2026년

ICH 가이드라인 교육

Training on ICH Guideline 2026

2026.10. 01.(Thu) – 10. 02.(Fri) I EL Tower(엘타워), Seoul

DAY 1 I 품질 & 복합 교육

Q2(R2)/Q14



Jean-Francois Dierick

GSK R&D/ 분석개발 전략적 분석법 검증 및 라이프사이클 관리 책임자

GSK R&D/ Analytical Development, Strategic Analytical Validation and Lifecycle Lead

Jean-Francois Dierick은 벨기에 University of Namur에서 세포 노화의 프로테오믹스(proteomics of cellular ageing) 분야로 생물학 박사(Ph.D.) 학위를 취득했으며, 이후 벨기에 Université libre de Bruxelles에서 프로테오믹스 분야의 박사후연구원(Postdoctoral Researcher) 과정을 수행했습니다.그는 SGS에서 제약 분야 경력을 시작했으며, 벨기에 비에르주(Bierges) 사업장의 생물학 부서장(Head of Biology Department) 을 맡아 조직을 이끌었습니다.18년 전 GSK Vaccines에 합류한 이후에는 개발 및 상업화 부문에서 생물학적 제제의 분석(Analytics) 과 관련된 다양한 직책을 수행해 왔습니다.현재는 GSK의 Analytical R&D 부서에서 Strategic Analytical Lifecycle Lead(전략적 분석법 라이프사이클 리드) 로 근무하며, 분석법 라이프사이클 전략을 총괄하고 있습니다. 그의 주요 업무는 분석법 밸리데이션(Analytical Method Validation), 기술이전(Transfer), 분석용 물질(Materials) 관리 등을 포함한 분석법 라이프사이클 전략의 수립과 운영입니다.
Jean-Francois Dierick holds a PhD In Biology from the University of Namur (Be), in the field of proteomics of cellular ageing and a post-doc in proteomics from the University of Brussels (Be). Jean-Francois Dierick entered the pharmaceutical world working for SGS, where he was leading the Biology Department from the site of Bierges (Be). Heigtheen years ago, he joined GSK Vaccines where he has occupied several positions related to analytics of biological products both in the development and the commercial areas. Today, he is working for GSK, in the Analytical R&D department, as Strategic Analytical Lifecycle Lead, being in charge of Analytical Lifecycle strategies (Analytical Method Validation, Transfer, Materials, ···).

Program

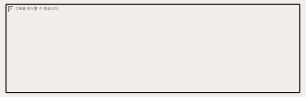
ICH Q2(R2) 및 Q14에 따른 분석법 수명주기 관리의 기회와 과제

Opportunities and Challenges from ICH Q2 (R2) and Q14 for the Analytical Lifecycle

The new version of ICH Q2 (R2) “Validation of Analytical Procedure” and the new ICH Q14 “Analytical Procedure Development” have been approved recently. Beside modernizing the text and addressing topics in the mood of time (Real-Time-Release, multivariate models, ···), these two guidelines bring the concepts of Analytical Quality by Design through the description of an “enhanced approach”. Opportunities like reuse of development data and abbreviated validation of platform procedures are addressed but not in great details, and probably to an extent that does not allow the immediate realization of the game changing potential of the application of AQbD concepts to (platform) analytical procedures development, validation and lifecycle.The objective of the presentation is to share a vision where the concepts from the enhanced approach (ATP, risk management, knowledge management, validation, assay control strategy, change management) can accelerate the availability of more robust validated (platform) analytical procedures, can facilitate the extension of usage to new products, and contribute to the reduction of product development lead time. The positioning will be knowingly progressive in order to stretch towards the most ambitious vision and to envisage together the long-range benefits that are possible but not promised and, in any case, depend on how we will implement ICH Q2 and Q14.

Opportunities and Challenges from ICH Q2 (R2) and Q14 for the Analytical Lifecycle

Jean-Francois Dierick



October 2026

Disclosure statement

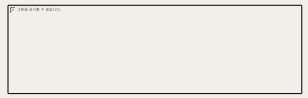
Jean-Francois DIERICK is an employee of the GSK group of companies.

This work was sponsored by GlaxoSmithKline Biologicals SA.

Content of the presentation

- ICH Q2 (R2) and Q14, what's new?
- ICH Q2 (R2) and Q14, "new" concept.
- ICH Q2 (R2) and Q14, opportunities.
- ICH Q2 (R2) and Q14, Platform Analytical Procedures.
- ICH Q2 (R2) and Q14, Established Conditions.
- ICH Q2 (R2) and Q14, where it may lead us?

ICH Q2 (R2) and Q14, what's new?



ICHQ2 (R2) and ICHQ14

What's new? (1/2)

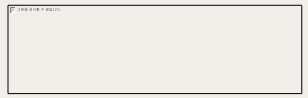
- These guidelines describe an **enhanced approach** that can be applied in full or partially as an alternative to a **minimal** (also known as **traditional**) **approach** for the **development** (Q14)**, validation** (Q2) **and maintenance** (Q14) of analytical procedures.
- This enhanced approach relies on the concepts of **Analytical Quality by Design** : **science and risk-based** approaches, the use of **prior knowledge** and **ATP**.
- Q14 proposes to evaluate **robustness as from the development phase,** using the principles of the enhanced approach (identification and evaluation of critical method parameters,…). But it can still be part of validation.
- New validation expectations in Q2 regarding generation and interpretation of confidence intervals
  - "*…interval should be compatible with the corresponding accuracy/precision acceptance criteria, unless otherwise justified*"
- Q14 and Q2 propose that, <u>in some cases and according to proper justification and documentation</u>, procedure **development data can be used in lieu of validation data**.
- Adaptation of some requirements related to the evaluation of linearity to support biological methods (Q2).

ICHQ2 (R2) and ICHQ14

What's new? (2/2)

- The guidelines describe considerations for the development/validation of
  - **platform methods**: abbreviated validation
  - **multivariate** analytical procedures: validation requirements
  - and for **real time release testing.**
- Using the tools described in **ICH Q12**… the guidelines describe principles to support **change management** opportunities for **more efficient regulatory approaches** to related post approval changes
- Proposing the establishment of an Analytical Procedure Control Strategy that will be used to monitor the performance of the method during its usage.

ICH Q2 (R2) and Q14, “new” concept



The concepts

The essence

Less of a
systematic « check the boxes » approach
More of a
systematic « understand and manage your risks » approach

Systematic

Science-driven

Identify the risks (risk=knowledge)
Score the risks (this is also knowledge)

Identify what knowledge is needed
to score / manage the risk
(do DoE when it helps)

- Analytical Quality by Design principles (AQbD): Science and Risk-based approaches throughout the entire analytical lifecycle

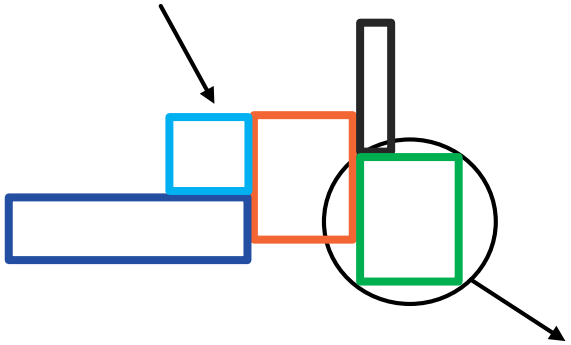
Integrated approach
from development
to routine use
and subsequent changes

The concepts

A schematic vision of the operating principles

A product

and its different attributes



Some of these attributes

will require control

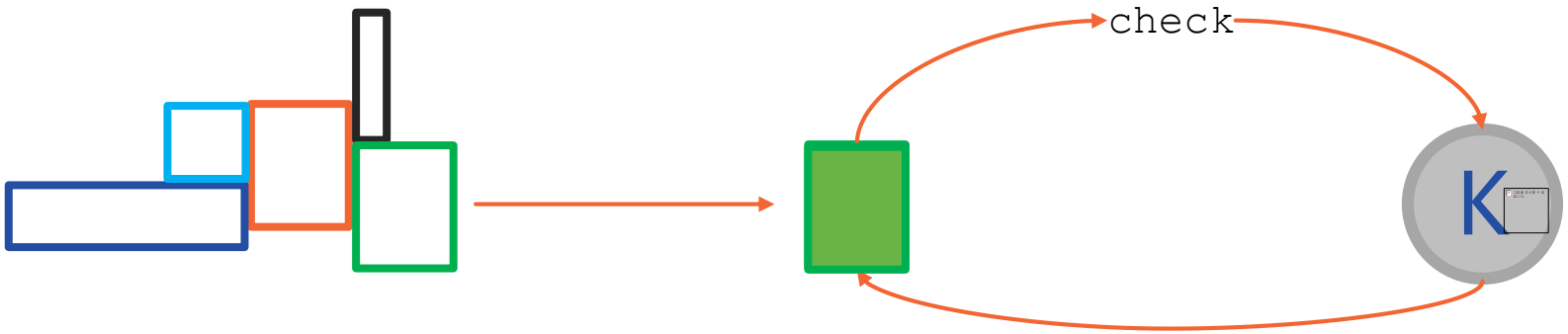
through measurement with an Analytical Procedure

This is the start of the Analytical Lifecycle … and AQbD

The concepts

A schematic vision of the operating principles

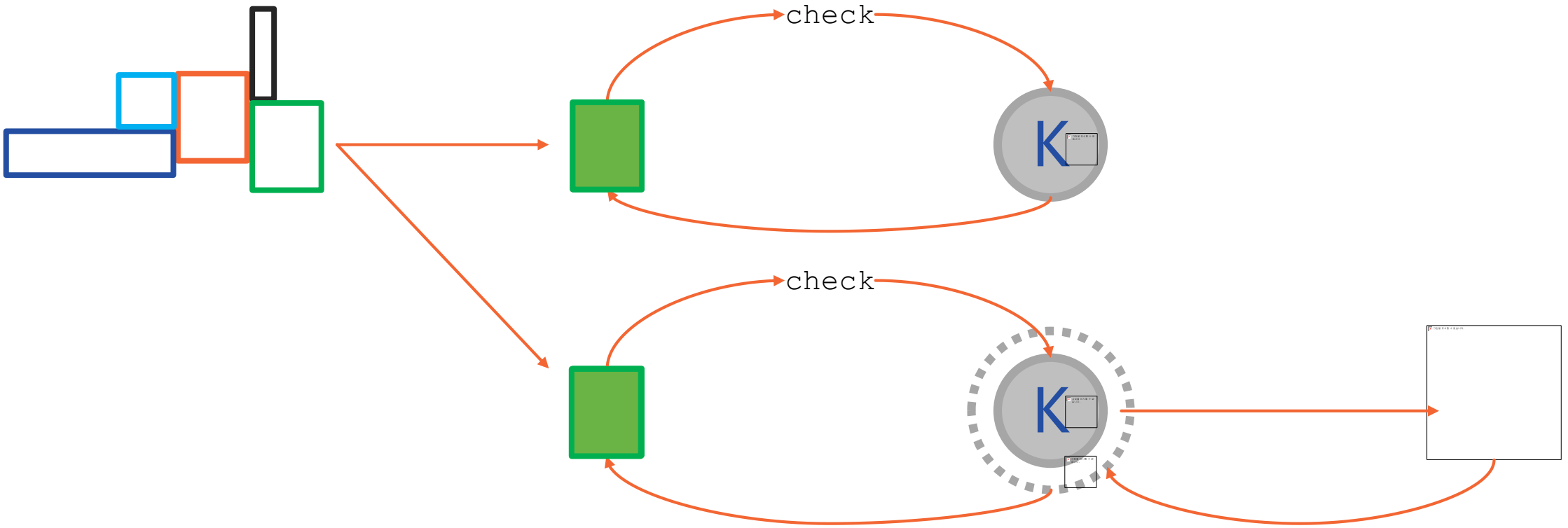
Product **R**equirement **K**nowledge



The concepts

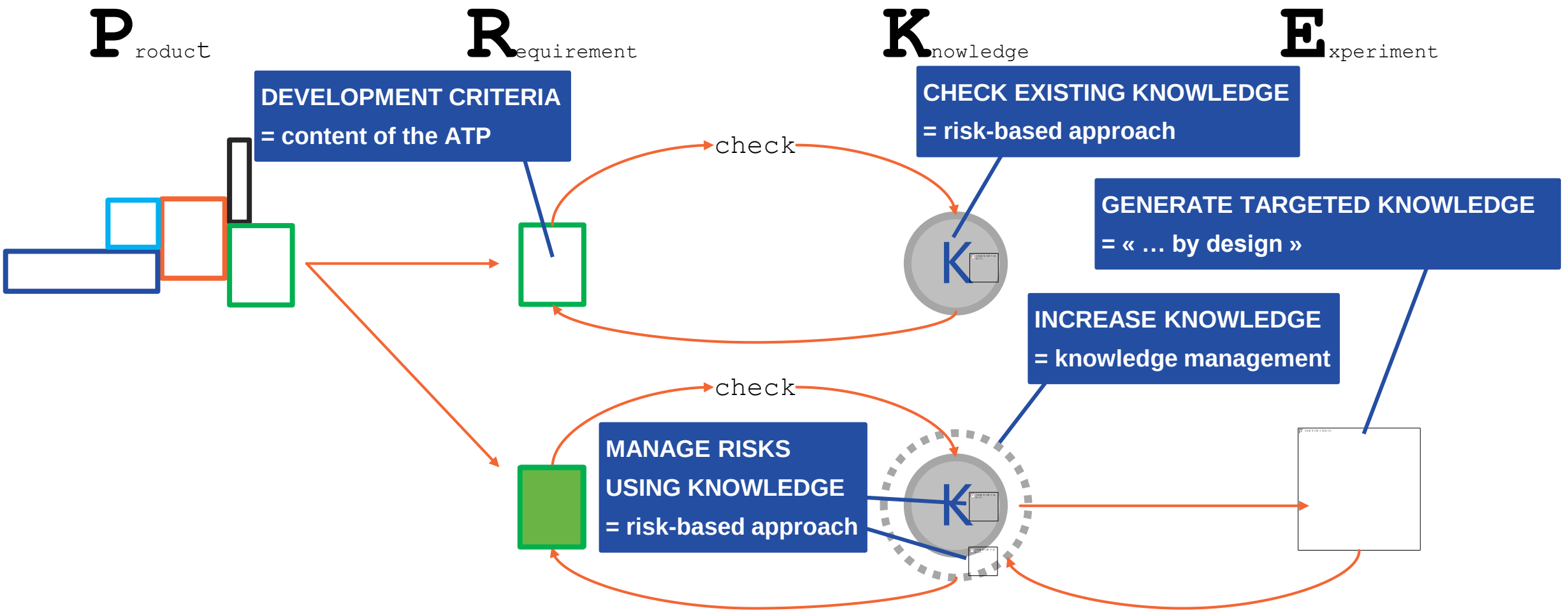
A schematic vision of the operating principles

Product **R**equirement **K**nowledge **E**xperiment



The concepts

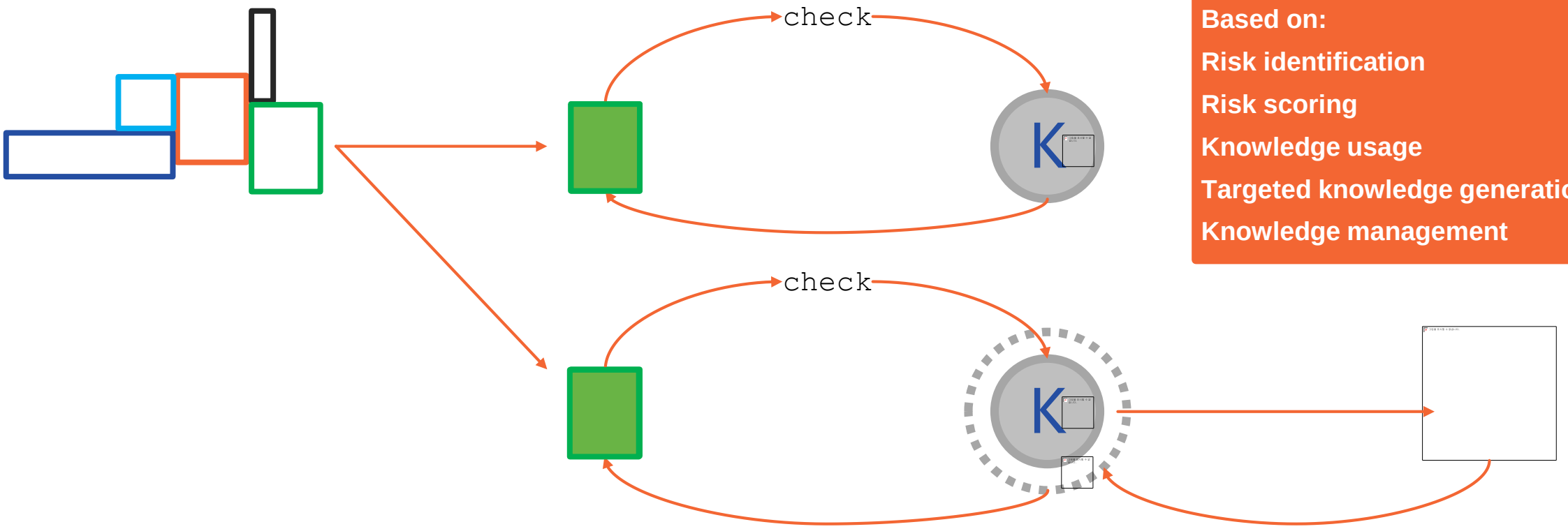
A schematic vision of the operating principles



The concepts

A schematic vision of the operating principles

Product **R**equirement **K**nowledge **E**xperiment



SPECIFIC ITERATIVE APPROACH

Based on:

Risk identification

Risk scoring

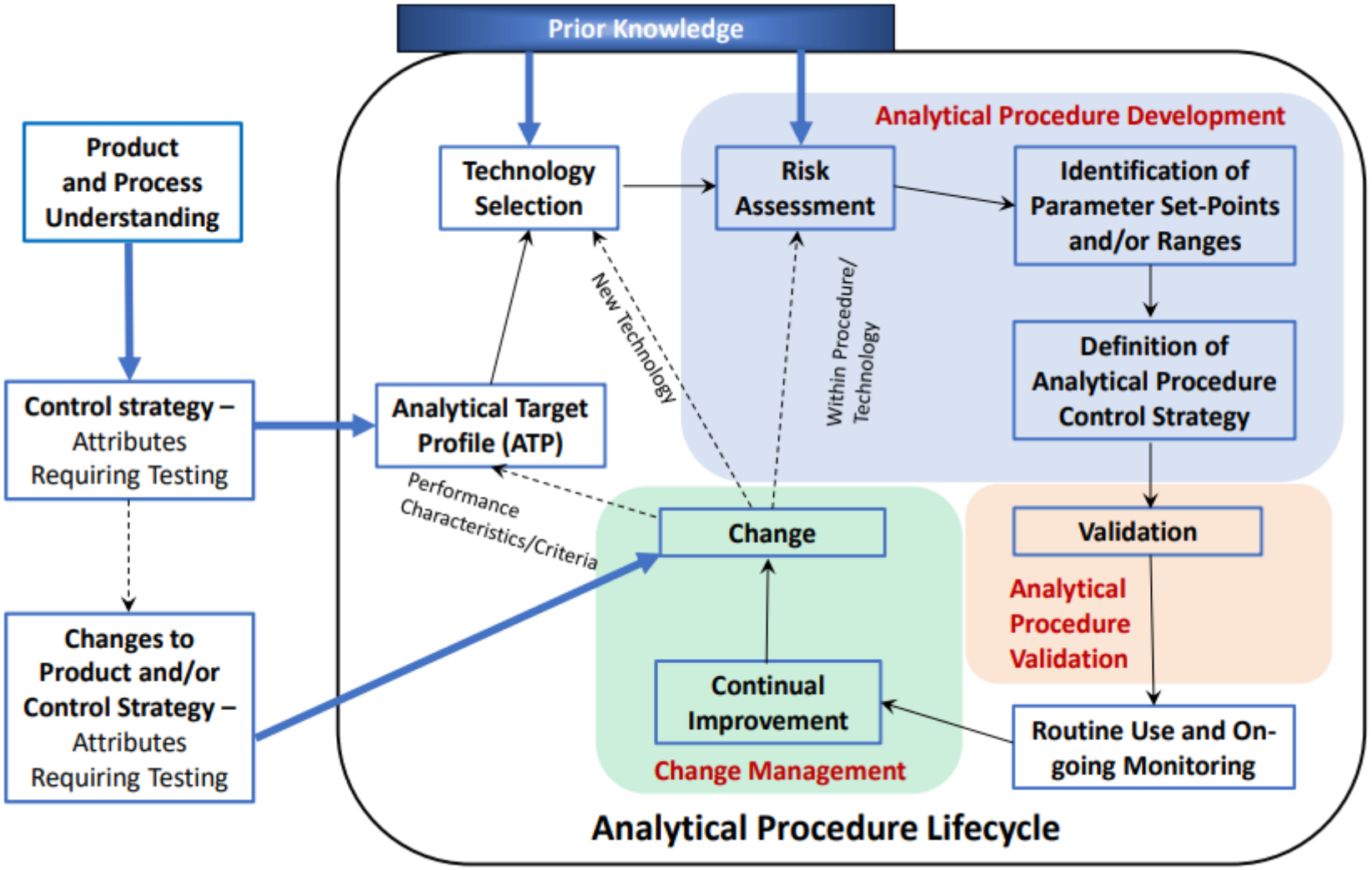
Knowledge usage

Targeted knowledge generation

Knowledge management

ICHQ2 (R2) and ICHQ14, “new” concept

Vision of the analytical lifecycle

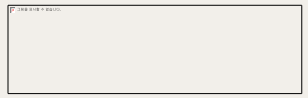


Extracted from ICH Q14

These operating principles are used all along the analytical lifecycle described in ICH Q14:

- Development of Analytical Procedure
  - Technology selection
  - Characterization of method parameters
  - Definition of set points for method parameters
  - + *Iterative dimension*
  - Establishment of Analytical Procedure Control Strategy (APCS)
- Validation of Analytical Procedure
- Definition of Established Conditions for an Analytical Procedure
- Post-Approval Changes management

ICH Q2 (R2) and Q14, opportunities



ICHQ2 (R2) and ICHQ14, new opportunities

Procedure Development

- Technically speaking, the principles of AQbD are widespread and well understood in the field.
- It is also acknowledged that applying these principles brings robust procedures.
- Sometimes there is the perception that applying the enhanced approach proposed by ICH Q14 relies (only/mainly) on huge Designs of Experiments (DoEs) that consume a lot of resources and this, for outcomes similar than those obtained when using the minimal approach and scientific expertise.

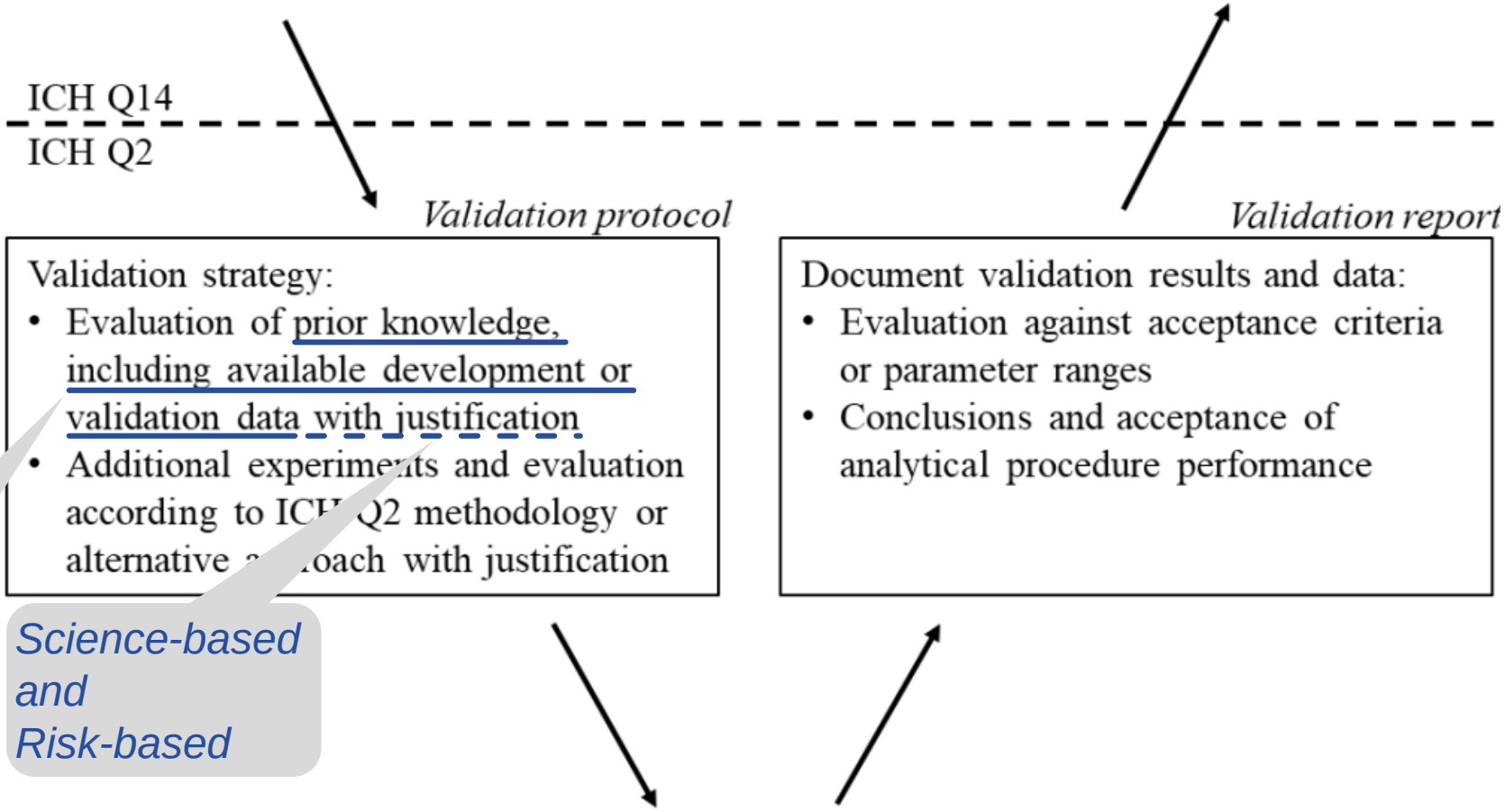
  This perception should evolve towards a systematic approach of risk management through the use of prior knowledge (including scientific expertise) and the generation of targeted knowledge (potentially through DoEs). This would lead to focusing resources and efforts where needed.
- The value of the knowledge generated during development for the validation and commercial spaces is still not fully understood from an operational perspective (see further).

