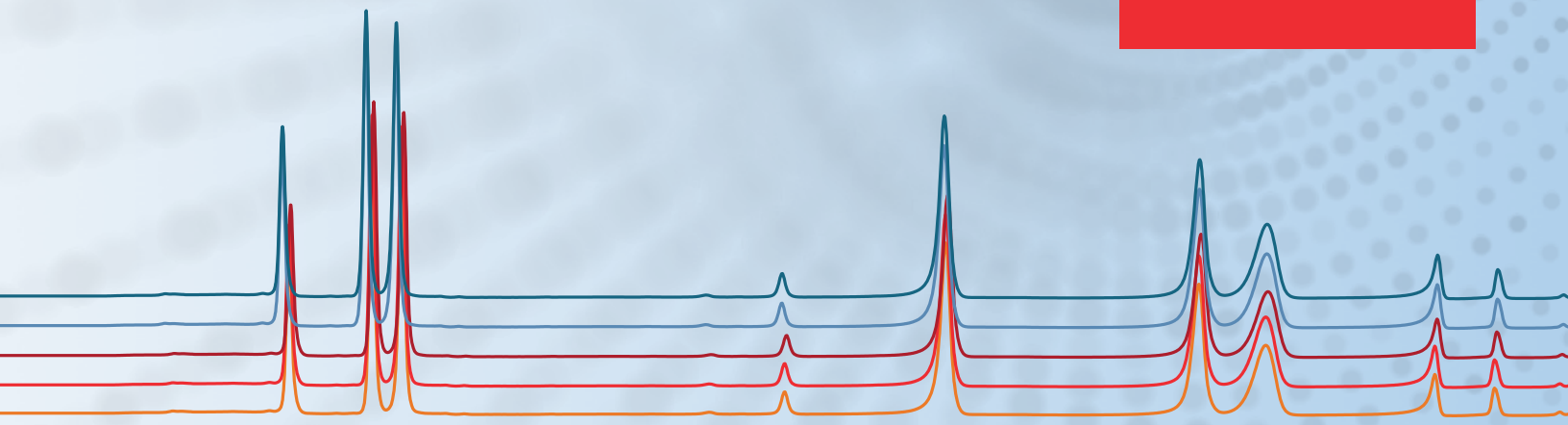
White paper | 002327



Biopharma

ICH guideline update: Method lifecycle

Authors

Crystal Welch, Thermo Fisher Scientific

Keywords

Chromeleon CDS, ICH, ICH Q2, method validation, method development, method qualification, MAM, CQA, BioPharma Finder, Ardia, Chromsword, Fusion, DoE, Specificity, Accuracy, Range, Precision, Robustness, Assay, Impurities, LOQ, LOD, Pharma, BioPharma

Introduction

If you've ever worked in process development in the research to pre-IND phase of a molecule you understand the chicken and egg syndrome of how to prove measured quality attributes against current characterization information.

It's generally understood in these phases that analytical methods are still a work in progress, and they will likely go through many changes while still be used to track attributes about the product in the meantime. The evolution of these methods can get complicated if changes are undertaken without a structured capture system or any records for the reasons 'why'.

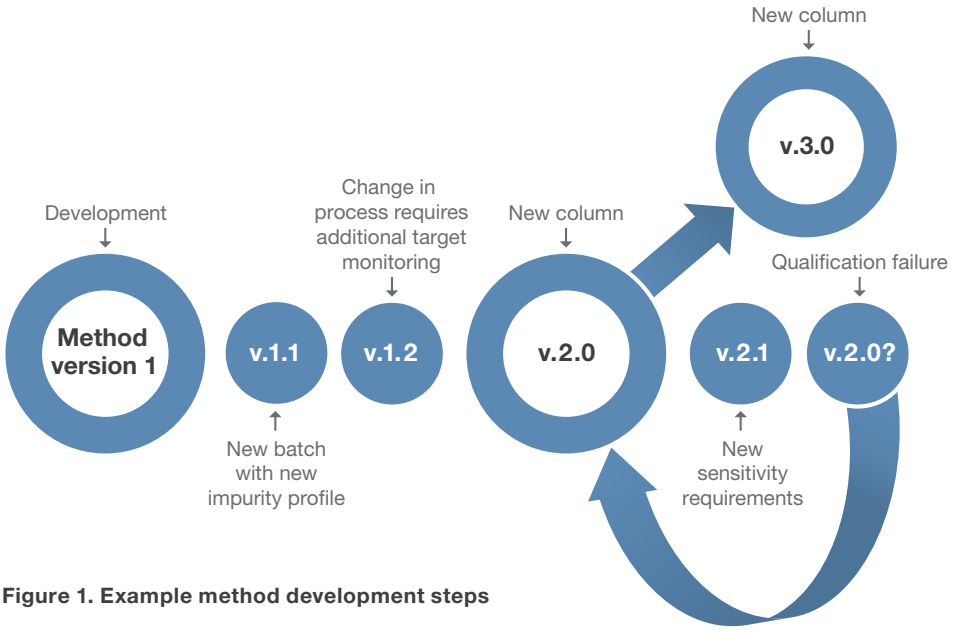


Figure 1. Example method development steps

thermo scientific

Despite method development having traditionally resided in the realm of research or process development and not under strict regulatory oversight, there is an encroaching emphasis to include method development in the method lifecycle and encourage controlled development steps utilizing guidelines for lifecycle management.

