Performance and Context Based Established Conditions for Analytical Procedures

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Introduction and Problem Statement

- **The different risk understanding** in view of the regulatory assessment of a change results in country specific reporting categories **(Figure 1)**
- **Pharmacopoeias** have different understanding in view of adjustments and modifications. Raw material, drug product, and general monographs are not fully harmonized (e.g. dissolution stage concepts of Ph.Eur and Ch.Ph.)
- **Different Timelines and Requirements** for regulatory change control processes are daily challenges for the regulatory life cycle management of analytical procedures **(Figure 2)**
- **Regulatory Compliance Oversight** is nearly impossible and higher resources are needed to control the logistic complexity instead of facilitating continuous improvement

Example	US	Europe	Japan
Change of Water determination (KF to Coulometric)	**Minor**	**Type IB**	**Notification**
Replacement TLC by HPLC for (purity)	**Moderate**	**Type IB**	**Partial Change Application**
Alternative analytical method: conventional and fast HPLC	**Minor**	**Type IB**	**Partial Change Application**
Pharmacopoeias	**Different Approaches (e.g. Adjustment sections)**		

Figure 1: Different Risk Understanding of Authorities

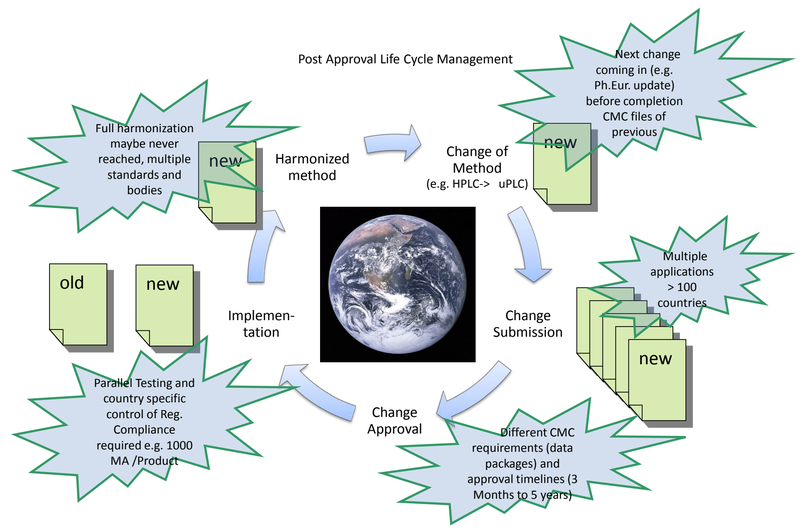

Figure 2: Increasing Logistic Complexity

ATP - Definition, Example, and Terminology

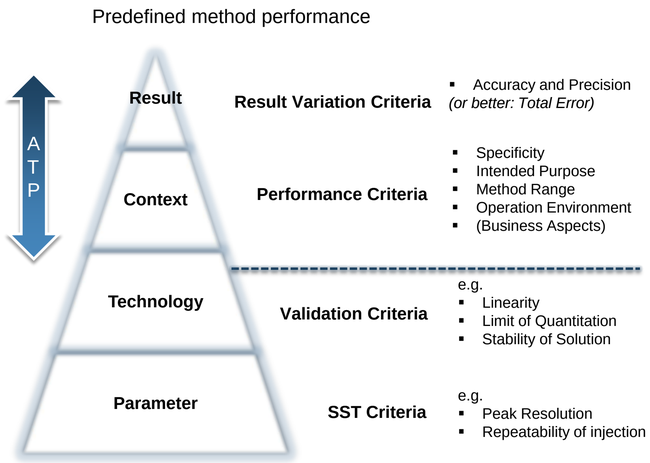

Figure 3: Analytical Target Profile (ATP)

Requirement	Method performance criteria
Accuracy	Impurity A: ≤ 80-120 % of true value Impurity B: ≤ 75-125% of true value
Precision of reportable result	Impurity A $_{srel}$ ≤ 10% Impurity B $_{srel}$ ≤ 15%
Intended Purpose	Quantification of manufacturing process related impurity (not a degradation product)
Range	Impurity A: at least 0.05%-0.6% Impurity B: at least 0.05%-0.12%
Specificity	No interference of the quantification of the specified impurities by • other related substances C, D, and E • the salt forming agent with Impurity A,B or the API.
Operating conditions and Environment	The analytical procedure must be applicable for use in a standard analytical QC laboratory environment of ADS Pharma for routine analysis. The test procedure must be stable for at least 24 h of consecutive analyses.

Figure 4: ATP Example

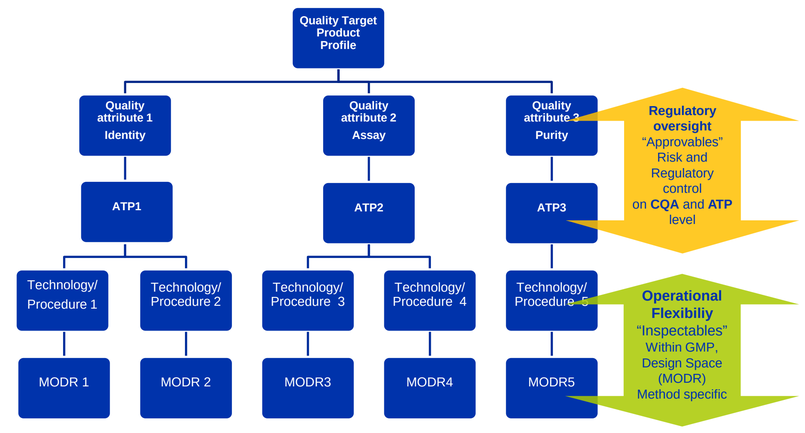

Figure 5: ATP Hierarchy

Regulatory Context of an ATP (Examples for Assay and Related Substances)