The concepts from ICH Q2 Q14

Validation of analytical procedure: a guiding principle

- Objectives/performance characteristics
- Analytical procedure
- Appropriate development data
- Prior knowledge

- Analytical procedure lifecycle management



Prior-knowledge

Science-based and Risk-based

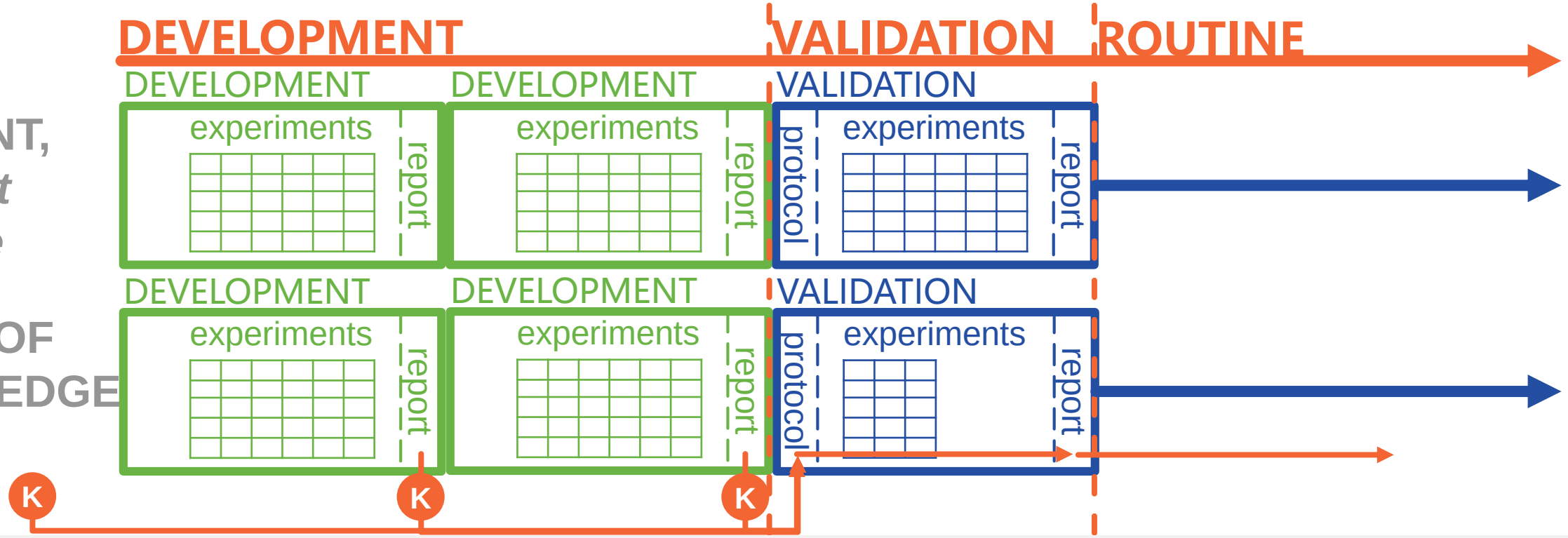
Extracted from ICH Q2 (R2) – Figure 1 Validation study design and evaluation

ICHQ2 (R2) and ICHQ14, new opportunities

Procedure Validation

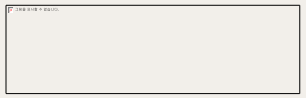
CURRENT, ***one shot exercise***

REUSE OF KNOWLEDGE



- Knowledge is transferred and reused from one stage to the next. (Knowledge = conclusion from previous study)
- The conditions of acquisition of knowledge must be auditable and justified as representative of future procedure.
- More difficult to apply on quantitative performance parameters: Precision, Accuracy, Linearity and Range

PLATFROM PROCEDURES and abbreviated validation



Platform Analytical Procedure

Definition

Practically, you can consider an entire procedure as the platform or only a part of a procedure (sample preparation *vs* read out, cell culture *vs* read out, …).

- From ICH Q2 Q14 Step 2 drafts:

PLATFORM ANALYTICAL PROCEDURE

An analytical procedure that is suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure. This type of analytical procedure can be used to analyse molecules that are sufficiently alike with respect to the attributes that the platform analytical procedure is intended to measure. *(ICH Q2)*

Extracted from ICH Q2 (R2) – 4 Glossary

Must be understood as « multiple products » or « multiple production intermediates from a same product »

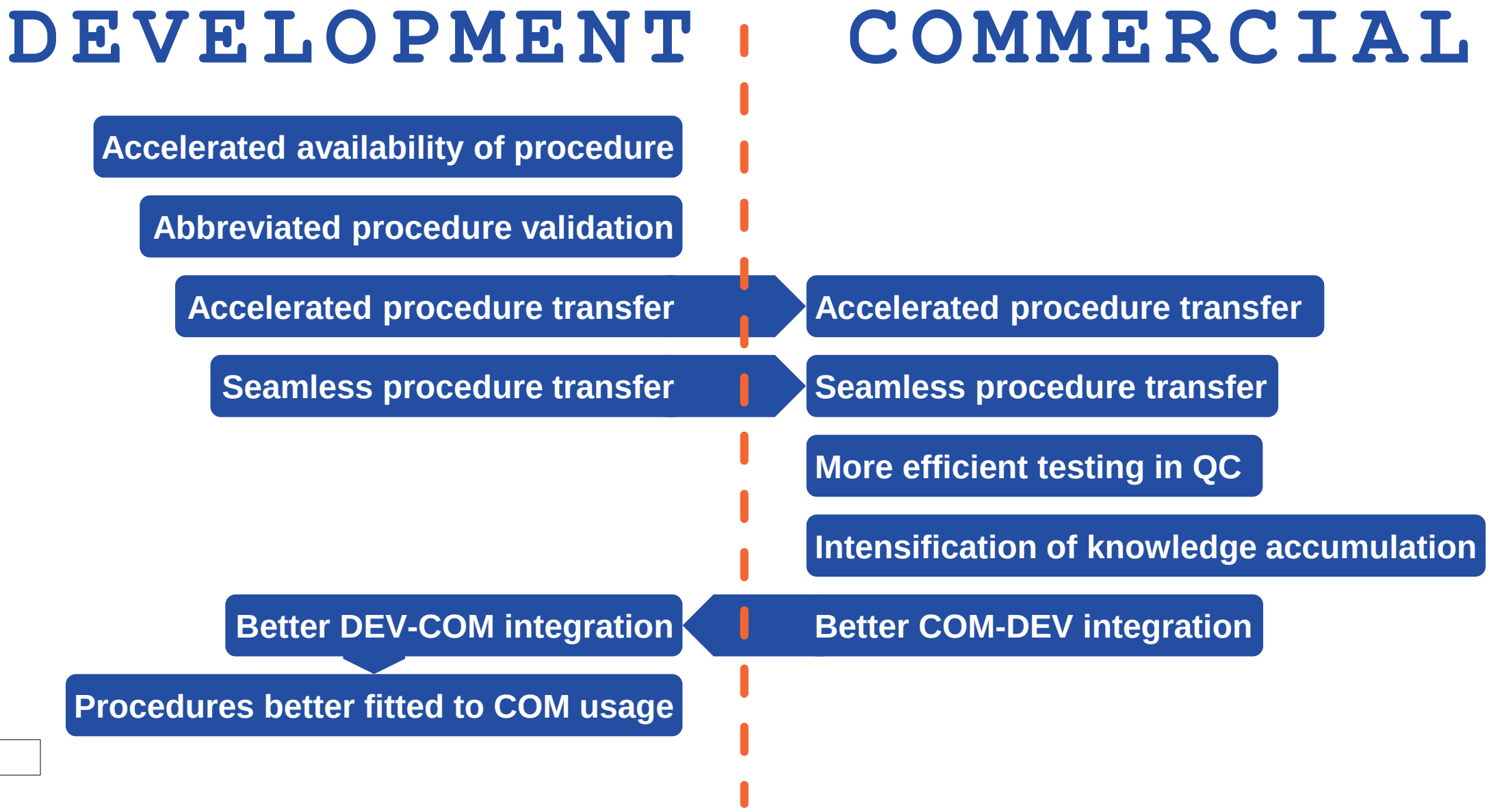
A rule of the thumb would be to be able to analyse samples from different products in the same analytical session.

« significant »→ depending on risk

A platform TECHNOLOGY (HPLC, FACS) is another level compared to platform METHOD/PROCEDURE

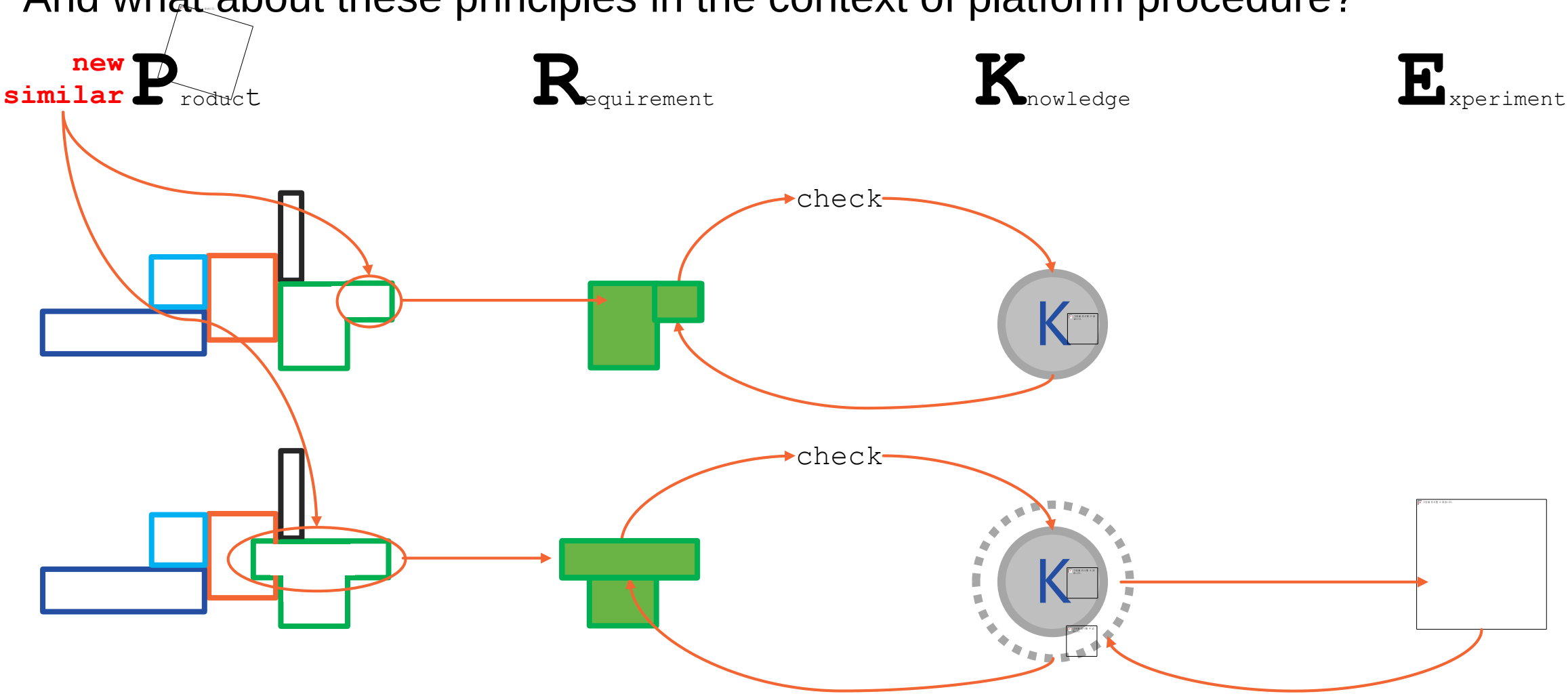
A platform TECHNOLOGY might be deployed, developed or validated in standard/harmonized way but its validation for its use on one product cannot stand for another product

Opportunities from Platform Analytical Procedures?



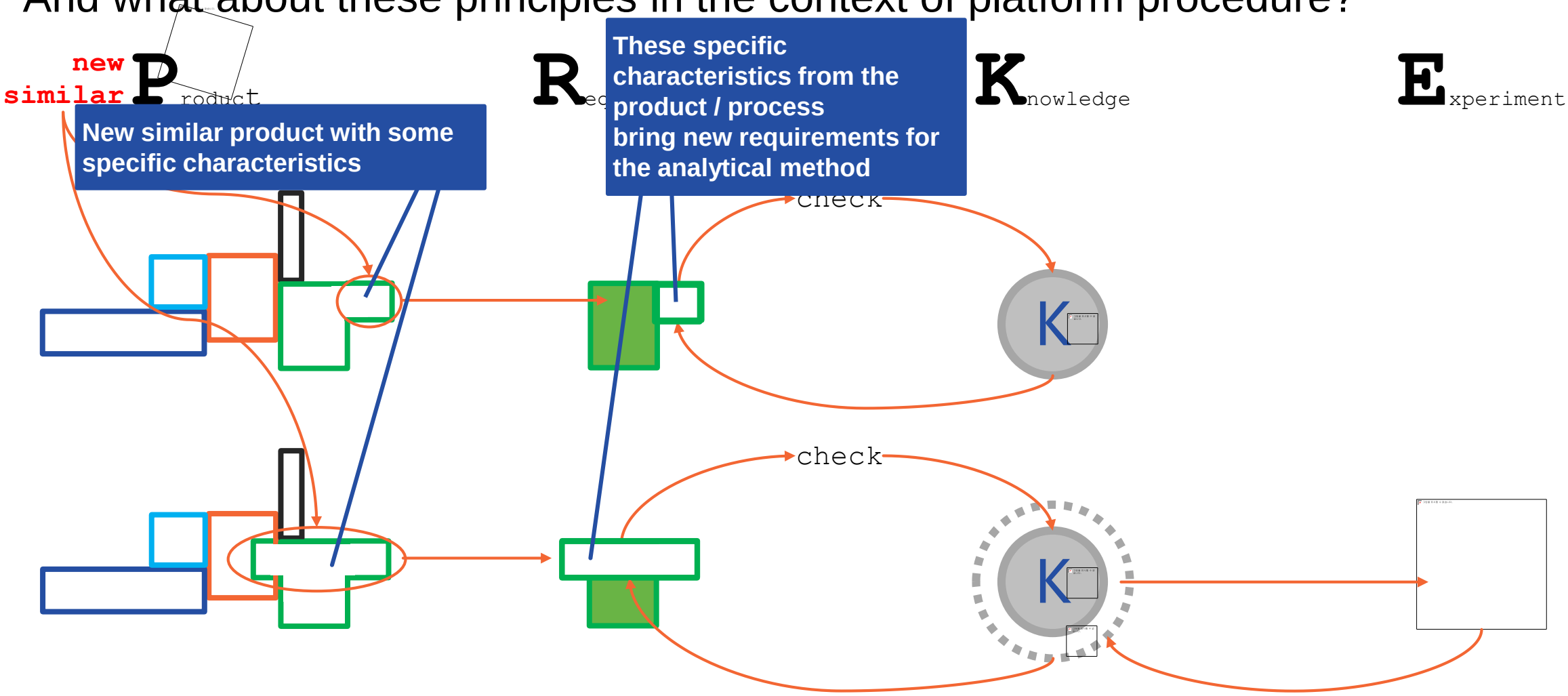
The concepts

And what about these principles in the context of platform procedure?



The concepts

And what about these principles in the context of platform procedure?



Platform Analytical Procedure

Progressive interpretation

- From ICH Q2 Q14 Step 2 drafts:

PLATFORM ANALYTICAL PROCEDURE

An analytical procedure that is suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure. This type of analytical procedure can be used to analyse molecules that are sufficiently alike with respect to the attributes that the platform analytical procedure is intended to measure. *(ICH Q2)*

Extracted from ICH Q2 (R2) – 4 Glossary

studies (see ICH Q14) can be used as part of validation data. When an established *platform analytical procedure* is used for a new purpose, validation testing can be abbreviated, if scientifically justified.

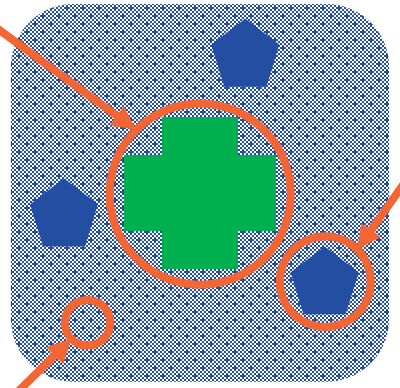
Extracted from ICH Q2 (R2) – 2 General considerations for analytical procedure validation

Science-based and Risk-based

Consideration for an abbreviated validation strategy

The different types of methods

Measuring an attribute of an active component.
Ex: - content
- identity
- purity
- aggregation
- modification
-…

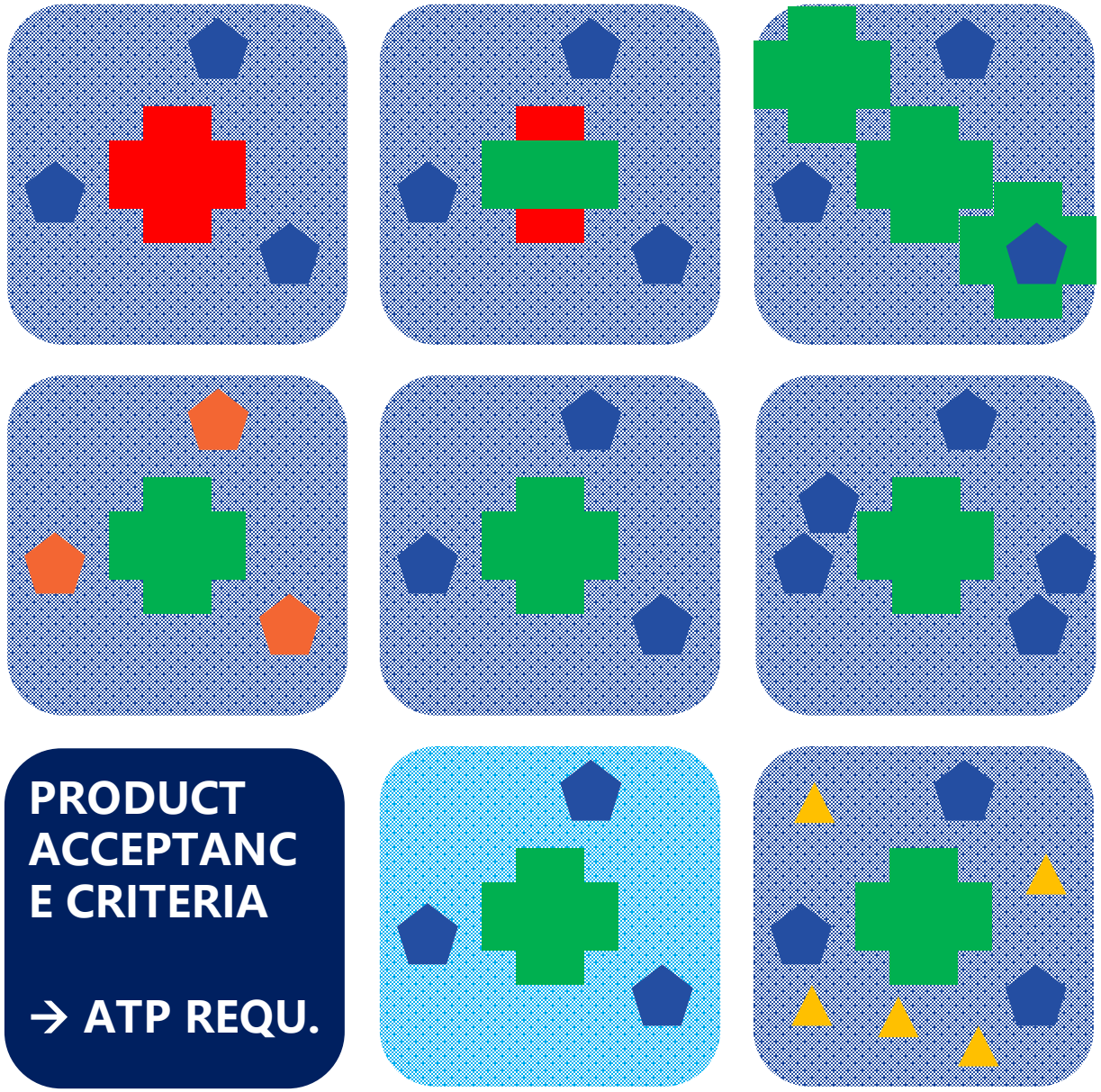


Measuring the nature or content of:
- a process impurity
- a product impurity
- an excipient

Measuring a property from the sample solution.
Ex: - pH
- osmolarity
- bioburden
- sterility
- endotoxin
-…

Consideration for an abbreviated validation strategy

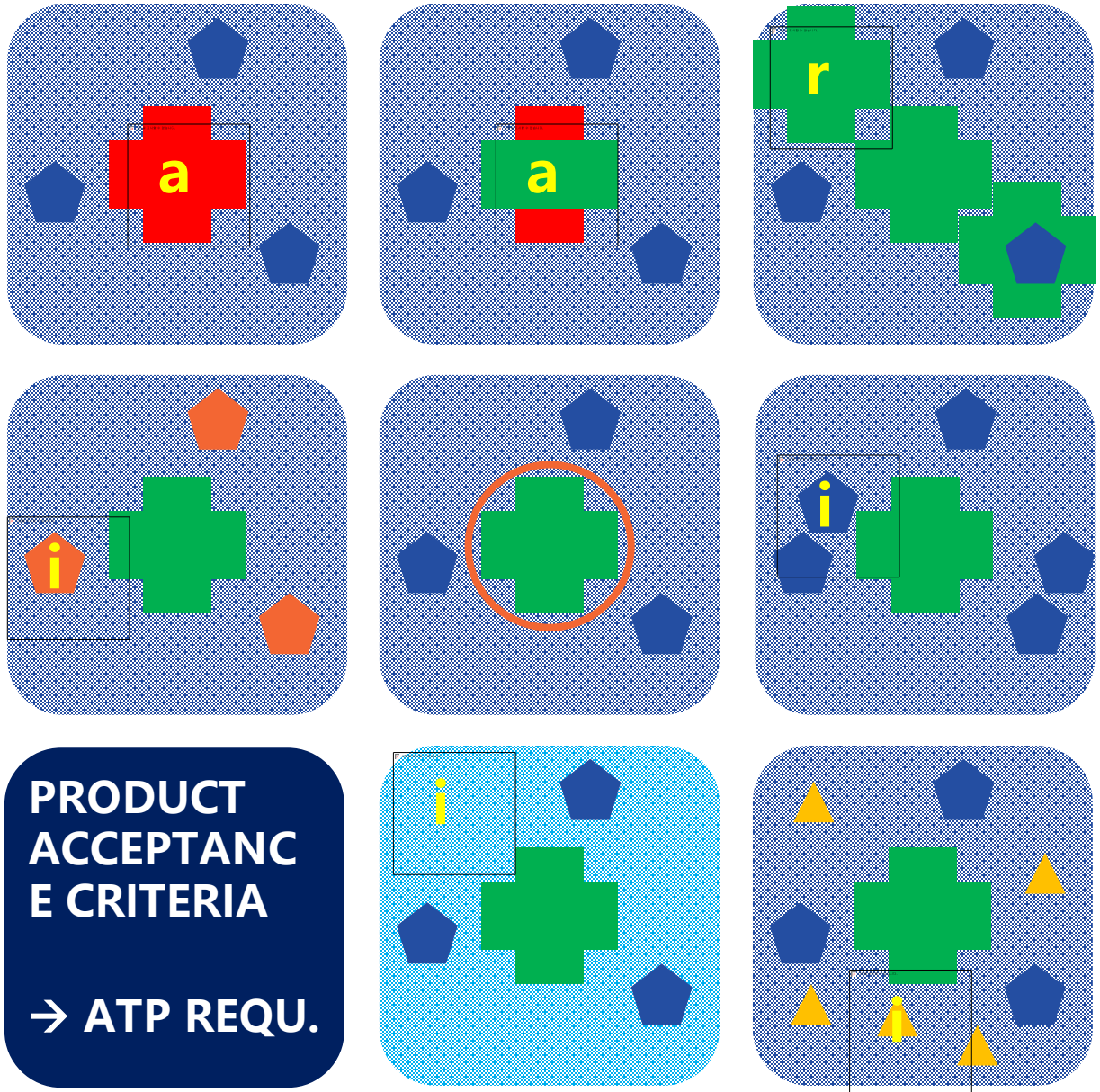
The different types of changes



As well as all the possible combinations between those cases.

Consideration for an abbreviated validation strategy

The different types of impacts of those changes



CHANGES IN:

a

Analyte nature or properties

r

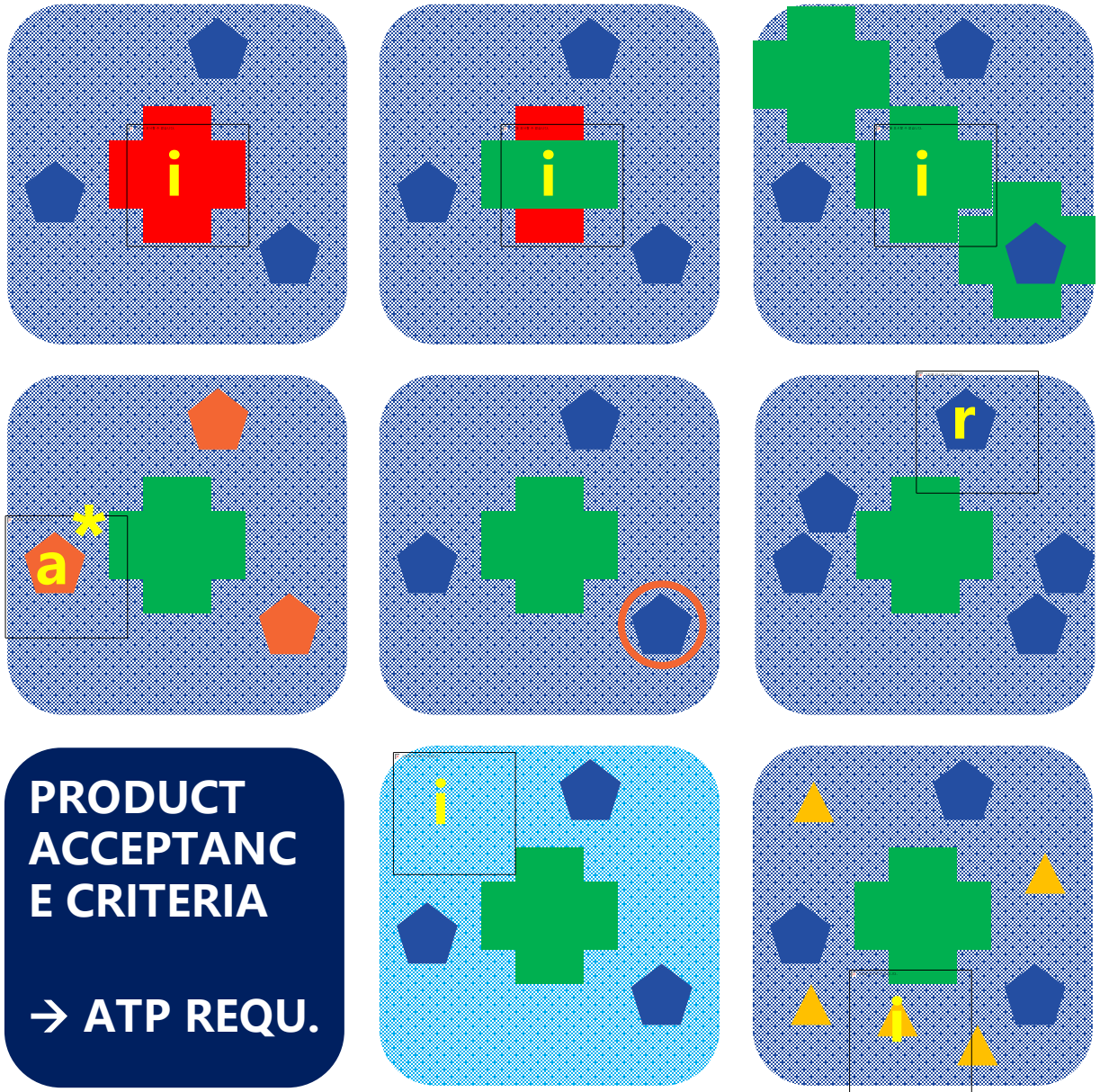
Range of analyte

i

Interference, nature or intensity

Consideration for an abbreviated validation strategy

The different types of impacts of those changes



CHANGES IN:

a

Analyte nature or properties

r

Range of analyte

i

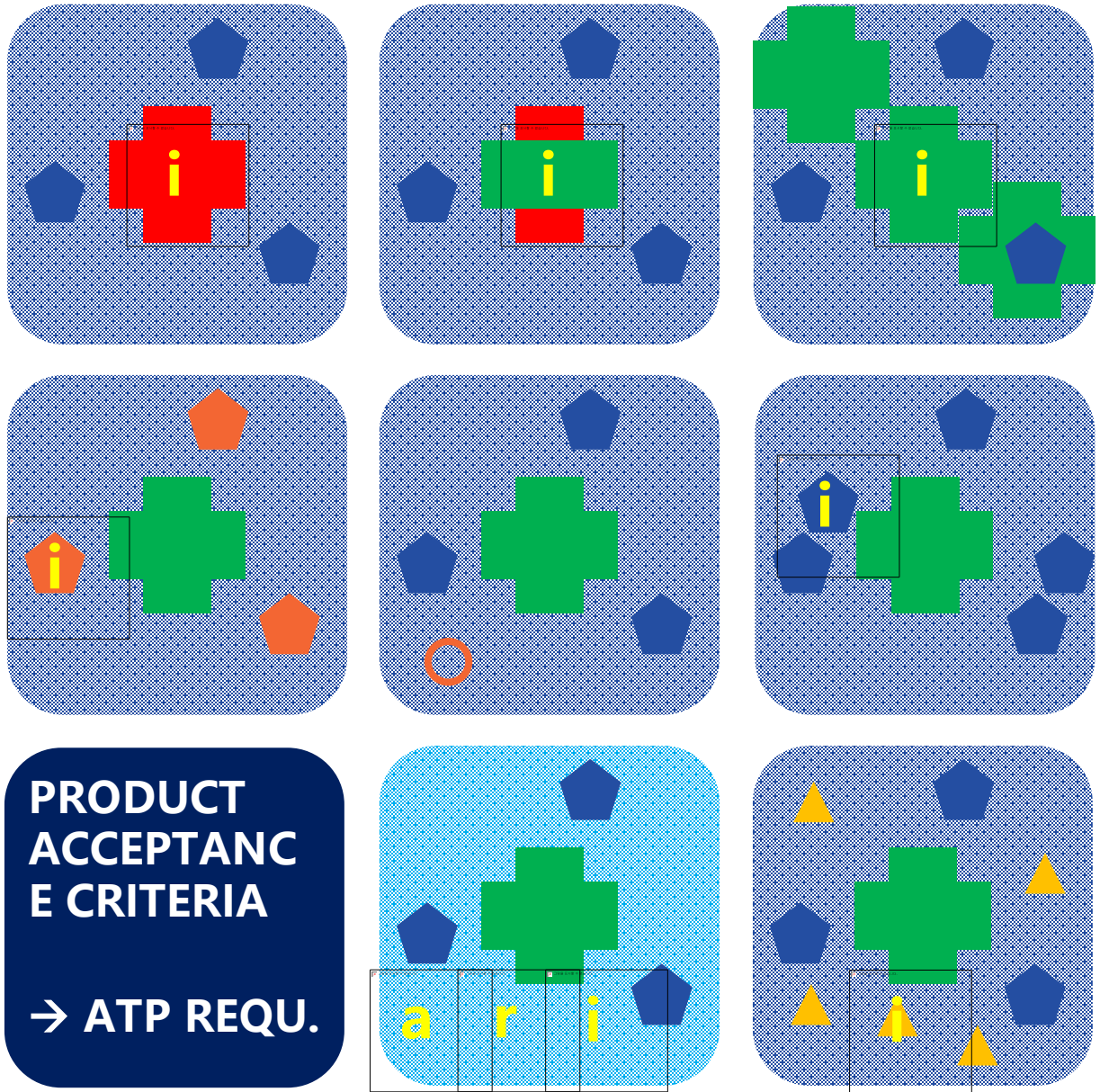
Interference, nature or intensity

*

Or N/A if a different method is used

Consideration for an abbreviated validation strategy

The different types of impacts of those changes



CHANGES IN:

a

Analyte nature or properties

r

Range of analyte

i

Interference, nature or intensity

Consideration for an abbreviated validation strategy

How to shape a platform validation strategy regarding those impacts?

