Introduction to New General Chapter <1220> Analytical Procedure Life Cycle

Amanda Guiraldelli, Ph.D.,
Scientific Affairs Manager
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Analytical Procedure Life Cycle

Concept

- “framework for analytical procedures that **holistically incorporates all the events** that take place over the procedure life cycle that are designed to demonstrate that a procedure is, and remains, **fit for the intended purpose**” USP GC <1220>

Analytical Quality by Design (AQbD)

AQbD Concept

QbD concept:
"A systematic approach to development that begins with predefined objectives and emphasizes product and **process understanding** and **process control**, based on **sound science and quality risk management**"
ICH Guideline Q8: Pharmaceutical Development

AQbD Concept:
"Systematic approach that begins with predefined objectives (ATP) and emphasizes **analytical procedure understanding** and control based on **sound science and quality risk management**."

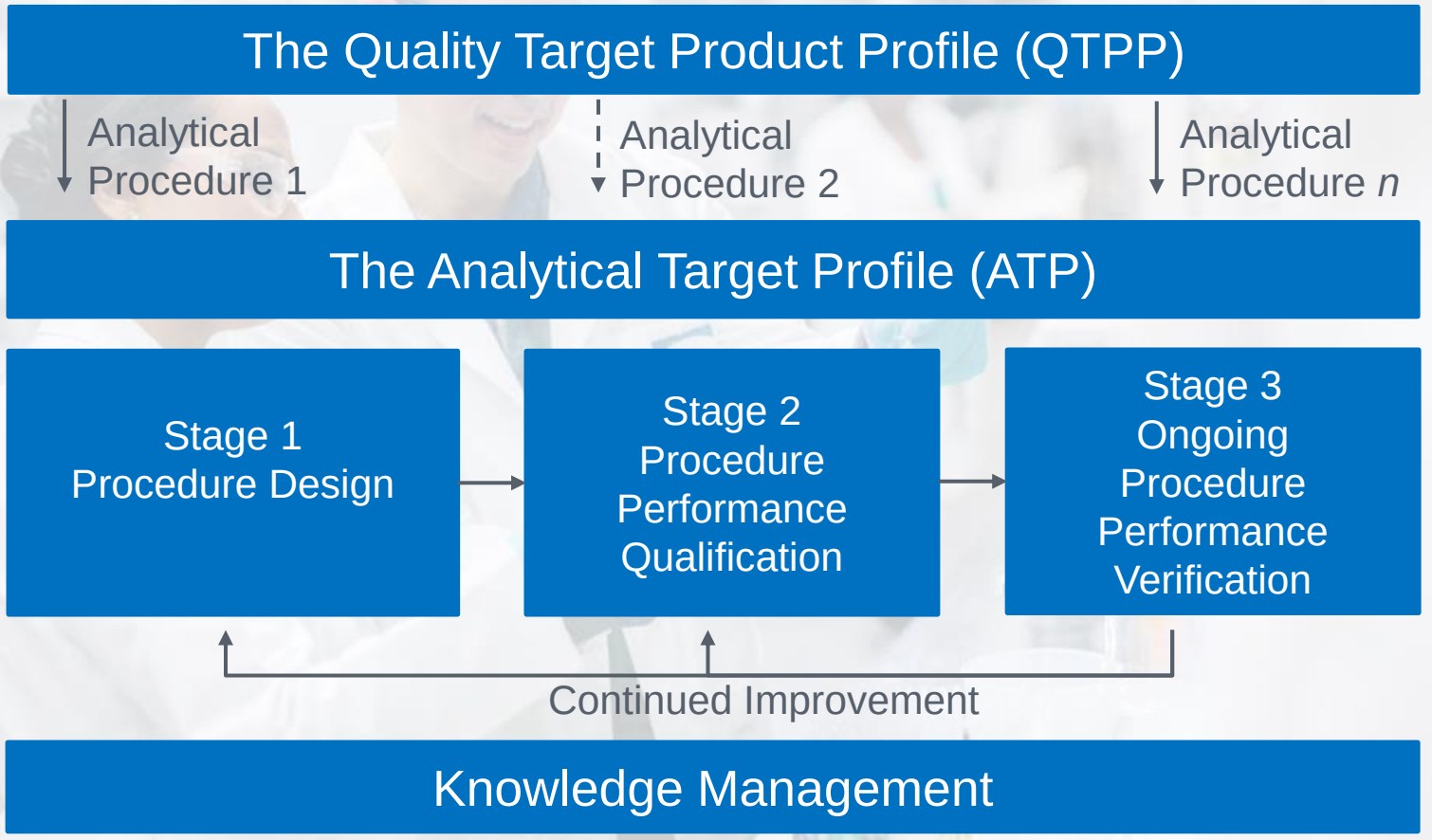
USP GC <1220>

"The procedure life cycle approach emphasizes the importance of **sound scientific approaches** and **quality risk management** for the development, control, establishment, and use of analytical procedures."

Analytical Procedure Life Cycle

Framework

- Key enablers:
  - Quality Risk Management (QRM)
  - Sound scientific approaches



USP GC <1220> Analytical Procedure Life Cycle

ICH guidelines outline QbD concepts
2004: Q8 Pharmaceutical development
2005: Q9 Quality risk managment
2007: Q10 Pharmaceutical quality system
2012: Q11 Development and Manufacture of Drug Substance

ICH Q12
Pharmaceutical Product Lifecycle Management

Q14/Q2(R2) Working Group

Public Consultation
ICH Q14 draft guideline
Procedure Development

ICH Q2(R2) draft guideline
Procedure Validation

2004-2012

1 — 2013

Stimuli Article
PF 39(5) Lifecycle Management of Analytical Procedures

2 — 2016

Stimuli Article
PF 42(2) Fitness for Use
PF 42(5) ATP
PF 42(5) Analytical control strategy

2014-2017

2018

2020

3 — 1st Sep 2020

USP GC <1220> published in PF46(5)

BP/MHRA Consultation response **application of AQbD concepts** to pharmacopoeial standards

2021

4 — 1st Dec 2021

USP GC <1220> became online in USP-NF

BP
Supplementary chapter proposed

March 2022

5 — 1st May 2022

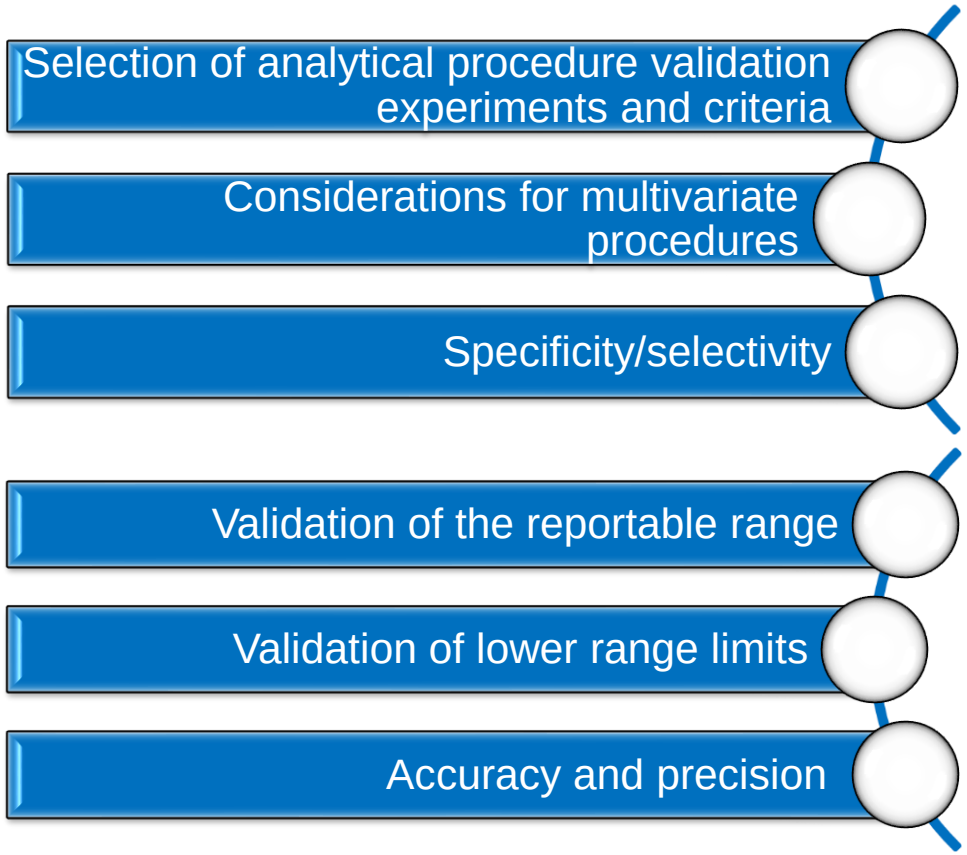
USP GC <1220> become official

USP GC <1220> & ICH Q14/Q2(R2)

Topics Covered in Q14 Procedure Development

GC <1220>: Stage 1 and 3

Topics Covered in Q2(R2) Procedure Validation



GC <1220>: One step of Stage 2

Quality Paradigm Shifts in an Evolving Global Environment

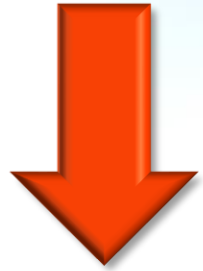
Compliance driven approach

Integrated Risk-based Approaches

Quality by Testing and Inspection

Quality by Design

Static / Reactive



Proactive Continuous Improvement

"The shift toward QbD and a culture of quality is already underway, and new compendial and regulatory approaches are needed that can support and help advance this transformation."

Understanding Quality Paradigm Shifts in the Evolving Pharmaceutical Landscape
AAPS J (2021) 23:112 Vol(0123456789) https://doi.org/10.1208/s12248-021-00634-5

Analytical Target Profile (ATP)

Concept

- ATP is the predefined objective that stipulates the performance requirements for the analytical procedure

- It states the required quality of the results in terms of:
  - the acceptable total error in the measurement **or**
  - the maximum measurement uncertainty