New year, new implementations

Continuing with this look into lifecycles, the ICH drafted a concept paper[1] in late 2018 with the intent to modify the ICH Q2 (R1) *Validation of Analytical Procedures: Text and Methodology*[2] to include guidelines that covered the method development stage.

In the end of the undertaking to revise this guidance, the ICH has kept the focus of ICH Q2 (R2)[3] on method validation, but also drafted a new chapter, ICH Q14 *Analytical Procedure Development*,[4] to address method development. Since ICH Q14 has its own developed nomenclature, ICH Q2 (R2) refers to ICH Q14 in text, and both of these revisions have been available for comments that were due in fall of 2022, it is more likely there will be two guidance documents coming out for implementation in the fall of 2023.[5]

Reviewing method validation changes—comparing ICH Q2(R1) to Q2(R2) draft

The problem statement for revising the 2005 ICH Q2(R1) version for *Validation of Analytical Procedures: Text and Methodology* includes references to covering the recent application of new analytical procedures such as Near Infrared (NIR) Spectroscopy that typically prove statistical significance for fit with multi-variable regression models. Since most of the previous language written around method validation takes advantage of external standards and linear regression to set statistical significance and measure variance based on ANOVA principals, this edit was essential to address multi-variable analytics.

Some of the other noted concessions and additions are highlighted in the table below for further discussion:

Topic	Notes about ICH Q2 (R2) intended changes
References	Includes called-out references to ICH Q14 as well as ICH Q8, Q9 and Q10 with emphasis on risk-based language.
Multi-variable analytics rework	The term 'Linearity' was changed to 'Suitability of Calibration Model' with expanded information in section 3.4.
Revalidation expansion	The revalidation procedure is more detailed in section 3.1 with generalized reference to lifecycle management and includes co-validation and cross-validation approaches.
Sample stability during an analysis	Sample stability is given more description in section 3.3.

The differences highlighted here for discussion do not represent the total of all differences.

Overall, there aren't any huge revelations of new requirements here, but the reorganization, re-stressed information, and just the new number of total pages does provide a much clearer outline for the method validation process than previously given.

Within the document itself, the outlined testing for validation has gone through some changes as well, but the overall message from the original version remains.

For the individual sections in the validation outline, the following was noted:

Topic	Notes about ICH Q2 (R2) intended changes
Specificity and identity	This section was expanded in 4.1 to include the allowance for orthogonal procedure comparisons or a technology inherent justification.
Assay and/or impurity	This section was expanded in subsection 4.1.4 under recommended data and includes more experiment structure descriptions.
Range	There is a tabulated explanation in section 3.2 and an expanded recommendation in section 4.2 for range requirements specific to analysis types.
Accuracy and precision	This section combines two topics with expanded information and recommendations in section 4.3 to include more alternative approaches to demonstrate accuracy in mixtures.
Robustness	This section now has a reference to ICH Q14.

The notes highlighted here for discussion do not represent the total of all noted changes.

Changes to Specificity and Identity to allow scientific justification when validating analytical methods such as mass spectrometry shows open flexibility to study design, as does the reference to ICH Q14 and allowance for the use of prior collected data to demonstrate Robustness. For Assay, Impurity, Range, Accuracy and Precision, the approaches outlined follow logic that is commonly demonstrated in the field, however, the expansion on these sections works toward enhanced clarification.

Overall, the changes in the body represent more clarification and flexibility allowances for validation of different analysis types and on different technologies.

A large portion of the addendums to the document includes a glossary of defined terms, a diagram of validation tests based on an objectives flow chart (Figure 2), and a tabulated list of examples for validation design.

The effort to include more examples in the guidance revision is a valuable addition for anyone, but especially for those who are new to method validation study design.

