The Future is Now:
ICH Q14: Analytical Procedure Development
ICH Q2(R2): Validation of Analytical Procedures

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.
www.fda.gov

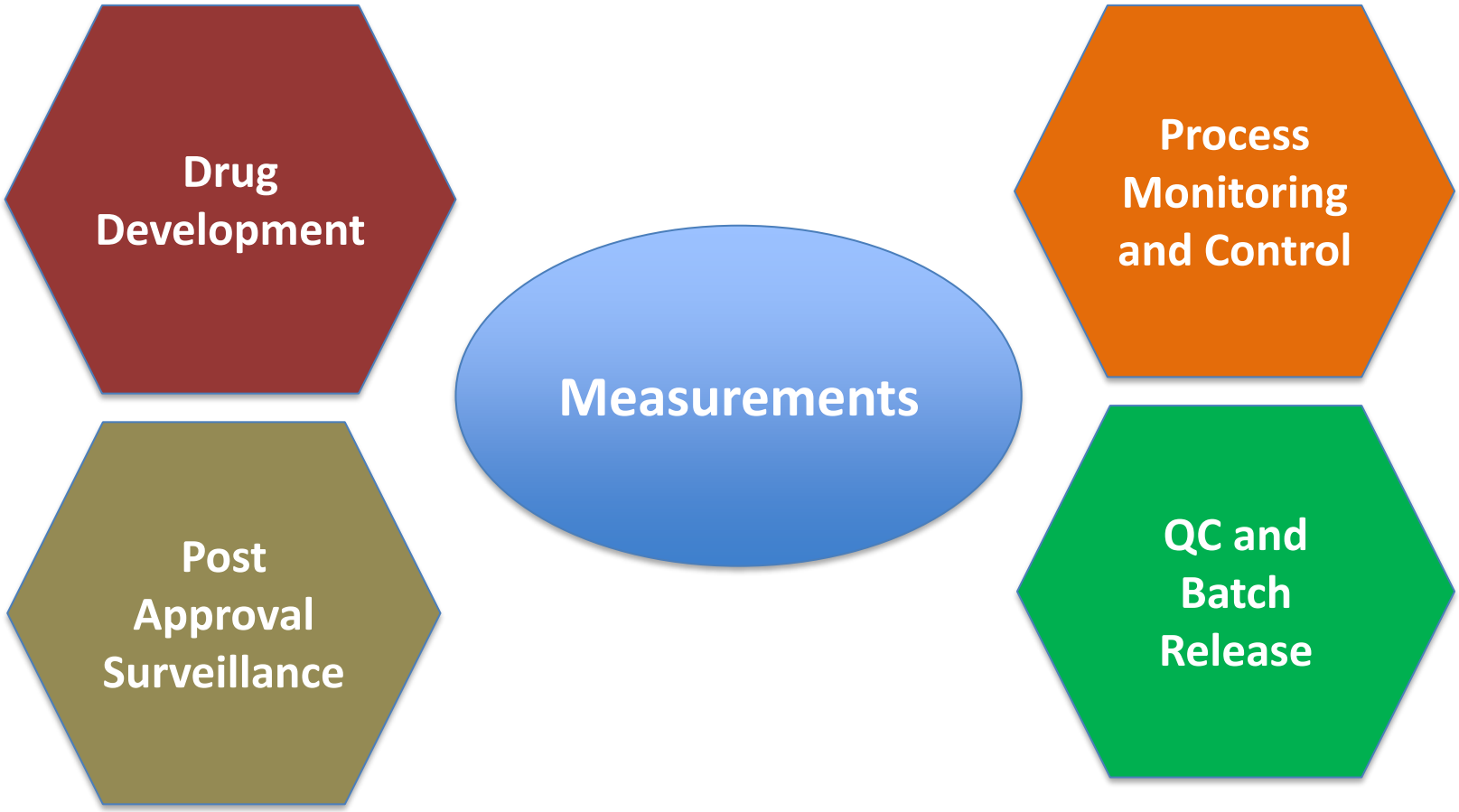
Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

