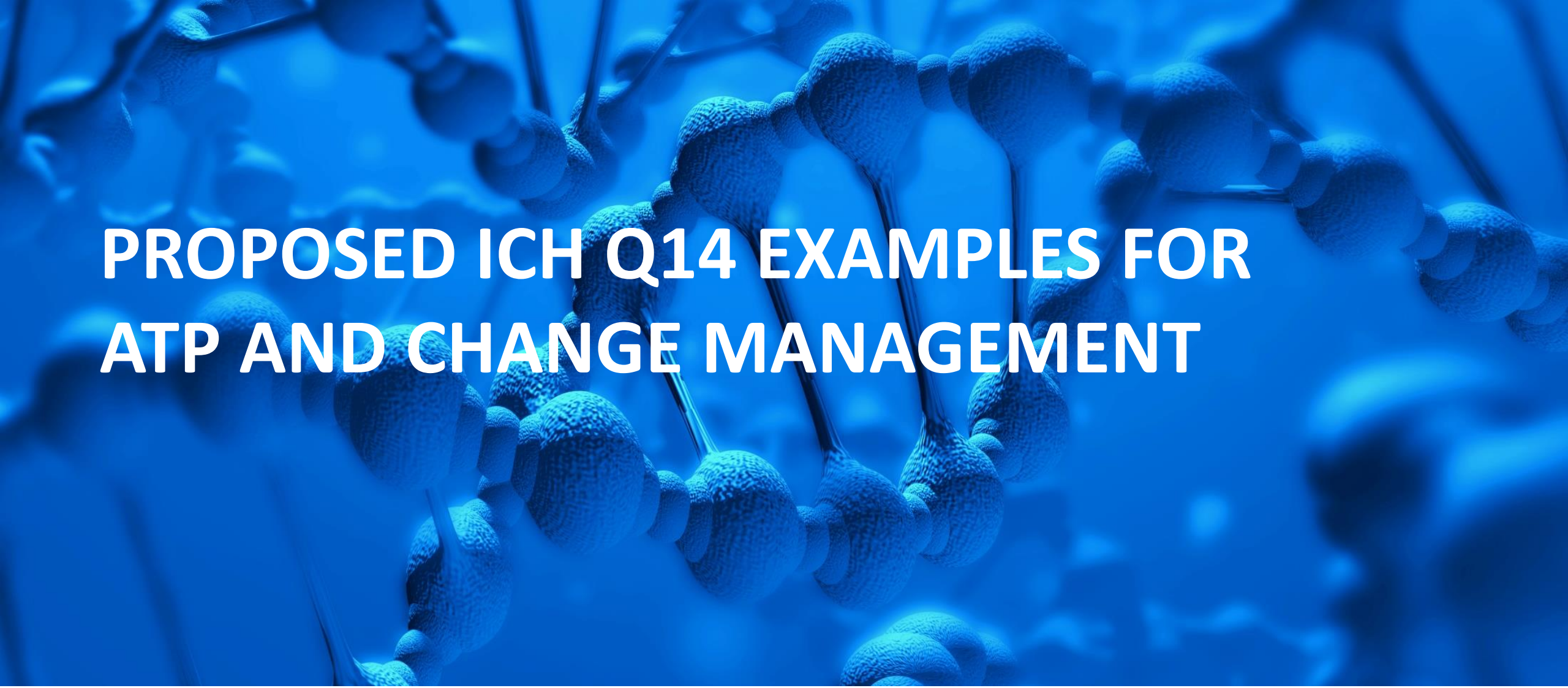

PROPOSED ICH Q14 EXAMPLES FOR ATP AND CHANGE MANAGEMENT

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DISCLAIMER

Materials presented in the following slides are meant to illustrate the potential application of Analytical Target Profile (ATP) in Analytical Procedure (AP) lifecycle development. All content are hypothetical, including the illustrative potential regulatory outcomes in post-approval change management.

A further goal of this presentation is to illustrate ways Established Conditions (EC's) can be leveraged to ensure post-change method quality and regulatory acceptance.