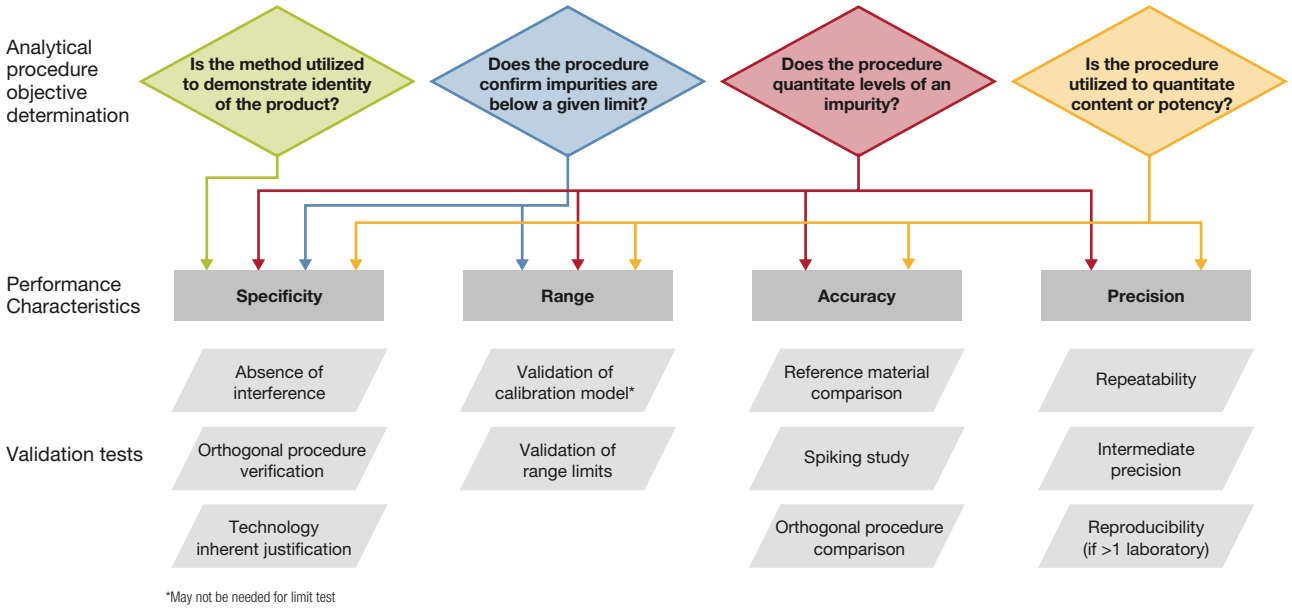


Figure 2. Selection of validation tests based on the objective of the analytical procedure[3]

Reviewing new method development information—ICH Q14

Overall, this guidance introduction represents a more conservative stance on regulation as applied to analytical methods since it seeks to give guidance for method development.

Some observations of the biggest contributing factors in the new guidance are listed below.

In addition to these general observations, there is a detailed set of recommendations for the analytical procedure lifecycle which is graphically represented by Figure 3.

Topic	Discussion on ICH Q14
Continual references are made throughout this document to: **ICH Q8 Pharmaceutical Development** **ICH Q9 Quality Risk Management** **ICH Q10 Pharmaceutical Quality System** **ICH Q12 Lifecycle Management**	For researchers looking to develop a new method, the recommendation to incorporate regulatory documentation in a systematic approach could seem like a new frontier.
Multi-variable calculations	A specific outline is made for multi-variable analytical procedure development due to the complexity of demonstrating suitability for these n-variable calculations.
Real Time Release Testing (RTRT)	A specific outline is made for RTRT procedures to address the emergence of methods to support time-sensitive products in the newer molecule modalities coming to market.
Platform methods, prior knowledge and robustness for validation	Concessions are made in the development process for utilization of platform methods, prior knowledge, and allowing robustness studies to be utilized in method validation steps to reduce method validation efforts.

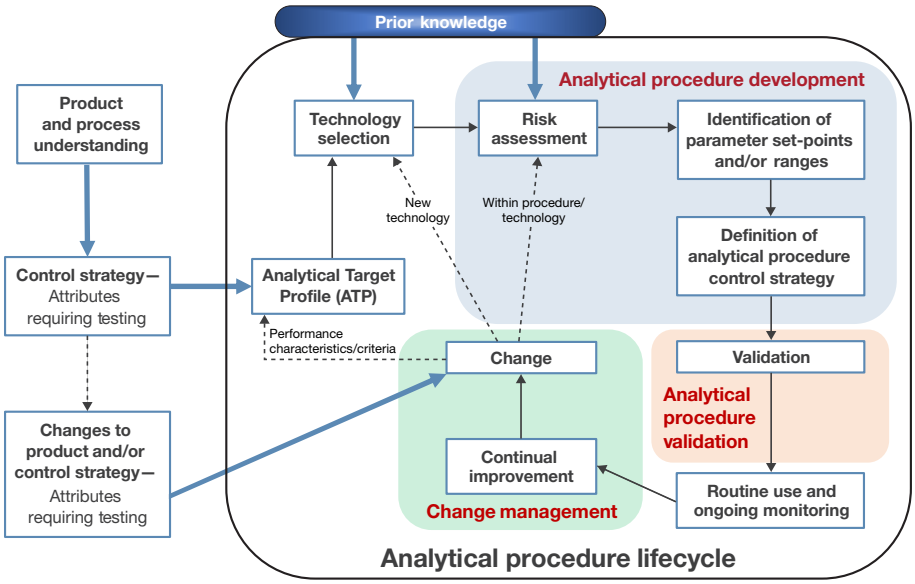


Figure 3. The analytical procedure lifecycle[4]

Emphasis in text is made on establishing a change control strategy, incorporating a risk assessment, and identifying procedural controls within the method itself to monitor during the development phases. These types of regulated steps may not currently exist in many method development labs, or be formally captured.

As with the revision to ICH Q2 the document includes several outlines and incorporated examples including some risk assessments. These examples are helpfully given as fishbone diagrams for readers to reference such as in Figure 4.

Each of the parameters illustrated here are typically assessed as a part of Robustness. The message within these examples is that there should be an established structure for determining the analytical procedure attributes. Ideally, those variables along with performance characteristics that determine method fitness should be set prior to testing and refined prior to movement into a quality environment.

In summary, the addition of this quality chapter to the ICH guidelines would impact traditional method development in general and may not currently be on the radar of most people involved in method development, qualification, transfer, or validation efforts.