- These changes when testing one product or another represent potential impacts.
- AQbD principles instruct us to perform a **risk assessment.**
- We must thus risk assess the potential impact of those changes on the **performances of the analytical methods**.
- And then take action according to the level of risk represented by these changes.
- The action can be to:
  - **Justify** that the current performances are applicable to the new product.
  - **Confirm** that the current performances are applicable to the new product.
  - **Evaluate** the performances of the method when testing the new product.

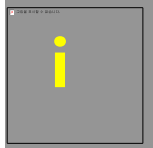
CHANGES IN:



Analyte nature or properties



Range of analyte



Interference, nature or intensity

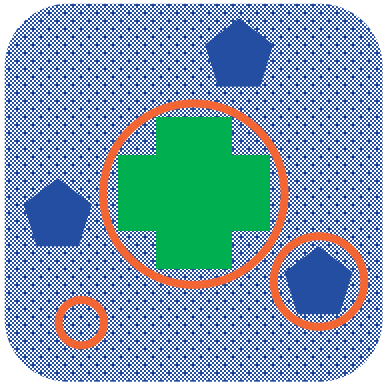
Consideration for an abbreviated validation strategy

How to shape a platform validation strategy regarding those impacts?

CHANGES IN:



Range of analyte



- In this situation, only the amount of the measured analyte is evolving, it should be quite straightforward to understand if the current validated range of the method is able to cover the new range with the same method performances.
- And this in both cases:
  - (a) When the sample dilution has not been adapted to accommodate with the different amount of analyte. In this case, a different range of amounts are measured but the sample dilution has not been modified.
  - (b) When the sample dilution has been adapted to accommodate with the different amount of analyte. In this case, the same range of amounts are measured but the sample dilution has been modified.
- In case (a) it is obvious if the current validated range is sufficient to cover new product.
  - If the range is covered: document justification. If not: perform validation complement
- In case (b) the question is to understand if the change in dilution impacts method performance.
  - This might potentially be justified.
  - If not, a confirmation from existing data should be possible.
  - In other cases (confirmation is not possible or not successful) a validation complement will be required to show fitness for purpose.

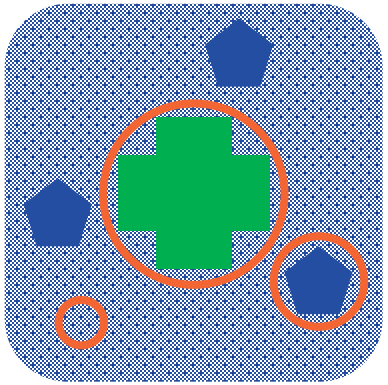
Consideration for an abbreviated validation strategy

How to shape a platform validation strategy regarding those impacts?

CHANGES IN:



Interference, nature or intensity



- In this situation the amount of something that is not measured with the method is changing. It is thus “only” a problem of potential interference, and it is about understanding if the new testing conditions can affect the performances of the method.
- Two main situations can be developed:
  - (a) The platform method has not been adapted to this new situation with the hypothesis that the potential new interference should be acceptable.
  - (b) The platform method has been adapted (but is still platform) to remove the interference (ex: adding a sample purification step).
- In case (a), the justification/confirmation that the potential interference has no impact on method performance might be sufficient. Otherwise, a validation complement should be executed in order to confirm the performances of the method are applicable to the new situation or measure new performances in this specific situation.
- In case (b), the justification/confirmation that the method adaptation does not impact method performance might be sufficient. Otherwise, a validation complement should be executed in order to confirm the performances of the method are applicable to the new situation or measure new performances in this specific situation.

Consideration for an abbreviated validation strategy

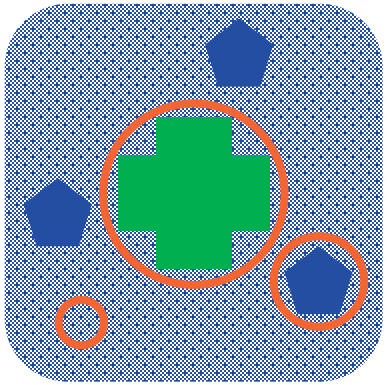
How to shape a platform validation strategy regarding those impacts?

CHANGES IN:

a

Analyte nature or properties

- In this situation the analyte itself is changing which probably represents a bigger technical challenge in the perspective of using a single platform method.
- However, some technologies allow to address some products attributes in a generic manner (SEC-UV or SEC-MALS for size, CGE for protein purity,…) and might be used to obtain true platform methods in those cases.



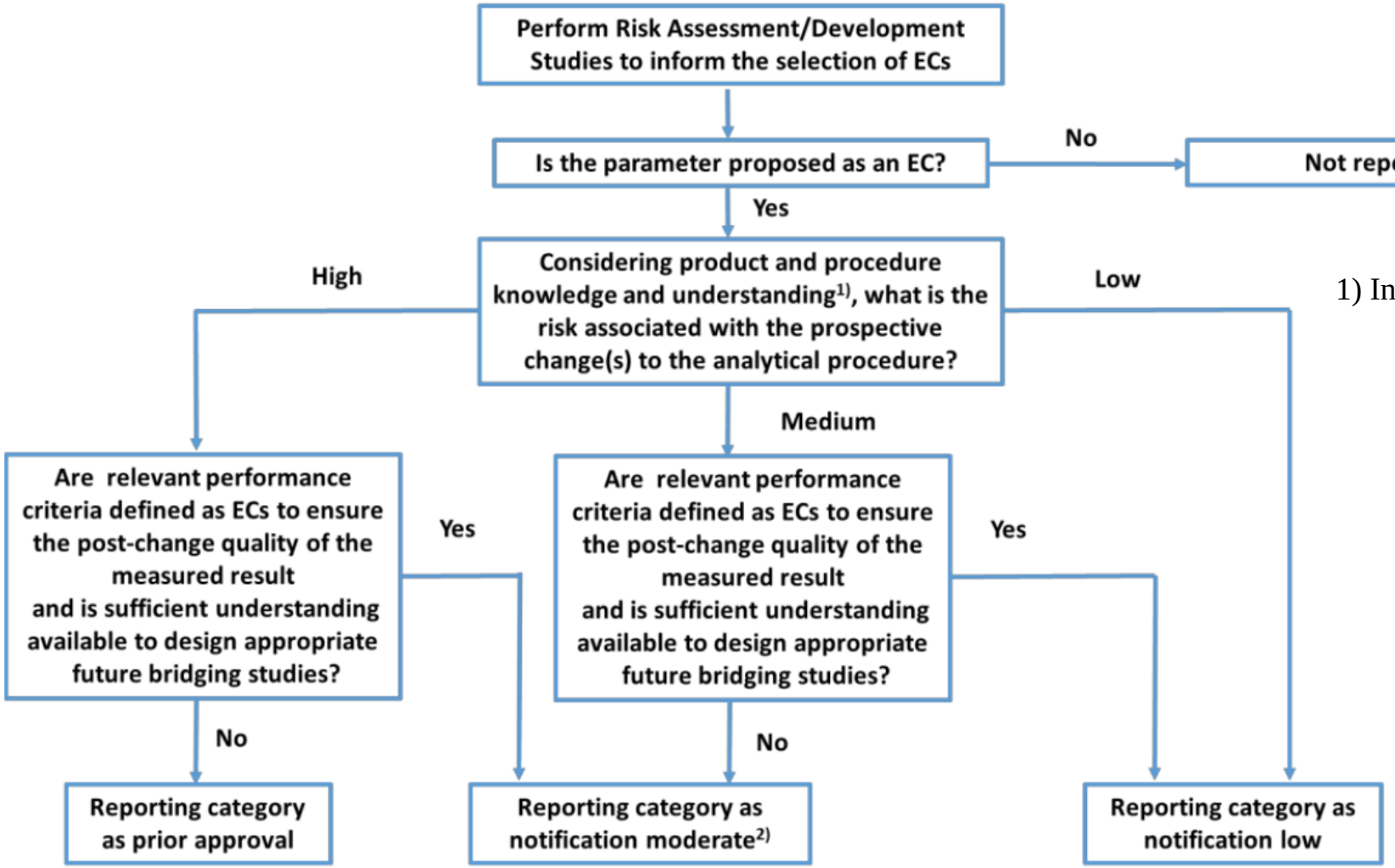
- In those situations, the validation strategy could rely on full validation on samples/products that can be justified/demonstrated to be representative of the diversity of the entire set of analytes. For the other analytes, a confirmation through abbreviated validation is probably required (and a simple justification might not be sufficient).

As the outcome of the exercise, it must be clear what performance we consider for the platform method for each of the analytes tested.

ICH Q2 (R2) and Q14, Established Conditions

ICHQ2 (R2) and ICHQ14, new opportunities and where it may lead us

Established Conditions and change management



1) Including analytical procedure control strategy

Extracted from ICH Q14

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

ICHQ2 (R2) and ICHQ14, new opportunities and where it may lead us

Established Conditions and change management

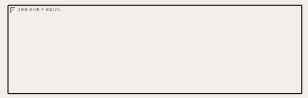
- The concept of Established Conditions (EC) is well understood in the field as well as the expected inputs from development phases in order to establish EC.
- While the application of the enhanced approach is recognized to lead to better characterized and more robust procedures; the registration of EC defined using the same enhanced approach might not yet be perceived to its full potential.

  Indeed, A) the parameters from the procedure covered by EC, in most cases, are anticipated as being totally under control and not subject to changes along the analytical lifecycle.

  B) exploring, validating and registering other parameters from the procedure, that are anticipated to be potentially subject to changes along the analytical lifecycle, is associated with a negative cost-benefits balance.

  This will evolve when the perception of EC will have evolved to established performances characteristics.
- The registration of Post-Approval Change Management Protocols, as valuable approach for the preparation of prospective management of changes along the analytical lifecycle.

ICH Q2 (R2) and Q14, where it may lead us?

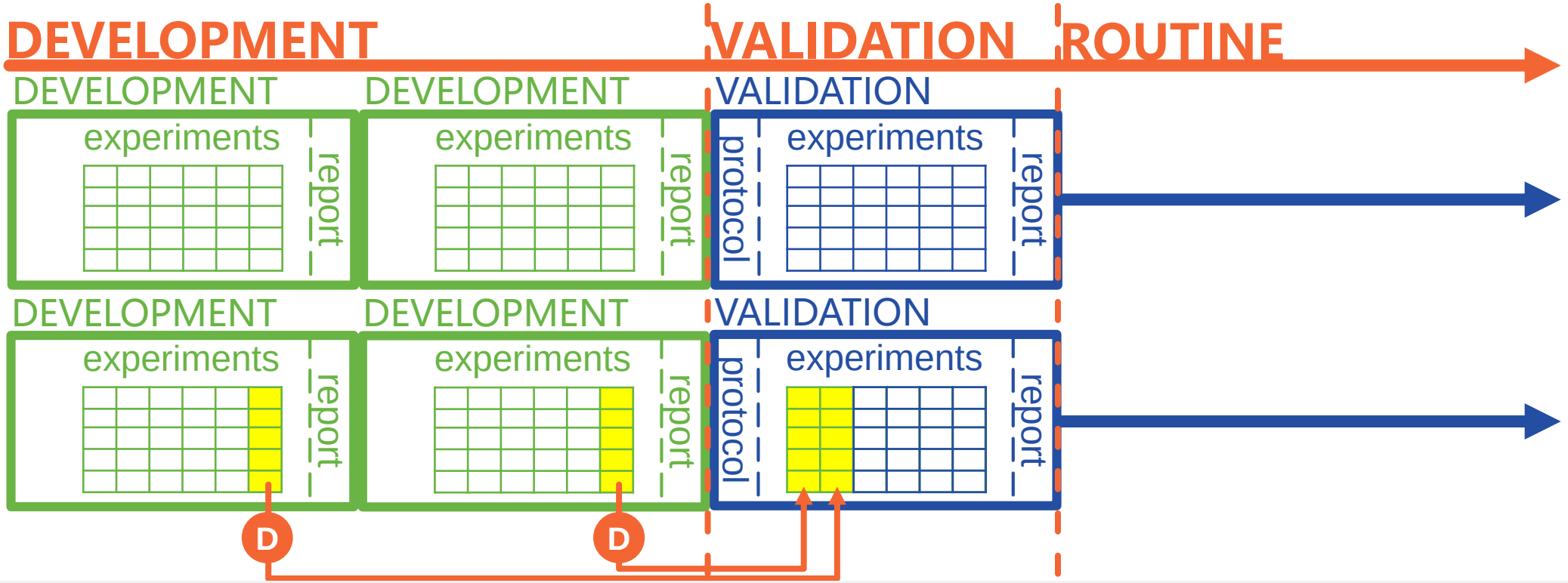


ICHQ2 (R2) and ICHQ14, new opportunities

Procedure Validation

CURRENT, ***one shot exercise***

REUSE OF DATA



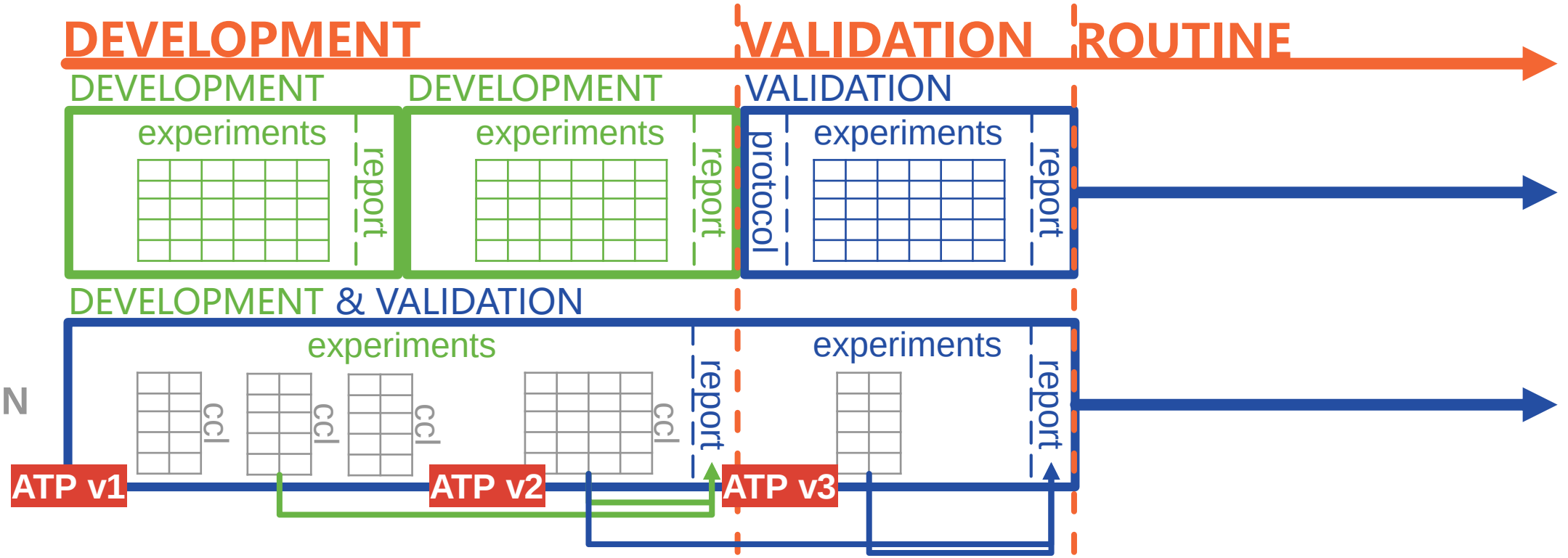
- Data from one stage are used, together with data from a further stage, into a statistical analysis.
- The conditions of acquisition of data must be auditable and justified as representative of future procedure.
- Same samples must be available and stable across the different stages.
- Applicable to quantitative performance parameters.
- Will require evolution of current paradigms and development of specific processes, statistics and digital tools.

ICHQ2 (R2) and ICHQ14, new opportunities and where it may lead us

Procedure Validation

CURRENT, ***one shot exercise***

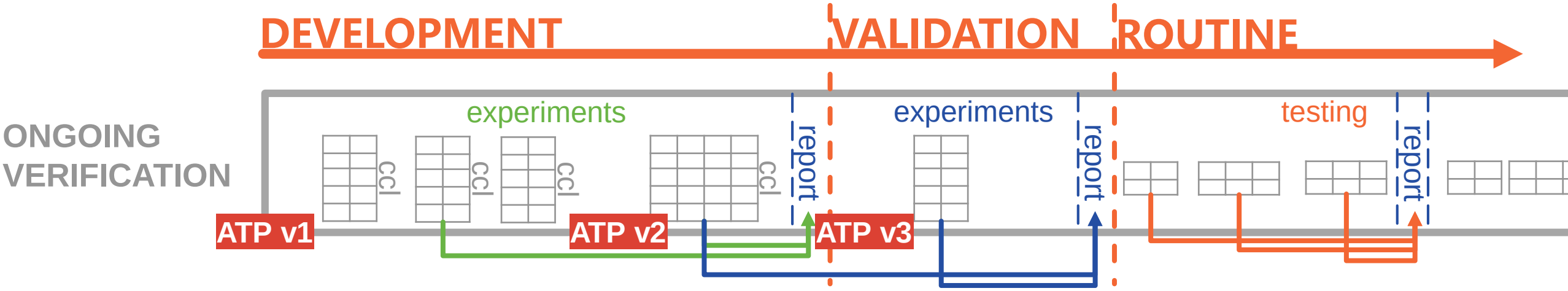
ONGOING VERIFICATION



- Main elements from the validation protocol are covered by a systematic iterative ATP process + pre-defined and conditionned experimental designs and supported by a Quality Risk Management Process.
- The conditions of acquisition of data and knowledge must be auditable and justified as representative of future procedure.
- Will require significant evolution of current paradigms and development of specific processes, statistics and digital tools.

ICHQ2 (R2) and ICHQ14, where it may lead us

Procedure Validation

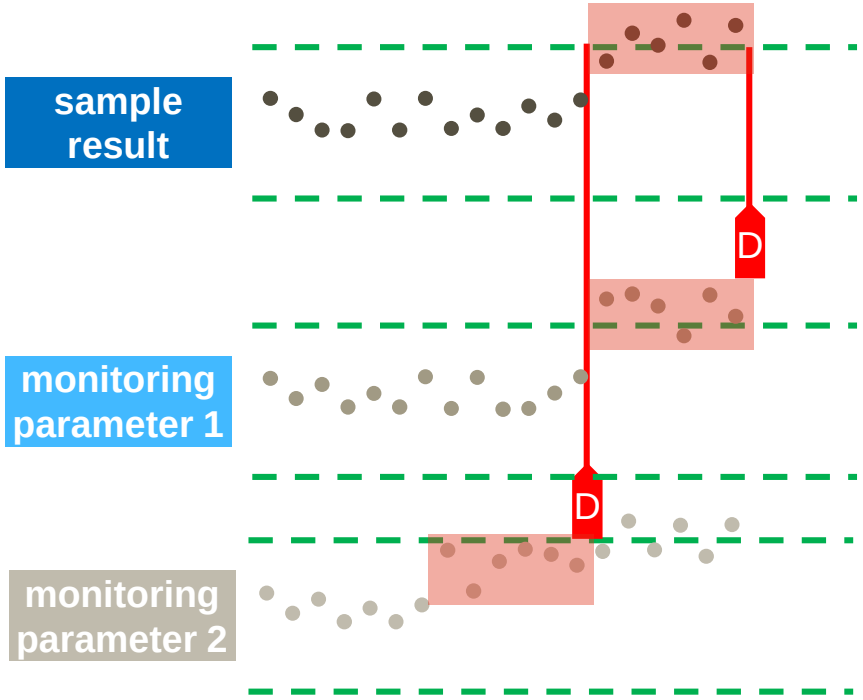


- The performance of the procedure is evaluated in a continuous fashion using data acquired during routine testing. The validated status can be verified at anytime.
- Will require significant evolution of current paradigms and development of specific processes, statistics and digital tools.
- Better understanding of the effect of procedure parameters on performance elements are provided by an evolved application of enhanced approach with the (additional) intention to prepare solid Analytical Procedure Control Strategy (APCS) and procedure performance monitoring.
- This considers that knowledge is also produced during routine use of the procedure.

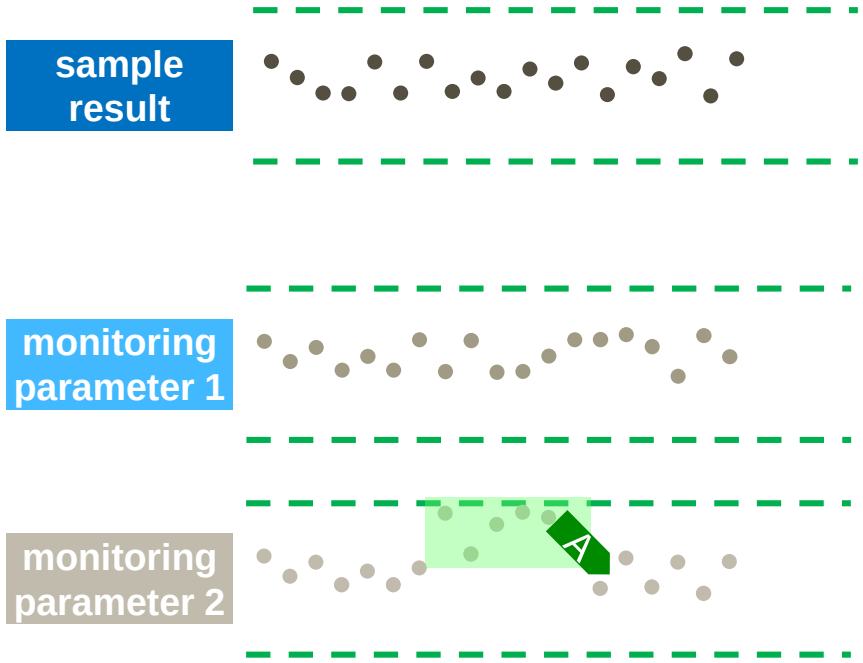
ICHQ2 (R2) and ICHQ14, new opportunities and where it may lead us

Analytical Procedure Control Strategy and Ongoing Procedure Monitoring

Towards advanced monitoring

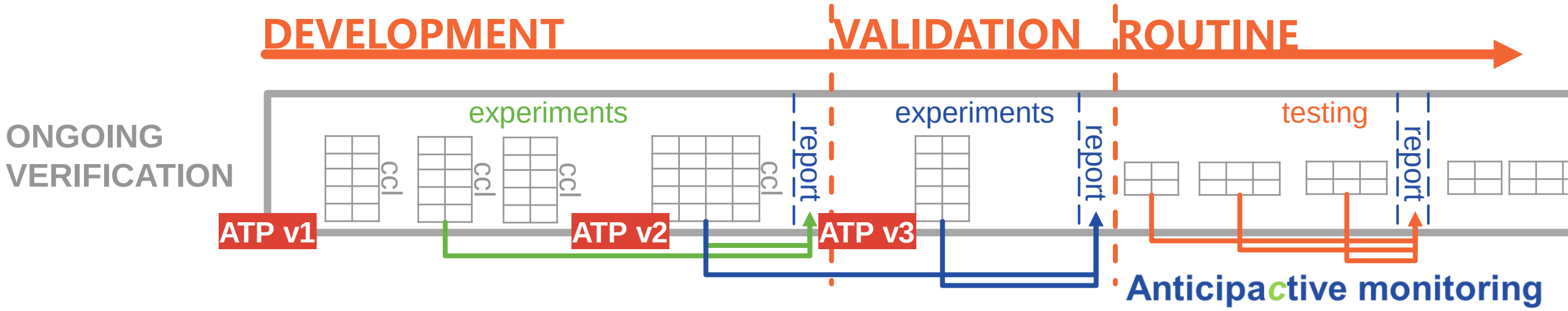


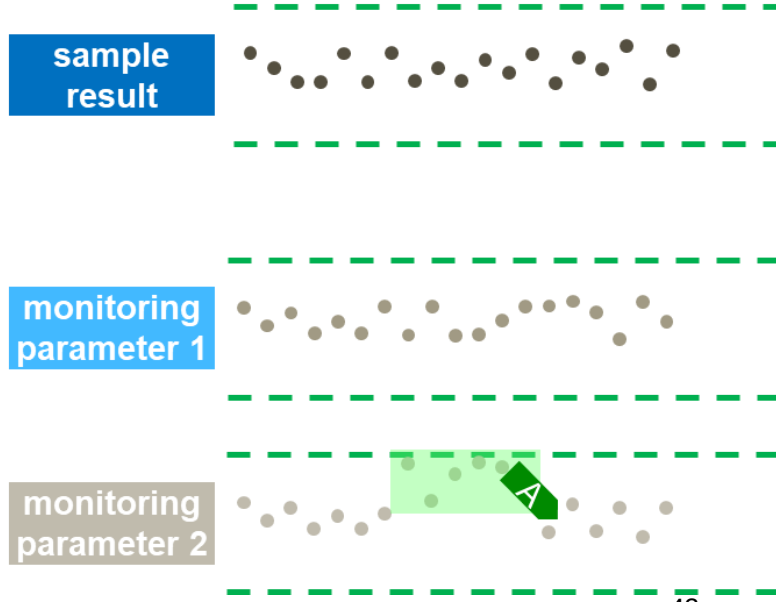
Up to anticipactive monitoring



- The performance of the procedure is evaluated in a continuous fashion using data acquired during routine testing. The validated status can be verified at anytime.
- Potential drifts and shifts can be anticipated and action can be taken in order to ensure the maintenance of the performance of the procedure before any unacceptable evolution.
- Such approach would also ensure full control of procedure performance upon changes.