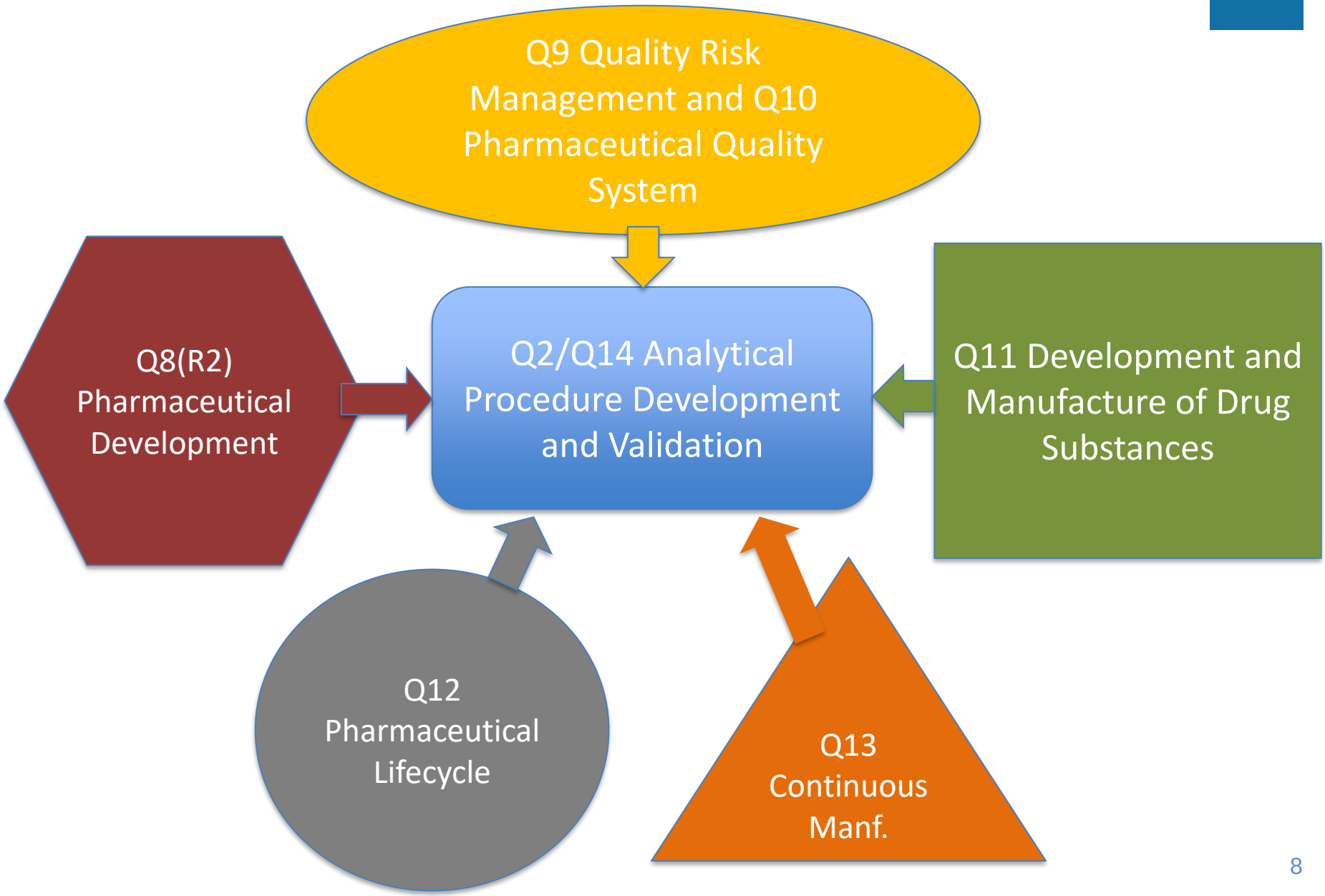
www.fda.gov


It is what gives patients confidence in their *next* dose of medicine.

The Central Science?



ICH Q-Guideline Continuum



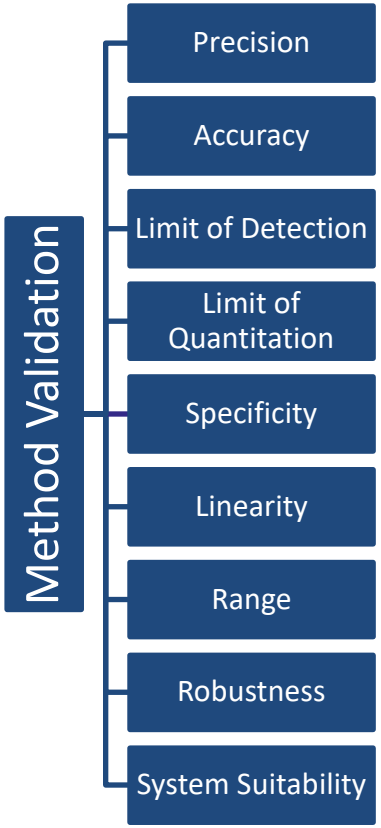
FDA Laboratory Experience

Purpose of the Methods Verification Program

- Reviewers often had questions about assay/impurity methods that could only be answered by laboratory-based verification
  - Analytical methods must be robust, accurate and suitable for use by the applicant **and** the regulatory agency
- OTR offered experts in the area of pharmaceutical analysis and the tools to verify most methods
- OTR began assisting in method verification in 1977 with NDA 1941/S-004, a topical anesthetic ointment called Diothane
- MVP is designed to aid reviewers by completing verification of methods in a laboratory-based setting and offering critical feedback

Why Verification?

Validation



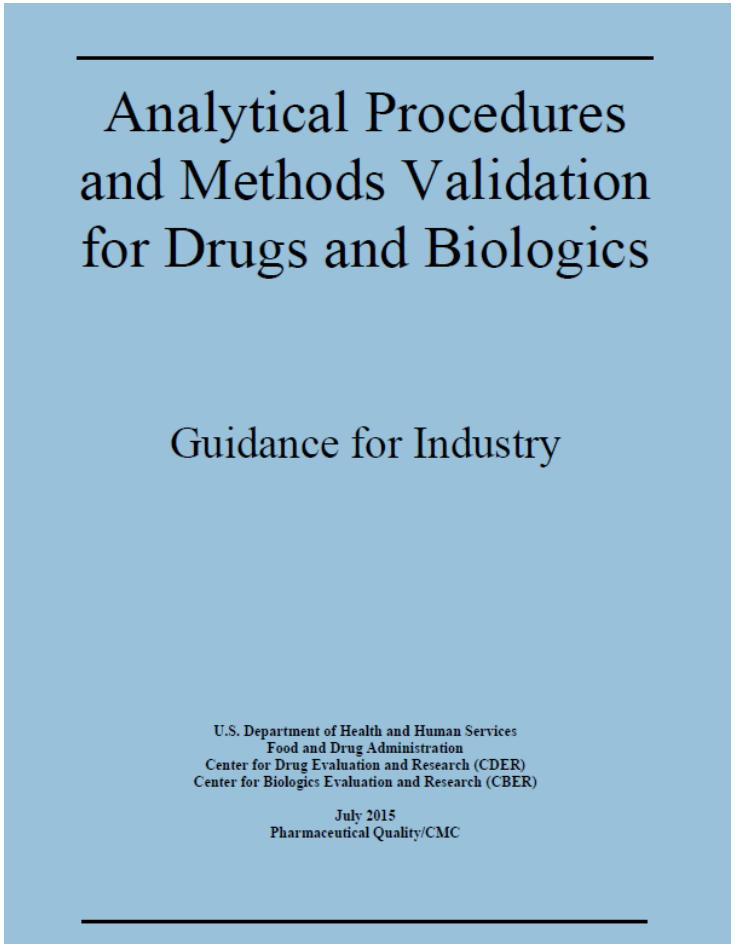
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

vs.