	Efficacy	Drug Product Specifications	Manufacturing Process	Packaging Material	Analytical Procedure
Regulatory Context level of the Assay ATP	95.0 – 105.0% (e.g. narrow therapeutic index drug)	Degradation rate D=2% for targeted shelf-life (2 years) Lower bound at release: 98.0% to account for stability losses Upper bound: 105% Release target =100% (no stability overage; manufacturing overage may be allowed)	Allowed Batch variability (BV) = ± 2%	Permeability of oxygen and water may have an influence on the degradation rate (D)	*Remaining available Analytical Variability (AV): 1%* *"Uncertainty Approach"*
Result level of the Assay ATP (only principle without statistical treatment)	**95.0-105.0% =**	**RT - D** RT =100% (no stability overage) D = 2%	**± BV** BV = 2%	**-PL** PL = 0%	**± AV**

Figure 6: Regulatory Context for an "Assay ATP"

- For regulatory processes (e.g. Change Controls) besides the **predefined method performance** the related **Regulatory Context** has to be known and adequately described
- **Figure 6** provides more regulatory background for an assay specification based on **CRS** (**C**linically **R**elevant **S**pecifications[2]). Taking into account allowed batch variability (e.g. = ± 2%) and degradation rate of API of 2%, the total error has to be better than 1%
- **Figure 7** should stimulate discussions for the most challenging topic to switch between technologies for an "Related Substances ATP". The Quality and reliability of the context description forms the basis to what extent operational flexibility can be implemented for impurity testing methods
- The Ph.Eur the monograph (e.g.) „2.2.40 NIRS" in conjunction with EMA Guidance *EMEA/CHMP/CVMP/QWP/17760/2009 Rev2* already provides context and performance based conditions to be established

2) Clinically Relevant Specifications (CRS): A Regulatory Perspective, Richard (Rik) Lostritto, Ph.D. Acting Deputy Director for Science & Policy and Acting Biopharmaceutics Lead, Office of New Drug Quality Assessment (ONDQA) CDER/FDA IFPAC, Washington, January, 2014

	Safety	API	Drug Product	Manufacturing Process	Packaging Material	Analytical Procedure
Regulatory Context Level of the Impurity ATP	Safety Related Specifications (e.g. ICH M7)	**API related degradation pathways** Transparency list (Ph.Eur.) ICH Q11	Formulation Specific Impurities; **Degradation Pathways** ICHQ1A, Q3A, Q8	Process understanding, e.g. Process related Impurities NfG on Process Validation	Understanding on the origin and interaction of drug product and primary packaging in view of impurities NfG on Primary Packaging materials	Discriminatory and stability indicating ability mass balance Compliance to acceptance criteria of ICHQ2 validation parameter (e.g. Specificity)
Result Level of the Impurity ATP						Precision and accuracy

Figure 7: Regulatory Context for "Related Substances ATP"

Level Concept for Established Conditions and Conclusion

Scope of the Change	Established Conditions	Proposed mechanisms / Regulatory Assessemnt	Operational Flexibility
Change/Implementation of an Analytical Performance Level (ATP) (New condition to be established)	Not Applicable	**Prior Approval** Authority risk assessment needed Major Change: Type II, PAS, PCA	None
Change within same Performance Level	Conformance to **ATP** and **appropriate description of Regulatory Context (RC)**	**Do and tell** Change Category has to be evaluated upfront (CMP) or Type II /PAS (Initial Submission)	Movement **outside** Technology Sect./ Switch **between** Technologies
Change outside valid. and registered ranges but within a method principle	Conformance to **ATP/RC** or existing, performance based **Pharmacopoeia Technology Section**	**Non-Reportable Change** **Minor Changes within PQS; only GMP actions**	Movement **within** same Technology (e.g. within a Ph. Eur. or USP Chapter)
Changes within validated, registered, or compendial ranges	**Traditional Registration based on "registered Details"**	**Non-Reportable Change** **Minor Changes within PQS; only GMP actions**	Movement within DS, MODR, Adjustments (already achieved)

Figure 8: Level Concept to support ICH Q12

In order to be able to proceed as **'Do and Tell', for method changes that involve a different analytical technique** (e.g. moving from chromatographic to spectroscopic) three main regulatory elements may be required

- **Performance based**[3] **Established Conditions: ATP** for a specific CQA as part of the Control Strategy (ICHQ8)
- **Regulatory Context based Established Conditions** to enable the ATP as regulatory element (Risk and knowledge based approach ICH Q9, 10)
- Change Management Protocols: **PACMP**

Conclusion

- The proposed **Performance Based Level Concept**[4] will work with ICHQ8 - 12 and intends to provide a framework to harmonize and facilitate the post approval change management in a more predictable and efficient manner (**Figure 8**)

3) **"We Are Moving to Performance-based Regulation"** CDER's Office of Pharmaceutical Quality (OPQ): Delivering on the 21st Century Quality Goals, Lawrence X. Yu, Ph.D. Director (acting), Office of Pharmaceutical Science, Food and Drug Administration, IFPAC Annual Meeting, Jan. 21 - Jan. 24, 2014, Arlington, VA (Washington DC), U.S.A

4) **"Advanced Concepts for Change Control of Analytical Procedures with ICH Q12 Coming",** Dr. Jörg Hoffmann, MS-QAO-Regulatory Compliance & CMC, Merck KGaA (EMD Serono in US) IFPAC® Annual Meeting, Jan. 25 - 28, 2015, Arlington, VA (Washington DC), U.S.A