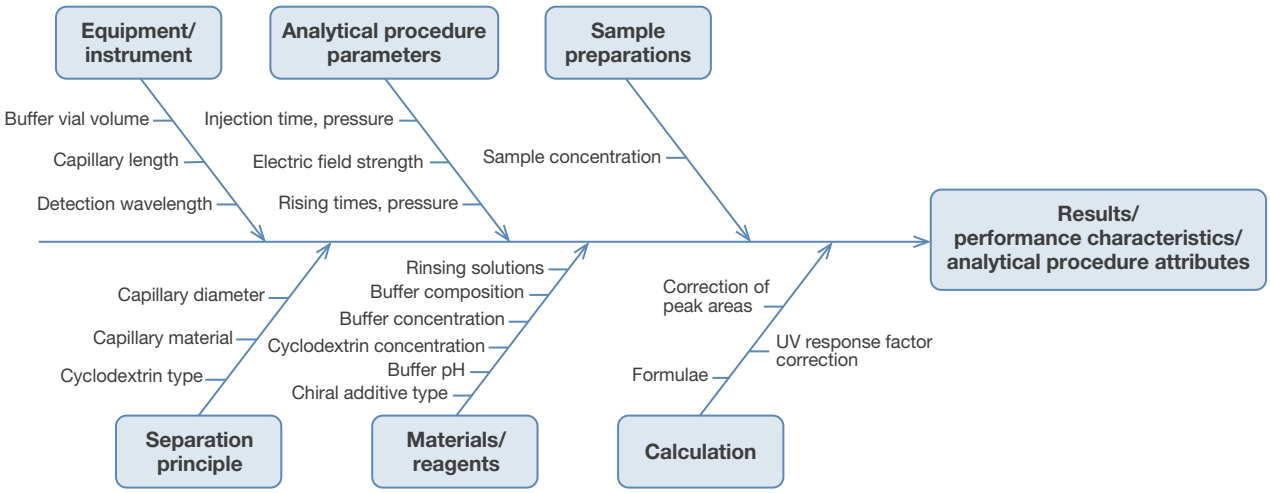


Figure 4. Ishikawa-diagram[4]

Investing in quality—compliance is more than a claim

Companies are always looking to reduce costs. While it is not always glamourous, an investment in quality often results in a positive feedback loop of savings. Well-developed methods result in fewer deviations and eliminate the need to reinvest effort to redevelop later.

For us at Thermo Fisher Scientific, we invest in our products with the goal to maximize ease and useability while minimizing the time to realize it. We believe that departments involved in method development should have access to the technology that monitors more attributes in one analysis, helping them to reduce the time spent equal to the number of orthogonal methods that don't have to be developed, qualified, validated, and regularly utilized across hundreds of thousands of samples over the life of a product.

For labs looking to expand technology in all molecule phases and for all departments, our multi-attribute method (MAM) solution allows for quality use of our Thermo Scientific™ Orbitrap™ technology supported by our compliant software package Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS).

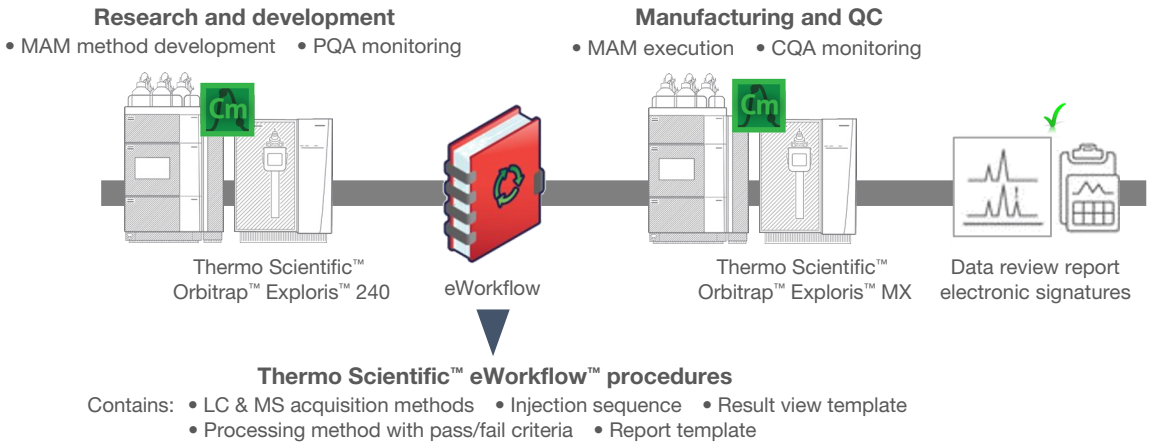


Figure 5. Workflow diagram for MAM 2.0

Chromeleon CDS is capable of controlling and summarizing data collected from our family of detectors including quadrupole and high-resolution MS, as well as an extensive list of instruments from other vendors.* This unifies the interface to collect and work with data ultimately giving users the ability to expand their knowledge and streamline use over a library of applications.