ICHQ2 (R2) and ICHQ14, where it may lead us





- Could the development of continuous validation and anticipactive monitoring lead us to an enhanced paradigm for the validation and the control of analytical procedure performance?

- Could we move

from **Established Conditions** to **Established Performances?**

THANK YOU,



Claudia Magagnoli

Cristiana Campa

Delphine Vanham

Francesca Rech

Giovanni Vitali

Maranda Noyes

Mila Toppazzini

And many inspiring passionate scientists

Jean-francois.m.dierick@gsk.com

Q2(R2)/Q14



Bryan Castle

일라이릴리 릴리 리서치 랩 합성 분자 설계 및 개발 담당 상무

Eli Lilly and Company, Lilly Research Labs, Associate Vice President – Synthetic Molecule Design and Development

브라이언 캐슬(Bryan Castle) 박사는 일라이 릴리(Eli Lilly & Company)의 합성 분자 설계 및 개발(Synthetic Molecule Design and Development) 부서에서 상무(Associate Vice President)로 재직 중입니다. 그는 25년 이상 '팀 릴리'의 일원으로 활동하며 원료의약품(drug substance) 및 완제의약품(drug product) 분석 개발 분야에서 다양한 기술 및 행정적 역할을 수행해 왔습니다.그는 분석화학 분야의 기술 리더로서, 현재 소분자(합성) 의약품 상업화 포트폴리오의 분석 전략을 주도하고 있습니다. 또한 기술 리더십 팀의 일원으로서 성공적인 글로벌 품목 허가(registration)를 포함해 최근 6개 소분자 의약품의 상업화를 실현하는 데 공동의 책임을 다하고 있습니다.캐슬 박사는 인재 개발, 그리고 크로마토그래피 분리 기술의 우수성, 자동화, 실험실 데이터의 효율적 관리를 통한 연구원 역량 강화 등 효율화 도구 도입에 깊은 열정을 가지고 있습니다. 릴리 외부적으로는 ISPE-PQLI의 팀 공동 리더로서 ICH Q2(R2) 및 Q14 가이드라인 관련 활동에 참여하고 있습니다.

Bryan Castle, Ph.D. is an Associate Vice President in Eli Lilly & Company's Synthetic Molecule Design and Development organization. He has been part of Team Lilly for over twenty-five years and has held many technical and administrative roles in drug substance and drug product analytical development. He is a technical leader in analytical chemistry and is currently engaged in driving the analytical strategy for the small molecule commercialization portfolio. He is also part of the technical lead team with a shared responsibility in enabling the commercialization of the last six small molecule products, including successful global registrations. Dr. Castle is passionate about people development, efficiency tools, which include excellence in chromatographic separations, automation, and enabling of scientists through better handling of laboratory data. External to Lilly, he is engaged in ICH Q2(R2) and Q14 activities by co-leading a team at ISPE-PQLI.

Program

ICH Q2(R2) 및 Q14: 분석법 수명주기 관리를 위한 기반 – 분석법 개발, 밸리데이션 및 수명주기 관리 사례

ICH Q2(R2) and Q14: The Enabler for Analytical Procedure Lifecycle, Examples across analytical procedure development, validation and lifecycle management

The recent revision of ICH Q2(R2) “Validation of Analytical Procedures” and finalization of ICH Q14 “Analytical Procedure Development” guidelines lay the foundation for increased flexibility in the lifecycle management of analytical procedures. However, these updates bring uncertainty for interpreting and translating new expectations from the guidelines into practical application as well as for global regulatory acceptance of approaches that are taken. Case studies will be shared to illustrate how these expectations are being interpreted and applied. Overall, guideline implementation should result in improved method knowledge and robustness, supporting method changes throughout the analytical procedure lifecycle.

ICH Q2(R2) & Q14: The Enabler for Analytical Procedure Lifecycle

Examples across analytical procedure development, validation and lifecycle management

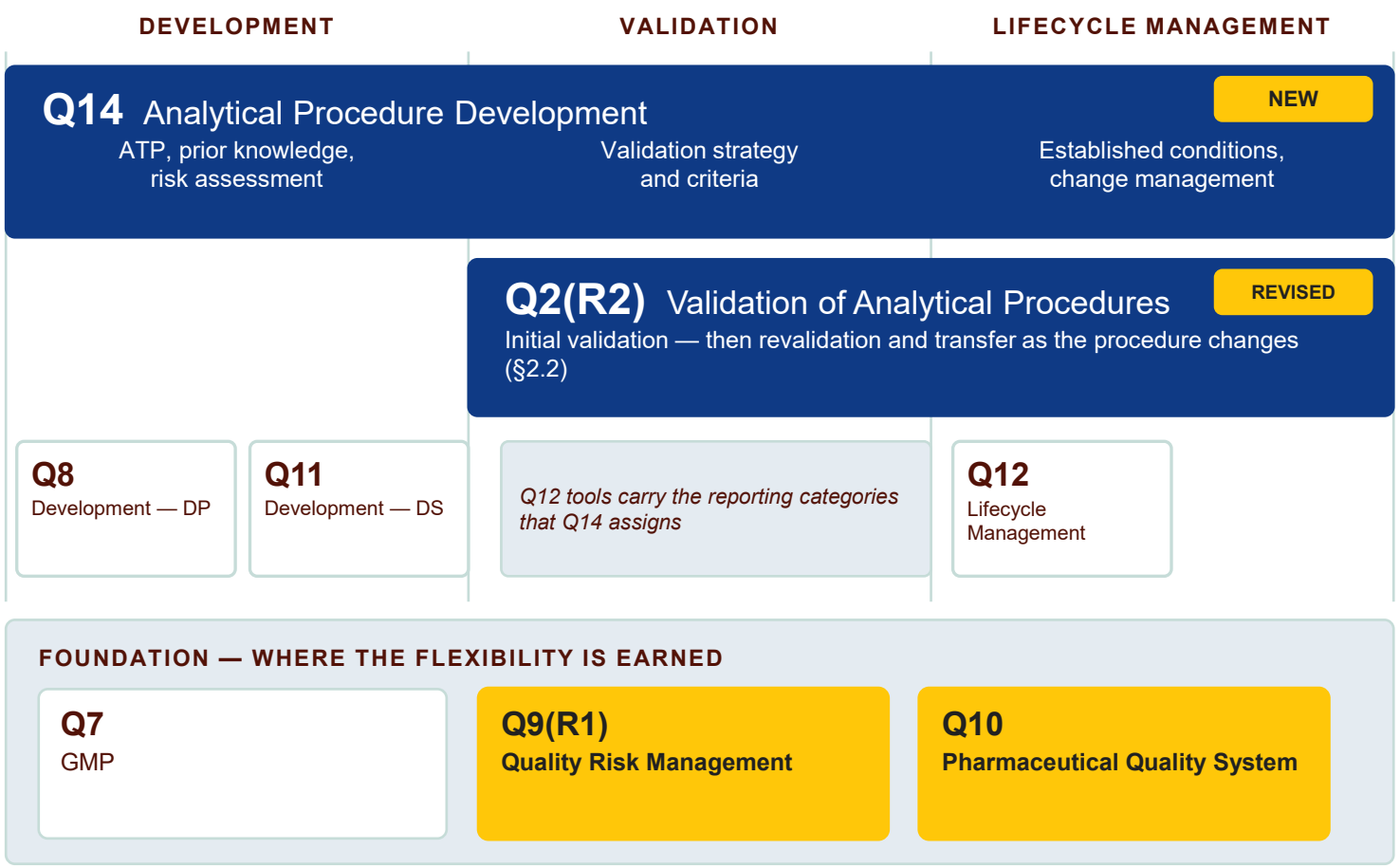
Bryan C. Castle, Ph.D.

01-Oct-2026

Lilly A MEDICINE COMPANY

ICH CONNECTIVITY

Q2(R2) and Q14 span development, validation and lifecycle



Q9(R1) — how much scrutiny?

- Risk assessment weighs test complexity, extent of change and how directly the procedure controls a CQA
- Its output is a risk level per established condition, with a rationale a reviewer can audit

Q10 — can it be executed reliably?

- The change management system evaluates, approves and records the change
- Knowledge management, management review and CAPA make the system inspectable

Oversight moves, it does not shrink

From case-by-case pre-approval review of every low-risk change, to assessment of a risk and quality framework — agreed once, applied repeatedly, and verifiable on inspection.

ICH Q2(R2) and ICH Q14, Step 4, November 2023. Q14 covers development, validation strategy and change management; the reporting categories it assigns are carried by the Q12 tools.

WHAT WE WILL WORK THROUGH

Three examples across the procedure lifecycle

CASE STUDY 1

Confidence intervals

Q2(R2)

- What the new reporting requirement requests
- Two borderline results accepted on documented reasoning
- One genuine failure that drove a method improvement

CASE STUDY 2

Established conditions and a PACMP

Q14 · Q12

- ATP/established conditions/PCAMP in the original filing
- A change pathway agreed with the application
- One bridging exercise, one global implementation

CASE STUDY 3

NIR for tablet release

Q2(R2) · Q14 §8

- An alternative procedure replacing HPLC at release
- Multivariate validation against Q2(R2) Annex 2
- Development, validation and lifecycle in one case

CASE STUDY 1 · DIRECT FROM ICH Q2(R2)

What Q2(R2) requires — and how a result is judged

What must be reported

§3.3.1.4 accuracy · §3.3.2.4 precision

- Mean percent recovery for accuracy; standard deviation and %RSD for both
- An appropriate 100(1−α)% confidence interval, or a justified alternative statistical interval
- The observed interval should be **compatible** with the acceptance criterion — "unless otherwise justified"

What sits behind the interval

§3.3.2.1 repeatability · §3.3.3 combined approaches

- Repeatability from a minimum of nine determinations (three concentrations × three replicates), or six at 100% of test concentration
- Accuracy and precision may instead be assessed together against one combined criterion — a prediction or tolerance interval
- Module 2 of the ICH training material emphasises the combined approach

What industry said about it

76% **of survey respondents raised concerns about implementing this requirement**

40%	Limited replicates may make the interval uninformative
21%	Insufficient experience to set acceptance criteria
16%	No internal statistical expertise to implement it
15%	No concern — already reporting intervals

How a reported interval is judged

1 Report
SD, %RSD and the interval for accuracy and precision

→

2 Choose the criterion
Separate criteria for accuracy and precision, or one combined criterion

→

3 Compare
Is the observed interval **compatible** with the acceptance criterion?

→

COMPATIBLE
The procedure meets the criterion.

NOT COMPATIBLE — JUSTIFIED
Acceptable, with the justification on record.

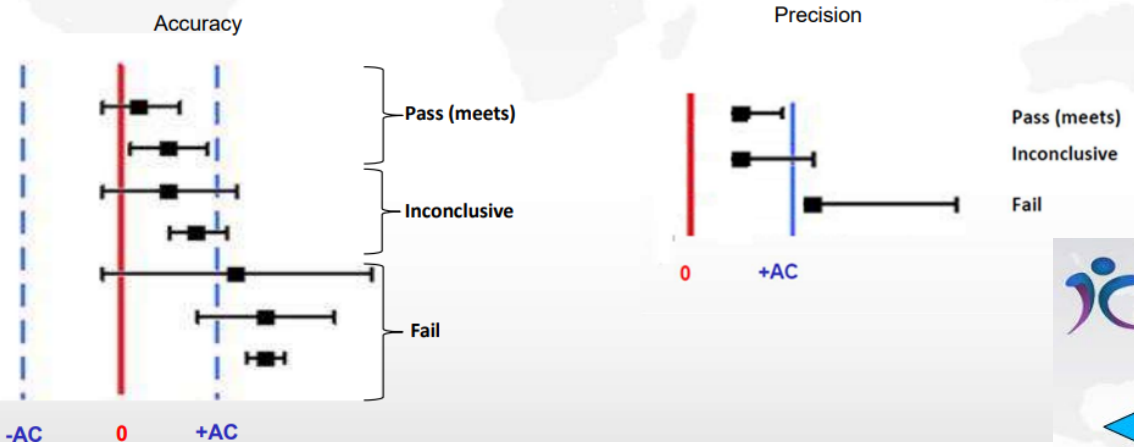
NOT COMPATIBLE — NOT JUSTIFIED
Investigate: improve the procedure, or increase replication.

ICH Q2(R2), Step 4, 1 Nov 2023 — §3.3.1.4, §3.3.2.4, §3.3.2.1, §3.3.3. Survey: Wang Q, Castle BC, Graul TW, Cauchon NS, Gellermann G, Pelletier MB. Pharmaceutical Engineering 2025;45(5):40–47.

ICH Q2(R2) / Q14 Training Module 3

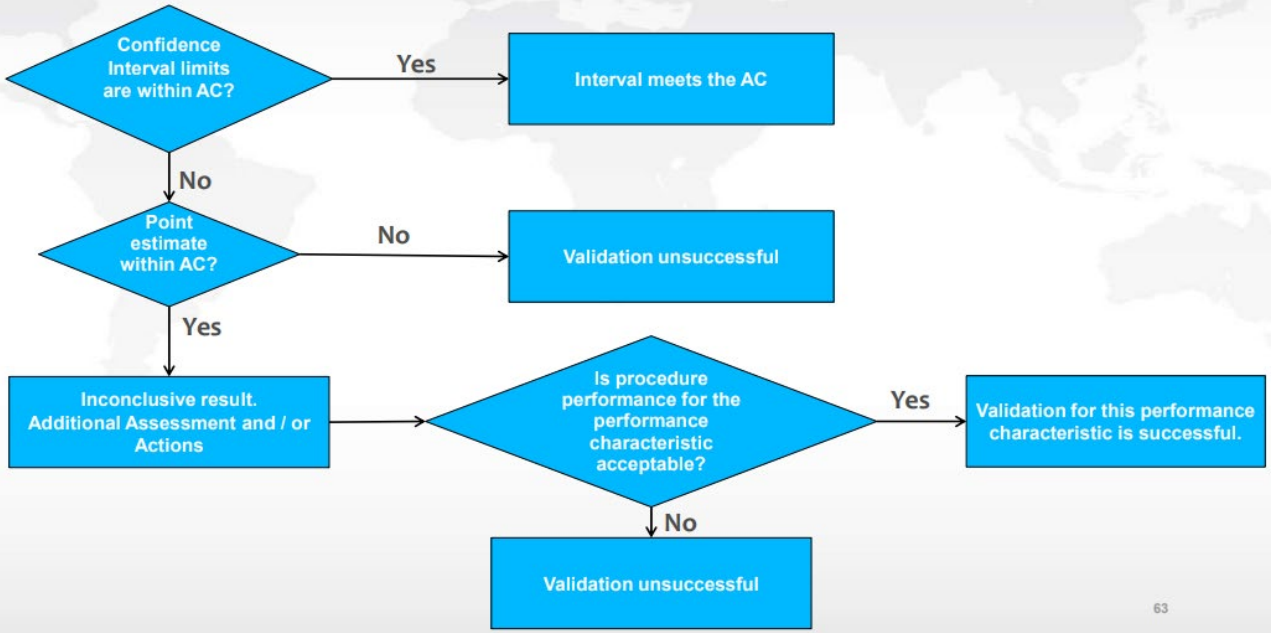
Interval Compatibility with Acceptance Criteria

- If the point estimate and the confidence interval are within the Acceptance Criteria (AC), validation of the performance characteristic is successful.
- If the point estimate is within the AC and the confidence interval exceeds the AC, the validation of the performance characteristic is inconclusive. The result may be considered compatible with the AC based upon additional assessments and / or actions (see slide 64).
- If the point estimate is outside of the AC, validation of the performance characteristic is unsuccessful.



ICH Q2(R2) / Q14 Training Module 3

Assessment of Confidence Interval Results



ICH_Q2(R2)Q14_TrainingMat_Module_3_2025_0620

CASE STUDY 1 · DRUG SUBSTANCE METHOD

Confidence Interval Outcomes & Decisions

Drug Substance Methods (n=18):

- In scope methods included:
  - assay
  - impurities (multiple methods)
  - solvents (multiple methods)
  - water
  - elemental impurities
- CI intervals not collected for 6 methods (description, ID, characterization)
- 83% of methods met CI acceptance criteria (10 of 12 methods)

Situation 1: Impurities Method (Accuracy)

Expt: 5 impurities each spiked at 3 levels

Accuracy:

- Acceptance Criteria (AC): 90-110%
- One impurity at 0.15% spike: 95% LCL = 89%
- All other impurities met criteria

Assessment:

- Point estimate for recovery = 91% (within AC)
- All other impurities met criteria
- Impurity not expected based on updated process controls

✓ Acceptable based on CI logic + process knowledge

Summary: Borderline case acceptable using CI-based decision logic + prior knowledge.

CASE STUDY 1 · DRUG SUBSTANCE METHOD

Confidence Interval Outcomes & Decisions

Situation 2: Impurities Method (Accuracy)

Accuracy Experiment: 3 impurities each spiked at 3 levels

- **Two impurities had low levels in matrix**
- **One impurity had high level in matrix**

Accuracy:

- Acceptance Criteria: 95-105%
- high matrix level – low spike level: 90% LCL = 93%
- Point estimate = 97% (within AC)
- All other impurities met criteria

✓ Accuracy acceptable for expected level

Situation 2: Impurities Method (Precision)

Precision Expt: n=6 reps in each of 3 set-ups for repeatability and intermediate precision

Precision:

- Repeatability:
  - One low result outlier: 90% UCL 5.9% RSD
  - Acceptance Criteria: NMT 5% RSD
  - Point estimate: 2.8 % RSD (within AC)
  - Other set-ups met criteria
- Intermediate Precision
  - pooled intermediate precision 90% UCL = 2.7%

✓ Acceptable based on pooled evidence

Summary: Borderline case acceptable using CI-based decision logic.

CASE STUDY 1 · DRUG PRODUCT METHOD

Confidence Interval Outcome & Decision

Drug Product, Assay method repeatability (n=6):

Sample	% Label Claim, Strength 1 (original validation)	% Label Claim, Strength 2 (original validation)	% Label Claim, Strength 3 (addendum validation for higher strength)	% Label Claim, Strength 3 (After Method Improvement)
1	100.511	100.120	101.711	100.111
2	102.040	100.725	102.582	101.069
3	101.704	100.458	99.798	100.356
4	102.436	100.540	102.839	99.999
5	102.307	99.599	102.090	100.271
6	101.892	100.542	101.988	99.249
Average	101.8	100.3	101.8	100.2
SD	0.7	0.4	1.1	0.6
95% Upper CI of SD	**1.4**	**0.9**	**2.3**	**1.2**

Experiment:
Prepare 6 independent sample preparations per method

Criteria:
The 95% upper confidence limit for the SD (n=6) of the % label claim results must be NMT 1.7%.

Decision:
- Review of collective data suggested higher variability was real
- no intermediate precision data was available
- investigation focused on sample prep
- larger pipet and VF sizes remedied the issue

Summary: Method improvement (sample preparation) initiated after inconclusive result; passed after implementation.

The situation

- Small-molecule solid oral product for a solid tumour indication — an area of unmet medical need
- Discovered and developed by a small biotechnology company, then acquired months before submission
- First-in-human to first approval in approximately three years, with expedited designations across multiple indications
- Assay procedure was validated and fit for purpose at submission — but not robust

Observed robustness liabilities

- Short column lifetime — roughly 100 to 150 injections
- Main peak splitting
- Impurity elution order changing and peak shifting
- Contributing factors: column temperature 55 °C against a 60 °C limit; aggressive phosphate mobile phase at pH 6.8; 95% acetonitrile at end of gradient with a phosphate precipitation risk

Interim controls put in place at submission

Enhanced system suitability

Impurity marker solutions to confirm elution order, plus peak shape criteria

Enhanced column wash

Extended wash program to improve robustness and column lifetime

Performance monitoring

Systematic monitoring of method performance across batch and stability testing

Documented risk item

Risk assessment formally identified analytical procedure risk as a post-submission action

Also driving the change: the QC laboratory wanted a shorter assay method, one procedure supports identity, assay, uniformity of dosage units and dissolution endpoint determination, so run time affects every batch and every stability time point.

Castle BC, et al. "Streamlining Post-Approval Changes: Industry Insights on ICH Q14." Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2.

CASE STUDY 2 · ENHANCED APPROACH

Step 1 — an analytical target profile defines what must stay true

The ATP states the intended purpose, the link to the CQA, and the performance the reportable result must deliver. Any future version of the procedure is judged against it — which is what makes a change to the procedure separable from a change to the control.

Element	Definition
Intended purpose	Quantification of the API in drug product for release and stability
Link to CQA (assay)	Procedure should quantitate API in drug product to verify the CQA of assay, values between 90.0 – 110.0%
Characteristics of the reportable result (performance characteristics)	
Accuracy	Recovery between 98.0 – 102.0% at three levels (80%, 100% and 120% of nominal concentration); %RSD ≤ 2.0% at each level
Precision	%RSD for intermediate precision samples ≤ 2.0% for each analyst; ≤ 3.0% for both analysts combined
Specificity	Capable of separating impurities (process impurities and degradation products) from API; any interference from placebo components < 0.5% of the nominal API concentration
Reportable range	70 – 130% of nominal

These numbers are not invented — check them against ICH Q2(R2) Table 2

Q2(R2) Table 2 gives recommended reportable ranges: 80–120% of declared content for assay of a product, and 70–130% for content uniformity. This one procedure covers identity, assay, uniformity of dosage units and dissolution, so uniformity sets the wider range and the ATP states 70–130%. The justification for each criterion belongs in the submission and is omitted here only for space — a reviewer assesses the ATP on the strength of that justification.

Castle BC, et al. "Streamlining Post-Approval Changes: Industry Insights on ICH Q14." Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2. Reportable ranges: ICH Q2(R2) Table 2.

CASE STUDY 2 · ENHANCED APPROACH

Step 2 — each established condition carries a reporting category

Q14 is used to identify the established conditions for the revised procedure. A risk assessment then places each one in a high, medium or low category, and each category maps to a reporting category — high risk to prior approval, low risk to a minor notification.

Established condition	Risk	Reporting category	Justification / rationale
Analytical target profile (ATP)	**High**	**Prior approval**	If widening the ATP is necessary, it will be reported as prior approval
Technology: HPLC	**Low**	**Notification low**	ATP must be met, and the defined bridging strategy must be met using representative materials
System suitability tests **SST 1 — system precision** **SST 2 — blank interference** **SST 3 — resolution** **SST 4 — peak symmetry**	**Low**	**Notification low**	SST were established from a risk assessment and considering compendial expectations. A change to SST should ensure similar control of the factors listed

Deliberately not established conditions

- Mobile phase composition
- Instrument conditions
- Sample and standard preparation

Each of these requires justification in the submission — the case rests on the ATP and the bridging strategy controlling the outcome.

Where Q9 enters

The risk column is not asserted. It is the output of an assessment of test complexity, extent of modification and how directly the procedure controls the CQA — reviewed against product, process and prior analytical knowledge. The agency reviews that reasoning once, at the point of agreement, and the categories follow from it.

Castle BC, et al. "Streamlining Post-Approval Changes: Industry Insights on ICH Q14." Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2.

CASE STUDY 2 · PRE-AGREED CHANGE PATHWAY

Step 3 — a PACMP submitted with the original application

The change was foreseeable at submission, so it was planned for at submission. Q12 provides the mechanism: a protocol describing the proposed change, the studies, the acceptance criteria and the proposed reporting category — reviewed and approved as part of the marketing application.

1. **Proposed change and rationale**
   Replacement of the assay procedure to resolve robustness liabilities and reduce run time

2. **ATP and established conditions**
   The ATP and the risk-based EC table, agreed as part of the protocol

3. **Development studies proposed**
   Characterisation of the chromatographic operating space; samples representative of process impurities and degradation products; selection of conditions robust to typical sources of variability

4. **Validation commitment**
   Commitment to validate the new procedure to ICH Q2(R2) expectations

5. **Bridging protocol**
   Experimental design and pre-defined acceptance criteria, using samples spanning manufacturing variability

6. **Proposed reporting category**
   Notification low, conditional on the acceptance criteria being met

The bargain: the agency agrees the evidence standard before the work is done. The sponsor then executes against it — and if the acceptance criteria are met, implementation follows the agreed reporting category without a further review cycle.

Castle BC, et al. "Streamlining Post-Approval Changes: Industry Insights on ICH Q14." Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2.

CASE STUDY 2 · EXECUTION

Step 4 — the bridging exercise settles it

Experimental design

Six set-ups across three days, two analysts, two instruments and four batches — so the comparison spans manufacturing variability, not one favourable run.

Set-up	Day	Analyst	HPLC	Batch
1	1	A	1	1, 2
2	1	B	2	3, 4
3	2	A	2	3, 4
4	2	B	1	1, 2
5	3	A	1	3, 4
6	3	B	2	1, 2

Result — assay

Mean % label claim from the current and proposed assay procedures, judged against a criterion fixed in advance in the protocol.

Assay procedure	Mean % label claim
Current procedure	99.9
Proposed procedure	100.3
Absolute difference	**0.4**
Acceptance criterion	NMT 1.4
Result	**Pass**

The difference uses 29% of the allowance the protocol permitted — the two procedures produce comparable assay results.

More than just validation

- Bridging is key to understand impact of the change
- Important to have samples that represent the process
- Final assessment managed in the PQS

Castle BC, et al. Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2.

CASE STUDY 2 · OUTCOME

The same change, with and without the pre-agreed pathway

WITHOUT THE Q12 / Q14 TOOLS

What the change actually required

- Staggered regional submissions produced staggered prior approval supplements
- Regional expectations for method changes differed, including bridging study design and data
- Current and new procedures run in parallel on stability for extended periods
- Method versions managed per market, packaging configuration and line extension
- Inventory segregation or duplicate testing to bridge the gap between markets
- Implementation stretched across several years before all markets were aligned

WITH ESTABLISHED CONDITIONS AND/OR A PACMP

What the change could require

- One protocol, agreed with the application, defining the evidence standard up front
- Bridging executed once against pre-defined acceptance criteria
- Acceptance criteria met, so the agreed reporting category applies — notification low (e.g. annual reportable)
- Change approved and implemented through the pharmaceutical quality system
- Health authorities notified through the annual report, per the protocol
- A single procedure in use globally, with no parallel method management

Why this serves patients as well as sponsors: a fragile procedure is a supply risk. Every year a robustness fix waits for sequential approvals is a year of parallel testing, segregated inventory and stock-out exposure. Harmonised reporting expectations also let reviewers spend their time on the changes that carry real product risk.

Castle BC, et al. "Streamlining Post-Approval Changes: Industry Insights on ICH Q14." Pharmaceutical Engineering 2025;45(5):28–39 — Case study 2.

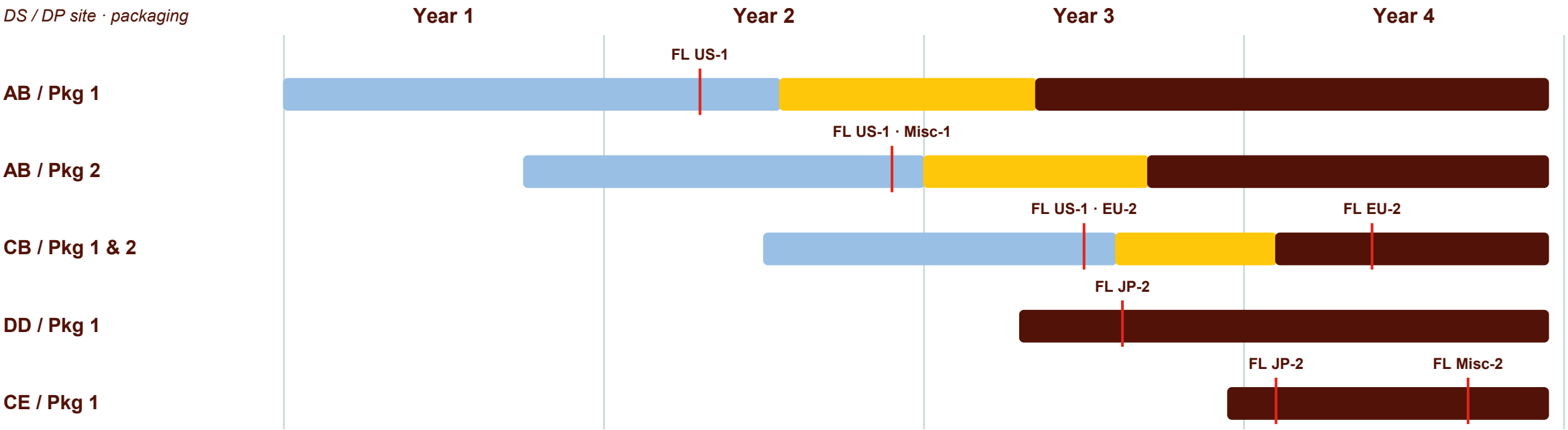
CASE STUDY 2 · LIFE WITHOUT Q14

Every market on its own method version, for years

One approved change does not mean one implementation. Each supply chain configuration converts on its own regulatory clock, so several method versions are live at once — here across four years.