Verification

- Analytical procedures are suitable for the drug product or drug substance
- Demonstration that a laboratory is capable of replicating a method with an acceptable level of performance
  - Meeting system suitability specifications
  - Meeting specific method specifications
- Acceptable for quality and regulatory purposes

FDA Methods Verification



"Part of the approval process for NDAs and ANDAs may include FDA laboratory assessment to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes. If a laboratory assessment will be conducted, the FDA laboratory will send you a request that will detail what samples and supplies to send to the FDA laboratory. These could include product samples, standards, critical reagents, material safety data sheets, and supplies. Laboratory results and comments will be forwarded from the FDA laboratory to the product quality reviewer."

- Similar wording available in 21 CFR 314.50(e)

Essential Information for Analytical Procedures

- Principle/Scope
- Apparatus/Equipment
- Operating Parameters
  - *Optimal settings; critical ranges*
- Reagents/Standards
  - *Grade, source, state, purity correction factors, storage controls, shelf life*
- Sample Preparation
  - *Procedures, replicate preparations for quantitative tests,* ***stability and storage conditions***
- Standards and Control Solution Preparations
  - ***Stability and storage conditions***
- Procedure
  - *Detail to allow a competent analyst to reproduce the method!*
- System Suitability
  - *Ensure system (equipment, electronics, analytical operations) will function correctly*
- Calculations
  - *Representative calculations*

Frequent Inadequacies

- **Incomplete analytical procedure description** (mobile phase, sample prep, minimal system suitability requirements or complete absence thereof)
- **System suitability issues**
  - *LOQ sample does not meet S/N specification for system suitability*
  - *Analytical procedure LOQ is above specification limit*
  - *Resolution*
- Column or detector overload causes chromatography problems
- Missing stability information for prepared samples or standards
- Need for a diluent blank
- Observed relative retention time of impurities does not closely match method
- **Unidentified peaks**
- **Incorrect calculations**

What Do We Want?

- Fewer Failures
- Minimize/Eliminate Recalls
- Regulatory Flexibility (fewer filings)
- Lower Barriers for New Analytical Technology
- Quality Drugs for Consumers

How Does ICH Help?

- Standardize
  - Provide guidance on the contents of Section S4, P4, and P5 of the Common Technical Document.
- Harmonize
  - Common requirements globally.
- Framework
  - Adaptable to technological change.
  - Allows continuous improvement.

ICH Background

- Unique harmonization project involving regulatory authorities and pharmaceutical industry
- Started in 1990
- Well-defined objectives:
  - **To improve efficiency of new drug development and registration processes**
  - **To promote public health,** prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonized guidelines and standards

ICH Mission

- Achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

Harmonization Under ICH Leads to…

- More efficient regulatory review
- More efficient exchange of information between regulatory authorities
- Reduced time to get a product to the market
- Reduced patient burden through prevention of unnecessary duplication of clinical trials and post market clinical evaluations
- Reduction of unnecessary animal testing without compromising safety and effectiveness

ICH Members

- **Founding Regulatory Members (permanent Management Committee (MC) Members):**
  - EC, Europe; FDA, US; MHLW/PMDA, Japan
- **Founding Industry Members (permanent MC Members):**
  - EFPIA, JPMA, PhRMA
- **Standing Regulatory Members (permanent MC Members):**
  - Swissmedic, Switzerland; Health Canada, Canada
- **Elected MC Members:**
  - Regulatory Members: CFDA, China; HSA, Singapore; MFDS, Korea
  - Industry Members: BIO, IGBA
- **Regulatory Members:**
  - ANVISA, Brazil; TFDA, Chinese Taipei
- **Industry Members:**
  - WSMI

Harmonization

versus

Harmonisation

Q2(R1) Was Finalized In The 90's

- Scientific and technological progress made since the document was written
- Advanced therapies are in drug development and commercialization
- Necessarily associated analytical techniques are multiplying
  - hyphenated-techniques (LC-MS), spectroscopic methods requiring multivariate statistical analyses (*e.g.,* NIR, Raman)

