and the new Arc HPLC System will be installed in adherence to the control strategy as determined by the risk assessment. IQ/OQ will be executed and Stage 2 of the iQbD approach is then performed.

Stage 2: Demonstration of instrument suitability

This is performed by running the Waters QCRM gradient instrument suitability test solution(s) on both the existing and new/upgraded instruments. The tests are executed following a protocol and the results are documented in a report that compares the outcome from each of the instruments against the requirements of the IST. An identical column, mobile phase, test method and test solutions are utilized on both instruments.

If the IST is met, then the new equipment can be included in the ongoing monitoring program in accordance with Stage 3 of the iQbD approach. This is usually achieved through the instrument's calibration and maintenance program. The use of independent prepared test solutions like QCRMs are ideal for instrument performance monitoring, having established an instrument performance baseline during the IST.

Link between instrument and analytical procedure performance

The system suitability test solutions and their acceptance criteria described in individual analytical procedures bridge the gap between instrument and analytical procedure performance. Analytical system suitability solutions and analytical procedure performance is outside the scope of this paper. However, it can be seen from the risk assessment that any special requirements needed for a particular system suitability/analytical procedure intended for use on the new instrument can be considered during the knowledge gathering and risk assessment parts of the process. This allows the assessment of any instrument function relating to specific analyte behaviour to be proactively identified independent of the analytical procedure and differences identified as high-risk with regards to switching instruments can be controlled at the time of installation.

In these special cases, there may be additional advantages to running the system suitability solutions listed in the analytical procedure, in addition to the instrument suitability test on the new/upgraded instrument, as part of performance qualification. This enables minor changes to instrument configuration or parameters outside of the regulated environment.

CONCLUSION

Modern technologies and enhancements create an environment that promotes innovation. Innovation is the pathway to improve product quality and efficacy and ultimately to increase commercial success.

An iQbD and lifecycle approach has been designed to fill a gap in the industry to proactively identify and resolve potential instrument differences leading to problems when running validated analytical procedures on new or upgraded LC systems. Stage 1 of the process gathers knowledge on the existing instrument and identifies differences between it and the new instrument/upgrade under consideration. The outcome of Stage 1 is a recommended control/adjustment strategy to reduce impact of physical differences. Stage 1 also provides a tool to help customers assess the suitability of an upgrade or new instrument for their intended use and hence make an informed decision, based on good science. All this takes place prior to purchase and without the need of a demo instrument onsite. Once the decision to purchase the new/upgraded instrument is made, stage 2 and 3 of the iQbD process are performed.

The examples in this paper were selected based on an upgrade and purchase of Waters-to-Waters equipment in order to introduce the concepts of iQbD. This process can be used across different models and vendors as well as for the switch from HPLC to UPLC/UHPLC systems. The complexity of the iQbD process will depend on the types of differences between systems and the necessary adjustments or controls required to accommodate them. While the iQbD process may seem long, it is about due diligence – even if in the end the instruments being compared meet the IST and no control strategies are needed, the due diligence is done, and confidence is gained around the LC asset replacement. Furthermore, the lab will have documented a solid instrument knowledge base and gained an understanding of how instrument parameters/settings may impact analytical procedure performance. This is a powerful troubleshooting tool that can assist with future analytical investigations.

Proactively identifying and mitigating the risk of potential instrument differences that contribute to problems with validated analytical procedures, independent of the analytical procedures, will allow for faster investigations of questionable results because it will be clear that the differences are not due to using a different instrument. The iQbD process may also be performed as part of the gap analysis prior to transferring validated analytical procedures between laboratories when different instrument models are involved. This allows the laboratories to proactively identify and control for potential risks, and an investment at this stage yields efficiencies in short term and long term investments.

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