For researchers in the development space tasked with method development and transfer, the steps taken on our family of Orbitraps on Thermo Scientific™ Xcalibur™ software and processing applications such as Thermo Scientific™ BioPharma Finder™ software can be translated to Chromeleon CDS through our connected Thermo Scientific™ Ardia™ Platform for use in process development or quality; saving time in analytical development and reducing the data loss from transferring detection to different technologies.

For scientists looking to move into a method lifecycle management approach, Thermo Fisher offers a variety of software and hardware tools supported by helpful resources.

*A complete list is included in the media files for each version of Chromeleon CDS

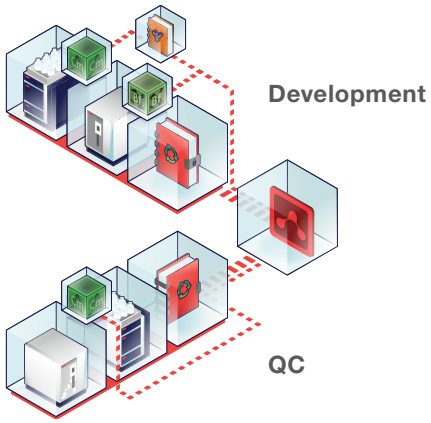


Figure 6. Connecting Development to QC

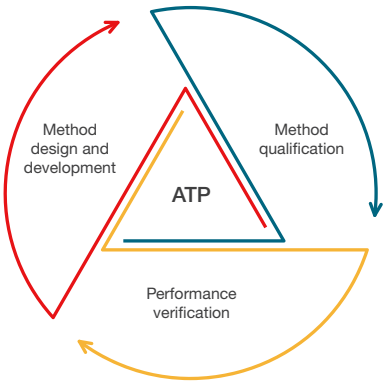
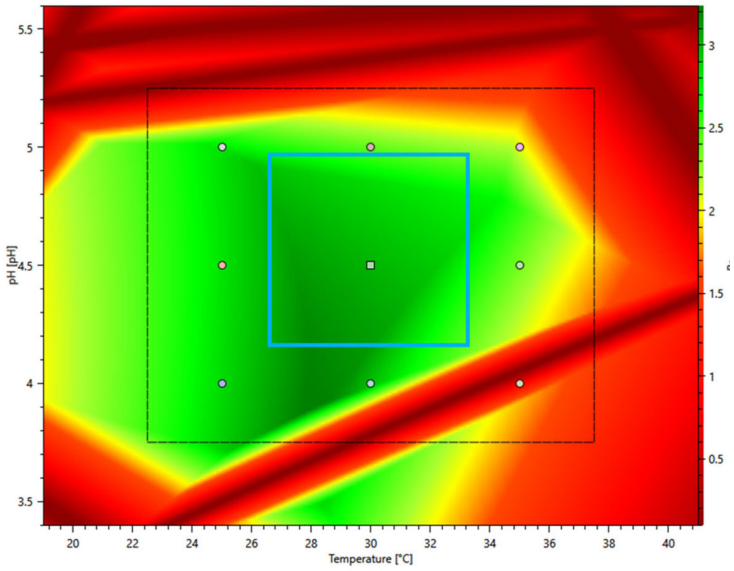


Figure 7. Stages of method lifecycle management

Automation of comprehensive robustness testing or matrixed method development screening can be orchestrated from ChromSword® or Fusion QbD™ connections to the Chromeleon CDS software. Each of these powerful add-on-products support Design of Experiment (DoE) studies and can summarize multi-variate statistical analysis.



Design of robustness tests

	-5 °C temp.	pH = 4	+1.5 % conc.	+0.6 min b.time.	-1.5 % conc.	-0.6 min b.time.	pH = 5	+5 °C temp.
Run #2 -5 °C temp. DAD	✓							
Run #3 -5 °C temp.; pH = 4; +1.5 % conc.; +0.6 min b.time. DAD	✓	✓	✓	✓				
Run #4 -5 °C temp.; pH = 4; -1.5 % conc.; +0.6 min b.time. DAD	✓	✓		✓	✓			
Run #5 -5 °C temp.; pH = 4; -1.5 % conc.; -0.6 min b.time. DAD	✓	✓			✓	✓		
Run #6 -5 °C temp.; pH = 5; +1.5 % conc.; +0.6 min b.time. DAD	✓		✓	✓			✓	
Run #7 -5 °C temp.; pH = 4; +1.5 % conc.; -0.6 min b.time. DAD	✓	✓	✓			✓		
Run #8 -5 °C temp.; pH = 5; -1.5 % conc.; +0.6 min b.time. DAD	✓			✓	✓		✓	
Run #9 -5 °C temp.; pH = 5; -1.5 % conc.; -0.6 min b.time. DAD	✓				✓	✓	✓	
Run #10 -5 °C temp.; pH = 5; +1.5 % conc.; -0.6 min b.time. DAD	✓		✓			✓	✓	
Run #12 +5 °C temp.; pH = 4; +1.5 % conc.; -0.6 min b.time. DAD		✓	✓			✓		✓
Run #13 +5 °C temp. DAD								✓
Run #14 +5 °C temp.; pH = 5; -1.5 % conc.; -0.6 min b.time. DAD					✓	✓	✓	✓
Run #15 +5 °C temp.; pH = 5; -1.5 % conc.; +0.6 min b.time. DAD				✓	✓		✓	✓
Run #16 +5 °C temp.; pH = 5; +1.5 % conc.; -0.6 min b.time. DAD			✓			✓	✓	✓
Run #17 +5 °C temp.; pH = 5; +1.5 % conc.; +0.6 min b.time. DAD			✓	✓			✓	✓
Run #18 +5 °C temp.; pH = 4; -1.5 % conc.; -0.6 min b.time. DAD		✓			✓	✓		✓
Run #19 +5 °C temp.; pH = 4; -1.5 % conc.; +0.6 min b.time. DAD		✓		✓	✓			✓
Run #20 +5 °C temp.; pH = 4; +1.5 % conc.; +0.6 min b.time. DAD		✓	✓	✓				✓
Run #22 pH = 5 DAD							✓	
Run #23 pH = 4 DAD		✓						
Run #24 -1.5 % conc. DAD					✓			
Run #25 +1.5 % conc. DAD			✓					
Run #27 -0.6 min b.time. DAD						✓		
Run #28 +0.6 min b.time. DAD				✓				