Current method · Both methods in use · New method

FL = first launch; suffix -1 / -2 = method version in that market



Parallel stability testing
Current and new procedures run side by side on stability programmes for extended periods

Conversion windows
New stability studies started for other reasons — a site change, for case study — become the opening to switch method

Lifecycle spread
Paediatric formulations and line extensions each add another configuration and another method version to manage

CASE STUDY 3 · TRANSMISSION NIR FOR TABLET RELEASE

One measurement, three attributes

Compression
Batch process under a defined control strategy

→

Stratified sampling
Units collected at multiple locations across the compression run

→

FT-NIR transmission
30 intact core tablets measured offline

→

PLS model
Assay, identity and uniformity of dosage units from one measurement

Why core tablets

- The coating contains no active ingredient, and the coating operation does not alter drug content
- The core therefore carries all the information relevant to assay, identity and uniformity

Why NIR rather than HPLC

- Nondestructive — the dosage units remain available, including for HPLC investigation
- Rapid, so more units are tested per batch
- Assay, identity and uniformity from a single procedure

Which part of Q14 applies?

Alternative analytical procedure — Q14 Section 8

- Tablets collected during or after compression, measured offline
- Release decided on a representative sample of dosage units
- Aligned with the compendial test for uniformity of dosage units

Real time release testing — Q14 Section 9

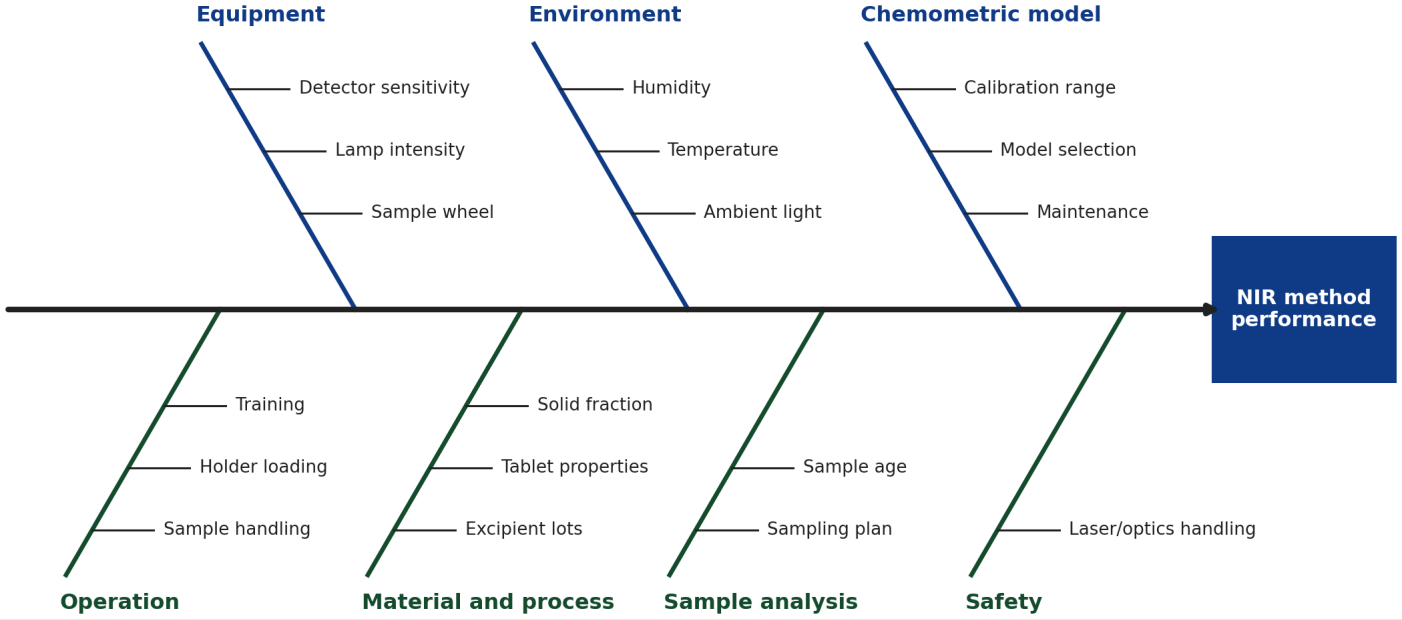
- In-line, on-line or at-line measurement integrated into the process
- Release derived from process data during manufacture
- Sample interface and measurement point are design elements

This case is the general case, not real time release testing. Either strategy holds the same quality standard — but only one of them is being proposed here.

CASE STUDY 3 · Q14 DEVELOPMENT

Robustness is designed into the model, not tested for afterwards

ICH Q14 Section 4 and ICH Q9(R1): sources of variability were identified with an Ishikawa diagram, then evaluated by FMEA — severity, occurrence and detection scored against a defined risk priority grid.



Ishikawa categorisation of potential causes of variation, taken into FMEA for the routine operation stage.

Variability built into the calibration

- Nearly orthogonal array DOE across multiple lots of active ingredient and excipients
- Tablet solid fraction and weight varied by design
- Production-scale batches represented in the model, across the dose range

Preprocessing and diagnostics

- Derivative, scatter correction and orthogonalisation evaluated — corrects instrument differences and physical property effects
- Q-residual detects spectral variation not present in the calibration
- Hotelling T^2 detects variation within the model space

The control strategy answers the risk assessment point by point:

- Instrument qualification: signal to noise, wavenumber accuracy, interferogram amplitude, single beam intensity
- Measurement: defined acquisition parameters, background referencing and sample presentation geometry
- Model: Q-residual and Hotelling T^2 statistical limits
- Procedure: defined spectral range, preprocessing and model type

Established conditions are assigned by risk, consistent with ICH Q12 — the same logic as Case study 3, applied to a multivariate procedure.

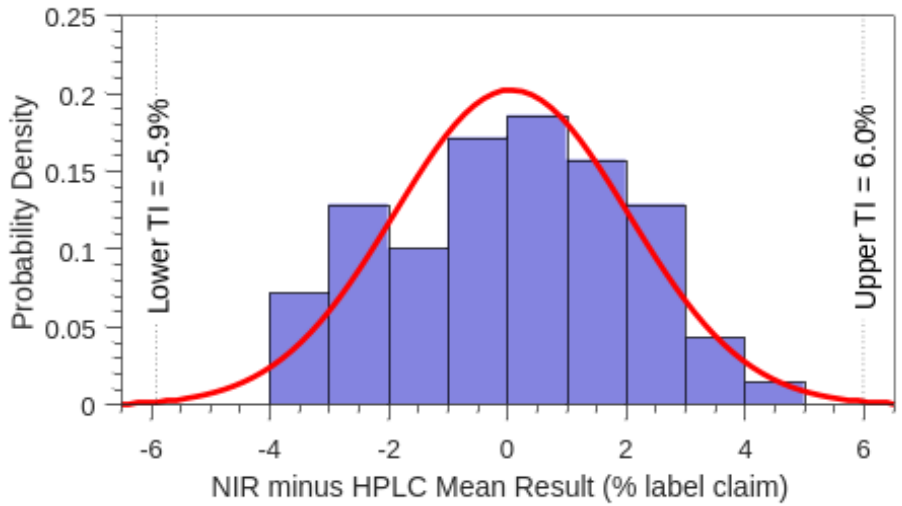
CASE STUDY 3 · Q2(R2) VALIDATION

Validated against the NIR case study in Q2(R2) Annex 2

Q2(R2) Annex 2 contains a worked case study for an NIR procedure for core tablet assay. Each performance characteristic below is the methodology the guideline itself specifies for this technology.

Performance characteristic	Methodology given in ICH Q2(R2) Annex 2	Outcome
Specificity / selectivity	Compare the drug substance spectrum with the loading plots of the model; reject outliers not covered by the multivariate procedure	**Met**
Precision	Repeated analysis with the sample removed from the holder between measurements	**Met**
Accuracy	Comparison with an orthogonal procedure across the range, predicted against reference values	**Met**
Reportable range	Demonstrate the relationship between predicted and reference values, and how error changes across the range	**Met**
Robustness	Deliberate variation of the chemical and physical factors that affect the spectrum and the model prediction	**Met**

Accuracy and precision as total error



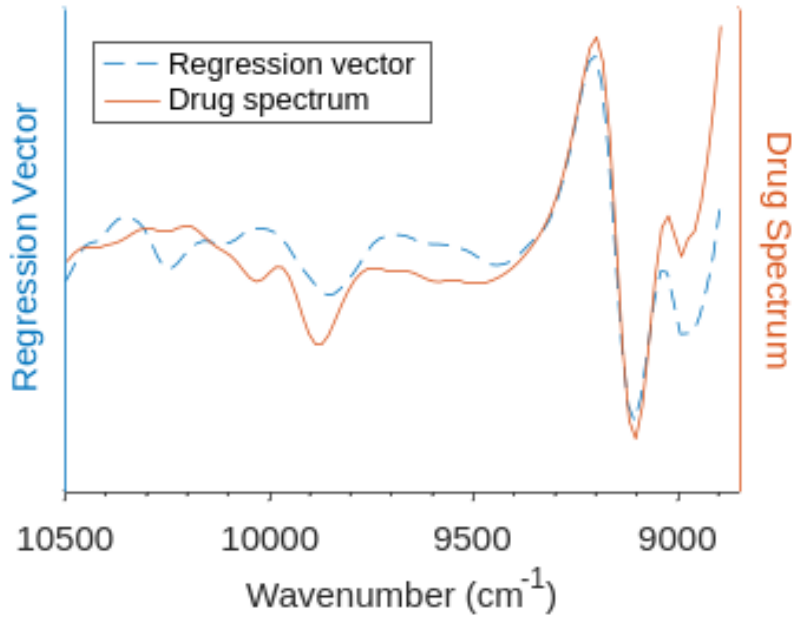
Paired NIR and HPLC results on external validation batches, n = 70 (DOE and pilot scale). 95% confidence / 99% coverage tolerance interval: −5.9% to +6.0% label claim.

This is the combined approach Q2(R2) §3.3.3 introduced. Rather than separate accuracy and precision criteria, the two are assessed against one criterion using a tolerance interval — which is the quantity that actually matters at release, since a release decision is affected by bias and variability together. Intermediate precision was confirmed on a second spectrometer, and the external validation range was 85 to 115% label claim.

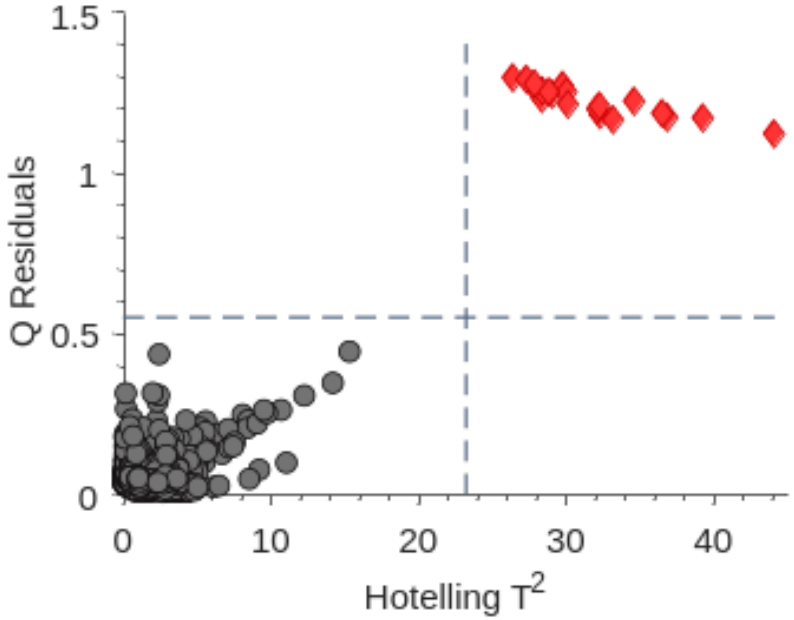
CASE STUDY 3 · SELECTIVITY

The same model that measures content also proves identity

The regression vector tracks the drug substance



Placebo tablets fall outside the diagnostic limits

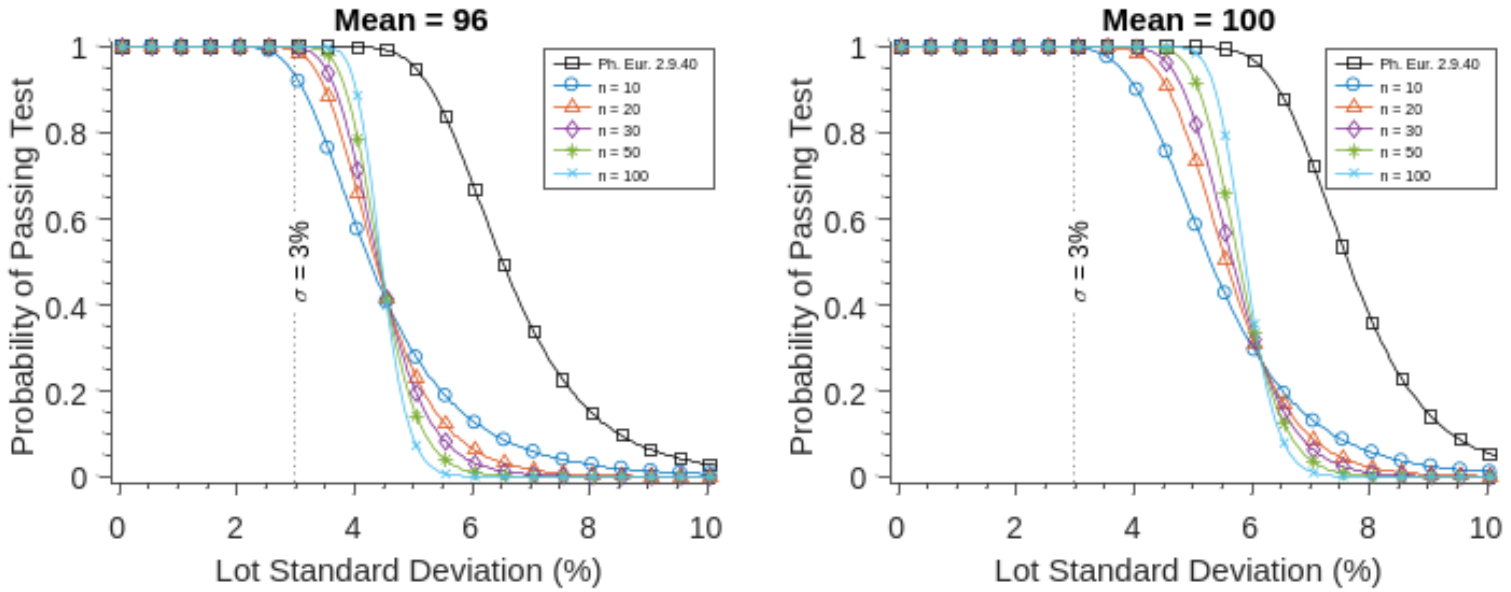


Two independent lines of evidence, consistent with ICH. The regression vector features match the drug substance spectral features, so the model is measuring the analyte rather than a correlated property. Separately, placebo tablets are flagged as outliers by the model diagnostics — high Q-residual and high Hotelling T². A tablet containing no drug substance cannot be reported as conforming, which is precisely what an identity test is required to establish. Orthogonal confirmation against the validated HPLC procedure completes the case.

CASE STUDY 3 · SAMPLING ADEQUACY

Why 30 dosage units is enough

Operating characteristic curves by Monte Carlo simulation: probability of passing a conservative two-sided normal tolerance interval criterion as a function of lot standard deviation, at n = 10, 20, 30, 50 and 100, against the Ph. Eur. 2.9.40 criterion.



Lot mean 96% label claim (left) and 100% label claim (right). Dotted line marks the 3% standard deviation observed in the process.

Within the observed range, n barely matters

Below 3% lot standard deviation — which covers the observed process — sample sizes from 30 to 100 give an almost identical probability of passing. The curves only separate well above the variability the process actually shows.

And the criterion is the conservative one

At every level of variability the validation criterion sits below the Ph. Eur. 2.9.40 curve. Method capability was qualified against the tighter of the two standards, not the compendial one.

The sampling design and the acceptance criterion make the release decision sound — not the ratio of sample size to batch size. A batch platform and a continuous platform do not require the same analytical strategy. ICH Q13 ties sampling amount, frequency and location to process dynamics, so a continuous process takes in-line measurements and a high sample number is intrinsic to it. For a batch process, the compendial uniformity test applied to a stratified sample is the platform-appropriate basis for release.

CASE STUDY 3 · LIFECYCLE

Staged implementation, verified for as long as the model is used

1. **Process transfer**
   Model transferred to the site and its performance checked against the original validation criteria

2. **Process validation**
   Release decisions still made by HPLC, with NIR run in parallel to build the comparability data set

3. **Commercial**
   NIR used for release once the site is certified

Ongoing verification

- Periodic paired NIR and HPLC comparison
- Frequency set by statistical analysis rather than convention
- Defined accuracy and precision criteria for the comparison

When the model must be reviewed

- Known events such as a material or process change
- Unexpected out-of-limit diagnostics
- Periodic trending of predictions

The model is classified as high impact

Updates run through change control, with revalidation where necessary. That classification is the honest one for a model whose output decides batch release, and it is what allows the ongoing verification programme above to be treated as a control rather than as reassurance. The result is a procedure that stays fit for purpose under ICH Q14 and Q10 for as long as it is in use.

BRINGING IT TOGETHER

What we would like you to take away

CASE STUDY 1 · Q2(R2)

Confidence intervals

A borderline interval (inconclusive) is not a failed method.

- Judge the point estimate and collective set of validation data
- The justification is the reviewable object

CASE STUDY 2 · Q14 · Q12

Established conditions and/or a PACMP

Agree to expectations, in advance, enables lifecycle management.

- Risk assessment sets the reporting category, and it is auditable
- Leveraging established conditions and/or PACMP should enable lower risk analytical procedure changes to be managed in the PQS

CASE STUDY 3 · Q2(R2) · Q14

NIR for tablet release

A multivariate procedure can enable a release decision (as an alternative method).

- Validated against the NIR case study in Q2(R2) Annex 2
- Diagnostics and paired comparison keep it fit for purpose

None of this asks for confidence the agency has not already extended

Q9 supplies the risk reasoning. Q10 supplies the system that executes and records it. Both are already applied to every change to ensure on going control and monitoring.

Thank you

Acknowledgements: Cynthia Hammill, Mark Argentine, Denilson Mendes de Oliveira

Q14 makes method transfer a change

What Q14 introduced

- Expectations for method transfer are now explicitly in scope — the same procedure operated at a different site
- Transfer is classified as a change
- Risk assessment should be leveraged to inform the bridging strategy

Reference: ICH Q2(R2)/Q14 training material, Module 5 (July 2025)

What a transfer has to establish

Laboratory capability

Can the receiving site perform the analysis — and has process and product knowledge travelled with the procedure

Performance and variability

Robustness studies from development are what make the receiving site system suitability results interpretable

Ongoing performance

Method performance samples support continual monitoring after the transfer closes

Classifying transfer as a change is not burden for its own sake

It brings transfer inside the same Q9 risk assessment and Q10 change management already applied to every other change. That is precisely what makes it possible to cover eight receiving sites with one pre-approved protocol rather than negotiating each transfer separately.

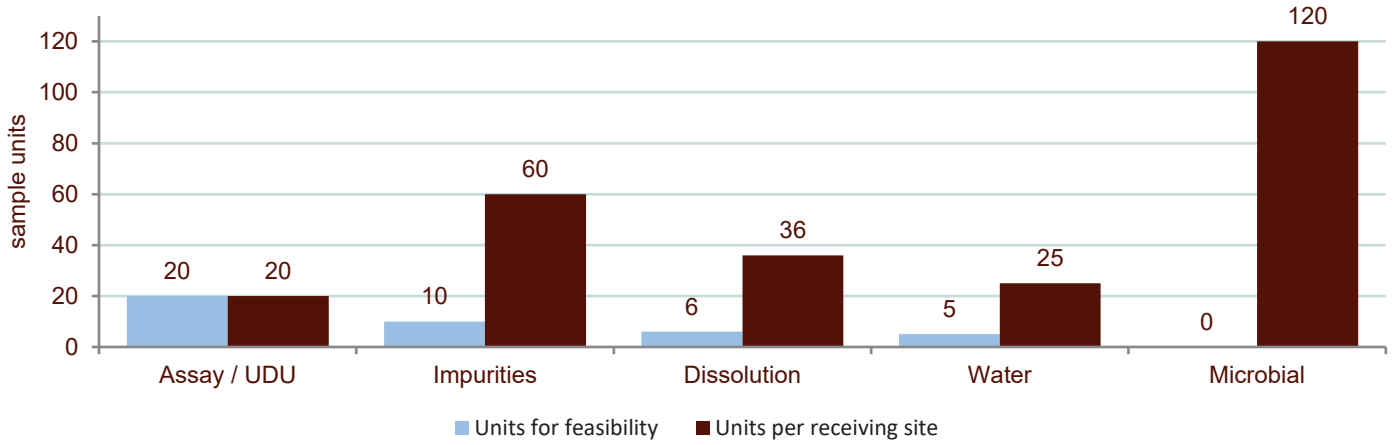
Direct from ICH Q2(R2) §2.2: transfer of a validated procedure is to be considered in the context of lifecycle changes in line with Q14, and moving a procedure to a different laboratory calls for partial or full revalidation of the affected performance characteristics, comparative analysis of representative samples, or both — with justification required if additional transfer experiments are not performed. Q2(R2) also defines covalidation: demonstrating that the procedure meets predefined performance criteria using data generated at multiple sites, which can itself satisfy the transfer requirement at those sites. That definition is the guideline basis for the hub-and-spoke model on the next slide.

A transfer kit turns each transfer into a repeatable exercise

Method transfer kit: centrally managed batches of representative material, held with pre-defined and pre-approved protocols and acceptance criteria, available for method transfers throughout the product lifecycle.

What makes a performance sample useful

- Stable and representative of routine material
- Impurity-rich, so an impurities procedure is meaningfully challenged
- Covers the range of strengths
- Quantity established up front to cover feasibility work and transfer to multiple sites



Microbial feasibility is not applicable; microbial quantity depends on unit mass. Roughly 400 units in total for one solid oral product — quantities are illustrative.

What the kit buys

- ✓ Streamlined transfers across multiple sites
- ✓ Objective, data-driven acceptance decisions
- ✓ Early detection of method performance issues
- ✓ Reduced transfer timelines and costs

For an impurities procedure, the sample has to be hard enough

Where the material comes from

- Impurity-rich development material
- Stable product material spiked with impurities
- Intentionally degraded material carrying the major degradation products

For less stable molecules, including large molecules, use a stressed sample with degradation representative of the end of shelf life.

What a stressed sample proves

- Valuable for any compound that degrades across its shelf life
- The receiving laboratory can demonstrate correct results at release and throughout stability
- It gives that laboratory a degraded sample it has never seen before

A clean release sample tells you the site can run the method on the easy case. It says nothing about the case that matters.

What it does afterwards

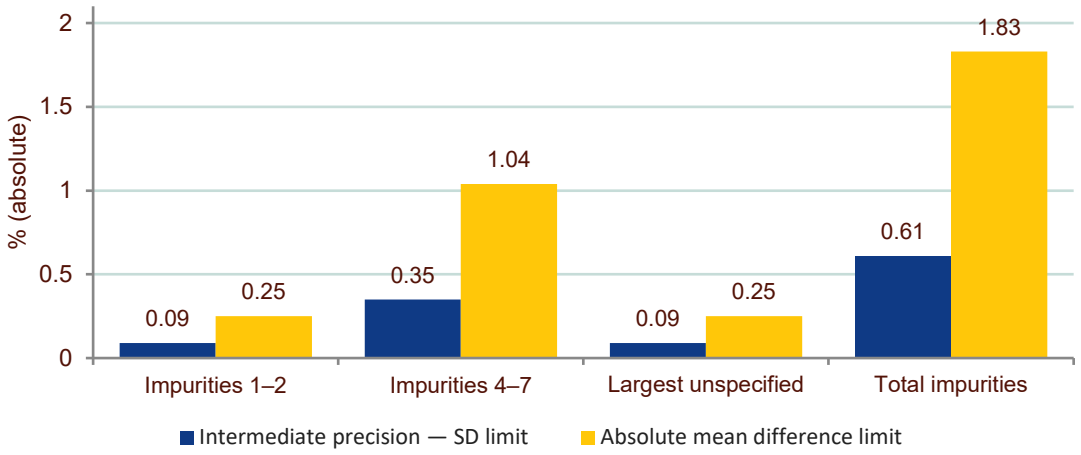
- Where the degradation mechanism is understood, it can be discussed as part of the transfer
- It supports troubleshooting during and after transfer activities
- A light-sensitive compound leads naturally into the need for amber vials

Robustness across laboratories is demonstrated on the hard sample, not the easy one.

One caution worth stating to a reviewer: a stressed sample may carry more degradation than the transfer activities actually require. That is acceptable — it is a transfer tool, not a stability sample — but the rationale for the degradation level should be documented, so the sample is not mistaken for a representation of the product at end of shelf life.

Criteria derived statistically, and only where they add value

The basis: criteria are set from n=6 set-ups in the receiving laboratory, the historical variability and experience of the originating laboratory (including intermediate precision from at least n=6 set-ups there), and the specification limits. Three inputs, none of them convention.



Why three impurities carry no criteria at all

No acceptance criteria were set for impurities 3, 8 and 9, because doing so affords no additional practical benefit. The analytes that do carry criteria were chosen because they have the greatest historical variability, are not easily resolved from adjacent peaks, and are most likely to sit near regulatory limits.

Two criteria, two different questions

The standard deviation test asks whether the receiving laboratory can produce results as consistently as required. The equivalence test asks whether its results agree with the originating laboratory. A site can pass one and fail the other, which is why both are set.

This is Q9 applied to a transfer protocol: effort is concentrated on the analytes where a difference between laboratories would actually matter, and the reasoning for excluding the others is written down.

Pack BW, Sailer DE, Argentine MD. Streamlining Method Transfer Across Global Sites. Pharmaceutical Technology. 2020;44(9).

BACKUP — ICH Q2(R2) TABLE 1

What the guidelines actually say

ICH Q2(R2) Table 1 — typical performance characteristics and related validation tests, by measured quality attribute

Performance characteristic	Identity	Impurity quantitative	Impurity limit	Assay content / potency
Specificity test	+	+	+	+
Response (calibration model)	–	+	–	+
Lower range limit	–	QL	DL	–
Accuracy test	–	+	–	+
Repeatability test	–	+	–	+
Intermediate precision test	–	+	–	+

+ normally conducted; – not normally conducted; QL quantitation limit; DL detection limit. Accuracy and precision may instead be evaluated together against a combined criterion (§3.3.3). Where reproducibility is performed and intermediate precision can be derived from it, a separate study is not required.

The clause behind Case study 1

Q2(R2) §3.3.1.4 and §3.3.2.4 both require the standard deviation, the %RSD and an appropriate 100(1−α)% confidence interval — or a justified alternative statistical interval — to be reported, and the observed interval to be compatible with the acceptance criterion, "unless otherwise justified."

The clause behind Case study 2

Q2(R2) §2.2 places transfer inside lifecycle change management per Q14, and defines covalidation — meeting predefined criteria using data from multiple sites, which can itself satisfy transfer at those sites.

The clause behind Case study 3 — and the reason Q9 sits underneath all of this

Q14 describes development, change management and submission using either a minimal or an enhanced approach. In the enhanced approach a risk assessment sorts changes into high, medium and low, and the reporting category for each is agreed with the regulator using the Q12 tools. That single sentence is the whole of Case study 3.