ICH Q14 DESCRIBES LEVERAGING QBD PRINCIPLES FOR FACILITATING AP DEVELOPMENT AND CHANGE MANAGEMENT

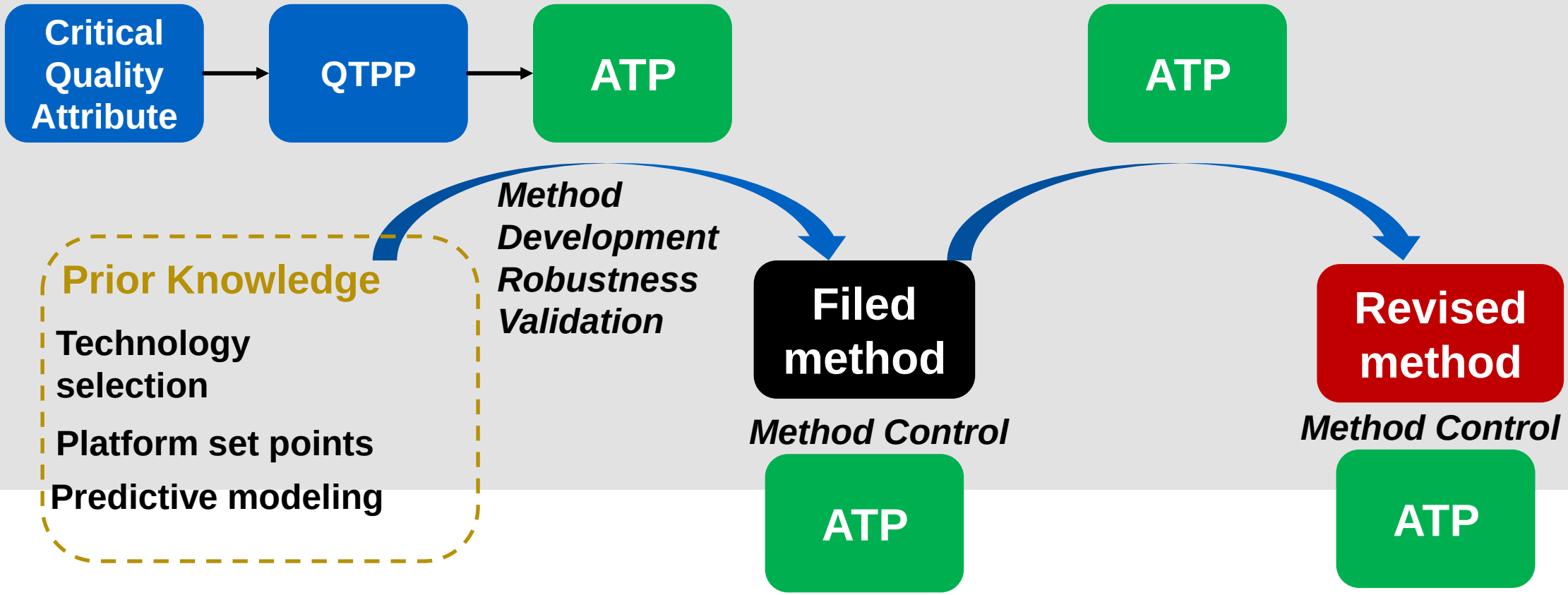
- The guideline provides guidance on science and risk-based approaches for developing analytical procedures to ensure the quality of marketed drug substances and drug products.
- Sharing additional knowledge and information related to development of analytical procedures with regulatory agencies may help demonstrate that the analytical procedure is appropriate for its intended purpose.
- In addition, a comprehensive understanding of analytical procedure based on risk assessment can support continual improvement of analytical procedure through the procedure's lifecycle and provide assurance of the quality of analytical data.

- Annex A: Examples of Analytical Target Profiles (ATP's)
- Annex D: Change Management of Analytical Procedures (Examples)