Figure 8. **Robustness testing created with ChromSword® Chromeleon Connect**

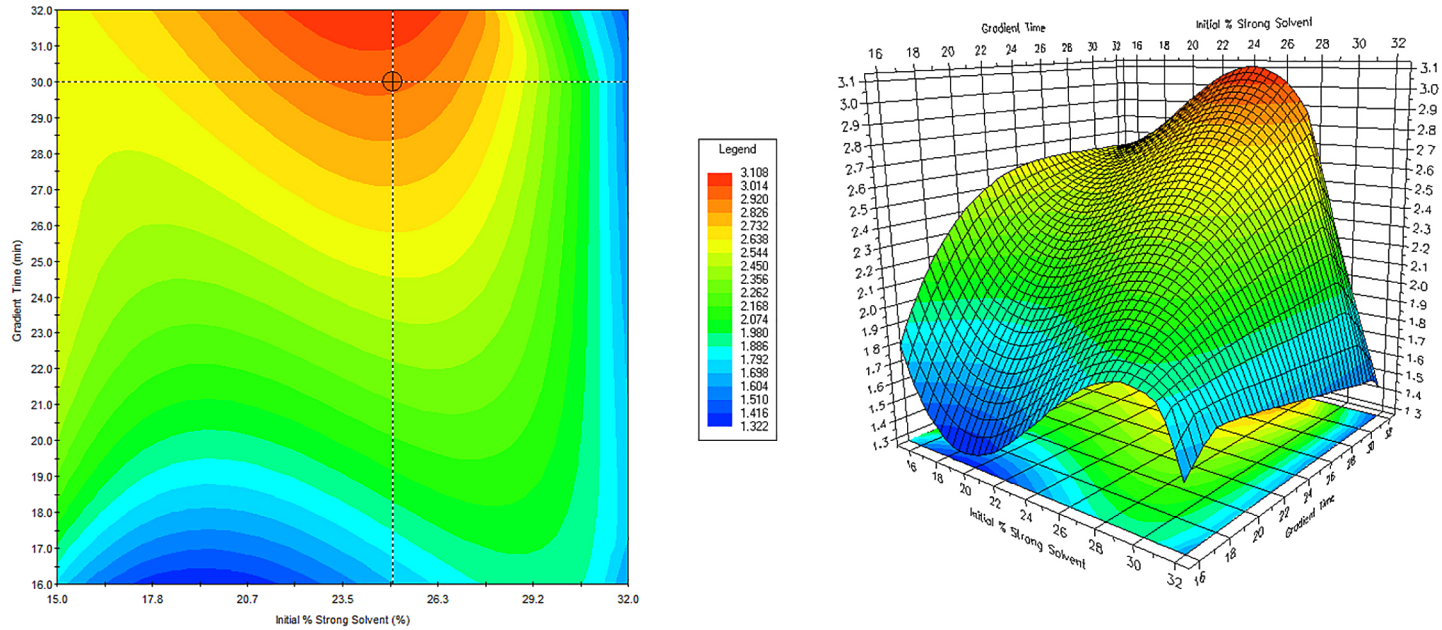


Figure 9. **Impurity separation optimization in method development with Fusion QbD**

Method development tools can also be orchestrated with eWorkflow procedures within Chromeleon CDS by our Thermo Scientific™ Vanquish™ Core HPLC systems to speed through method optimization tasks with helpful hardware scouting tools and settings.