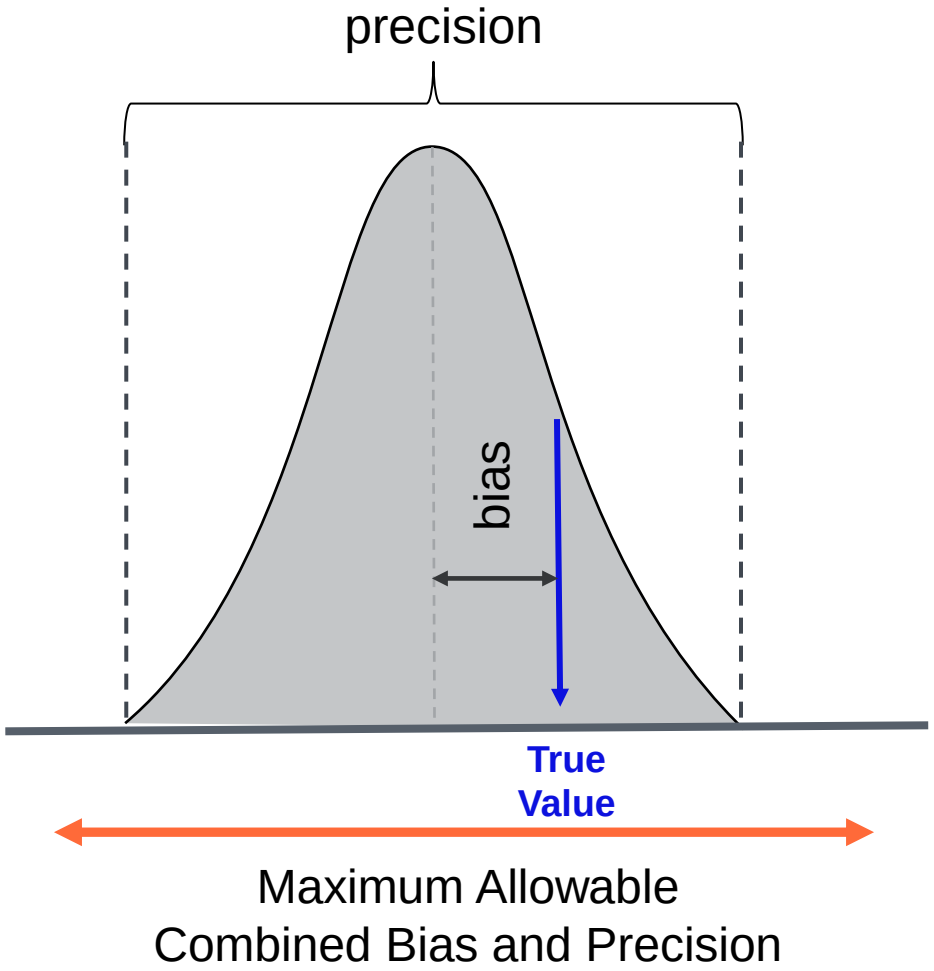
- It should include:
  - Definition of the analyte
  - Description of the analytical matrix
  - Range
  - The precision and accuracy (bias) acceptable for the reportable value

Analytical Target Profile (ATP)

Measured Value and Source of Errors

Procedure performance characteristics focus on **two** primary aspects of the measurement:

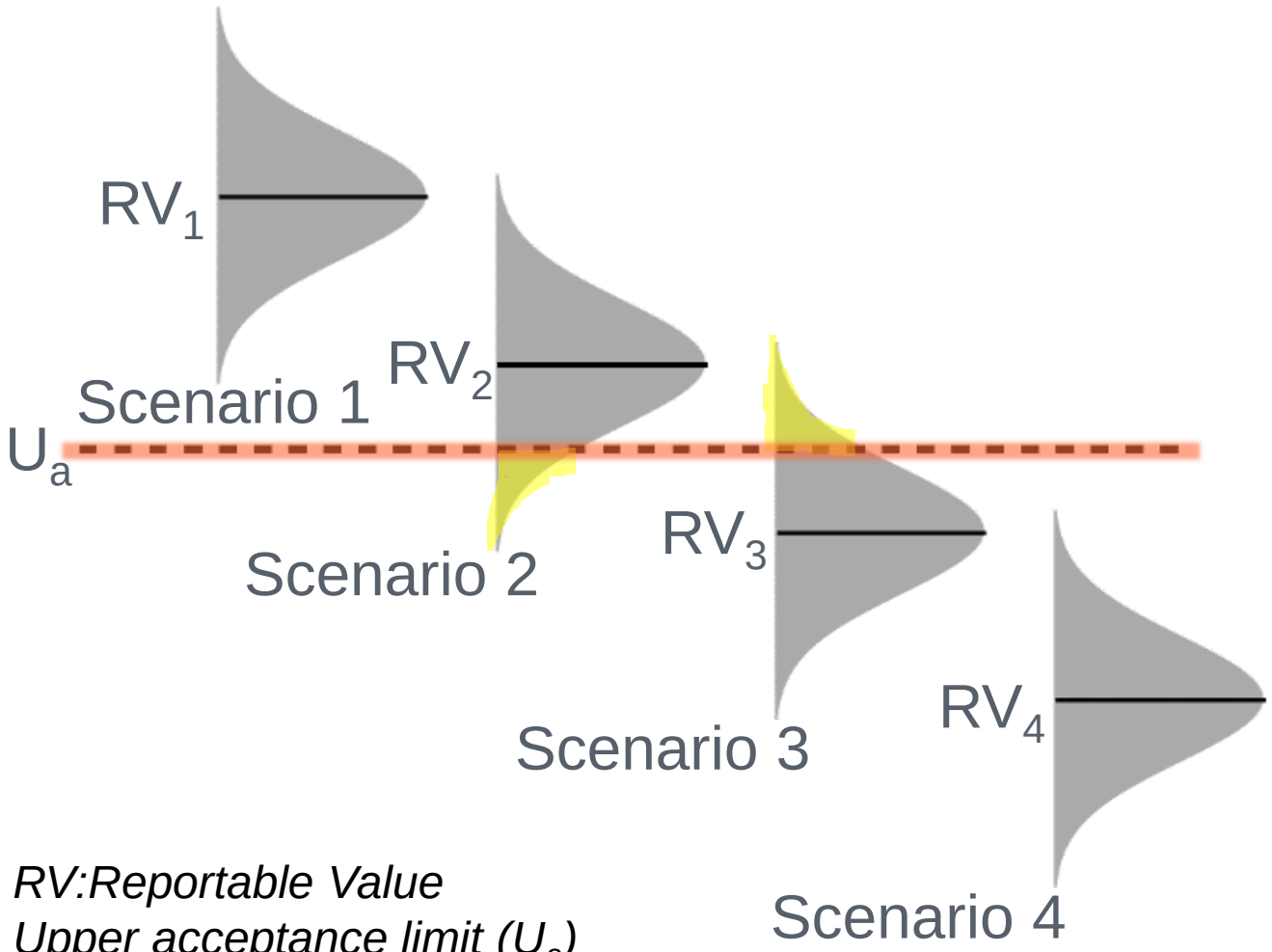
1. **Bias:** how close the measurement is, on average, to the true value that is being measured (systematic error)
2. **Precision:** how much the measurement will vary randomly under routine use; (random error)



USP GC <1220> Analytical Procedure Life Cycle

Analytical Target Profile (ATP)

Specifications and decision rules



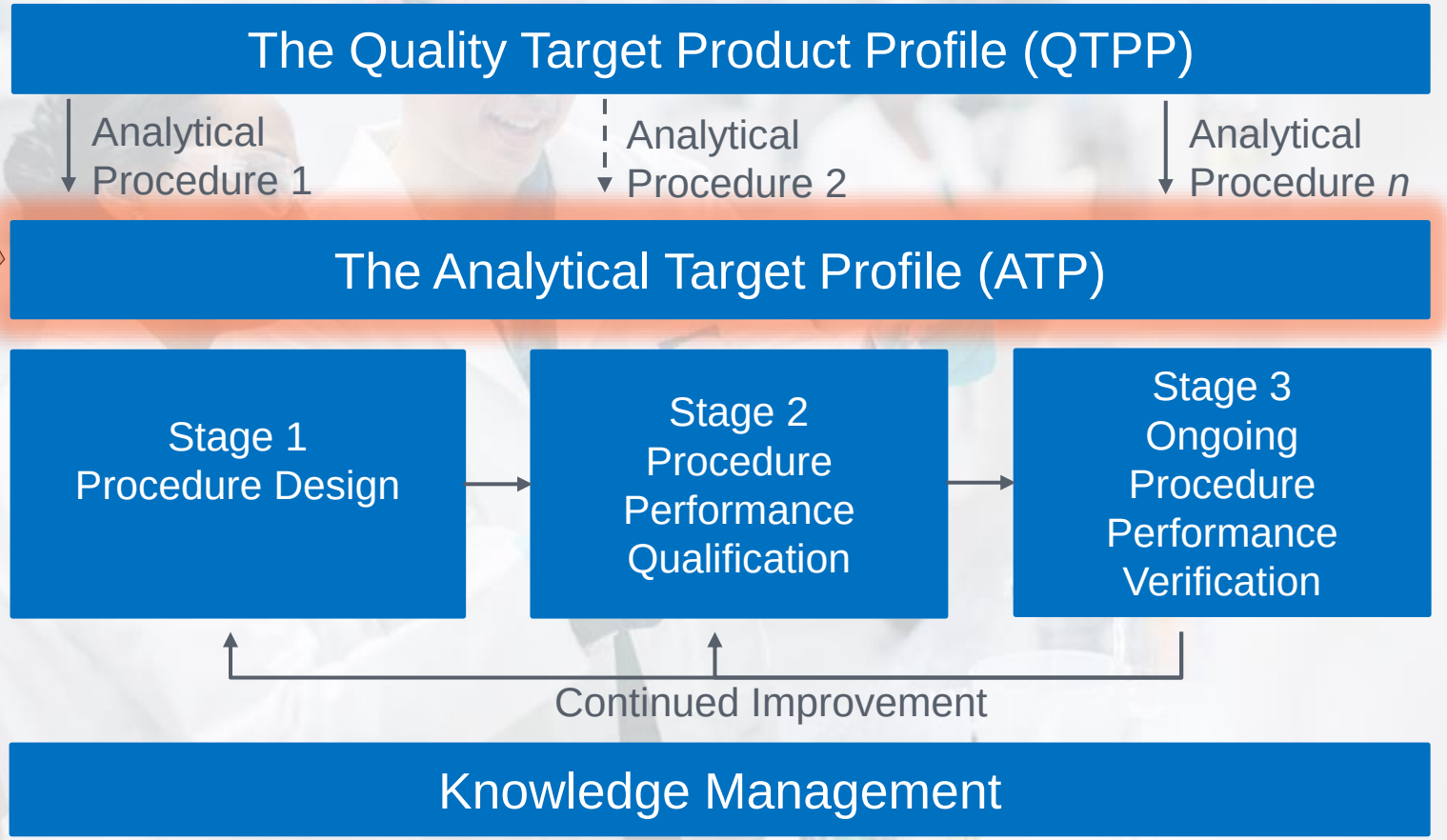
RV:Reportable Value
Upper acceptance limit (U_a)

- In scenarios 1 and 4 the decision is clear.
- In scenarios 2 and 3, it is less clear that the quality attribute is actually above or below the acceptance criteria
- There is a significant probability that the true value of the quality attribute is actually within (Scenario 2) or outside (Scenario 3) the acceptance range.