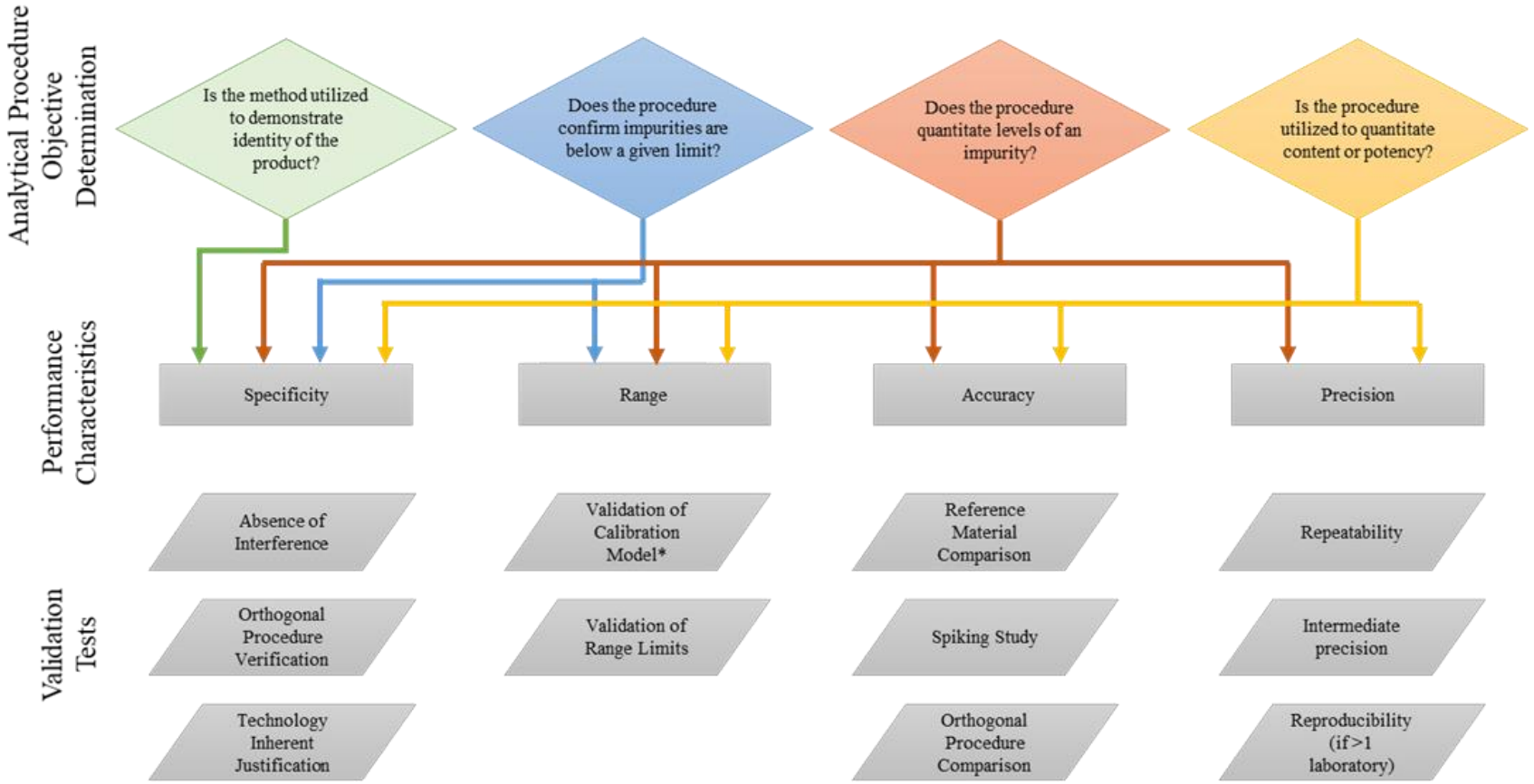
Q2: The Issue and Costs

- Q2(R1) not directly applicable to multivariate spectroscopy data.
  - Lack of clear guidelines leads to inadequate validation data in submissions to regulatory agencies.
    - Recursive information requests and responses leading to delay.
  - NIR commonly used for real time release testing.
- A barrier to innovation in analytical approaches for pharmaceutical quality assessment.

Q2 Revision

- ICH Q2(R2) will continue to provide a general framework for the principles of analytical procedure validation and has been modernized to include newer technologies (e.g., for biological products or multivariate analytical procedures)

Q2 Annex 1 - Selection of validation tests based on the objective of the analytical procedure



* May not be needed for limit test

ANNEX 2: Examples for Analytical Techniques

- Separation Techniques (assay, impurities, relative quant).
- Elemental Impurities by ICP-OES or ICP-MS as purity test
- Dissolution with HPLC as product performance test for an IR dosage form
- Quantitative ^{1}H-NMR (internal standard method) for Assay of an API
- Binding assay (e.g., ELISA, SPR) or Cell-based assay for determination of potency relative to a reference
- Quantitative PCR (quantitative analysis of impurities in drug substances or products)
- Particle size measurement (DLS; LD measurement) as a property test
- NIR method validation example for core tablet assay
- Quantitative LC/MS (quantitative analysis of impurities (e.g., genotoxic impurities) in drug substances or products)

Q14: The Issue and Costs

- No ICH Guideline on Analytical Procedure Development
  - Applicants rarely present performance evaluations
    - Can lead to recursive regulatory communication around non-conventional analytical procedures
      - *e.g.*, PAT driven multivariate models used for process control
    - Impedes applicant from presenting a scientific basis for flexible regulatory approaches (*e.g.,* QbD) to post-approval analytical procedure changes
- Delayed access to medication and increased cost

Q14 is New (sort of)

- Applying principles described in ICH Q14 can improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures
- ICH Q14 establishes harmonized scientific and technical principles for analytical procedures over the entire lifecycle in conjunction with Q2(R2)

What is Developed is Validated

Objectives / Performance Characteristics
Analytical Procedure
Related information from development

Analytical Procedure Lifecyle Management

Q14

Q2

Validation protocol

Validation report

Plan for validation strategy:

- Evaluation of existing development or validation data with justification
- Additional experiments and evaluation according Q2 (standard) methodology or alternative approach with justification

Document validation results and Data:

- Evaluation against Acceptance Criteria or Parameter Ranges
- Conclusions and acceptance of analytical procedure performance

Experiments and/or evaluation of data

Practical Matters: Test Performance Changes Over Time

- Change in product matrix
  - Raw material sources
  - New manufacturing equipment
  - Consumables, e.g., manufacturing filters or membranes
- Change in instrumentation and technology
  - Older model instrument versus newer model from the same vendor
  - Different vendor

Analytical Procedure Performance Changes

- Change in reagents or standards
  - New vendor
  - New manufacturing procedure for reagents
  - New batch of standard
- Change in analysts
  - Humans are involved in analytical measurements –skill, knowledge and experience
- Business decisions
  - Resource limitation
  - Spare parts (OEM versus other)
  - Change in CRO
- Environmental factors

Change and Analytical Procedure Validation

- Analytical procedure validation is a photograph.
- If the performance drifts can we still call the analytical procedure validated?
- What drift is acceptable?

Change and Analytical Procedure Validation

- Analytical procedure validation
  - Establishes the performance of test procedures
  - Decision point: Is it fit-for-purpose?
  - **Does not** provide data to understand and control potential sources of variability
- Typical analytical procedure validation addresses characteristics like;
  - Specificity
  - Linearity (response)
  - Accuracy (over some range)
  - Precision (that yields an LOD and LOQ)
- What should be monitored over time to check for drift in analytical performance versus product change?