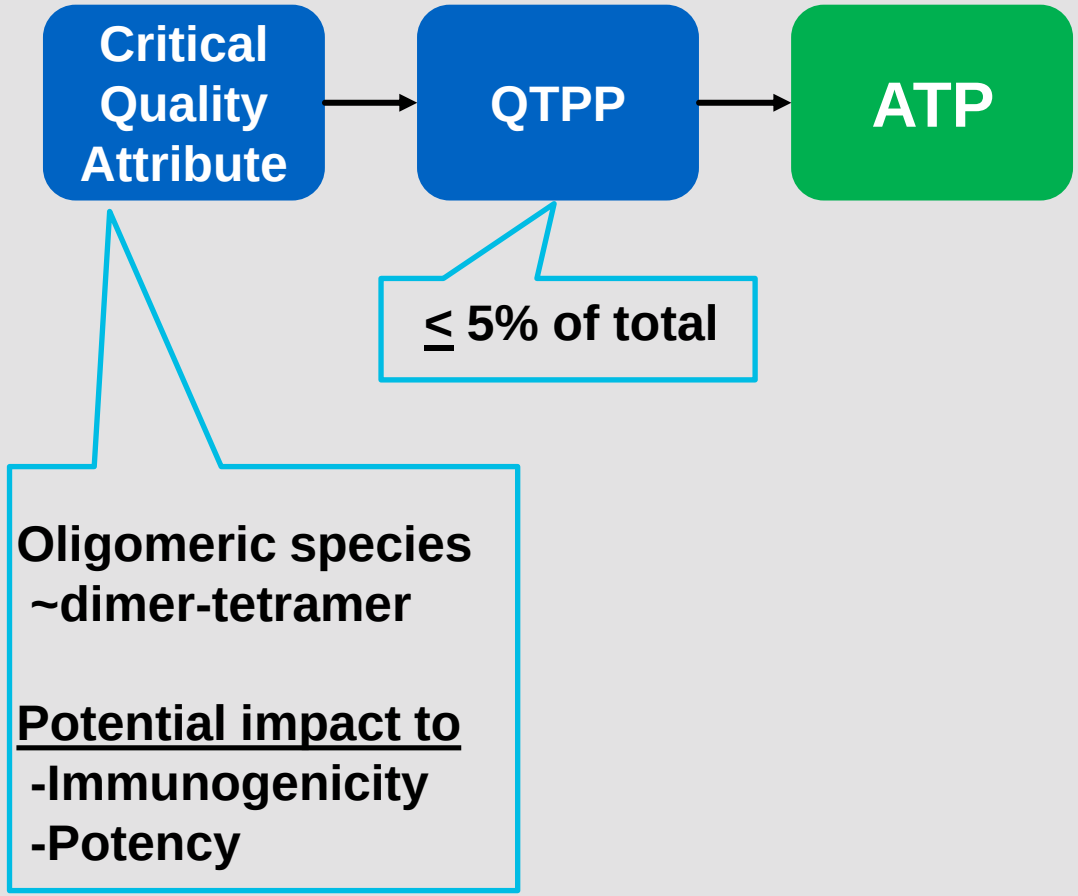
Language from draft ICH Q14 – subject to change

ANALYTICAL TARGET PROFILE AND CHANGE MANAGEMENT

- **The ATP is a predefined set of criteria for the analytical method(s) used to monitor a given product's quality attributes.**
  - **It is the "gate keeper" in development as well as ensuring the method remains fit for purpose**



ATP EXAMPLE – CONTROLLING FOR HIGH MOLECULAR WEIGHT SPECIES (HMWS) ATTRIBUTE IN A THERAPEUTIC MONOCLONAL ANTIBODY

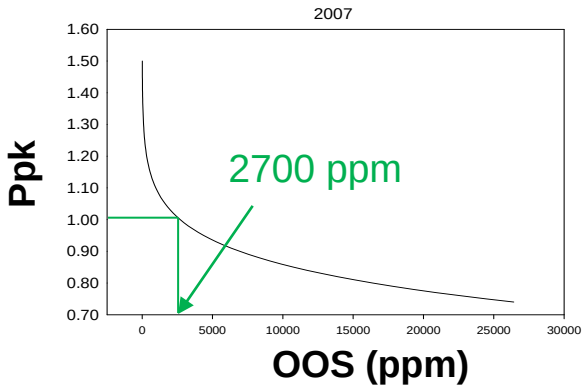


- Scope: Measurement of dimer and oligomer species in DS and DP release and stability testing
  - Throughput sufficient to monitor manufacturing process capability (ie, ≤ 2 days to generate result) and be validatable in a QC environment.
- Specificity: < 0.1% carryover or interference; quantifies species of interest
- Linearity: Linear ($r^2 > 0.99$) up to 120% of QTPP limit
- Precision: Total analytical error (TAE) ≤ 50% of allowable process capability to achieve Ppk 1.0 in QTPP range (SD ~0.9%)
- LOQ: ≤ 10% RSD at QL target ≤ 0.2% HMWS
- Range: QL to 120% of QTPP limit