Case Study: ATP

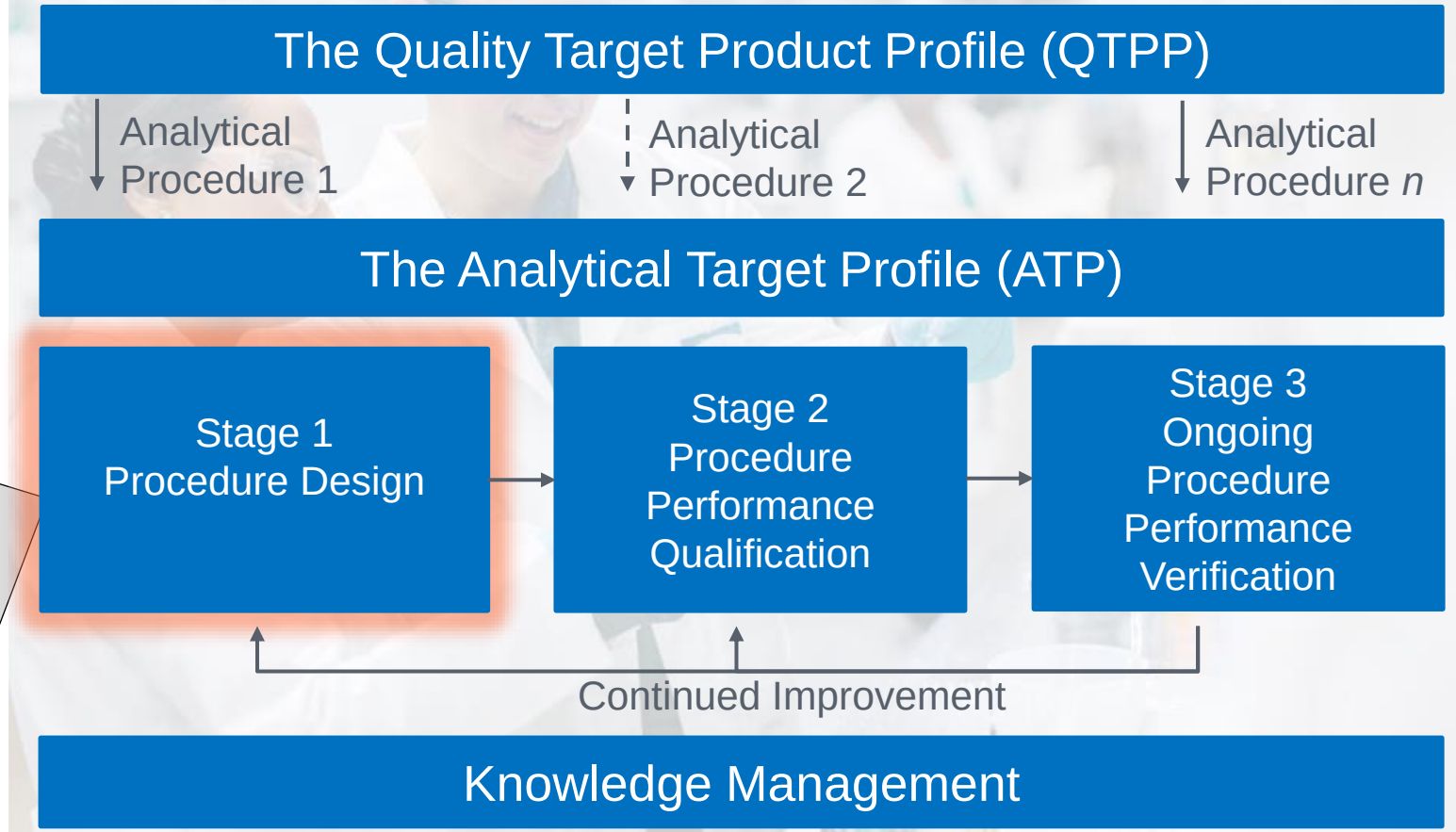
ATP

The procedure must be able to accurately quantify **degradation products** in a range from 0.1% to 1.0% in **Venlafaxine Extended-Release Tablets** in the presence of interfering compounds and API process impurities with an accuracy within 100.0% ± 10.0% and a precision ≤ 10.0% for the reportable value



Case Study: Stage 1

- Preparation for Procedure Design – Initial Risk Assessment
- Procedure Development: Experimentation
  - Screening and Optimization Studies DOE
  - Predictive Modeling
- Robustness and Method Operable Design Region (MODR)
- Replication Strategy
- Analytical Control Strategy (ACS)



Quality Risk Management (QRM)

Concept

- **QRM:** Systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the lifecycle of the analytical procedure
- Quality risk management supports a scientific and practical approach to decision making (ICH Q9)
- **Risk Management Methodologies**
  - flowchart, process mapping, cause and effect diagrams, failure mode effects analysis (FMEA),failure mode effects and criticality analysis (FMECA) etc.

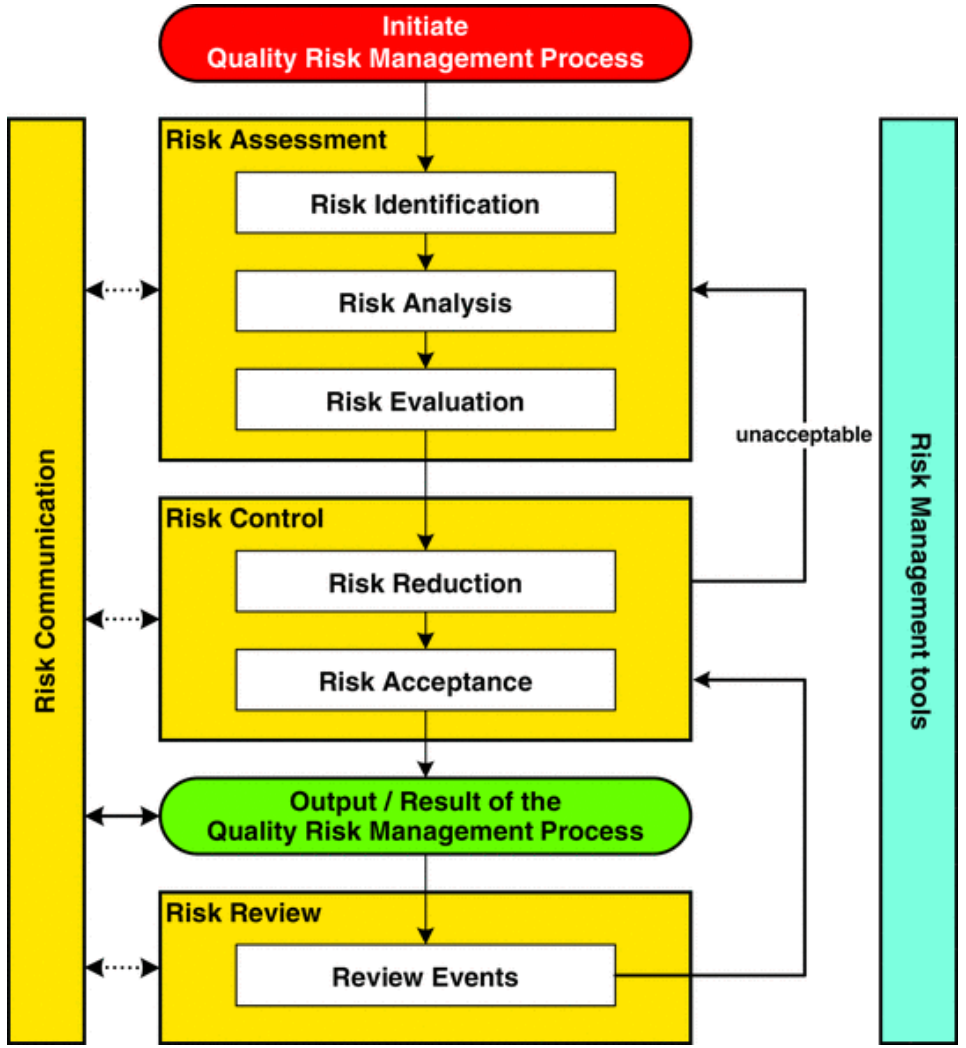


Figure 4. Overview of a typical QRM process (ICH Q9).

Case Study: Initial Risk Assessment

Assessment of sample constitution & compounds properties evaluation

Impurities	Venlafaxine HCl USP43-NF38	Venlafaxine Tablets USP43-NF38	Venlafaxine Extended-Release Tablets PF44(6)	Venlafaxine HCl Extended- Release Capsules USP43-NF38	Venlafaxine Hydrochloride EP 10.0	Venlafaxine Prolonged-release Tablets BP
Desvenlafaxine phenol impurity						
Venlafaxine EP Imp A	X	X	X		X	
Venlafaxine EP Imp B					X	
Venlafaxine EP Imp C	X				X	
Venlafaxine EP Imp D	X	X		X	X	X
Venlafaxine EP Imp E					X	
Venlafaxine EP Imp F*			X		X	X
Venlafaxine EP Imp G	X		X		X	
Venlafaxine EP Imp H					X	
Venlafaxine Acetamide			X			
*N-oxide Venlafaxine**						
Desvenlafaxine*						

Initial risk assessment: Prior knowledge on potential presence of impurities, excipients, degradation products

*Potential degradation products (API) – evaluated during pilot stress testing (API) LC-UV-MS/MS

Technology Assessment: RPLC-UV

Case Study: Screening Study

Procedure Performance - Knowledge Acquisition

Critical Procedure Parameters

INPUTS (x)

Procedure Variables
Material properties

Screening 1. Acidic pH range
Screening 2. Basic pH range

(x_1) Stationary Phase
(x_2) Organic solvent composition
(x_3) pH of mobile phase
(x_4) Gradient Slope

PROCESS/ PROCEDURE

Design of Experiments (DOE)
Predictive Modeling

$$\hat{y} = f(x)$$

Critical Quality Attributes

OUTPUT (y)

Observable response variables

(y_1) Number of peaks Rs > 1.5
(y_2) Total number of peaks
(y_3) Number of peaks Rs > 2.0
...