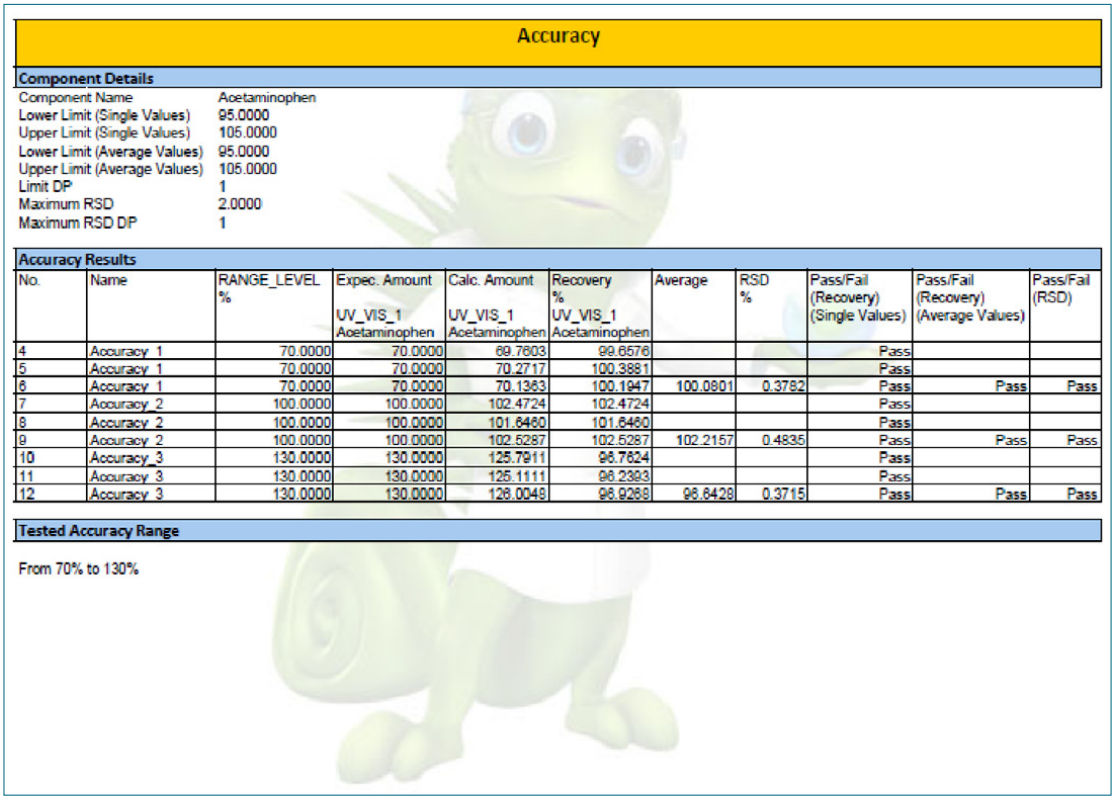
For quality scientists, results can be summarized with our Chromeleon Report Designer that looks, feels, and can be programmed with familiar equation logic like spreadsheets in Microsoft Excel™. This frees users to create validation reports without the need to learn a software specific code.

#	UV_VIS_1	Name	Type	Level	*PercentageASele	*PercentageBSele	*ColumnSele	*ColumnNam	*SSV_Pos	*BufferName	*FlowRate	*ColumnOvenTem
1	None	Column Switching	Blank		%A1	%B1	1	<enter nam..	1	<enter name of..	0.600	30
2	None	Equilibration	Unknown		%A1	%B1			1	<enter name of..	0.600	30
3	None	Blank injection	Unknown		%A1	%B1			1	<enter name of..	0.600	30
4	None	Standard, injectio..	Calibrat..		%A1	%B1			1	<enter name of..	0.600	30
5	None	Standard, injectio..	Calibrat..		%A1	%B1			1	<enter name of..	0.600	30
6	None	Equilibration	Blank		%A1	%B1			2	<enter name of..	0.600	30
7	None	Blank injection	Unknown		%A1	%B1			2	<enter name of..	0.600	30
8	None	Standard, injection..	Calibrat..		%A1	%B1			2	<enter name of..	0.600	30
9	None	Standard, injection..	Calibrat..		%A1	%B1			2	<enter name of..	0.600	30
10	None	Equilibration	Blank		%A1	%B1			3	<enter name of..	0.600	30
11	None	Blank injection	Unknown		%A1	%B1			3	<enter name of..	0.600	30
12	None	Standard, injection..	Calibrat..		%A1	%B1			3	<enter name of..	0.600	30
13	None	Standard, injection..	Calibrat..		%A1	%B1			3	<enter name of..	0.600	30
14	None	Equilibration	Blank		%A1	%B1			4	<enter name of..	0.600	30
15	None	Blank injection	Unknown		%A1	%B1			4	<enter name of..	0.600	30
16	None	Standard, injectio..	Calibrat..		%A1	%B1			4	<enter name of..	0.600	30
17	None	Standard, injectio..	Calibrat..		%A1	%B1			4	<enter name of..	0.600	30

Figure 10. Method scouting for Thermo Scientific™ Vanquish™ Horizon™ eWorkflow procedure

Extension packs for Chromeleon CDS are offered that cover the ICH Q2 method validation test matrix and include eWorkflow procedures, injection lists, processing methods, and report templates with demo data to help you get started.

Data can also be flexibly exported in .CSV to support use of common statistical analysis tools already available in some departments such as JMP® or even in Allotrope™ data format for connection to summary software beyond.