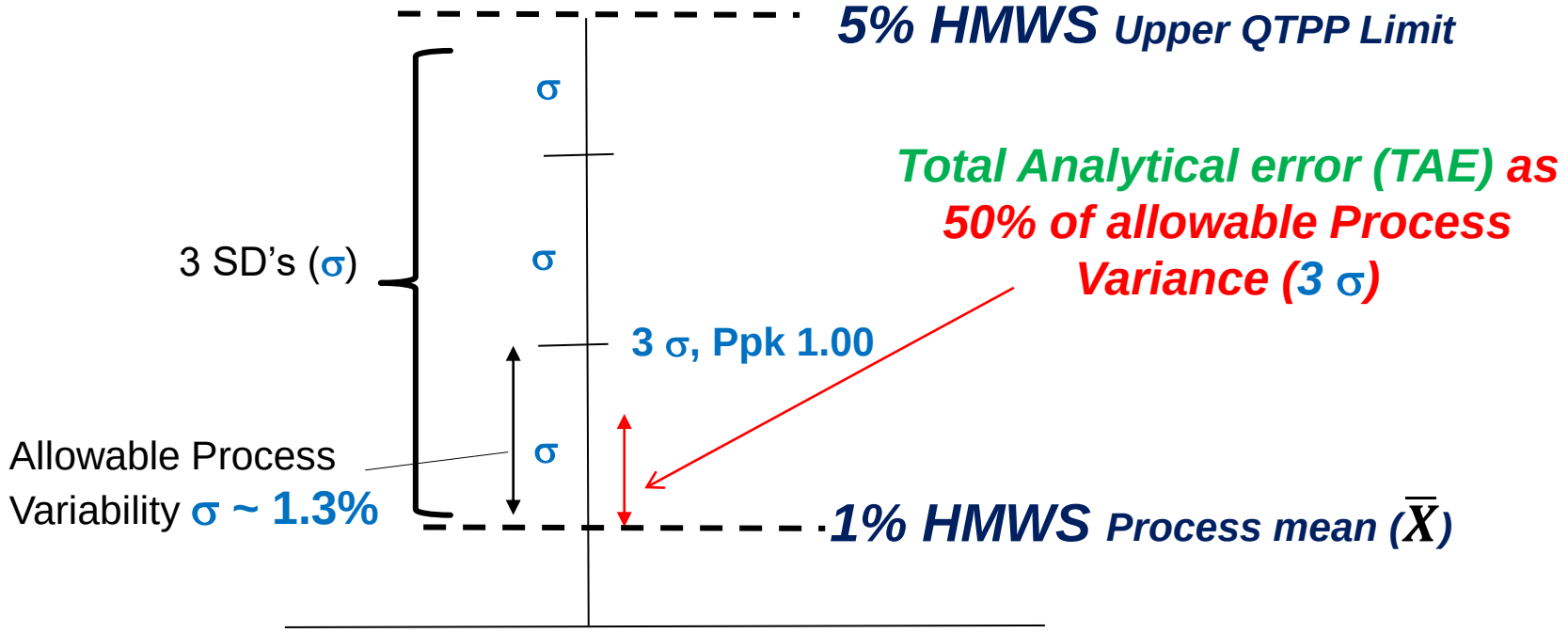
ILLUSTRATION OF TAE (PRECISION TARGET) VS. PROCESS VARIANCE VS. QTPP LIMIT *(HYPOTHETICAL EXAMPLE)*

Process performance Ppk

$$\text{Ppk} = \frac{(\text{Upper QTPP} - \bar{X})}{3SD}$$



Process and method performance targets



$$\textbf{TAE} = \sqrt{\{(0.5)[\text{Process SD Target}]^2\}}$$ **= 0.9% = method precision target**

In this example, Total Analytical (method) error (variance) (TAE) is limited to ≤ 50% of the allowable Process Variance to achieve Ppk 1.0