Case Study: Optimization Study

Optimization Studies using DOE

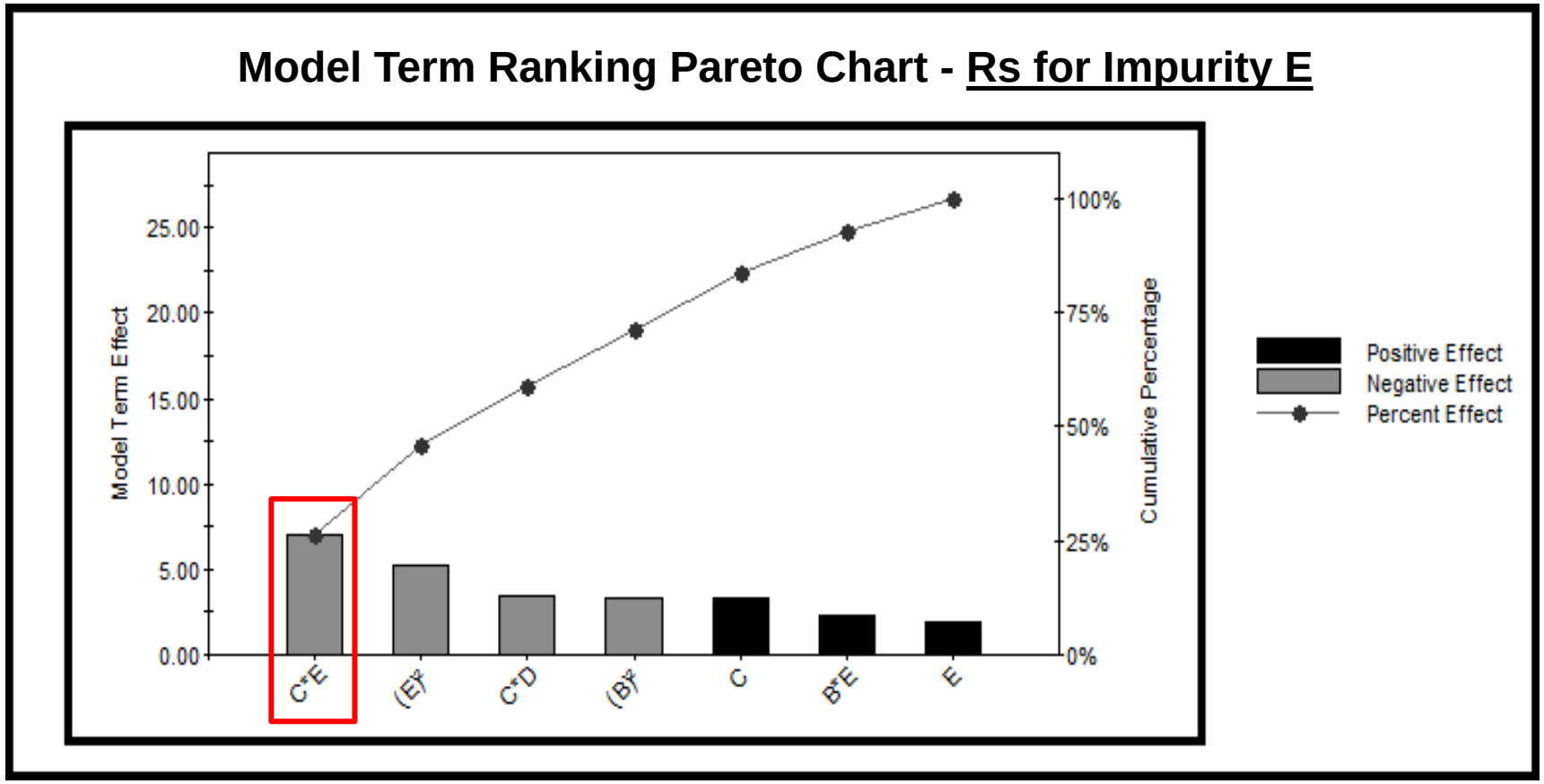
Analytical Factor or Variable	Optimization 1 (UHPLC) Optimal Design	Optimization 2 (UHPLC) Optimal Design	Optimization 3 (HPLC) CCD
	Factors Levels	Factors Levels	Factors Levels
x_1: pH value of mobile phase	8.8, 9.2, 9.6, 10.0, 10.4	9.6, 9.9, 10.2, 10.5	9.8, 10.1, 10.4
x_2: Solution B: % of ACN in MeOH	0 – 75%	60 – 75%	60 - 80%
x_3: Gradient slope	13 – 20 min	15 – 21 min	26 – 38 min
x_4: Column temperature	25 – 40°C	20 – 40°C	25 – 40°C
x_5: Flow rate	0.4 – 0.6 mL/min	0.4 – 0.6 mL/min	0.4 – 0.5 mL/min

Narrowing down the factors range

Case Study: Optimization Study

Risk Identification

- Evaluation of variables effects that have the most impact on procedure performance



Several 2-factors interaction and higher-order interaction effects significantly impact performance.

Study Variable	Code Name
Pump Flow Rate	A
Gradient Time	B
ACN	C
Oven Temperature	D
pH	E

Case Study: Optimization Study

Risk Identification

- Evaluation of variables effects that have the most impact on procedure performance

Analytical Factors	RISK HEAT MAP Identified Potential Risk for Critical Pairs					
	Imp A/C (Rs: 0 – 6)		API/Imp. E (Rs: 1.9 –12)		Imp F/H (Rs: 1.6 –10)	
	S	E	S	E	S	E
E - pH value of mobile phase						
C - Organic solvent: % of ACN in MeOH						
B - Gradient slope						
D - Column temperature						
A - Flow rate						

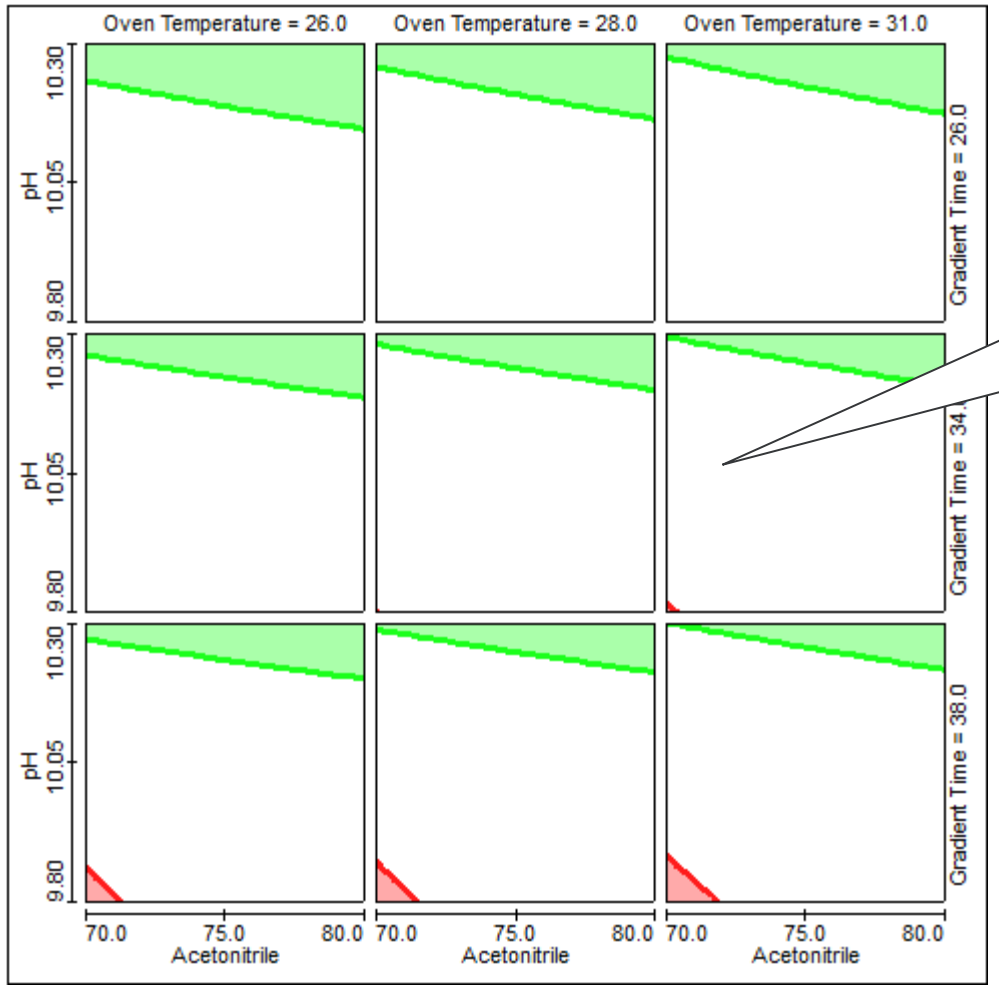
Legend:
S: Selectivity (resolution)
E: Efficiency (tailing factor)

	High risk
	Medium Risk
	Low Risk

Risk criteria:
- Rs = 3 for Imp. E & API
- Rs = 1.5 others

Case Study: Optimization Study

Knowledge Space



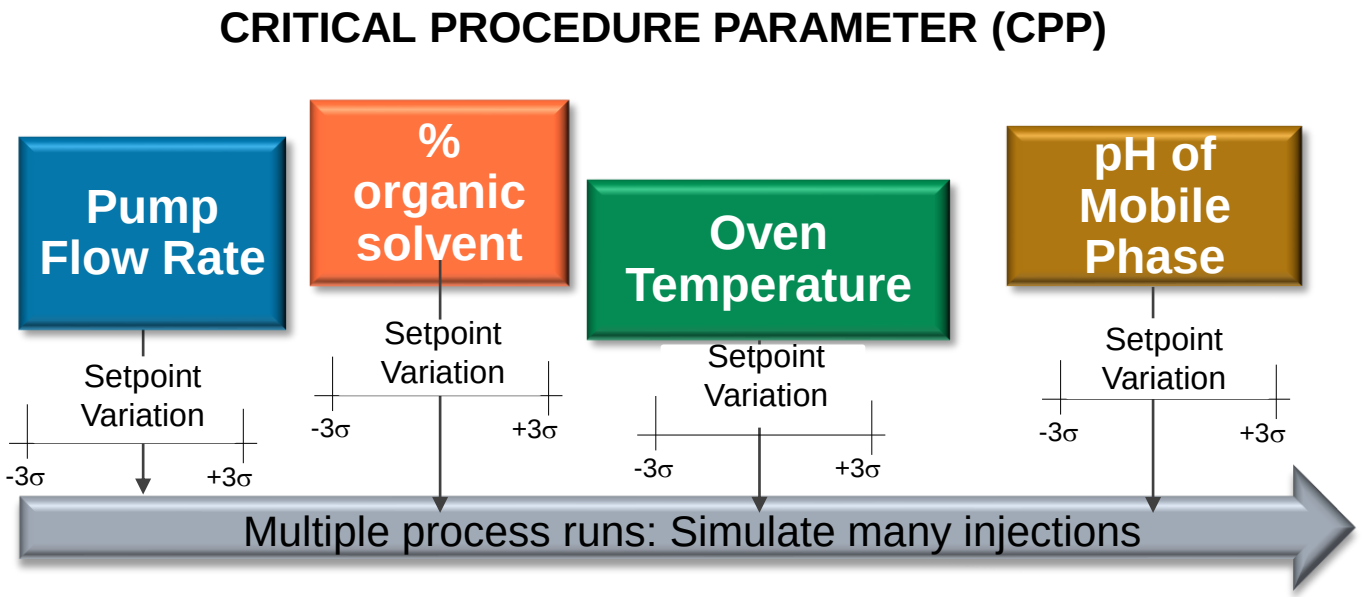
White area = acceptance criteria for all responses were met!!

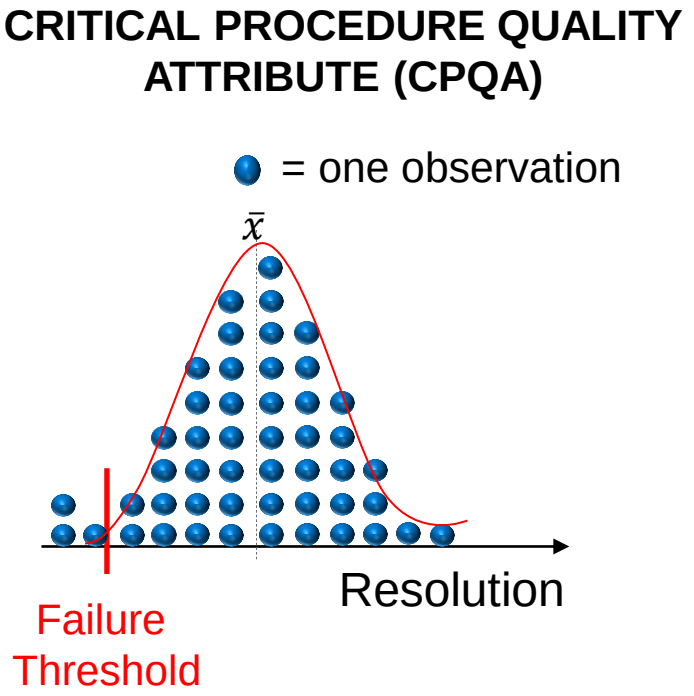
Before Robustness Study

Name	Units	Goal	Color	Lower Bound	Upper Bound
Imp A - USPResolution		Maximize	Red	1.50	
Imp E - USPResolution		Maximize	Green	4.00	