Life-cycle Management of Analytical Procedures

- Want: Valid method over the life-cycle of the analytical procedure
- ICH Q8 and Q10 provides guidance on life-cycle management of a manufacturing process
  - ❑ Continuous verification
  - ❑ Change management
- Paralleling ICH Q8: A performance target should be identified during development.
  - Data acquired and analyzed over time provides knowledge to identify critical attributes to be monitored and acceptance criteria to be developed (Analytical Target Profile or ATP)
- Concept of Analytical Quality by Design (AQbD)

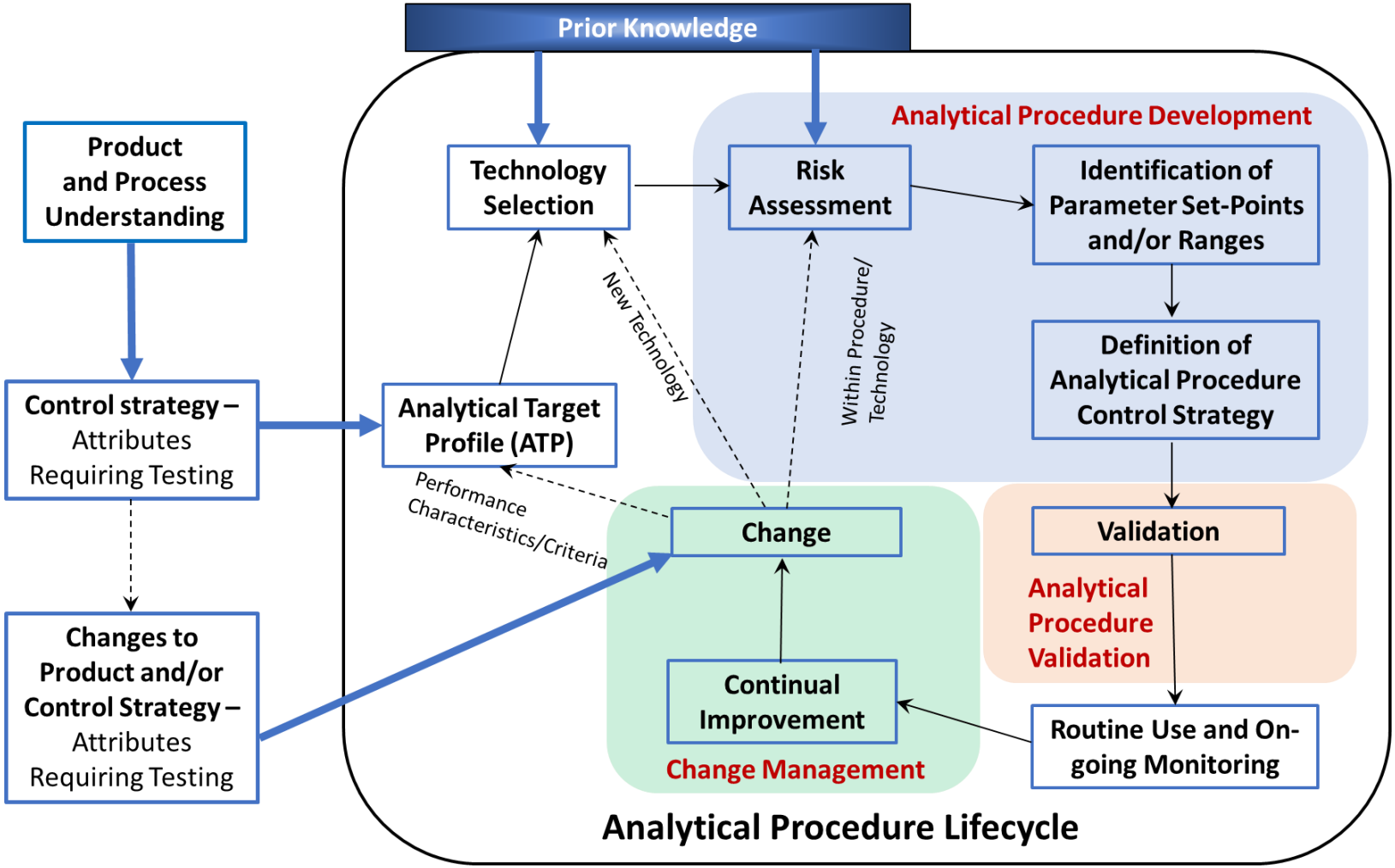
Q14 Analytical Method Development

- QbD is to QTPP as AQbD is to ATP
  - Quality by Design
  - Quality Target Product Profile
- Starts with the end in mind
- The end includes the entire lifetime of use
  - Not “one and done” but “constant verification”

Q8 to Q14

Product Development	Analytical Procedure Development
Quality Target Product Profile	Analytical Target Profile
Critical Quality Attributes	Critical Analytical Procedure Attributes
Risk Assessment	Risk Assessment
Design Space	Method Operable Design Region
Control Strategy	Analytical Procedure Control Strategy
Continued Process Verification	Continued Analytical Procedure Verification