Accuracy

Component Details

Component Name	Acetaminophen
Lower Limit (Single Values)	95.0000
Upper Limit (Single Values)	105.0000
Lower Limit (Average Values)	95.0000
Upper Limit (Average Values)	105.0000
Limit DP	1
Maximum RSD	2.0000
Maximum RSD DP	1

Accuracy Results

No.	Name	RANGE_LEVEL %	Expec. Amount UV_VIS_1 Acetaminophen	Calc. Amount UV_VIS_1 Acetaminophen	Recovery % UV_VIS_1 Acetaminophen	Average	RSD %	Pass/Fail (Recovery) (Single Values)	Pass/Fail (Recovery) (Average Values)	Pass/Fail (RSD)
4	Accuracy_1	70.0000	70.0000	69.7603	99.6576			Pass		
5	Accuracy_1	70.0000	70.0000	70.2717	100.3881			Pass		
6	Accuracy_1	70.0000	70.0000	70.1363	100.1947	100.0801	0.3782	Pass	Pass	Pass
7	Accuracy_2	100.0000	100.0000	102.4724	102.4724			Pass		
8	Accuracy_2	100.0000	100.0000	101.6460	101.6460			Pass		
9	Accuracy_2	100.0000	100.0000	102.5287	102.5287	102.2157	0.4835	Pass	Pass	Pass
10	Accuracy_3	130.0000	130.0000	125.7911	96.7624			Pass		
11	Accuracy_3	130.0000	130.0000	125.1111	96.2393			Pass		
12	Accuracy_3	130.0000	130.0000	126.0048	96.9268	96.6428	0.3715	Pass	Pass	Pass

Tested Accuracy Range

From 70% to 130%

Figure 11. Method accuracy report

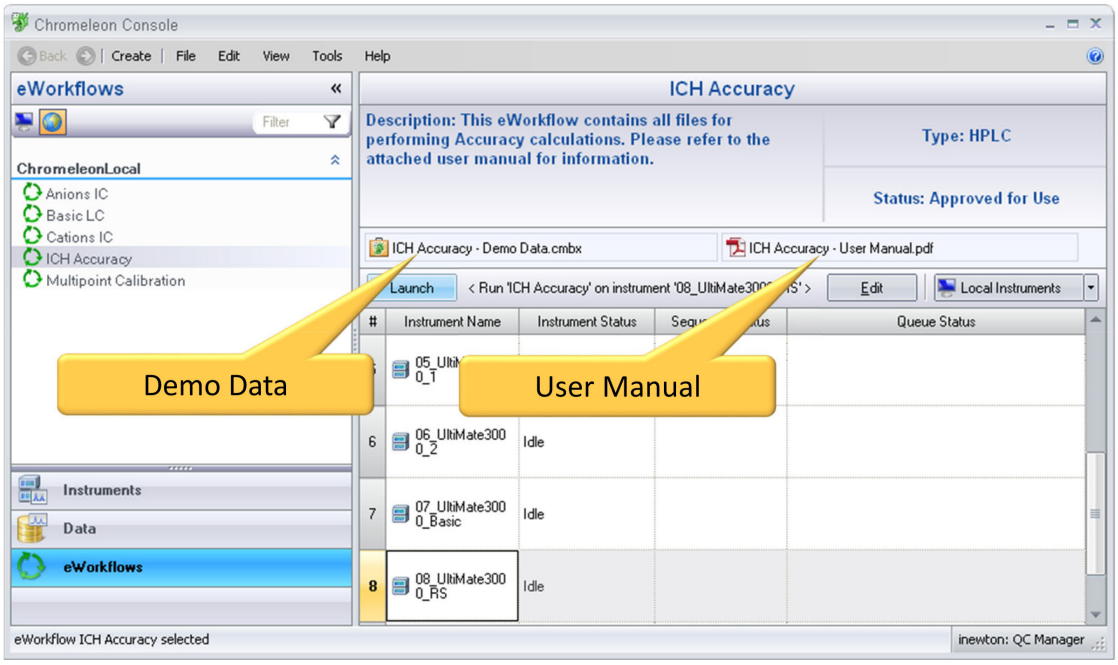


Figure 12. Example eWorkflow procedure in Chromeleon CDS Extension Pack for ICH accuracy

Quality in every step

Regardless of the department, we at Thermo Fisher support quality initiatives and understand that for you, compliance is more than buying specific products. For you, compliance is your system of procedures and your ability to adhere to your high level of quality standards. To enable that goal, you need supportive and comprehensive tools that encourage users not to "work around" their frustrations.

Let us help you incorporate quality into your every step to develop, produce, and provide life changing therapies, detect and eliminate disease, and treat a whole world of patients that rely on quality systems to help them.

Glossary	
ANOVA	Analysis of Variance
ATP	Analytical Target Profile
CQA	Critical Quality Attributes
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Initial drug application
MAM	Multi-Attribute Method
QbD	Quality by Design
QC	Quality Control
PQA	Product Quality Attributes

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1. ICH. Final Concept Paper ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation. [November 2018]. https://database.ich.org/sites/default/files/Q2R2-Q14_EWG_Concept_Paper.pdf. Accessed May 22, 2023.
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4. ICH. Analytical Procedure Development Q14 Draft. [March 2022]. https://database.ich.org/sites/default/files/ICH_Q14_Document_Step2_Guideline_2022_0324.pdf Accessed May 22, 2023.
5. ICH. ICH Q2(R2) / Q14 EWG Work Plan. [July 2022]. https://database.ich.org/sites/default/files/Q2%28R2%29-Q14_EWG_WorkPlan_2022_0916.pdf. Accessed May 22, 2023.

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