Figure. Acceptance Performance Region Graphic: Flow Rate 0.45mL/min

Case Study: Risk Assessment Robustness Study





Scheme 2: Method performance variation

Analytical Factor or Variable	Variation around the setpoint
Flow rate	± 0.05
Organic solvent: % of ACN in MeOH	± 1.0
Gradient time	± 2.0
Column temperature	± 3.0
pH value of mobile phase	± 0.15

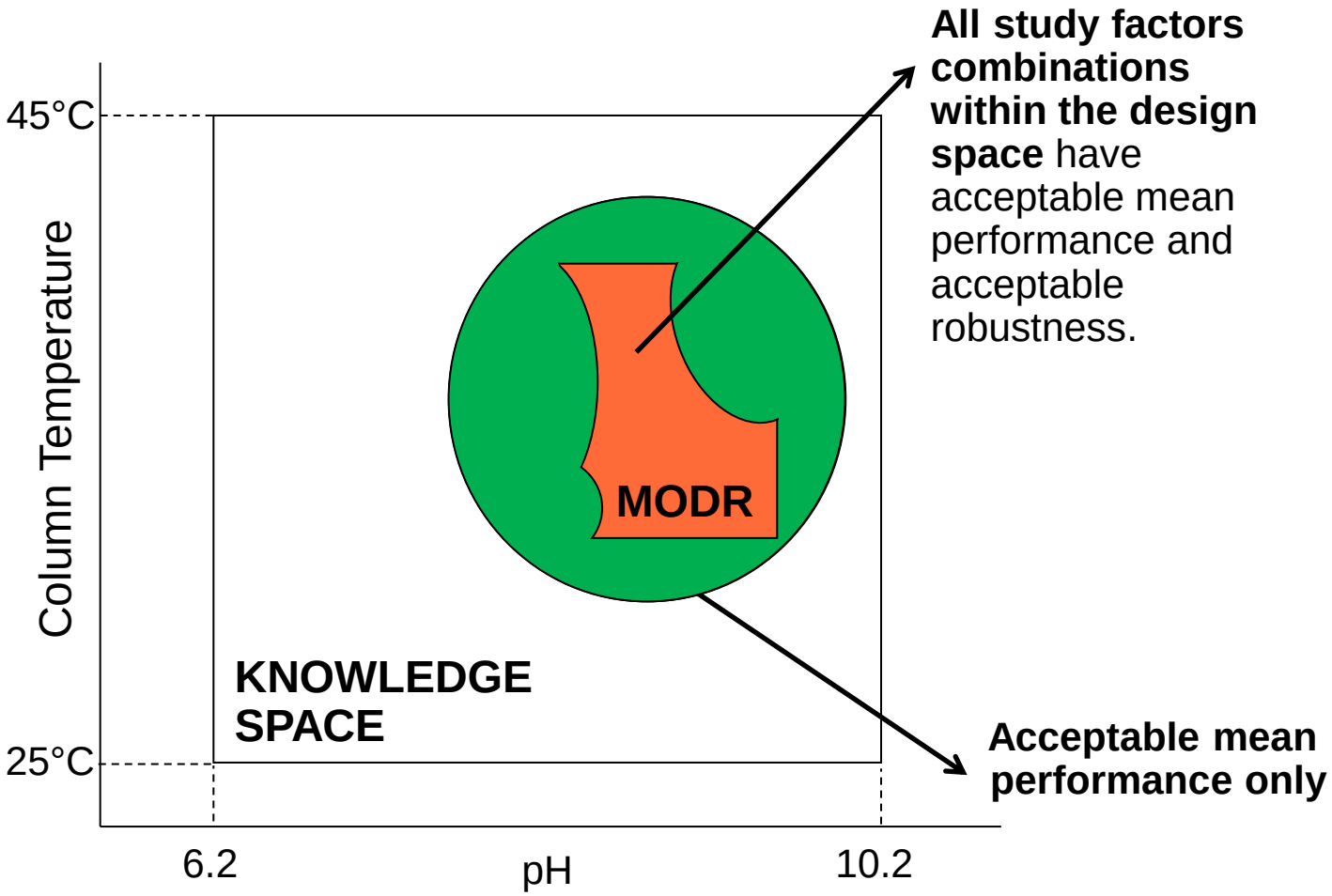
Establishing Risk Criteria

Resolution between Impurities	LSL
"Non-critical" target impurities	1.5
Impurity A/C	1.5
Venlafaxine/Impurity E	3.5

Process Capability Assessment

Method Operable Design Region (MODR)

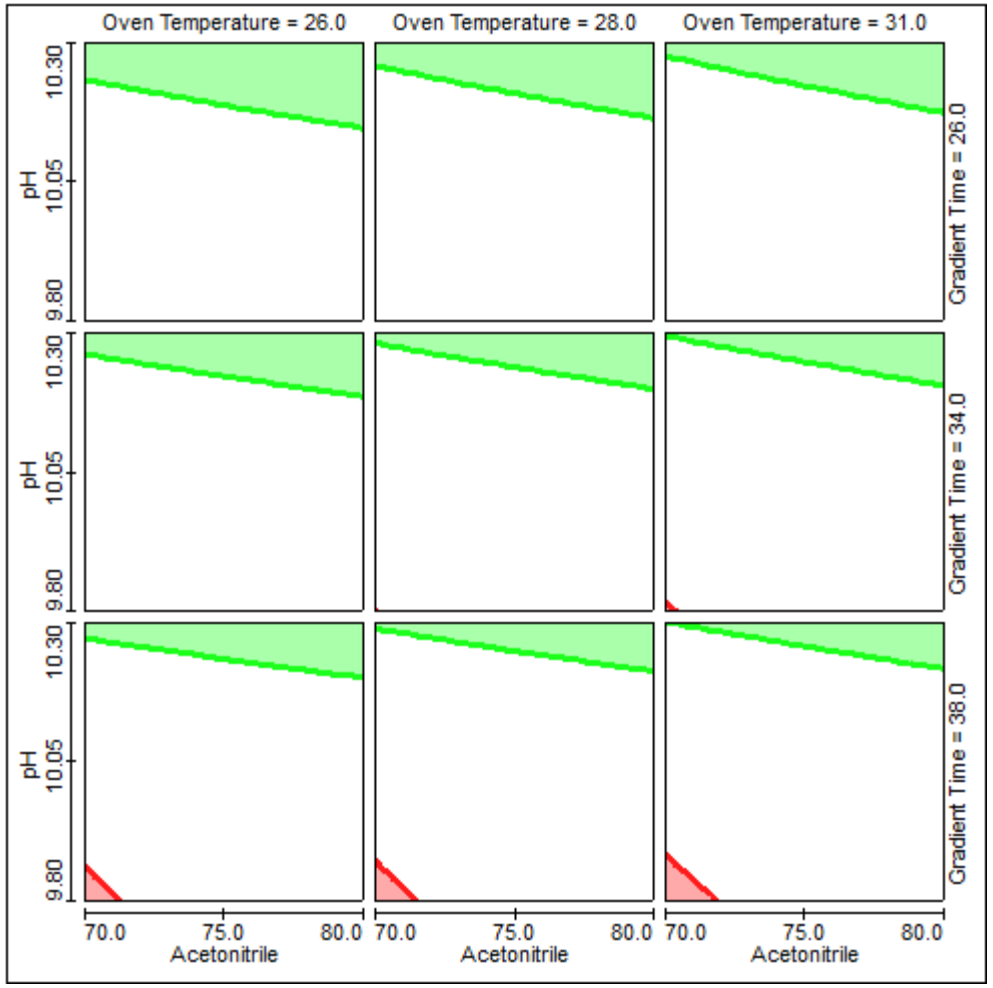
Concept



- MODR is a **multidimensional combination** and **interaction** of procedure parameters where all study factors combinations have been demonstrated to:
  - provide acceptable mean performance
  - provide acceptable robustness
  - ensure the ATP is fulfilled

- Robustness assessment plays an essential role

Case Study: MODR



Name	Units	Goal	Color	Lower Bound	Upper Bound
Imp A - USPResolution		Maximize	Red	1.50	
Imp E - USPResolution		Maximize	Green	4.00	

Figure. Acceptance Performance Region Graphic: Flow Rate 0.45mL/min

Before Robustness Study

Case Study: MODR

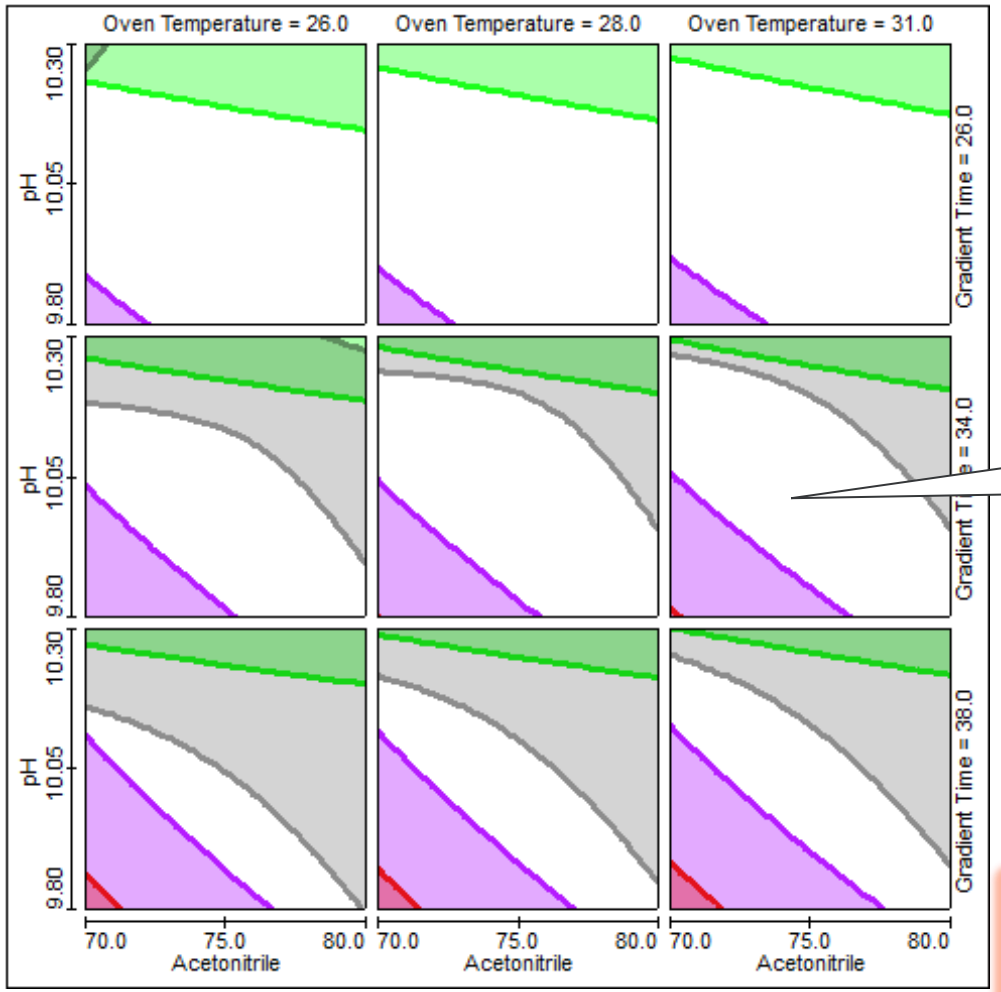


Figure. Acceptance Performance Region Graphic: Flow Rate 0.45mL/min

After Robustness Study

Narrower area with suitable acceptable performance and robustness!