HMWS ATTRIBUTE CONTROL – LEVERAGING PRIOR KNOWLEDGE

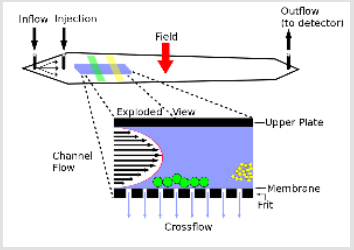
Critical Quality Attribute → QTPP → ATP

Prior Knowledge

- Technology selection
- Platform set points
- Predictive modeling

Analytical Ultracentrifugation

Field flow fractionation



Light Scattering

HPLC/UHPLC

HMWS ATTRIBUTE CONTROL – LEVERAGING PRIOR KNOWLEDGE

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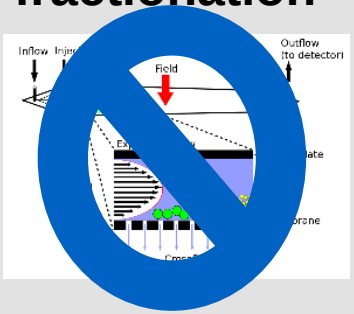

Light Scattering

HPLC/UHPLC

HMWS ATTRIBUTE CONTROL – LEVERAGING PRIOR KNOWLEDGE

Critical Quality Attribute → **QTPP** → **ATP**

Prior Knowledge

- **Technology selection**
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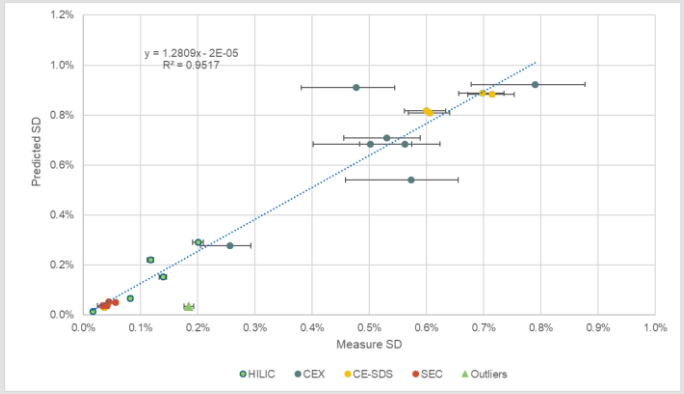
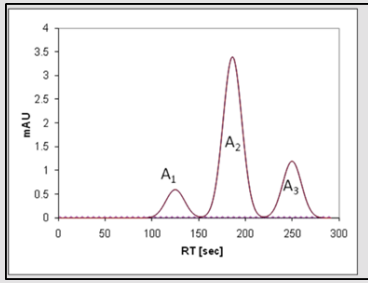




$Var(Pi) = f(A_i, R_i, w_i, w\_50_i, N_i, \sqrt{}, RSD\_w, RSD_{Inj})$

Error type	A_i	R_i	w_i	w_50_i	N_i	$\sqrt{}$	RSD_w	RSD_{instr}
Injection	x	x						x
Integration	x	x	x	x		x	x	
Noise			x		x		x	
Detector	x	x						

$$P_1 = \frac{A_1}{R_1 + A_1}$$

$R_1 = A_2 + A_3$

A_i- area under the peak
R_i- rest of the area on the chromatogram
w_i- width of integration domain
W_50_i – width at half height
N_i- Noise level
$\sqrt{}$ - frequency of acquisition
RSD_w - variability of integration width
RSD_{instr}- variability of injection

Uncertainty based on Current Information (UBCI) model – method performance characteristics as a function of signal, noise, hardware specs, and software settings

Apostol, I, Wu, R, Ko, M, et al. (2020) "Prediction of Precision for Purity Methods." Journal of Pharmaceutical Sciences. 109(4): 1467-1472.

HMWS ATTRIBUTE CONTROL – AP DEVELOPMENT, VALIDATION, AND CONTROL

ATP

Validation

- ✓ Specificity
- ✓ Linearity
- ✓ Precision
- ✓ QL
- ✓ Range

AP Development

Method Parameter	Screening	Minor variable	Significant variable	Multivariate Assessment
Column type				
Flow rate				
Column Temperature				
MP pH				
MP Ionic strength				
Protein load				
Injection Vol.				
Detector wavelength (λ)				