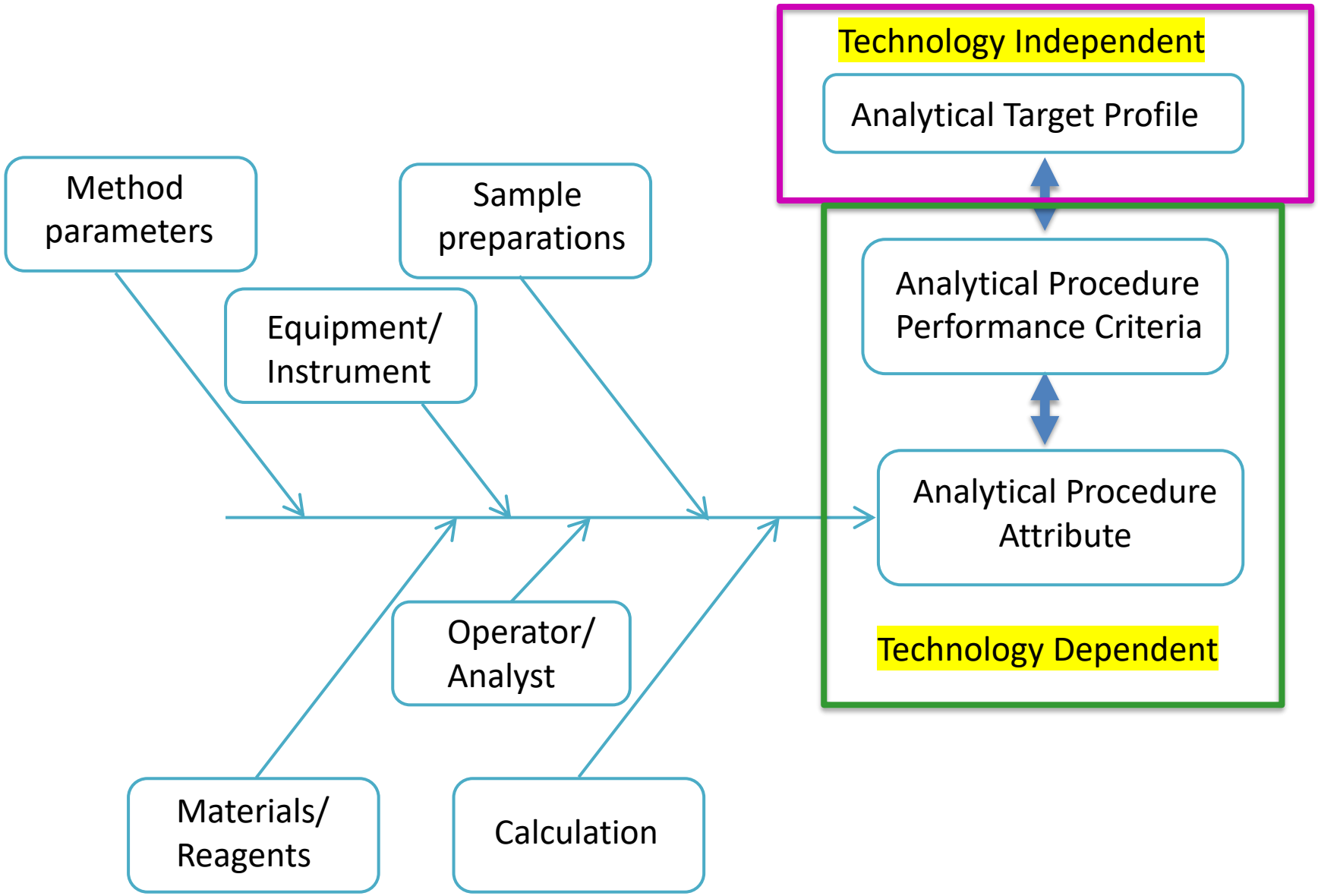
Analytical Procedure Lifecycle



ICH Seeks to Harmonise Definitions:

- ATP (Analytical Target Profile)—A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement
  - "Fit for purpose"
  - More than one technology may deliver this performance

Risk and ATP


Technology Independent
Analytical Target Profile
Method parameters
Sample preparations
Equipment/ Instrument
Analytical Procedure Performance Criteria
Analytical Procedure Attribute
Operator/ Analyst
Technology Dependent
Materials/ Reagents
Calculation

Minimal (traditional) *versus* Enhanced

- The traditional approaches of analytical procedure validation, transfer and verification need to be integrated into the analytical procedure life-cycle planning
  - Minimal: limited understanding of effects of variation on performance – generally does not permit understanding the root cause
  - Enhanced: Structured methodological approach to identify and explore variables.
    - Understanding the root cause of the variables
    - Ability to identify a change when it happens
    - Ability to identify the root cause of the change
- Not a new concept: Being adopted for manufacturing processes but not so much on the analytics side.

Minimal vs. Enhanced

Minimal (*a.k.a.* Traditional)

- Identify attributes to be tested
- Select appropriate technology and related instruments
- Conduct appropriate development studies (including robustness)
- Define analytical procedure description and control strategy (system suitability and parameter settings)

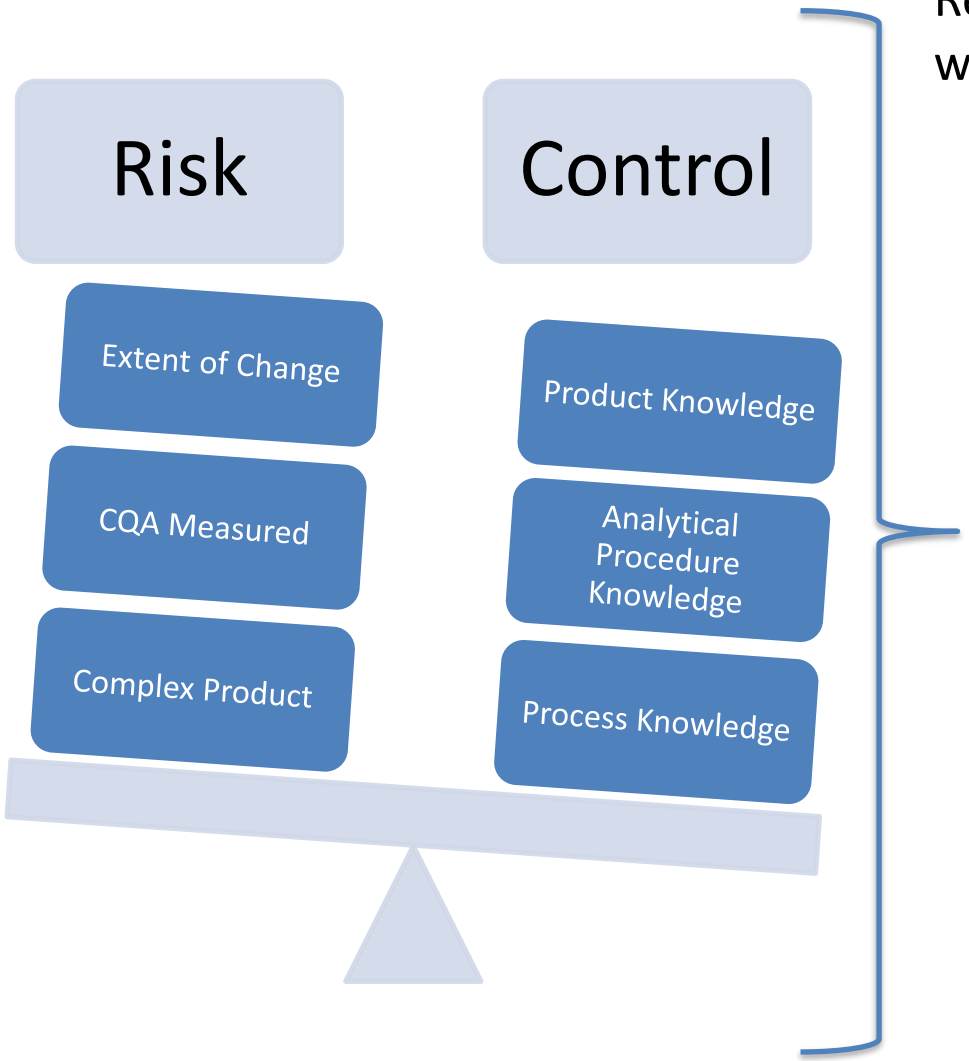
Enhanced (Minimal +)