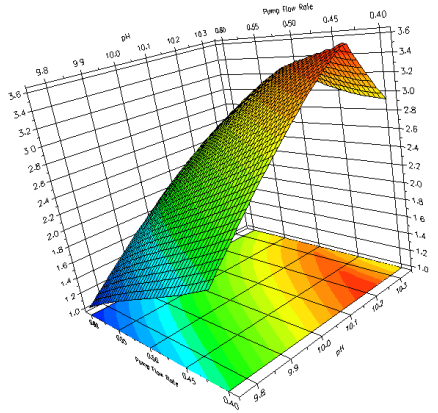
White area after ROBUSTNES STUDY = MODR

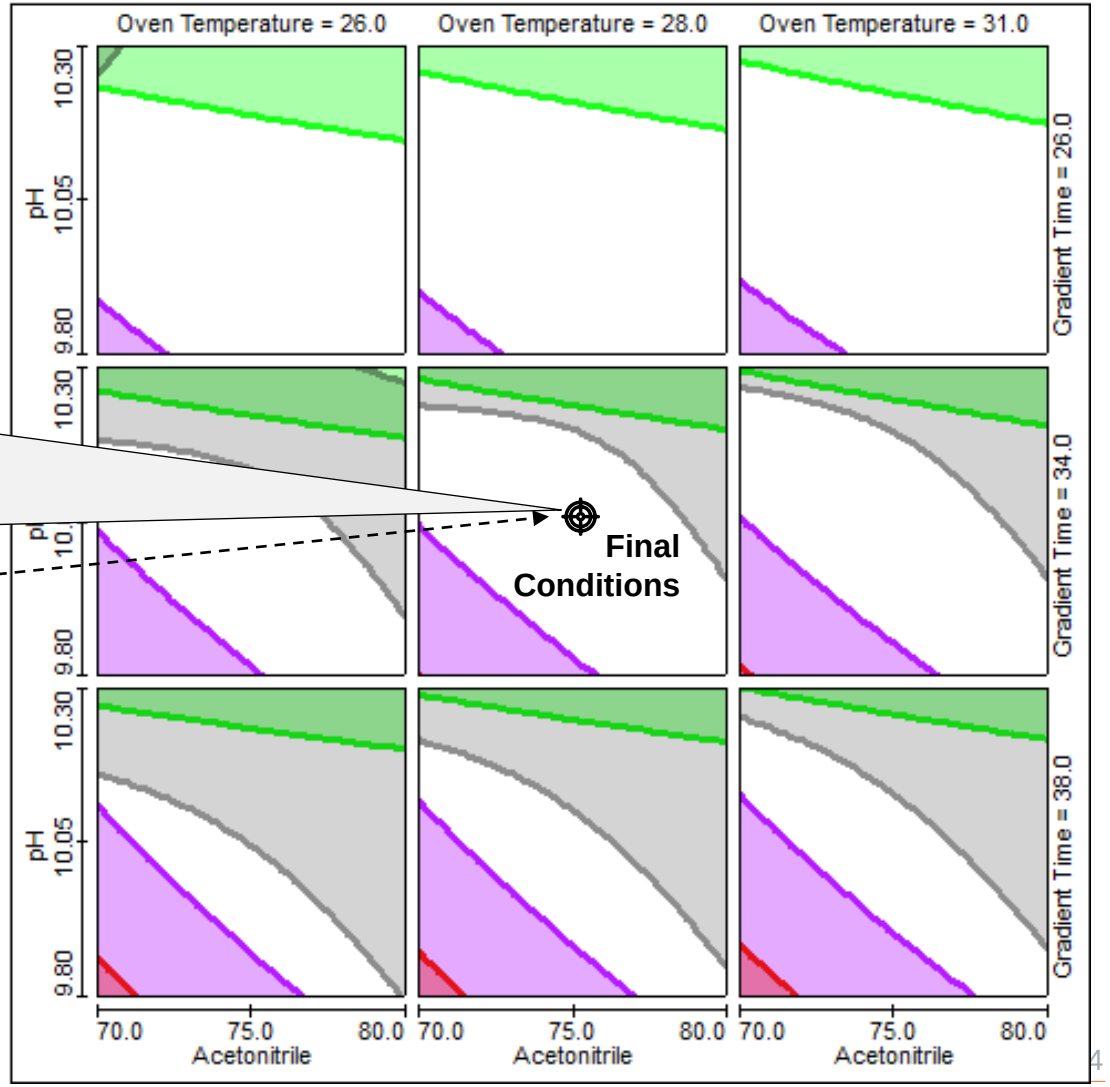
Name	Units	Goal	Color	Lower Bound	Upper Bound
Imp A - USPResolution		Maximize	Red	1.50	
Imp E - USPResolution		Maximize	Green	4.00	
Imp A - USPResolution - Cpk		Maximize	Purple	1.33	
Imp E - USPResolution - Cpk		Maximize	Gray	1.33	

Case Study: Optimization Study

Change of analytical conditions within the MODR

Analytical Factor or Variable	Robustness (around set point)
pH	± 0.15
% of ACN	± 1
Gradient slope	± 2
Col. temp.	± 3
Flow rate	± 0.15





Final (Target) Conditions
Flow rate: 0.45mL/min
Temperature: 28°C
Gradient slope: 34 min
pH: 10.1
Sol B: 75% ACN

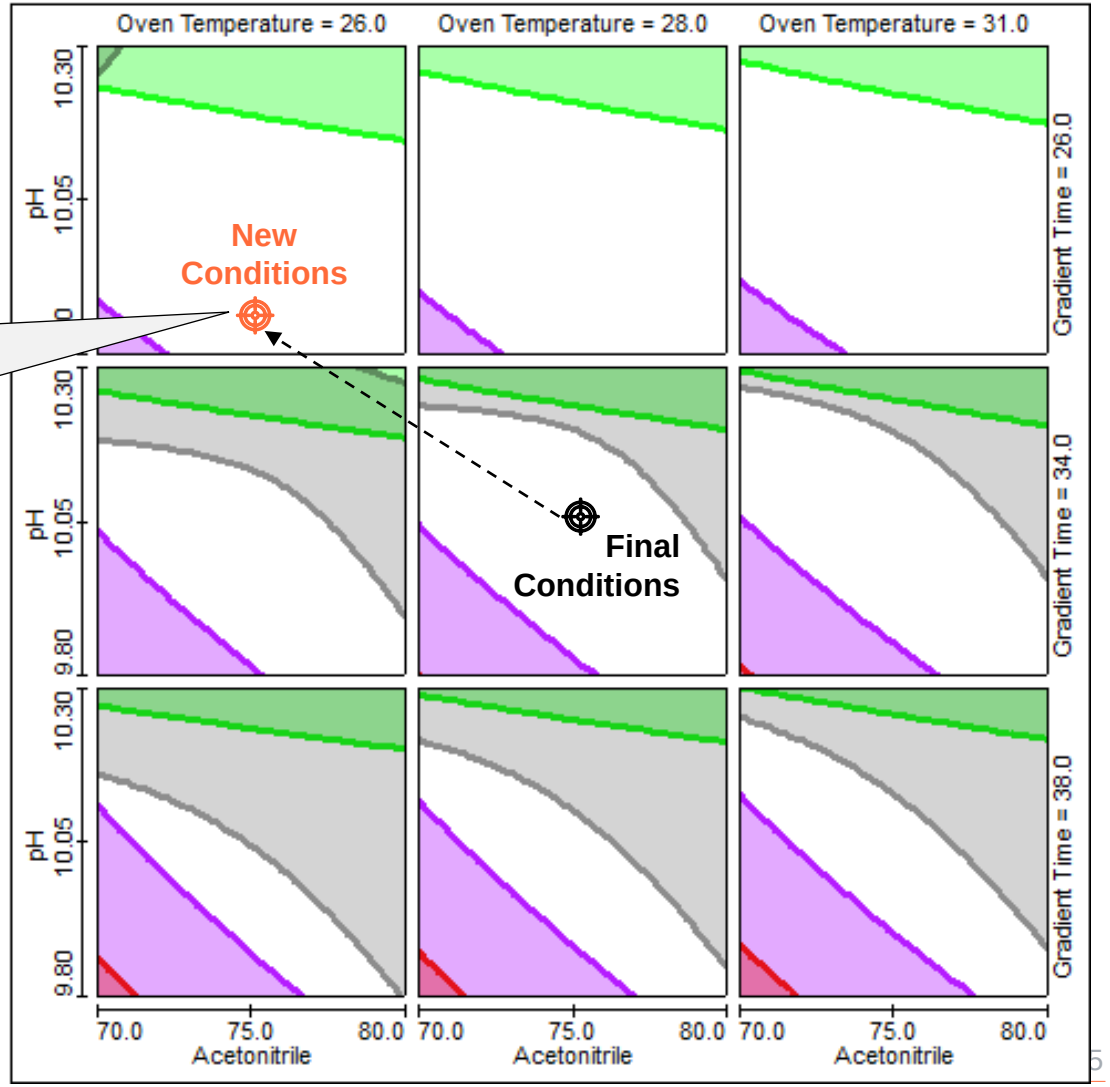
Scientific Projects: Case Study

Change of analytical conditions within the MODR

Analytical Factor or Variable	Robustness (around set point)
pH	± 0.15
% of ACN	± 1
Gradient slope	± 2
Col. temp.	± 3
Flow rate	± 0.15