High risk | **Medium risk** | **Low risk**

Prior approval · intermediate · notification

Reporting category agreed with the regulator using ICH Q12 tools — the framing used by FDA in its own regional consultation on Q2(R2) and Q14.

Source: ICH Q2(R2) and ICH Q14, Step 4, November 2023; as adopted and published by FDA, March 2024. Section numbers follow the ICH organisational breakdown.

BACKUP · METHOD TRANSFER — HUB AND SPOKE

One protocol, one reference data set, eight receiving laboratories

Originating laboratory

One-time generation of the data set used to set the statistical acceptance criteria



RECEIVING LABORATORIES

Site 1	Site 2
Site 3	Site 4
Site 5	Site 6
Site 7	Site 8

A common pre-approved protocol

Every receiving site executes the same protocol against the same criteria. Nothing is renegotiated per site, and results are comparable across the network.

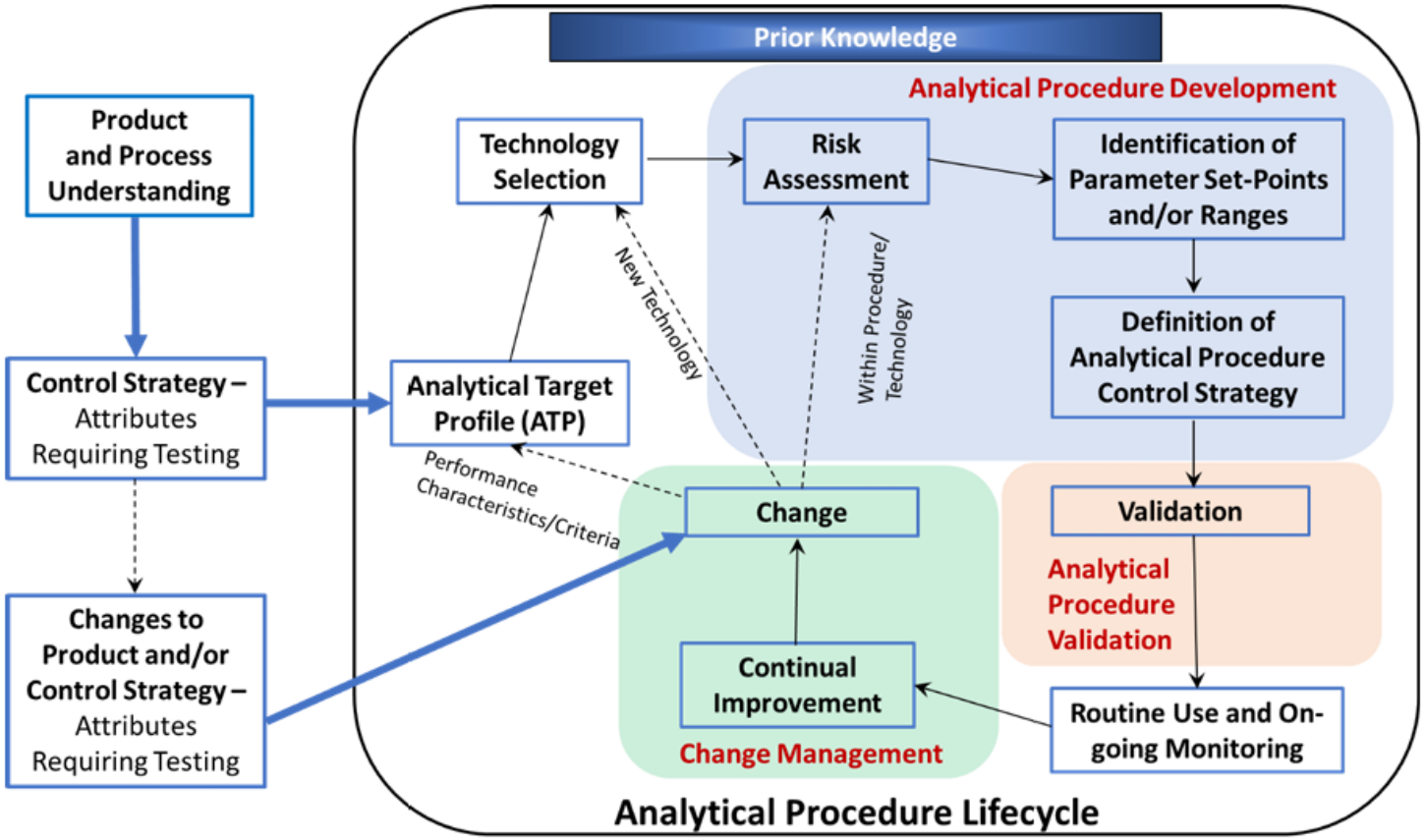
Issues surface early

A deviation at one site is immediately interpretable against the originating data set and the other sites, so system or preparation problems are caught before routine use.

The same samples keep working after the transfer closes

A method performance sample is not consumed by the transfer — it becomes a standing reference for laboratory performance over time. In one instance a set of low results was traced to an assignable sample preparation problem: every result in that set-up was low, which pointed directly at the system set-up rather than the method. The cause was identified, mitigated for future occurrences, and could be deliberately reconfirmed by inducing the same preparation error.

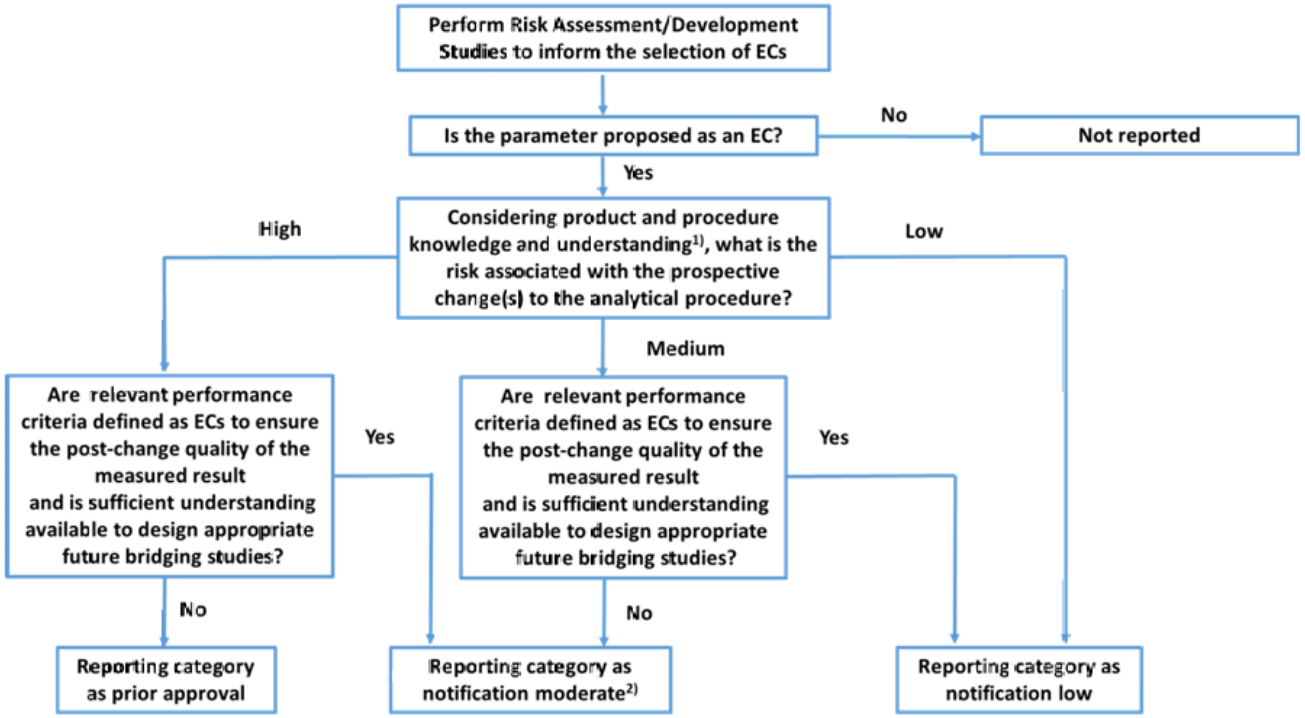
Figure 1: The Analytical Procedure Lifecycle



ICH Q14, Step 4, November 2023, Figure 1: The Analytical Procedure Lifecycle.

Figure 2: Risk-Based Reporting Categories for Changes

Figure 2: Risk-based approach for identification of ECs and reporting categories for associated changes in the enhanced approach



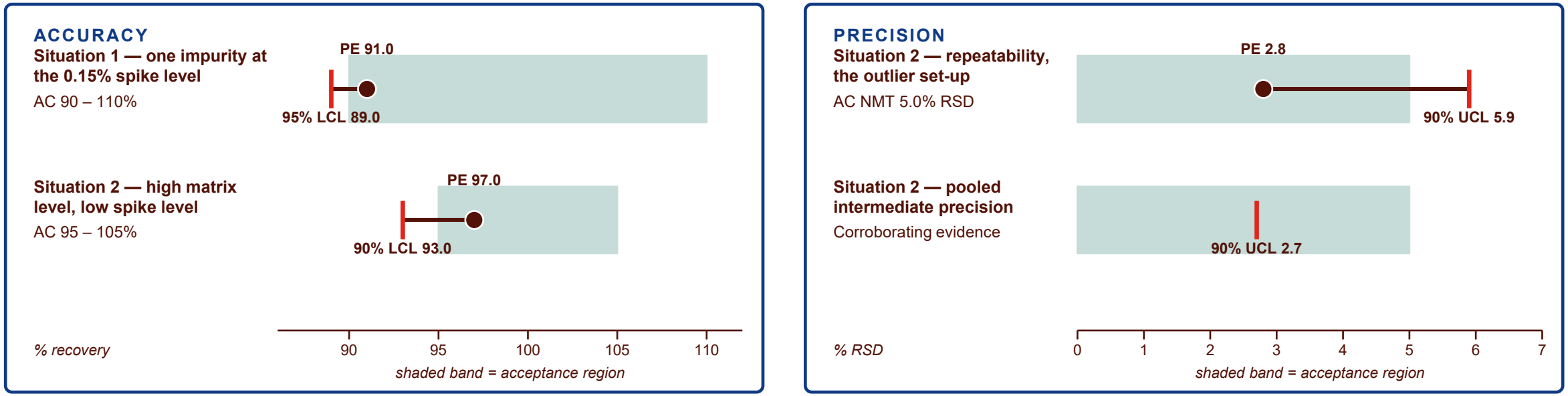
1) Including analytical procedure control strategy
2) In some cases, moderate risk changes proposed by the company may require prior approval based on health authority feedback

ICH Q14, Step 4, November 2023, Figure 2: Risk-based approach for identification of ECs and reporting categories.

CASE STUDY 1 · WHAT A BORDERLINE INTERVAL LOOKS LIKE

The same three results, plotted against their criteria

The tick marks the reported one-sided confidence limit; the dot marks the point estimate. In every case the point estimate sits inside the shaded acceptance region and only the limit falls outside it — which is exactly the situation the justification clause in Q2(R2) exists for.



Bottom line:

The repeatability upper limit of 5.9% breaches a 5.0% criterion, and on its own that looks like a failed method. The pooled intermediate precision limit of 2.7% sits well inside the same criterion, drawn from all three set-ups rather than the one containing the outlier. When the isolated statistic and the higher-level statistic disagree this sharply, the higher-level statistic is the better estimate of what the procedure actually does — and that is the reasoning that was documented.

Q12



Joseph Kutza

일라이릴리 글로벌 규제업무(GRA) – 화학·제조·품질관리(CMC) 및 의료기기 부문(GRA-CMCD) CMC 정책 담당 수석 이사

Eli Lilly and Company, Global Regulatory Affairs – Chemistry, Manufacturing, and Controls, and Devices (GRA-CMCD), Senior Director – CMC Policy

Kutza 박사는 2023년 4월 일라이 릴리(Eli Lilly)에 합류했으며, 현재 글로벌 규제 정책 및 전략(Global Regulatory Policy and Strategy) 팀의 수석 디렉터(Senior Director)로 근무하면서 모든 제품 유형에 걸친 글로벌 CMC(화학·제조·품질관리) 이슈를 담당하고 있습니다.그는 이전에 아스트라제네카(AstraZeneca)의 규제업무(RA) – CMC 부문 허가 후 바이오의약품 전략(Post-Approval Biologics Strategy) 팀에서 수석 디렉터 겸 그룹 매니저로 근무했습니다.Kutza 박사는 여러 전문 학회 및 제약산업 협회(Trade Association) 그룹에서 활발히 활동하고 있으며, 미국약전(USP) 전문가 패널(Expert Panel) 위원을 역임했습니다. 또한 CASSS 이사회(Board of Directors) 이사이자 CASSS 재무담당(Treasurer)으로 활동하고 있습니다.아스트라제네카에 합류하기 전에는 미국 FDA에서 의약품 심사관(Product Reviewer) 및 팀 리더(Team Leader)로 근무하면서 단일클론항체(monoclonal antibody) 제품에 대한 IND(임상시험계획 승인신청), BLA(생물학적제제 허가신청) 및 관련 변경·보완 신청(amendments and supplements)을 심사했습니다.

Dr. Kutza joined Lilly in April 2023 and is currently a Senior Director in the Global Regulatory Policy and Strategy Team with a focus on global CMC issues across all product types. He was previously a Senior Director and Group Manager in the Post-Approval Biologics Strategy Team in Regulatory Affairs – CMC at AstraZeneca. Dr. Kutza is active in several professional societies, trade association groups, has served on USP Expert Panels and is a member of the Board of Directors of CASSS as well as the Treasurer of CASSS. Prior to joining AstraZeneca, Dr. Kutza was an FDA product reviewer and Team Leader reviewing INDs, BLAs, and related amendments and supplements for monoclonal antibody products.

Program

ICH Q11 및 Q12: ICH Q10·Q9 기반의 발전-위험관리, 품질시스템 및 과학 기반 개발을 통한 허가 후 변경관리 체계 구축

ICH Q11 & Q12 Building on the ICH Q10 / Q9 Foundation-How risk management, quality systems, and science-based development converge into a workable framework for post-approval change management

ICH Q11 establishes principles for developing and manufacturing drug substances, including selection and justification of manufacturing processes and control strategies based on enhanced, science-based approaches. ICH Q12 builds on this foundation by providing a framework for managing post-approval changes across the product lifecycle, introducing tools such as Product Lifecycle Management documents, and Post-Approval Change Management Protocols. Neither guideline operates in isolation. ICH Q9 (Quality Risk Management) provides the risk-assessment methodology underlying control strategy design in Q11 and the risk-based categorization of Established Conditions in Q12. ICH Q10 (Pharmaceutical Quality System) supplies the organizational infrastructure—change management, knowledge management, continual improvement—required to implement Q12's lifecycle management tools effectively.This session will walk through each guideline's core concepts and demonstrate how they function as an integrated system with the core foundation concepts of Risk Management and the Pharmaceutical Quality System. Practical examples will illustrate how this integrated approach supports both regulatory predictability and manufacturing efficiency.

KOBIA SESSION

ICH Q11 & Q12

Building on the ICH Q10 / Q9 Foundation

How risk management, quality systems, and science-based development converge into a workable framework for post-approval change management



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FRAMING THE PROBLEM

Why This Training Matters

- Post-approval CMC changes are frequent and often trigger formal regulatory submission regardless of the actual risk to product quality or patient safety.
- ICH Q11 already gives us the scientific basis for knowing what matters — which process parameters and material attributes are truly critical to control.
- But that understanding doesn't automatically translate into how changes are classified and reported after approval — that is the gap Q12 was written to close.
- Q12 only works when applied together with Q10 (the quality system) and Q9 (risk management) — it is not a stand-alone tool.

Q11 asks:

"What do we need to control?"

Q12 asks:

"How do we manage change to it?"

One Integrated System, Through Four ICH Guidelines



Q10 is the operating system that governs how changes are handled; Q9 supplies the risk assessment and Q11 the science that determines what a change means; Q12 is the harmonized mechanism that ties it together.

FOUNDATION — ICH Q10

The Pharmaceutical Quality System

Defines the management framework within which every manufacturing and quality decision takes place — including how changes are evaluated, approved, and monitored.

- **Process Performance & Product Quality Monitoring**
- **Corrective Action / Preventive Action (CAPA)**
- **Change Management System**
- **Management Review of Process Performance & Quality**

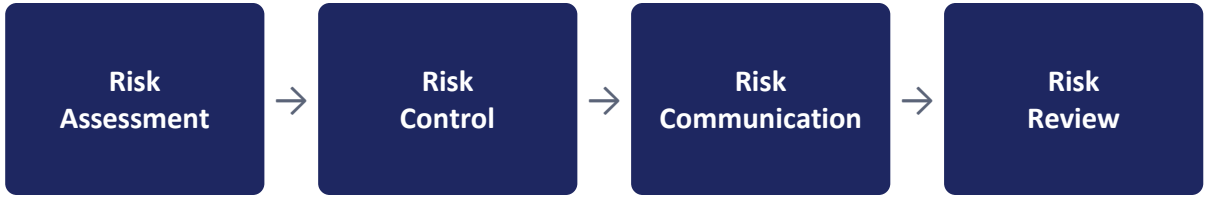
ROLE IN THE FRAMEWORK

Q10's PQS is the operating environment. Q12's post-approval change tools are not a replacement for the Q10 change management system — they extend it, giving it a risk-based, harmonized way to classify and report changes.

FOUNDATION — ICH Q9

Quality Risk Management

A systematic process for the assessment, control, communication, and review of risks to product quality across the lifecycle.



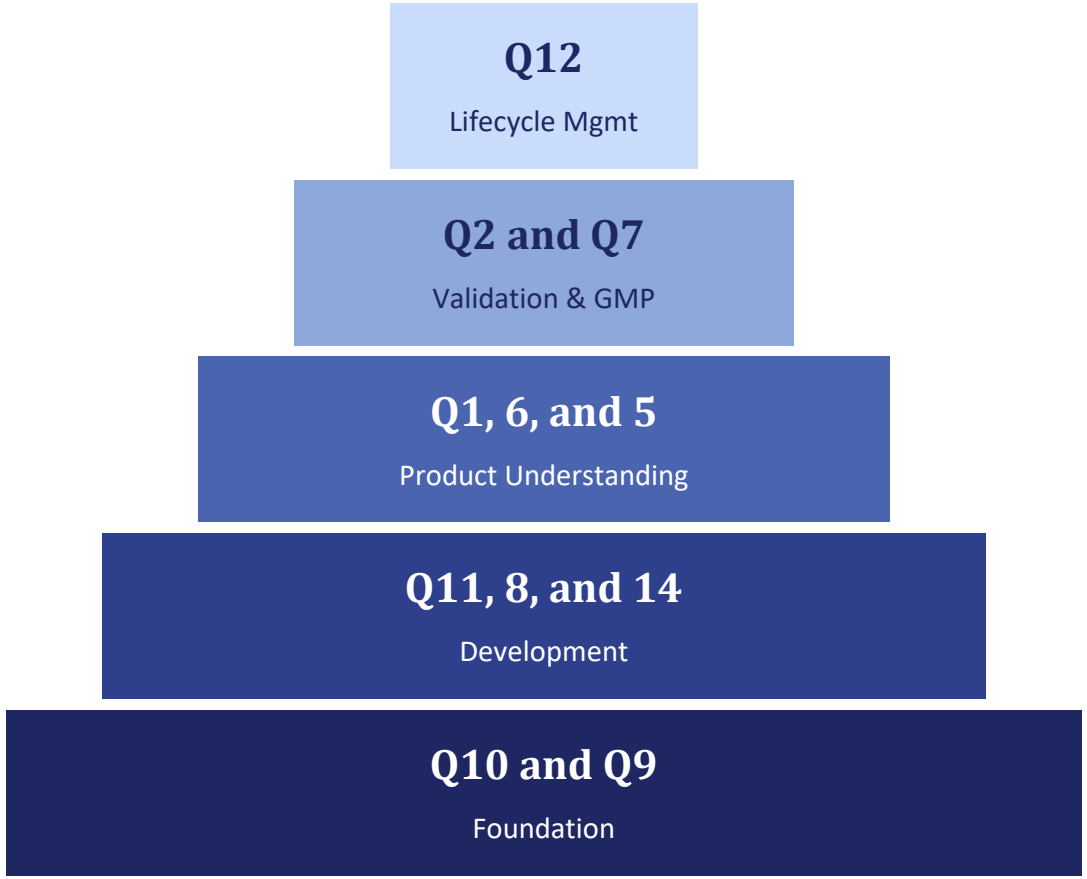
Provides the decision logic for proportionate action: not every change carries the same risk to the patient, so not every change should require the same regulatory scrutiny.

ROLE IN THE FRAMEWORK

Risk assessment tools underpin how quality attributes are identified in Q11, and how changes to them categorized under Q12.

Q10 and Q9: The Foundation for ICH Quality Guidelines

Q10 and Q9 aren't just the foundation for Q11 and Q12 — they underpin the entire ICH quality guideline system.



- **Q12**

  Lifecycle Management — draws on the product and process understanding built by everything below it.

- **Q2 and Q7**

  Analytical Procedure Validation (Q2) and GMP for Active Pharmaceutical Ingredients (Q7).

- **Q1, 6, and 5**

  Stability (Q1), Specifications (Q6), and Quality of Biotechnological Products (Q5).

- **Q11, 8, and 14**

  Development guidelines: Drug Substance (Q11), Drug Product (Q8), Analytical Procedure Development (Q14).

- **Q10 and Q9**

  Pharmaceutical Quality System (Q10) & Quality Risk Management (Q9) — the foundation everything above depends on.

Q11: Bringing Development Guidance to Drug Substance

Q8 had already brought a science- and risk-based approach to drug product development. Drug substances had no harmonized equivalent.

The Gap Before Q11 (pre-2012)

- No single ICH guideline described how drug substance development data should support a control strategy.
- Regional expectations for CTD Module 3 varied, driving inconsistent submissions and duplicated review effort.
- Sponsors often over-specified parameters to avoid regulatory risk, or under-justified them and drew review questions.

What Q11 Introduced

- A harmonized, science- and risk-based framework for describing drug substance development and manufacture.
- The concept of Established Conditions — distinguishing what needs regulatory control from what the firm's quality system can manage.
- A shared basis for linking process understanding directly to the control strategy.

Q11 gave sponsors and regulators a common language for what needs to be controlled — the next question was how to manage change to it. That's where Q12 comes in.

ICH Q11

Development and Manufacture of Drug Substances

Introduces a science- and risk-based approach to process development, and a concept that everything downstream depends on:

Post-approval Changes that Require a Submission (Established Conditions (ECs))

The parameters and procedures necessary to assure process performance and product quality — identified through development, prior knowledge, and risk assessment.

Post-approval changes of higher risk (ECs)

Require regulatory notification to change (reportability governed by Q12 categories).

Supporting Information

Managed within the firm's Q10 quality system; does not typically require prior regulatory approval to change.

This distinction — EC vs. supporting information — is the conceptual linchpin for proportionate post-approval change management. (More on where this stands globally in a moment.)

Why Q12 Was Needed

Q11 (2012) gave sponsors a harmonized way to identify what needs control — but not how to manage or report changes to it after approval.

The Gap After Q11

- Post-approval CMC changes remained one of the most burdensome parts of the lifecycle, with differing regional classification.
- Even well-justified, low-risk changes often required lengthy prior-approval submissions in multiple regions.
- Change backlogs could delay supply continuity and manufacturing improvements sponsors already understood were low-risk.

What Q12 Introduced (2019)

- A harmonized, risk-based lifecycle management framework for post-approval changes.
- Tools that let a change management plan look forward — rather than react change by change.
- A way to translate Q9/Q10/Q11 understanding directly into predictable, proportionate reporting.

Q12 closed the loop: Q11 defines what matters; Q12 defines how change to it gets managed and reported.

ICH Q12

Lifecycle Management

Provides harmonized tools to manage post-approval changes based on risk and established product/process understanding.

Risk-Based Reporting Categories

Classifies post-approval changes by risk — from notification to prior approval. Usable today.

PACMPs

Post-Approval Change Management Protocols — pre-agree the plan and criteria for a future change. Usable today.

Established Conditions & PLCM

The full EC/PLCM construct is the long-term vision — see the next slide for where it stands globally.

Post-Approval Change Management Protocols (PACMPs) and risk-based reporting categories are the tools we can leverage today, across ICH regions. The Established Conditions framework is still working toward full global implementation — covered next.

CURRENT STATE — GLOBAL IMPLEMENTATION

Established Conditions: Not Yet a Global Tool

The Barrier

- Established Conditions are a foundational Q11/Q12 concept — but submitting them as a formal regulatory category isn't yet possible in every ICH region.
- In the EU, variations classification is defined in law (the EU Variations Regulation), not by ICH guideline alone — adopting ECs requires legislative change, not just regulatory guidance.
- Until that alignment happens, a global strategy built around formal EC submissions creates inefficiency: a classification usable in one region may have no equivalent elsewhere.

What Works Today

- The risk-based logic behind EC reporting categories — classifying changes by risk, even without a formal “EC” designation.
- PACMPs, which several regions already accept in some form today.
- Practical takeaway: apply Q9/Q10 risk-based thinking now; treat formal Established Conditions submissions as a future-state tool once legal frameworks catch up.

BRINGING IT TOGETHER

A Worked Example

Scenario: scaling up a drug substance crystallization step to a larger vessel

Q11 Was agitation rate identified affecting product quality during development (EC?) — or as supporting information?

Q10 Is the change captured, evaluated, and approved through the site's change management system?

Q9 What is the risk to product quality if agitation rate shifts outside the historical range at the larger scale?

Q12 Does the risk category support reduced reporting or use of a pre-agreed PACMP in each region where the product is registered?

KEY TAKEAWAYS & DISCUSSION

One Integrated Framework

Q10 = the system · Q9 = risk management · Q11 = the science · Q12 = the mechanism

Established Conditions are the conceptual foundation — but PACMPs and risk-based reporting categories are the tools with the broadest use today. Apply those first.

Discussion Prompts

- Where in our own change management process or regulatory review process do we already apply Q10/9 risk-based thinking?
- Which upcoming changes might be good candidates for a PACMP?

Q12



Brix Bayuga

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Brix Bayuga는 현재 일라이 릴리(Eli Lilly)의 아시아·태평양(APAC) 지역 글로벌 규제업무(GRA) 화학·제조·품질관리(CMC) 및 국제업무 부문 리더로서, 아시아·태평양 지역의 CMC 규제 전략을 총괄하고 있습니다. 이를 통해 여러 치료 영역에서 성공적인 의약품 허가를 이끌어내고, 아시아·태평양 전역에서 환자들이 혁신 의약품에 보다 신속하게 접근할 수 있도록 하는 역할을 수행하고 있습니다.그의 전문 분야는 의약품 품질시스템, 우수의약품 제조관리기준(GMP), 제조 및 품질관리(CMC)이며, 제약업계에서 19년 이상의 경력을 쌓아왔습니다.일라이 릴리에 합류하기 전에는 화이자(Pfizer)에서 CMC 규제업무를 담당했으며, 미국, 유럽 및 아시아·태평양 지역에서 의약품의 품목허가 등록 및 허가 갱신·변경 등 전 생애주기(lifecycle) 허가 업무를 수행했습니다. 여기에는 중국, 일본, 대한민국 및 ASEAN 국가가 포함됩니다.Brix는 규제업무전문가협회(RAPS, Regulatory Affairs Professionals Society)에서 발간한 Fundamentals of Pharmaceutical and Biologics Regulations: A Global Perspective 제2판의 공동 저자로도 참여했습니다.

Brix Bayuga is the APAC Leader, Global Regulatory Affairs Chemistry, Manufacturing, and Controls (CMC), International Operations at Eli Lilly, leading regional CMC regulatory strategy across Asia Pacific enabling successful approvals across multiple therapeutic areas — accelerating patient access to innovative medicines throughout the region. His expertise spans pharmaceutical quality systems, GMP, and manufacturing and controls, built over 19 years in the pharmaceutical industry. Prior to Eli Lilly, he held CMC regulatory roles at Pfizer, delivering registrations and lifecycle approvals throughout the US, Europe, and Asia Pacific — including China, Japan, South Korea, and ASEAN. Brix is a contributing author to the Regulatory Affairs Professionals Society (RAPS) Fundamentals of Pharmaceutical and Biologics Regulations: A Global Perspective (Second Edition).