- Evaluation of the sample properties
- Defining the ATP
- Conducting risk assessment and evaluating prior knowledge
- Conducting uni- or multi-variate experiments
- Defining an analytical procedure control strategy (ranges or set points
- Defining a lifecycle change management plan (ECs, PARs, MODR)

Established Conditions

- ECs for analytical procedures in line with ICH Q12
- Nature and extent of ECs depends on development approach, complexity of the analytical procedure and demonstrated understanding
- With a minimal approach, the number of ECs may be extensive with fixed analytical procedure parameters and set points
- In the enhanced approach an increased understanding of analytical procedure parameters and impact on performance facilitates identification of which factors require control and thus enable a more appropriate set of ECs (examples in Q14 Annex A).
- ECs can be focused on performance characteristics (e.g., specificity, accuracy, precision)

Change, Risk and Reporting



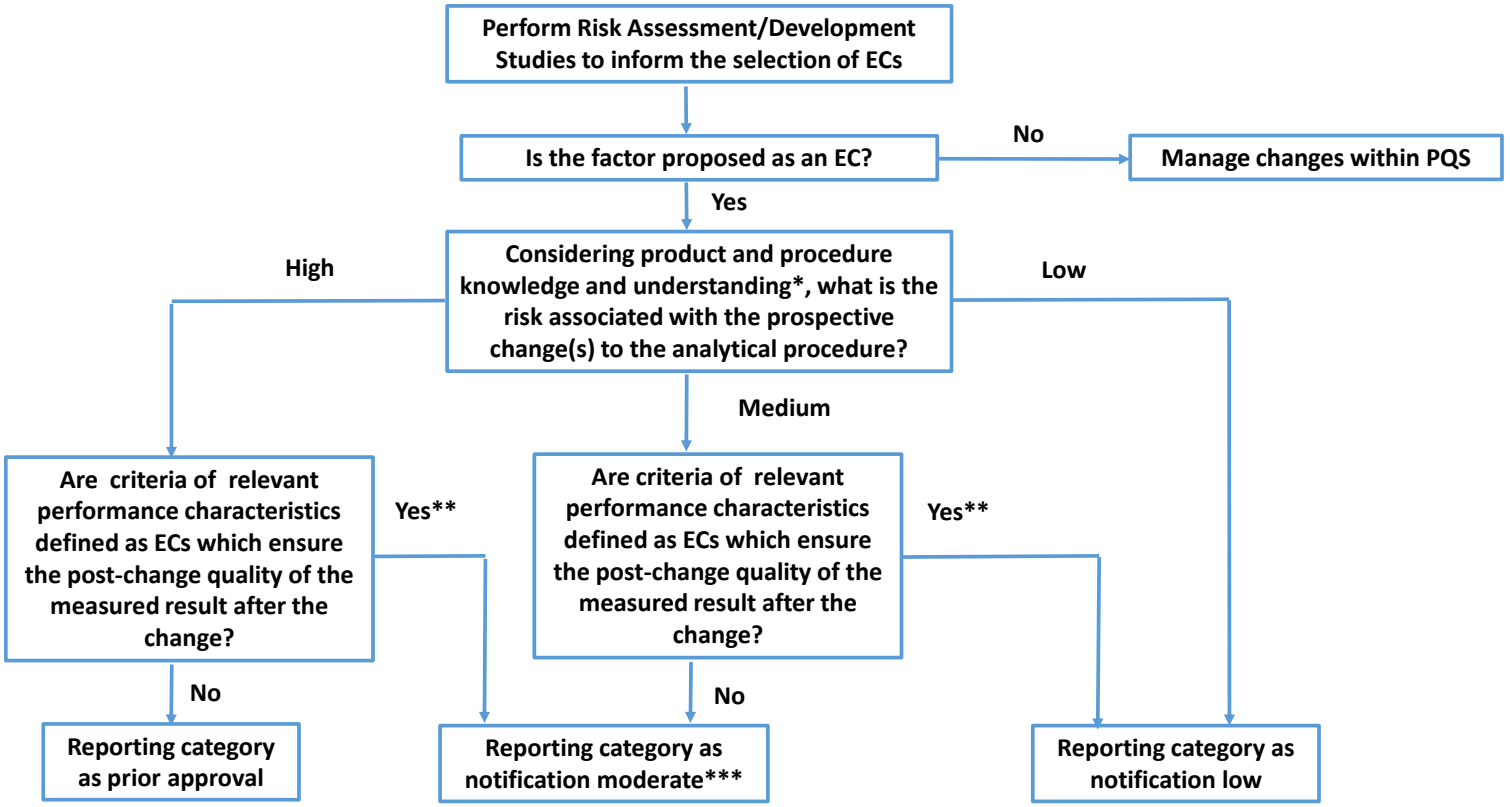
Reporting Category agreement with regulator using Q12 tools

High

Med

Low

Lifecycle Management and Post-Approval Changes of Analytical Procedures



* Including analytical procedure control strategy

** Sufficient information or prior knowledge should be available to design appropriate future bridging studies

*** In some cases, moderate risk changes proposed by the company may require prior approval based on health authority feedback