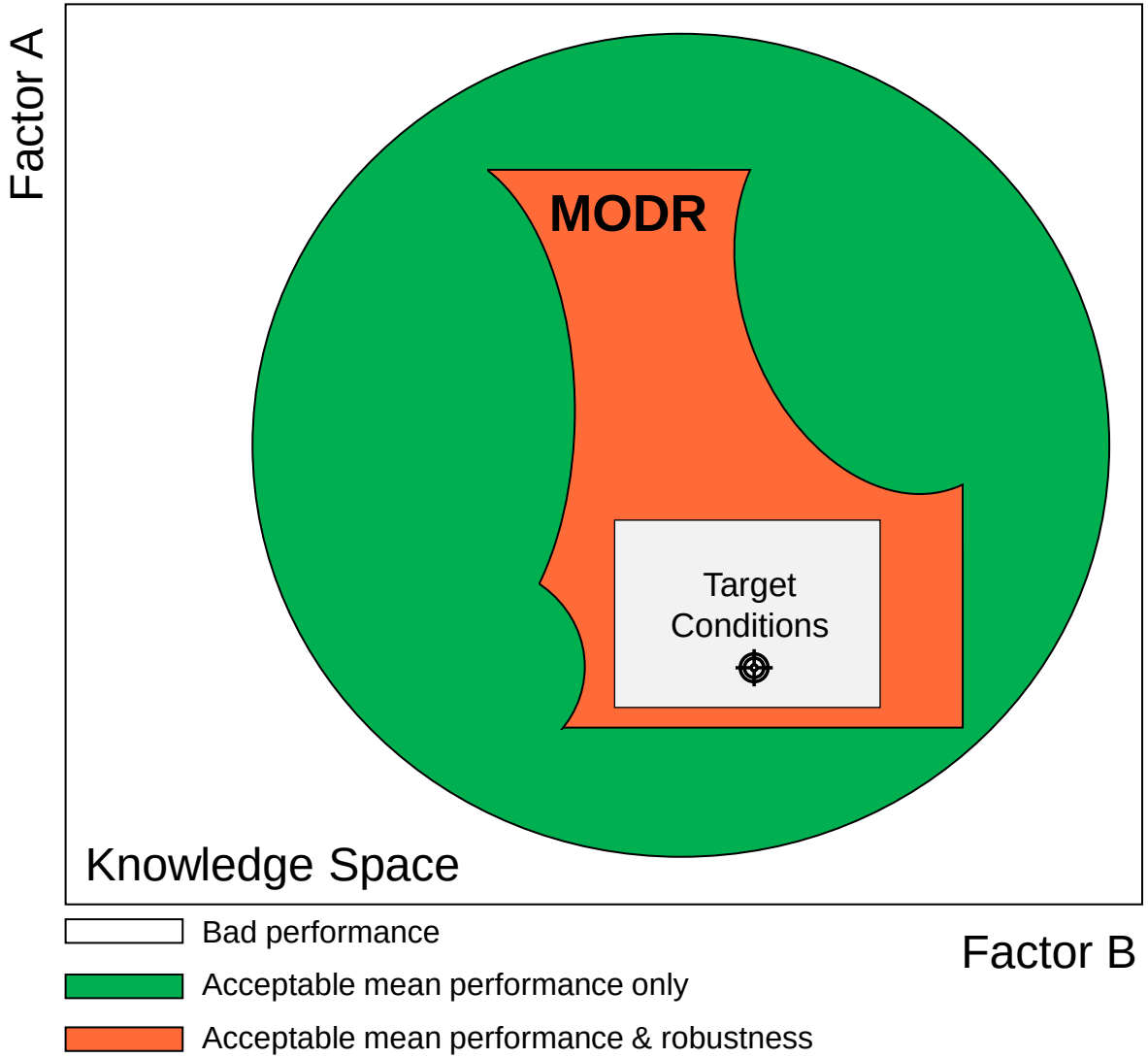
New Conditions

Flow rate: 0.45mL/min
Temperature: **26°C**
Gradient slope**: 26min**
pH: 9.8
Sol B: 75% ACN



Method Operable Design Region (MODR)

Analytical Conditions Change Management



- Change of analytical conditions
  - **within** the range previously qualified may **not** require additional experimentation before implementation.
  - **outside** the set point or range that was previously qualified would require a risk assessment.

USP GC <1220> Analytical Procedure Life Cycle

Scientific Projects: Case Study

Validation of a portion of the MODR

Chromatographic system

Column: 2.6 um x 3.0 mm × 15 cm; packing L1 (Kinetex EVO C18)
Target conditions and validated operating range:
- Gradient time: 34 min
- Flow rate: 0.45mL/min

Chromatographic Conditions	Target Value	Lower Value	Upper Value
pH	10	9.9	10.1
Solvent B - %ACN in MeOH	75	74	76
Column temperature (°C)	28	26	31

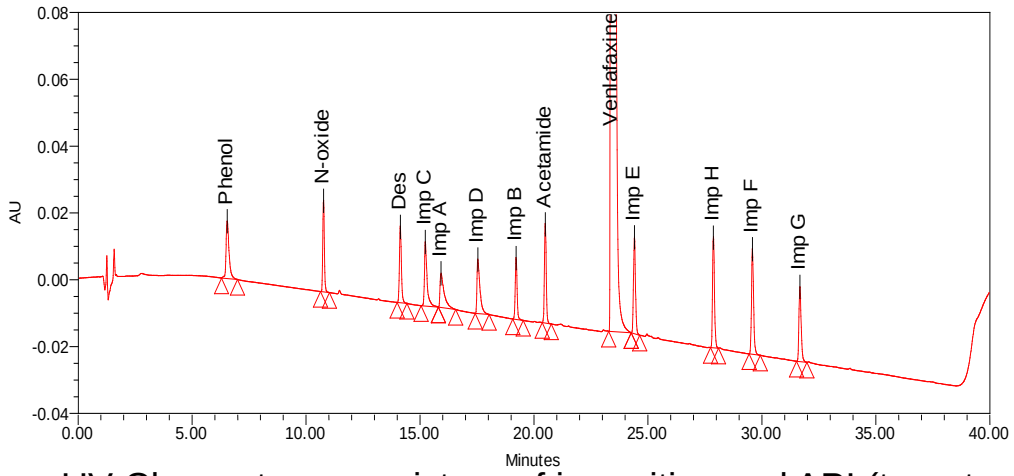
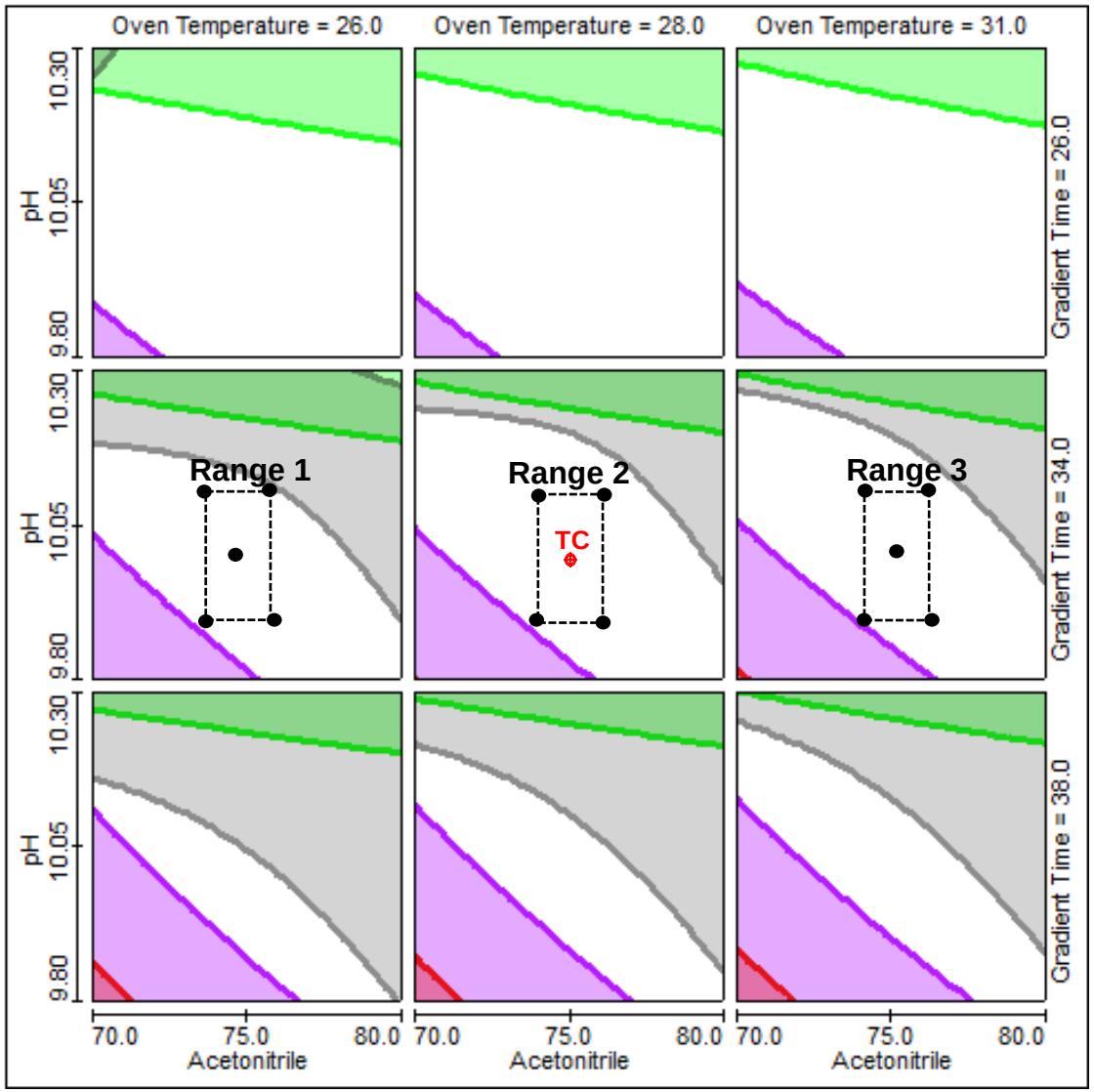


Figure. UV Chromatogram mixture of impurities and API (target condition)



Analytical Control Strategy (ACS)

- ACS is a planned set of controls, established to eliminate the risk or control it at an acceptable level.

- Case Study – Establishment of
  1. Target conditions and validated operating range
  2. SST Criteria
  3. MODR

Target conditions and validated operating range

Chromatographic Conditions	Target Value	Lower Value	Upper Value
pH	10	9.9	10.1
Solvent B - %ACN in MeOH	75	74	76
Column temperature (°C)	28	26	31