Program

기초에서 실무까지: 공급망 회복탄력성 강화를 위한 원료의약품 변경 및 PACMP의 리스크 관리와 의약품 품질시스템을 적용한 사례 연구

From Foundations to Practice: Case Studies Applying Risk Management and the Pharmaceutical Quality System to Drug Substance Variations and PACMPs for Supply Chain Resilience

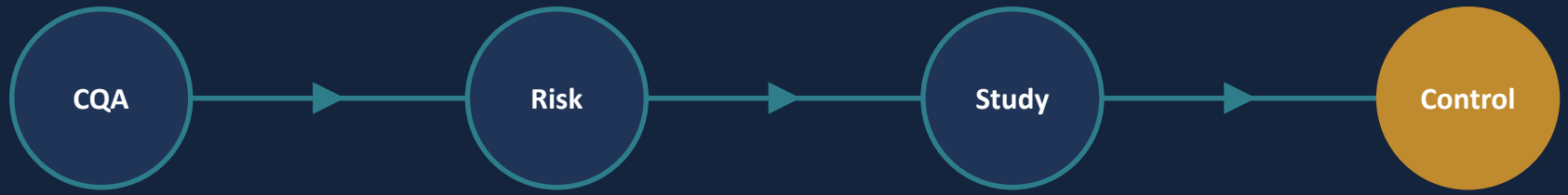
This session presents real-world case studies of drug substance variations and Post-Approval Change Management Protocols (ICH Q12), demonstrating how the principles of ICH Q9, Q10, Q11, and Q12 perform under the demands of live regulatory execution.Central to the discussion is ICH Q11. The manufacturing process description, designation of critical process parameters, and control strategy defined at original submission establish the baseline against which any subsequent variation is assessed and justified. The cases examine how the granularity and robustness of that foundational development work govern the categorization, scope, and reviewability of downstream changes, and how an enhanced development approach expands lifecycle flexibility, including opportunities for prospective change management under a PACMP.Collectively, they illustrate how risk-based change categorization and prospective change management operationalize these foundational principles into agile, predictable regulatory execution, reinforcing continuity of supply.

KOBIA WORKSHOP · A GRA-CMC PERSPECTIVE

ICH Q11 & Q12 in Practice

Development, Common Technical Document (CTD) placement, and a lifecycle strategy for stable supply

Part 2 of 2 — applying the framework · following J. Kutza (Foundations & Policy)



Brix Bayuga Director, Global Regulatory Affairs (GRA) — Chemistry, Manufacturing & Controls, and Devices (CMCD)

Eli Lilly and Company

SESSION OVERVIEW

Agenda

PART 1 · ICH Q11 IN PRACTICE

1. Deep dive on 3.2.S.2.6 — Manufacturing Process Development (Section VIII)
2. Lifecycle management (Section IX)

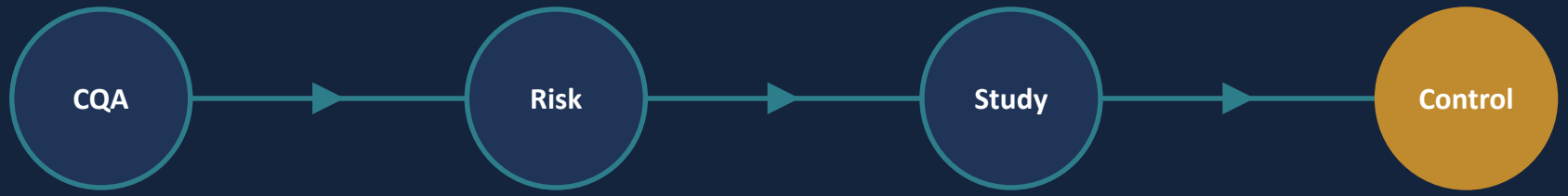
PART 2 · ICH Q12 IN PRACTICE

3. A Post-Approval Change Management Protocol (PACMP) case study — enabling "Do-Then-Tell"

GRA-CMCD · WORKED EXAMPLE

Deep dive: Section 3.2.S.2.6 of the Common Technical Document

Manufacturing Process Development — ICH Q11 principles as they appear in Module 3.



Aligned to ICH Q11, Section VIII — Submission of Manufacturing Process Development and Related Information in Common Technical Document (CTD) format

Where 3.2.S.2.6 sits in the dossier

- Section VIII maps process-development and related information to defined locations in the Common Technical Document (CTD), Module 3.
- 3.2.S.2.6 is the narrative section. It tells the development story, summarizes the control strategy, and cross-references the sections that hold each element.
- The enhanced (Quality by Design) approach does not change where content is placed; it raises the level of scientific justification carried in the summary.

3.2.S.2.2	**Description of Manufacturing Process & Process Controls** *Design space, if used*
3.2.S.2.3	**Control of Materials** *Starting-material specifications + selection justification*
3.2.S.2.4	**Controls of Critical Steps & Intermediates** *In-process controls, intermediate specifications*
3.2.S.2.5	**Process Validation / Evaluation** *Demonstration of consistent performance*
3.2.S.2.6	**Manufacturing Process Development** *Development narrative · control-strategy summary · comparability*
3.2.S.3.2 / .4.1	**Impurities · Specification** *Justified acceptance criteria*

Process validation data in the marketing application

Whether process validation/evaluation data is included in the marketing application depends on the type of drug substance (ICH Q11, Section VII, p.15).

1 Synthetic (chemical entity) drug substance

Not all geographies require process validation data in the marketing application; for non-sterile chemical entity processes, results are not normally included in the dossier.

2 Biotechnological or sterile drug substance

Inclusion of process validation data in the marketing application (3.2.S.2.5) is a typical regulatory requirement.

The concept: Submission of Manufacturing Process Development and Related Information

Each of the four subsections of Section VIII is summarised in the Manufacturing Process Development section, 3.2.S.2.6.

VIII.1

Quality Risk Management

Risk assessments; links of material attributes and process parameters to Critical Quality Attributes (CQAs)

Summarised in 3.2.S.2.6

VIII.2

Critical Quality Attributes

The CQA list and the rationale for their designation

Summarised in 3.2.S.2.6

VIII.3

Design Space

The development studies that form its basis

Summarised in 3.2.S.2.6

VIII.4

Control Strategy

Changes to the strategy across process evolution

Summarised in 3.2.S.2.6

Lifecycle management and continual improvement are handled under the Pharmaceutical Quality System (ICH Q10), not the dossier.

WORKED EXAMPLE · DOCUMENT STRUCTURE

Anatomy of a Q11-aligned 3.2.S.2.6

Six connected subsections — how Section VIII development information is summarised in 3.2.S.2.6.

.1 Introduction

Process and route overview; development guided by Critical Quality Attributes (CQAs).

Enhanced approach framed

.2 Synthetic Route Development

Route history with each change and its scientific rationale.

ICH Q11 Section III — process understanding

.3 Material Comparability

Science- and risk-based assessment across process changes.

Risk-based comparability

.4 Starting Material Designation

Selection justified against the ICH Q11 general principles.

ICH Q11 Section V

.5 Intermediate Specification Rationale

Controls set at isolated intermediates by Impurity fate and purge

Control strategy

.6 Commercial Process Development

Critical quality attributes; impurity fate and purge; proven acceptable ranges and critical process parameters.

ICH Q11 Sections III & VI

Summary sits in 3.2.S.2.6; detail is cross-referenced to home sections (3.2.S.2.2–.2.4, 3.2.S.3.1, 3.2.S.4.5).

The concept: knowledge and control across the lifecycle

Q10

Development does not end at approval. Under ICH Q10, process performance and the effectiveness of the control strategy are evaluated and improved across the lifecycle — development, commercial manufacture, and discontinuation — with knowledge managed systematically and every change governed by risk.

Continual improvement

Periodically evaluate process performance and control-strategy effectiveness; use commercial and prior knowledge to refine the strategy.

Pharmaceutical Quality System (ICH Q10)

Knowledge management

Systematic across development, technology transfer to internal sites and Contract Manufacturing Organisations (CMOs), validation over the lifecycle, and change management.

Pharmaceutical Quality System (ICH Q10)

Change management

Evaluate each proposed change for impact on drug-substance (and drug-product) quality on scientific grounds; determine appropriate testing.

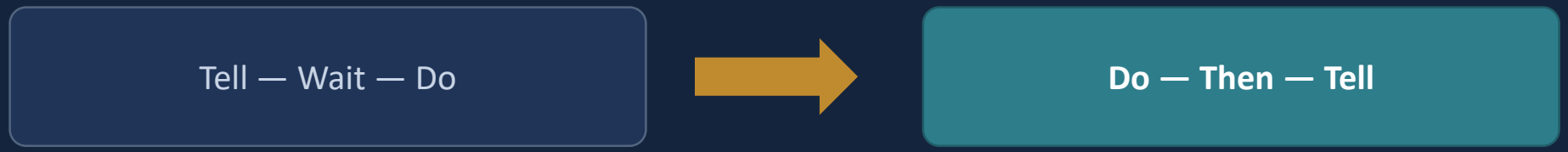
Pharmaceutical Quality System (ICH Q10)

Regulatory interface

Movements within an approved design space are not changes and need no regional approval. Changes to filed information are reported per regional requirements. The applicant may propose in the original submission how specific future changes — including to the control strategy — will be managed. The Post-Approval Change Management Protocol (PACMP) in Part 2 is one such pre-agreed mechanism.

Post-Approval Change Management Protocol

Structured approach for frequent CMC post-approval change



A pre-approved protocol enables a lower reporting category — the change is implemented once the agreed conditions are met, then reported.

The change and the objective

1

What

A change in the manufacturer of a starting material and/or intermediate used to manufacture the drug substance — applicable to both the linear process and the hybrid process.

2

Why

Additional manufacturers are anticipated over the product lifecycle to secure a reliable, resilient supply of drug substance.

3

The ask

A pre-approved Post-Approval Change Management Protocol (PACMP) that defines, up front, how each such change is assessed, controlled, and reported — supporting a lower reporting category.

Why the drug-substance control strategy is justified

Developed under an enhanced approach — risk management and process knowledge link parameters and unit operations to the Critical Quality Attributes (CQAs).

1 Impurities are understood

Formation, fate, and purge of impurities introduced from incoming starting materials and intermediates are well characterized across the process.

2 Materials are controlled

Starting materials and intermediates are controlled through an overarching control strategy: parameter ranges, in-process controls, and specifications.

3 Specification and control strategy restrict impurity entry

Starting-material specifications (3.2.S.2.3) and intermediate specifications (3.2.S.2.4) limit impurities at process entry; limits reflect demonstrated downstream purge capability.

4 A safeguard against new impurities

All starting-material and fragment-intermediate specifications carry an 'any unspecified impurity' limit or tighter, guarding against a new impurity above the drug-substance limit.

Acceptance criteria to be met

Based on this enhanced control strategy, any change in the manufacturer of a starting material and/or intermediate is reported as a 'Do-Then-Tell' variation — provided the acceptance criteria specified in the PACMP are met.

Material	Acceptance criteria
Starting material (both drug-substance processes)	Analytical data from at least two (2) commercial starting-material batches from the proposed manufacturer will be comparable to analytical data from the current manufacturer(s) and will meet the approved specifications.
Intermediates	Analytical data from at least two (2) commercial intermediate batches from the proposed manufacturer will be comparable to analytical data from the current registered intermediate manufacturer and will meet the approved specifications.

Comparability together with conformance to the approved specifications is the condition for implementation.

Quality risk management activities (based on ICH Q9)

The Post-Approval Change Management Protocol (PACMP) commits to the following quality risk management (QRM) activities — following ICH Q9 principles — for any change in the manufacturer of a starting material and/or intermediate.

1	**Identify and assess risks**	Identification and assessment of the potential risks associated with the proposed change, and the risk-mitigation steps.
2	**Account for known process elements**	Accounting for known elements of the process — robustness, existing controls, and potential impact on product quality.
3	**Apply prior process knowledge**	Incorporating prior process knowledge gained from development and commercial manufacturing experience.

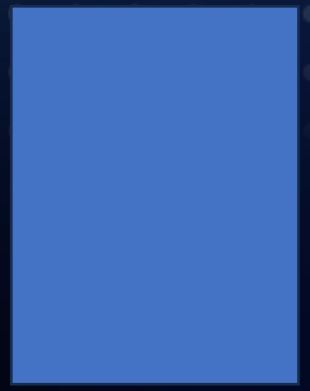
A managed 'Do-Then-Tell' change

Any change in the manufacturer of a starting material and/or intermediate within the scope of the Post-Approval Change Management Protocol (PACMP) is reported as 'Do-Then-Tell' — provided the acceptance criteria are met.

- **Supply resilience**
- **Reduced lead time**
- **Regulatory predictability**
- **Continued control oversight**

Approved in Europe: this protocol was accepted under the EU framework

Q8/Q9/Q10



이명모 (Myungmo Lee)

노바티스 코리아 품질 관리부 QA 매니저 Novartis Korea, Novartis Country Quality QA Manager

이명모 박사는 서울대학교 약학대학을 졸업하고 약품화학 전공으로 약학박사 학위를 취득한 약사이며 정부, 다국적 제약기업, 학계에 걸쳐 10년 이상 의약품 품질 분야에 종사해왔다. 식품의약품안전처 심사관으로 원료의약품 및 신약의 품질심사를 담당하며 관련 국가 가이드라인 제정에 참여하였고, 이후 한국룬드벡과 CG인바이츠를 거쳐 현재 한국노바티스에서 QA Manager 및 QP로 수입의약품의 품질보증과 출하를 총괄하고 있다. 이러한 실무와 병행하여 ICH Q9(R1) Quality Risk Management Working Group의 Expert Member로 글로벌 교육자료 개정 작업을 수행하였으며, 식약처 CHORUS의 첨단품질심사분과 전문가로 활동하였고, 현재 경희대학교 약학대학에서 국제 의약품 규제 동향을 강의하고 있다. 가이드라인을 기반으로 심사하는 자리, 그것을 현장에서 운영하는 자리, 그리고 가이드라인 자체를 만드는 자리를 모두 거치면서, 규제 문언이 실제 개발과 심사 현장에서 어떻게 작동하는지에 지속적인 관심을 두고 있다.

Dr. Myungmo Lee is a licensed pharmacist who received his Ph.D. in medicinal chemistry from the College of Pharmacy, Seoul NationalUniversity, and has worked in pharmaceutical quality for over ten years across government, multinational industry and academia. As aregulatory assessor at the MFDS, he reviewed the quality of drug substances and new drugs and contributed to the related nationalguidelines. He then worked at Lundbeck Korea and CG Invites, and is currently QA Manager and Qualified Person at Novartis Korea,overseeing quality assurance and release of imported medicines. Alongside this work he served as an Expert Member of the ICH Q9(R1)Quality Risk Management Working Group, leading the revision of its global training materials, and as an expert in the MFDS CHORUSadvanced quality review subgroup; he currently teaches international regulatory trends at Kyung Hee University. Having reviewed againstguidelines, applied them in practice and helped write them, he maintains a continuing interest in how regulatory text operates indevelopment and review.

Program

QbD 기반 제품 개발 사례: 위험평가의 재검토에서 관리전략 재수립까지

A Case Study in QbD-Based Product Development: From an Overturned Risk Assessment to a Rebuilt Control Strategy

ICH Q8, Q9, Q10의 개념은 이미 여러 차례 교육된 바 있다. 그러나 실무의 어려움은 개념을 아는 데 있지 않고,그것들이 하나의 제품 개발 과정에서 어떤 순서로 서로를 호출하는지를 경험하기 어렵다는 데 있다. 실제 개발 사례는 대부분 비공개이며, 공개된 사례조차 성공한 판단만을 담고 있기 때문이다. 본 강연에서는 규제기관이 공개한 예시자료를 토대로 구성한 가상의 제품 개발 사례를 처음부터 끝까지 따라간다. 구체적으로 1) 목표제품품질프로파일에서 중요품질특성을 도출하며 무엇을 중요하다고 판단하고 무엇을 제외했는지, 2) 위해평가 도구와 등급 기준을 어떻게 설정하였으며 그 결론이 제조규모 확대 과정에서 어떻게 뒤집혔는지, 3) 드러난 상호작용을 반영하여 설계공간과 관리전략을 어떻게 재설정하였는지, 4) 재설정된 관리전략이 변경관리와 제품품질검토로 이관되며 어떤 문서로 남았는지를 다룬다. 아울러 초기 판단이 어긋난 지점을 ICH Q9(R1) 개정이 지적한 위해평가의 subjectivity 및 formality 문제와 연결하고, 동일한 문서가 심사자의 자리에서 어떻게 읽히는지를 함께 제시한다. 성공한 결정뿐 아니라 재검토가 필요했던 판단을 함께 보여줌으로써, 참석자가 자사의 개발 문서를 같은 순서로 점검할 수 있도록 하는데 목적이 있다.

The concepts of ICH Q8, Q9 and Q10 have been covered in previous sessions. The difficulty in practice liesnot in knowing them but in rarely seeing the order in which they call on one another while a single product isdeveloped. Most real development cases remain confidential, and those that are published tend to show only thedecisions that worked. This presentation therefore uses a hypothetical development case built from publiclyavailable regulatory example materials, and follows it from beginning to end. Four areas are addressed: 1) Howcritical quality attributes were derived from the quality target product profile, including what was judged criticaland what was excluded; 2) how the risk assessment tool and its scoring criteria were set, and how thoseconclusions were reversed during scale-up; 3) how the design space and control strategy were re-established oncethat interaction was understood; and 4) what documentation the revised control strategy produced in changecontrol and product quality review. The points at which the early judgement failed are linked to the subjectivityand formality issues addressed by the ICH Q9(R1) revision, and the same documentation is then considered froman assessor's position. By showing judgements that had to be revisited alongside those that worked, the sessionoffers participants a sequence they can apply to their own development records.

A Case Study in QbD-Based Product Development

From an Overturned Risk Assessment to a Rebuilt Control Strategy

Slido QR

2026 ICH Guideline Training Program
Pharmaceutical Quality System
ICH Q8 / Q9 / Q10
1 October 2026

Presented by
Myungmo Lee, Ph.D.
QA Manager / QP, Novartis Korea

IFPMA

Three Seats

IFPMA

1

Regulatory assessor

Ministry of Food and Drug Safety

Reviewing the file

Quality assessment of drug substances and new drugs

2

Industry QA / QP

Lundbeck Korea · CG Invites · Novartis Korea

Releasing against the file

Where the dossier meets the batch

3

ICH Q9(R1) Expert Member

Quality Risk Management Implementation Working Group / Training Group

(2024–2026, nominated by IFPMA)

Explaining the guidance

Revision of the global Q9(R1) training materials

Disclaimer · About This Case

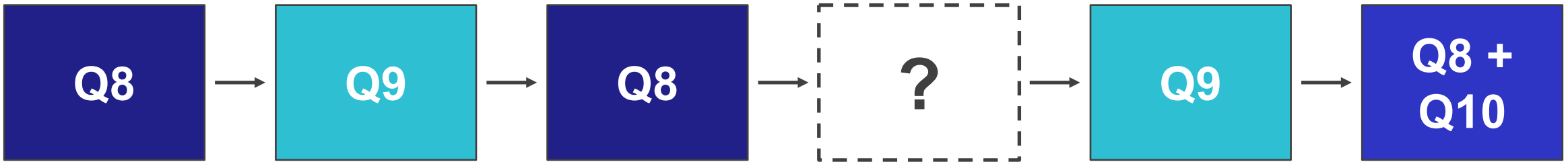
Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the positions of Novartis, IFPMA or ICH.

About this case

- Hypothetical product, process and data, created for explanatory purposes
- Document format follows published regulatory examples
- The direction and magnitude of effects are specific to this case and should not be generalized.

Today's Route



One product · three guidelines · one revised judgment

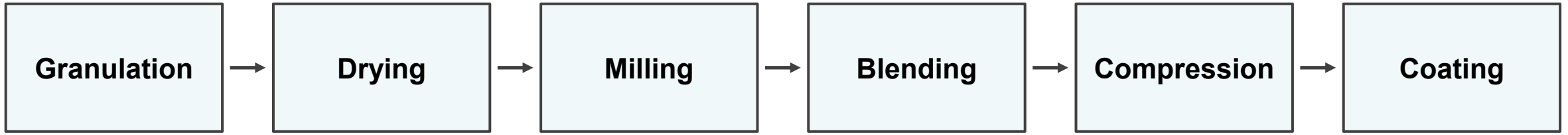
Up next — running a quality system across products: Session (II)

The Product

IFPMA

Model Drug A

- 20 mg immediate-release film-coated tablet
- BCS Class II — low solubility, high permeability



High-shear wet granulation process

Quality Target Product Profile

Granulation | Drying | Milling | Blending | Compression | Coating

IFPMA

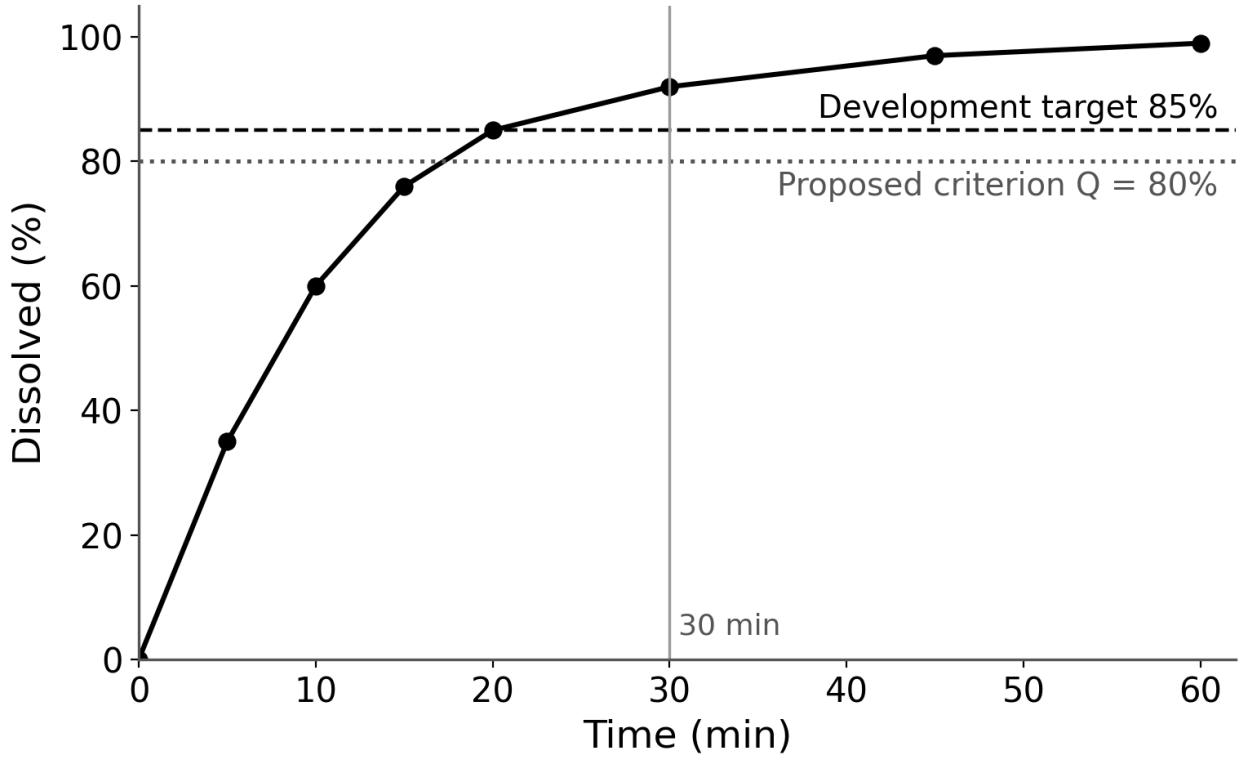
Proposed dissolution acceptance criterion

Q = 80% at 30 min

Development target

Mean dissolution at 30 min ≥ 85%

5% margin between the criterion and the target



Q8 | Q9 | Q10

From QTPP to CQAs

IFPMA

Attributes screened for patient impact

Quality attributes

Assay

Content uniformity

Degradation products

Dissolution

Hardness

Friability

Appearance

→ **CQA**

Dissolution

Absorption is solubility-limited

→ **Not designated as CQAs in this case**

Hardness · Friability · Appearance

No clinically relevant impact demonstrated within the proposed control range

Initial Risk Assessment — 2 kg

IFPMA

Risk to dissolution · severity × occurrence × detectability

Process step	Risk to dissolution
Granulation	High
Drying	**Low**
Milling	Medium
Blending	Low
Compression	Medium

Slido

How would you rate drying?

High · Medium · Low

Slido QR

Why Drying Was Rated Low

IFPMA

1

Data

All results ≥ 90% across LOD 1.5–3.0%; no trend judged significant

2

Prior knowledge

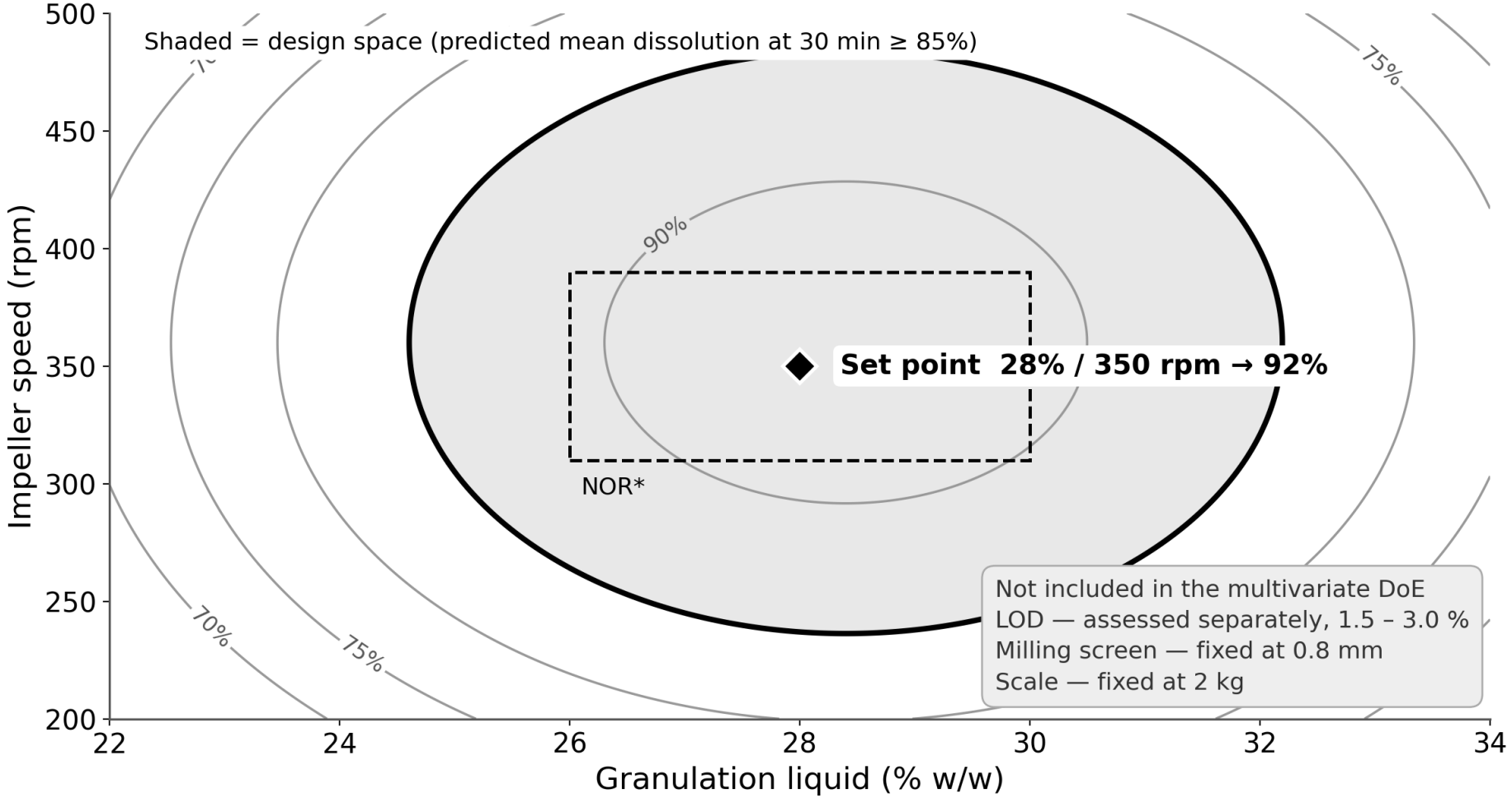
Suggested limited impact on dissolution under the studied conditions

3

Study design

LOD was assessed univariately; milling screen was held at 0.8 mm

Initial Design Space at 2 kg



*NOR: normal operating range — industry QbD term, not defined in ICH Q8

Scale-up

IFPMA

92% → 86% → **82%**

2 kg
screen 0.8 mm

30 kg
screen 0.9 mm

200 kg
screen 1.0 mm

Met dissolution acceptance criteria at S2 · below the development target of 85%

Mean dissolution at 30 min

Root Cause

IFPMA

1. **A significant interaction between residual moisture and milling screen was identified**

2. At the larger screen aperture, the milling response became more sensitive to residual moisture

3. The resulting PSD shift was associated with slower disintegration and dissolution

Interaction and direction are hypothetical and product-specific; references support the underlying milling principles (Metta et al., Int J Pharm 2018 · Karlsen et al., Int J Pharm 2025).