EC's

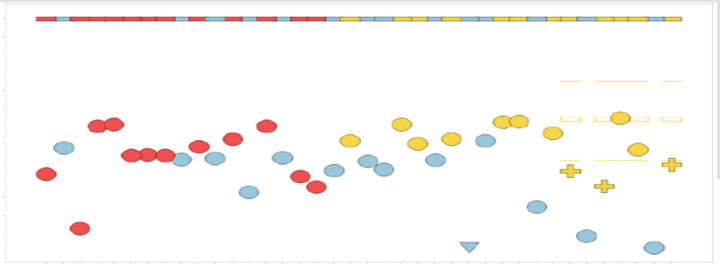
MP: Mobile Phase

Filed method

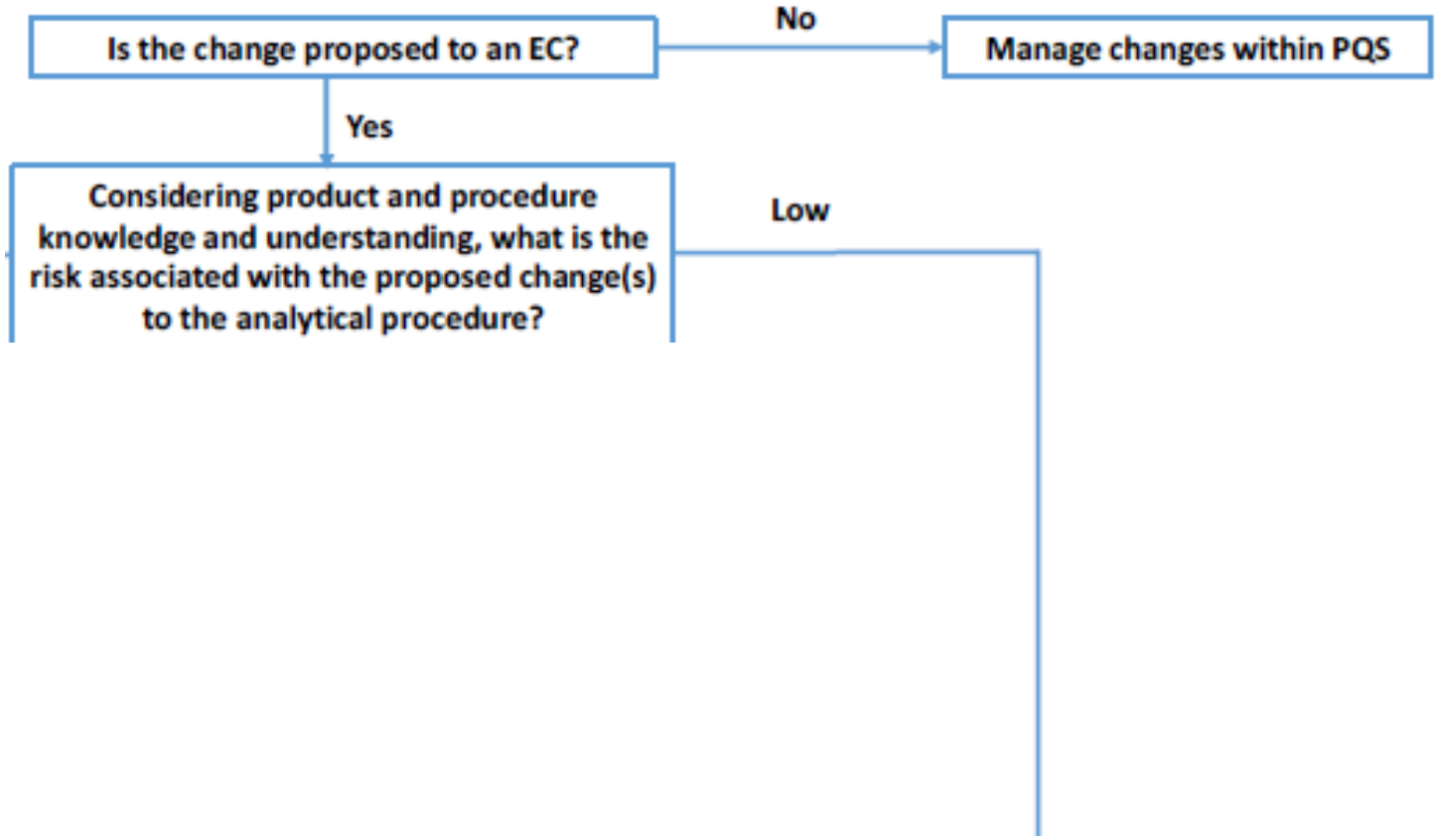
AP Control

ATP

- System Suitability
- Assay Control Monitoring



ATP AND LIFECYCLE MANAGEMENT OF CHANGES TO ANALYTICAL PROCEDURES USING AN ENHANCED APPROACH (ICH)