Gradient time: 34 min Flow rate: 0.45mL/min

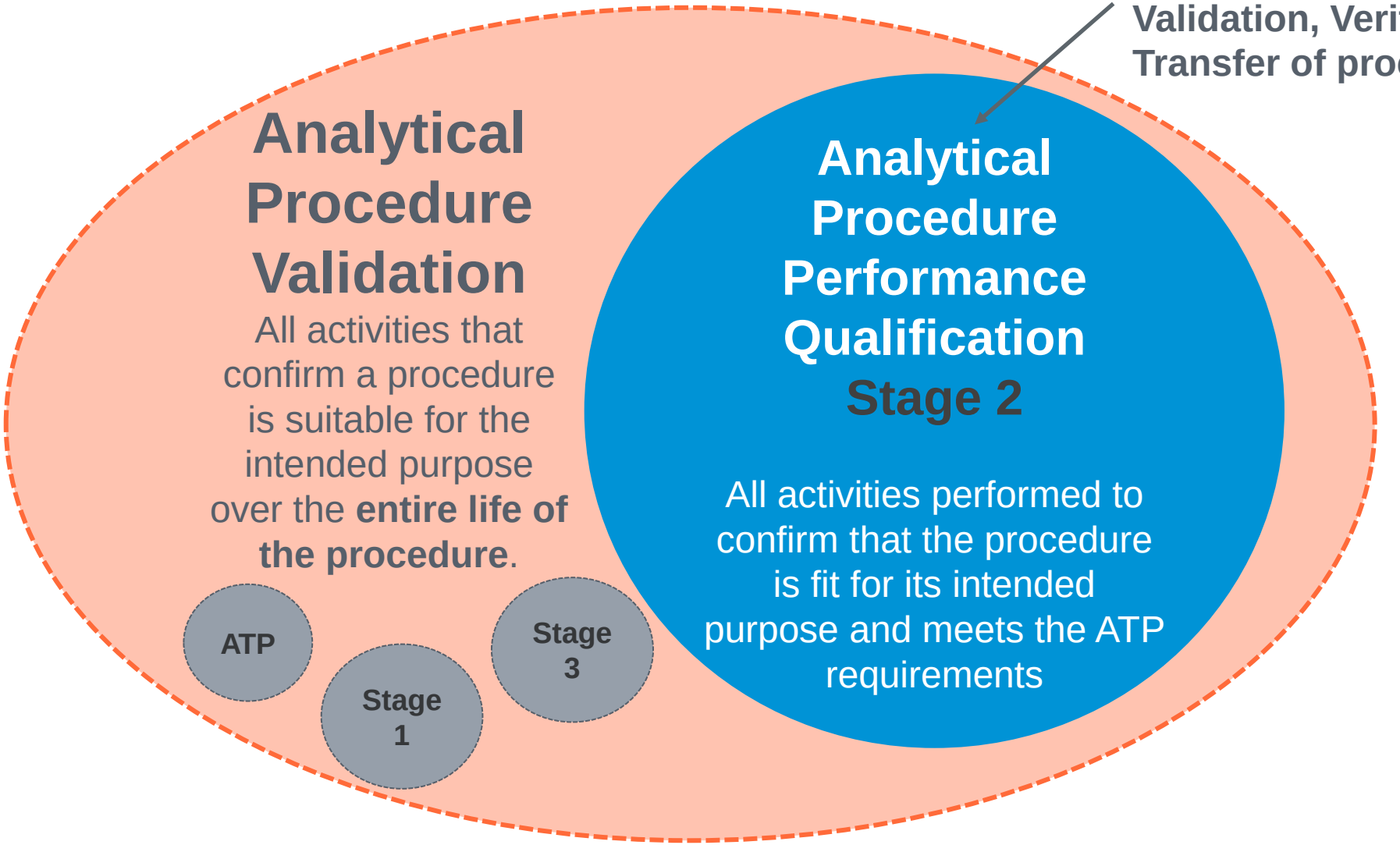
Gradient table not shown

System suitability requirements

Resolution: NLT 1.5 between Venlafaxine Impurity A and C and NLT 3.5 between Venlafaxine and Venlafaxine Impurity E (System Suitability Solution)
System precision: %RSD of replicate injections is NMT 5.0% for all impurities (sensitivity solution)
Sensitivity: signal-to-noise ratio NLT 20 (sensitivity solution)

Stage 2 - Analytical Procedure Performance Qualification

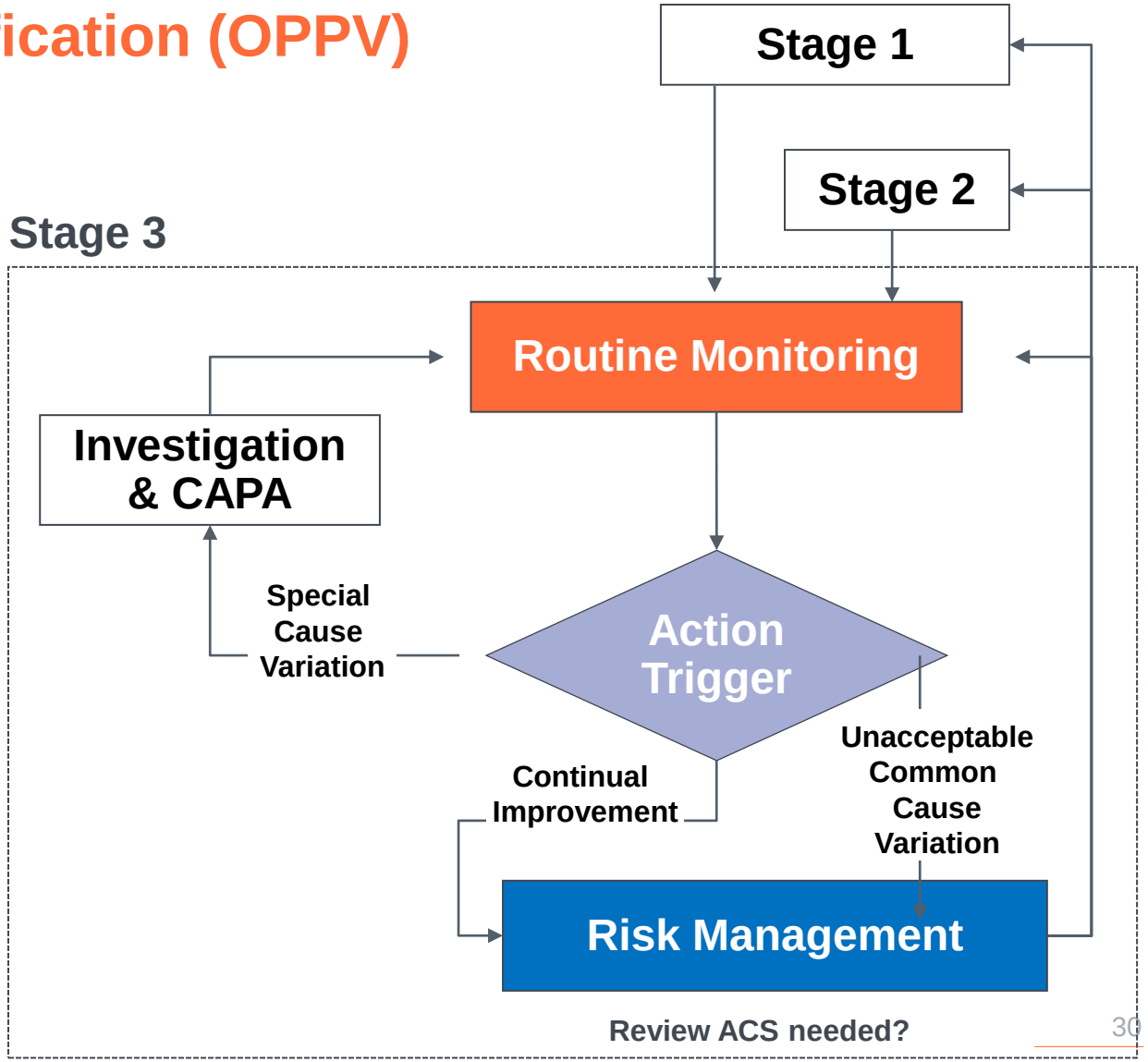
Analytical Procedure Validation vs. APP Qualification



Stage 3

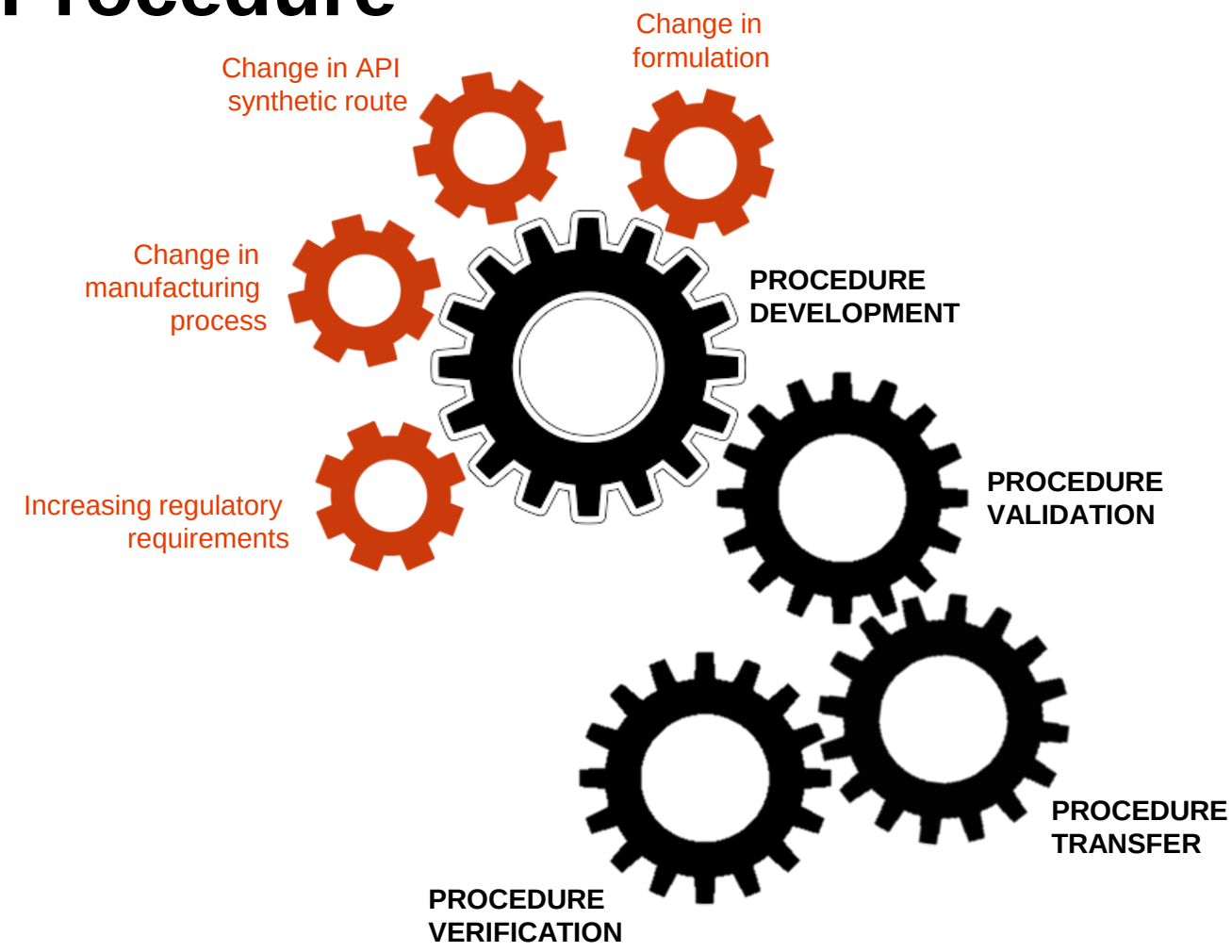
Ongoing Procedure Performance Verification (OPPV)

- This step involves
  - monitoring relevant analytical procedure attributes
  - confirming that the ATP criteria are still being met
- This stage may include
  - routine monitoring
  - Monitor relevant analytical procedure attributes
  - Statistical process control (SPC) techniques may be (e.g.: control charts)



Changes to an Analytical Procedure

- Changes to analytical procedures may be needed over the life cycle.



Adapted from R.W. Lee, et al. Life Science Connect. 2012.

Concluding Remarks

Benefits of AQbD principles Implementation

Analytical Procedure Knowledge

- Better understanding of the impact of analytical procedure parameters on performance
- Understand the sources of variability
- Establish the maximum variability that can be associated with a reportable result

- Design more robust analytical procedures (minimize variability)
- Establish a wider operating range (MODR)
- Establish suitable analytical control strategies (ACS)
  - for method transfer and verification
  - provide purpose driven protocols for validation
- Increase reliability of deciding if a product is OOS

- More flexibility for lifecycle management (and analytical procedure changes)
- Reducing the amount of effort/costs across the analytical procedure lifecycle
- Facilitating continual improvement by using more analytical procedure knowledge

Analytical Procedure Lifecycle & AQbD

Fundamental to the concept of quality by design (QbD) is to start with the end in mind.

42(5) Stimuli Article: Analytical Control Strategy

- Key Enablers:
  - Knowledge Management
  - Quality Risk Management

Unknown source

Thank You

Empowering a healthy tomorrow

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Amanda Guiraldelli, Ph.D. | *Scientific Affairs Manager* | *awg@usp.org*

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