Q2(R1) → Q2(R2)

- Q2(R1) was adopted in the 1990s and primarily described validation for univariate chromatography methods
- Previously has been widely adapted to other technology in a variety of ways
- Q2(R2) guidance helps incorporate analytical procedures that use newer technology with an adaptable framework approach
  - Analytical procedures based on multivariate measurements
  - Applies concepts of risk and change management

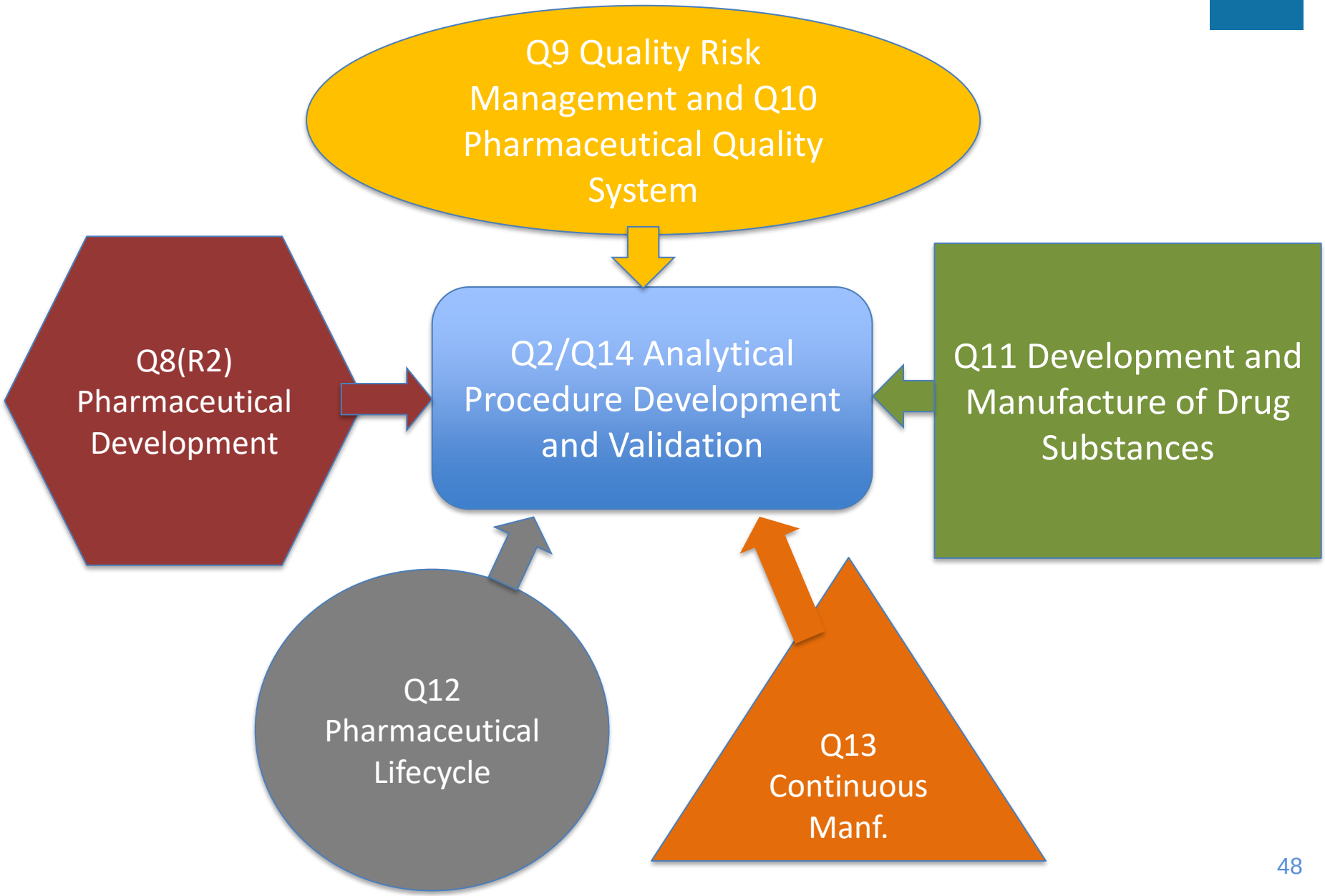
Q14/Q2

- Inextricably linked: What is developed is validated.
- For use to ensure the quality of DS, DP and the manufacturing process
- Traditional approach versus the enhanced approach as per ICH Q8: you have a choice
- Not a new regulatory requirement
- Robustness and System Suitability are established during development

Scope of Q2/Q14

- Keep univariate guidance for chromatography.
- Add multivariate guidance (*e.g.,* NMR, MS, NIR) for spectroscopic methods
- Add Real Time Release Testing validation
- Enhanced Approach versus Traditional Approach
- Analytical Procedure Lifecyle
  - Risk and change management
- Provide a framework that allows analytical innovation

ICH Q-Guideline Continuum



Possibilities

- Harmonized approach for submissions
- Greater level of analytical detail in applications
- Greater assessor understanding
- Fewer rounds of information requests
- Fewer ECs
- More approved MODRs
- Less post-approval supplements for analytical procedure changes

Current Status of Q14 and Q2(R2)

- The documents have been signed off as *Step 2* documents (endorsed on March 22, 2022) and are being issued by the ICH Regulatory Members for public consultation
- The documents were developed based on a Concept Paper (15 November 2018) and a Business Plan (15 November 2018)
- Targeting finalization as *Step 4* documents to be implemented in the local regional regulatory system: May 2023

Expert Working Group – Organizational membership

Rapporteur: Yukio Hiyama (MHLW/PMDA)
Regulatory chair: David Keire (FDA)
ANVISA, Brazil
BIO
EC, Europe
EFPIA
FDA, US
HSA, Singapore
IGBA
JPMA
MFDS, Rep. of Korea
MHLW/PMDA, Japan
NMPA, China
PhRMA
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