B. Kurtyka, FDA, IFPAC 2021. Draft ICH proposal – subject to change

HMW AP EXAMPLE - ESTABLISHED CONDITIONS AND PROPOSED NOTIFICATION CLASSIFICATION

Established Conditions

Prior Approval

Widening any of ATP performance characteristics

- Specificity
- Linearity
- Precision/TAE
- QL
- Range

ATP

Method technology platform change –
Size Exclusion Chromatography

Change of attributes reported

Notification Moderate

Widen SST –
-RS profile consistent with historical
-Plate count

Change detection platform (UV to fluorescence)

Notification Low

Widen other SST –
S/N criterion
Repeatability criteria

Change detection λ (280 nm)

Change injection load outside 5-20 µL

Change MP pH/Ionic strength

Not reported – manage in quality system

Change minor method parameters

-Column w/in USP L59 column class
-Column Temp
-Flow rate

HMWS QUANTITATION Q14 CHANGE EXAMPLE #1 – CHANGE OF COLUMN, COLUMN LOAD, AND DETECTOR WAVELENGTH

Background

- Column manufacture discontinued
- New UHPLC column selected from within USP L59 class – changes made to –
  - Injection volume (< 5 µL) to enable resolution
  - Detector λ to 214 nm to improve sensitivity

Application of enhanced understanding

- Extensive biophysical understanding of all HMWS variants and criticality determined and presented during product characterization (S31, S32)
- Multivariate evaluation of parameters during development covered the range of changes

Assessment of impact to EC's

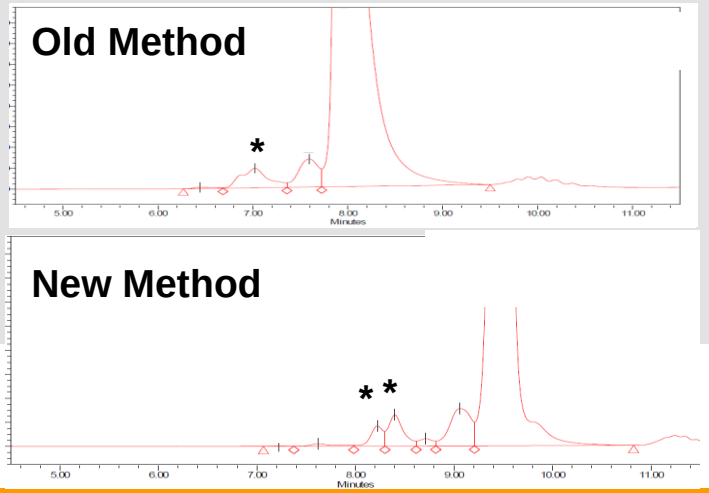
- No measurement bias between methods
- Chromatographic profiles consistent between methods
- Robustness experiments re-performed w/ DOE including detector λ and injection volume
- Method Validation passed vs. ATP criteria

Proposed regulatory assessment – Medium risk to method + performance characteristics met = Notification Low

HMWS QUANTITATION Q14 CHANGE EXAMPLE #2 – CHANGE OF COLUMN LEADING TO CHANGE IN CHROMATOGRAPHIC PROFILE OF REFERENCE STANDARD

Background

- Method performance not achieving TAE criteria
- New UHPLC column selected from within USP L59 class, however change observed in HMWS profile



Application of enhanced understanding

- Extensive biophysical understanding of all HMWS variants and criticality determined and presented during product characterization (S31, S32).
- Profile change due to *improved resolution - a*ll species observed known and previously characterized

Assessment of impact to EC's

- Bias between method results observed, statistically defined.
  - No impact to process meeting QTPP range (*no change to specifications proposed)*
  - Method meets TAE criterion of ATP
- Identities of additional resolved HMWS determined and presented (S31)
- Resolution improvement led to tightening of System suitability criteria
- Method Validation repeated and passed vs. ATP criteria.

Proposed regulatory assessment – High risk to method + performance characteristics met = Notification Moderate

SUMMARY

- **The ATP can be prospectively used to guide analytical procedure development to align with the QTPP and the process**
- **An aspiration of Q14 is to provide avenues for enabling post-approval analytical procedure changes through some combination of demonstrated enhanced method understanding and adherence to well-defined EC's, including ATP.**
  - **The hypothetical examples of ATP and change management presented here and by other contributors may illustrate ways EC's can be leveraged to ensure post-change method quality and regulatory acceptance.**

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