Risk Assessment, Revisited

Granulation | **Drying** | **Milling** | Blending | Compression | Coating

IFPMA

Same matrix · same scoring method

Process step	Risk to dissolution
Granulation	High
Drying	**Low → High**
Milling	**Medium → High**
Blending	Low
Compression	Medium

New data did not merely change the score.

It exposed the assumption behind the old score.

Through the Q9(R1) Lens



IFPMA

Subjectivity	Prior knowledge was used without documenting its assumptions and boundary conditions
Formality	The level of QRM was not commensurate with the uncertainty, importance and complexity of scale-up

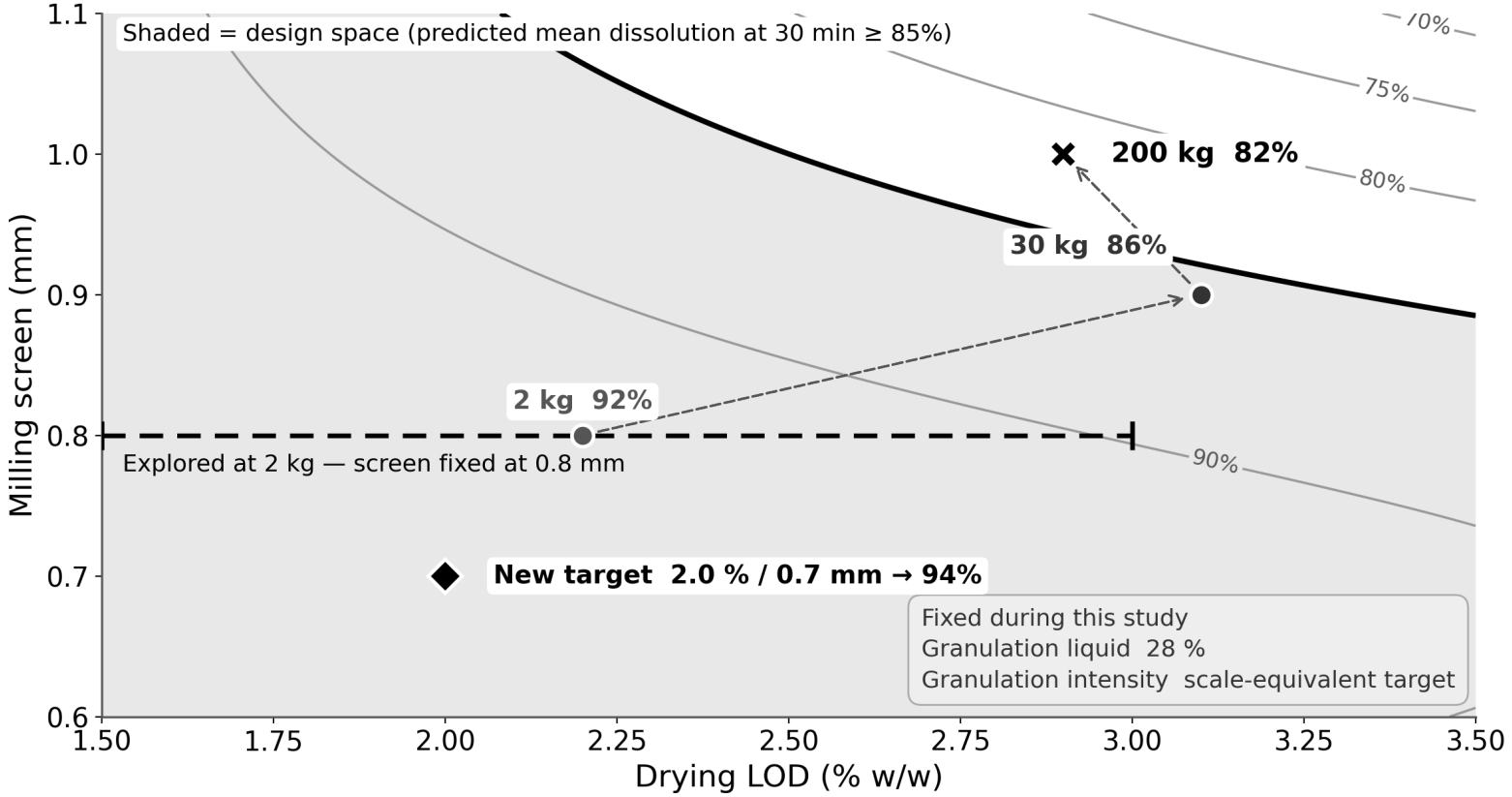
Published QbD mock examples have also evolved to address implementation challenges.

e.g. NIHS Sakura Tablet → Sakura Bloom Tablets (process-parameter-based → material-attribute-based design space)

Design Space, Redefined

Granulation | Drying | Milling | Blending | Compression | Coating

IFPMA



The effect of milling screen depends on LOD

Little at low LOD, pronounced at high LOD

The 2 kg relationship was not shown to be scale-independent.

Its boundary conditions changed during scale-up.

2 kg and 30 kg points show historical operating conditions and observed dissolution; they were not used to define the 200 kg response surface.

Q8 | Q9 | Q10

Control Strategy, Rebuilt

Granulation | **Drying** | **Milling** | Blending | Compression | Coating

IFPMA

Element	Role	Basis
Milling screen aperture	**CPP**	Revised multivariate study
Drying inlet temperature, airflow	**CPPs**	Demonstrated impact on dissolution through LOD variability
Granule LOD and D_{50}	**Intermediate attributes — controlled by IPC**	Not process parameters

Development change control links the revision to the risk assessment that triggered it

Q8 | Q9 | **Q10**

The Same File, From the Assessor's Seat

IFPMA

1. Assessors read for the link between risk assessment and control strategy

2. A CPP with no visible scientific rationale is likely to generate a question

3. **Section 3.2.P.2 should make the path from evidence → risk → control visible**

Where This Goes Next

IFPMA

One product

All of this lives in one product's development file

→

Across products

Making it repeatable is a quality system question

Session (II) — implementing ICH Q9 and Q10

Q8 | Q9 | **Q10**

Three Things to Take Back

IFPMA

1

The 2 kg design space was not wrong.

Its applicability was conditional.

2

Low risk at 2 kg

may not stay low at 200 kg.

3

A univariate result

cannot rule out an interaction.

Questions open for one week
— Slido #3404955 / 1–7 October

Please do not include information that could identify a specific company or product.

Q8 Q9 Q10

Publication

ICH Q9(R1) Briefing Pack — updated March 2026

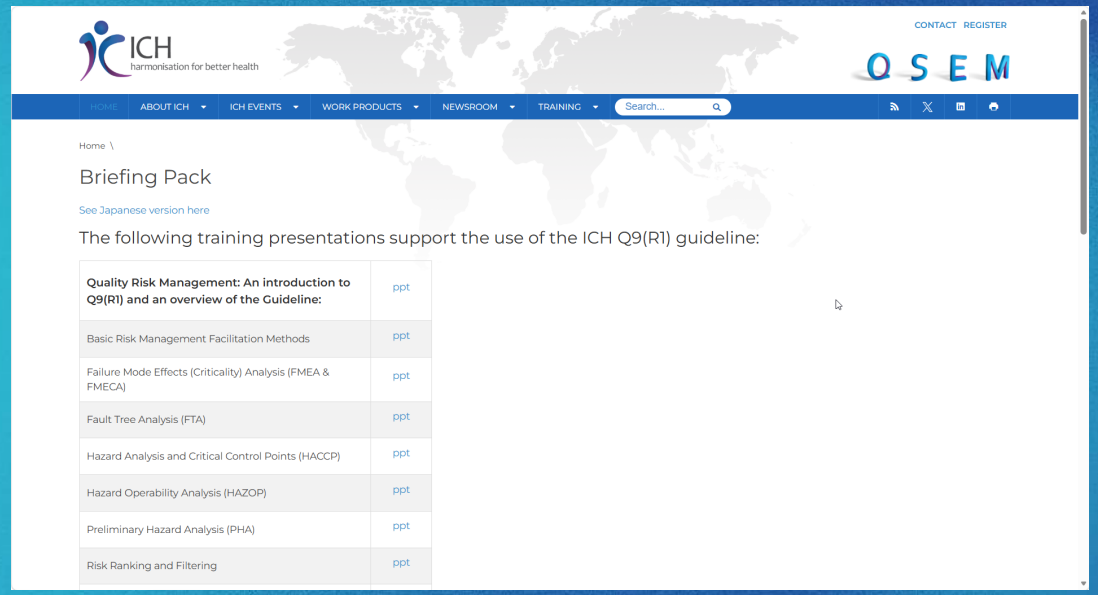
1 introductory module
9 modules on QRM methods and tools
9 modules on QRM applications

https://ich.org/page/q9r1-briefing-pack

Questions open for one week — Slido #3404955 / 1–7 October

Please do not include information that could identify a specific company or product.





Q13



정성훈 (Sunghun Jung)

삼성바이오로직스 Process Lifecycle QA 파트장

Samsung Biologics, Process Lifecycle QA Part Leader

정성훈은 University of California, San Diego 생화학 학사학위를 받은 후 녹십자에서 품질보증부서 4년 / 삼성바이오로직스 품질보증부서 7년간 재직중이다. 삼성바이오로직스에서 생산하는 항체 바이오의약품의 공정 다자인, 공정밸리데이션 및 제품 수명주기 관리를 담당하고 있다.
Sunghun received a bachelor's degree in biochemistry from University of California, San Diego. He joined Greencross for 4 yeas and 7 years in Samsung Biologics (SBL) in the Quality Assurance. He is responsible for process design, process validation, and product lifecycle management for the biological products manufactured in SBL.

Program

생물학적 제제 연속제조공정 도입 절차 및 일부 공정 적용 케이스

Introduction of continuous manufacturing for biological product and case study

생물학적 제제의 연속제조공정 도입을 위한 필요 요소 및 아래 적용 사례에 대한 논의

Rapid Microbiological Methods

원료의약품 배양 및 정제공정 in-line monitoring 적용 사례 (cell culture metabolite, UFDF concentration)

완제의약품 충전공정 in-line monitoring 적용 사례 (fill weight)

In this presentation, the feasibility of introduction continuous manufacturing process for biological product will be discussed with below example of unit operations

Rapid Microbiological Methods

API upstream and downstream in-line monitoring (cell culture metabolite, UFDF concentration)

DP filling in-line monitoring (fill weight)

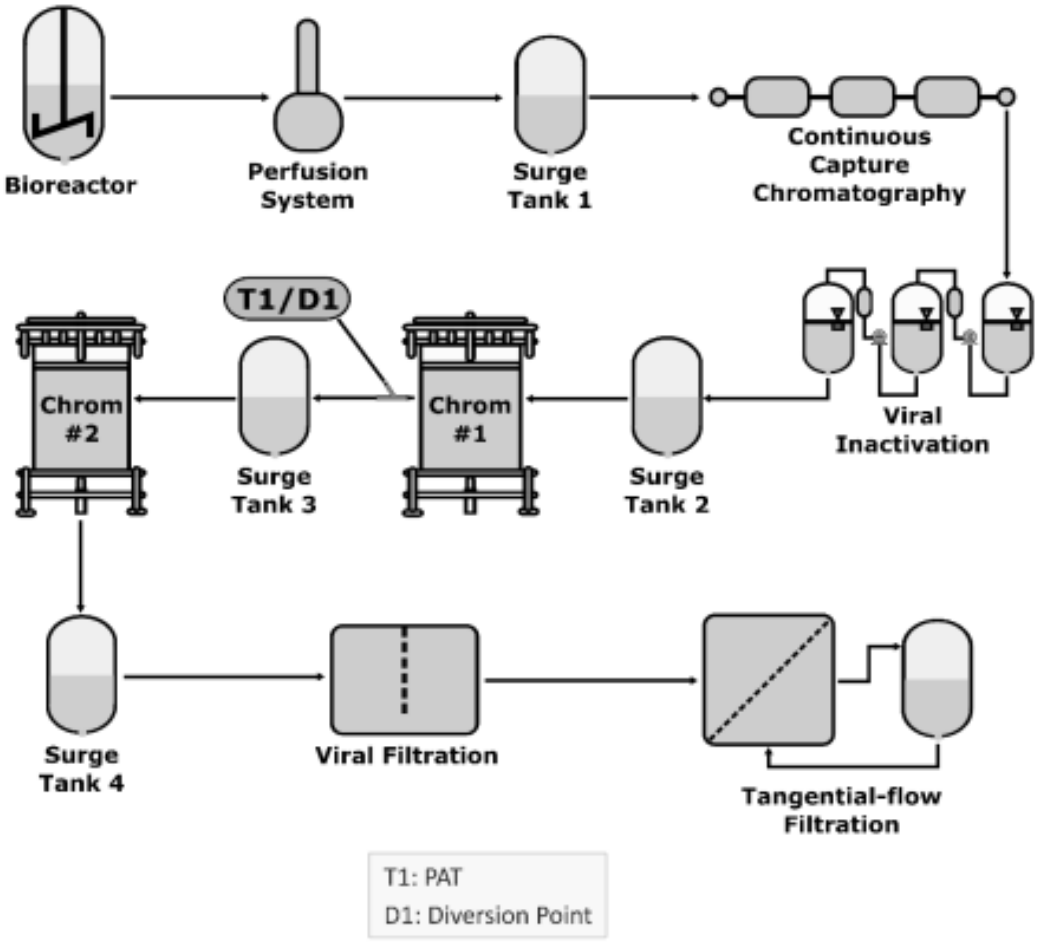
연속제조공정 관리 및 case study

ICH Q13
Enabling continuous manufacturing
Case 1 Alternative and Rapid Microbiological Methods
Case 2 UFDF, protein concentration
Case 3 Fill and finish, fill weight

ICH Q13

Annex 3 CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES (THERAPEUTIC PROTEINS)

Continuous Manufacturing (CM) of Drug substances



- Adventitious Agent Control
  - ICH Q5A, viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
  - Polymerase Chain Reaction (PCR)
- Process Monitoring and Real-Time Release testing
  - (USP) metabolite, VCD, viabilty
  - (DSP) pH, osmolality, protein concentration and online release tests for purity, charge heterogeneity, aggregation, and low-molecular weight impurities
  - microbiological analytical methods and other tests that require long processing times

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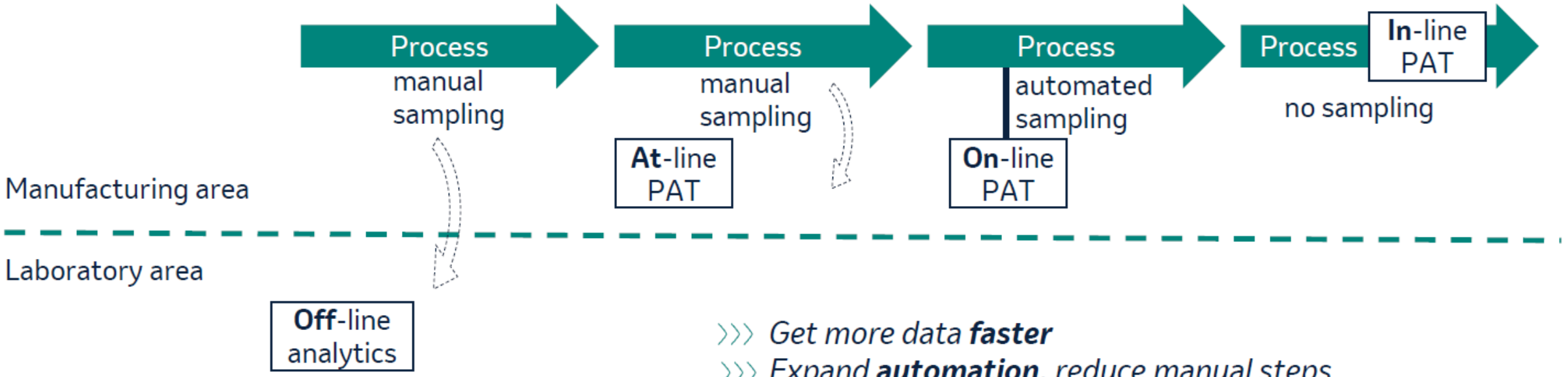
Enabling Continuous manufacturing

Process Analytical Technology (PAT)

PAT monitoring and control

FDA definition of PAT: A system for *designing, analyzing, and controlling manufacturing through timely measurements* of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

=> Analytics on the manufacturing floor



››› *Get more data **faster***
››› *Expand **automation**, reduce manual steps*
*=> Gain better **process understanding***
*=> Allow better **process control***

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PAT method development

Technology comparison of available PAT

- What are the desired attributes to monitor and or control?
- What are the business drivers?
- What instruments and technologies exist to achieve this?
- What external [vendor] support will be required?
- What is the desired timeline for deployment?

Early phase

- Bench scale models to provide data for POC
- Comparability studies between traditional and PAT based process
- Sufficient dataset to support claims
- Test the hypothesis
- Develop In Process Control strategy, with Regulatory guidance

Mid phase

- Establish parameter and control classifications
- Develop data analysis methodology to support In Process Control and Monitoring
- Democratize the data via Information System Infrastructure
- Develop a data analysis methodology: statistical techniques, pre-processing, exploratory, predictive, test and validate

Final phase

- Descriptive of Unit Ops and how the PATMC will be utilized/affect the operation
- List of materials, storage conditions, and hold times
- Finalized In Process Control and Acceptance criteria
- Method/Model Implementation and Validation

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PAT monitoring and control

Qualification and validation of PAT methods

Phase	Qualification	Validation*
Definition	Objective evidence that equipment or system and its ancillary systems are correctly installed, work as expected, and fit for the intended use	Assessment and collection of data from process design to commercial phase, which establishes objective evidence that a process can consistently deliver a quality product
Completion	In the development phase prior to commercialization	Around the time of PPQ and before commercial use
Scope	• Non-GMP or GMP (clinical stages: toxicology to Pre-PPQs) • IPC • RTRt • Process monitoring • Tech transfer	• GMP testing from PPQ onwards • IPC • RTRt • Process monitoring • Replacement of (offline) CQA testing

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PAT monitoring and control

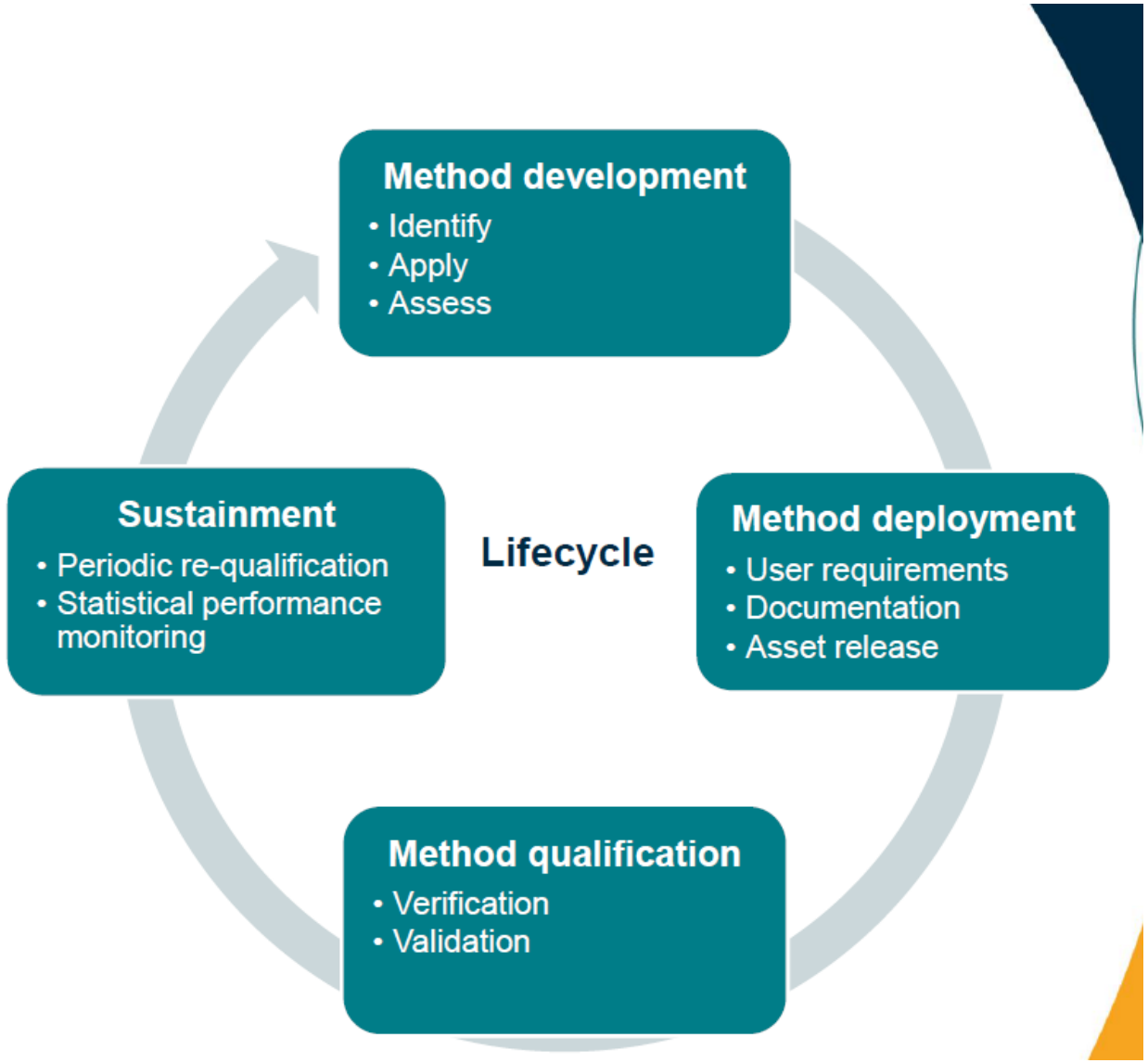
Lifecycle management

Lifecycle management process

- Ensures integrity and availability of the PAT method over time
- Addresses potential risk factors that could impact the product quality and/or the product control strategy

Implementation strategy

- Risk assessment and addressing key risk factors
- Outlier detection limits and acceptance criteria
- Updates to validated methods/models
- Method maintenance strategy (CPV)
- Method retirement



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Case study 1 (Alternative and Rapid Microbiological Methods)

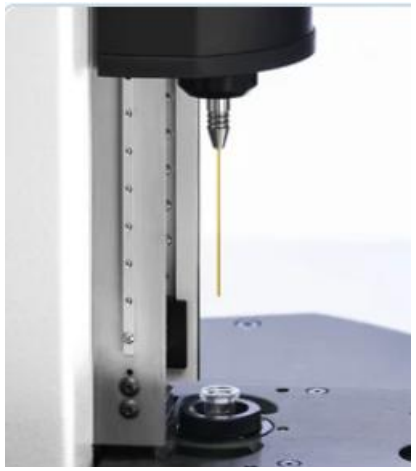
Alternative and Rapid Microbiological Methods

- **Alternative or Rapid Microbiological Methods (AMM/RMM) ***
  - Methods that differ from the Conventional Microbiological Method, CMM (e.g., USP General Notice 6.30). These AMM/RMMs use technology that differs in measurement end points, automation, and software for managing testing processes and analyzing the resulting quantitative, qualitative, and microbial identification data. Such AMM/RMMs must undergo full validation and demonstrate comparable results to the CMMs within acceptable limits, established on a case-by-case basis.
- **Comparability**
  - Demonstration that the qualitative or quantitative detection of microorganisms, related analyte, or measurement response in the AMM/RMM is equivalent, non-inferior or not statistically different than the detection of microorganisms in the existing test method, depending on the statistical method used to compare the data.
- **Point to consider for microbial control in ATMP (2022)**
  - Short product shelf life and short manufacturing turnaround time
  - Conditional product release based on in-process sterility testing

* PDA Technical Report No. 33 Evaluation, validation, and implementation of alternative and rapid microbiological methods

Case 2 UFDF, protein concentration

At line PAT vs On line PAT





- **At line PAT (SoloVPE vs A280)**
  - UV-Vis Concentration Measurement
- **On line PAT (flowVPX)**
  - Continuous in-line concentration measurement for real-time process control
- **Comparability**
  - Specificity
  - Accuracy
  - Precision
  - Linearity
  - Robustness
  - System suitability

Case 3 Fill and finish, fill weight

Definition

MAPP 5019.1 & .2

- **Deliverable Volume** (mL per vial) : Volume that can be withdrawn and delivered following procedures in USP General Chapter <697> / Extractable Volume. Deliverable volume needs to meet Net Container Content.

- **Net Container Content** : Net quantity of contents that appears on the container label as distinct item.

- **Gross Content** : Content of the drug product (mL) per vial including the excess volume. 0.3mL USP<1151>
  -Lower Limit : Ensure Net Container Content is delivered
  -Upper Limit : Avoid excessive overfill

Assessment of Gross Content

MAPP 5019.1 & .2

- **Multi-dose** :
  - Chemical and Microbiology information required for in-use period. (Default in-use period is 28 days after first entry)
  - Provide justification for stopper integrity after certain number of punctures.
  - Provide justification for reasonable amount of use over 28 days.

- **Single- dose** :
  - Excess volume after withdrawal of fixed does should be considered to prevent pooling.

- **Dosing based on Body weight /surface**:
  - Provide justification for container content to ensure dosing flexibility across intended population of US patients.

Example

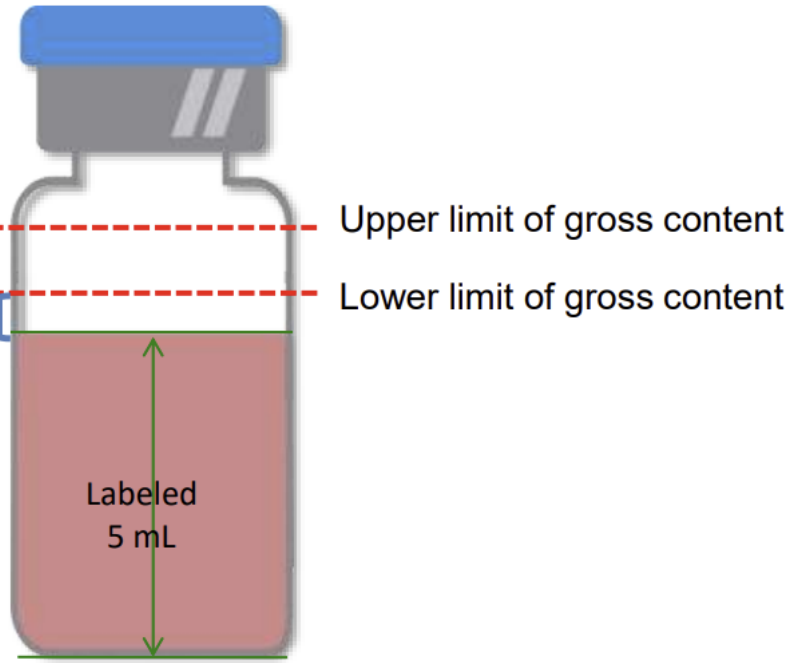
MAPP 5019.1 & .2

Liquid Single Dose Case Study

Label: 500 mg per 5 mL (100 mg/mL), 5 mL (net container content)

Max. Fill Vol.	Discourage pooling	≤ 5.8 mL
Min. Fill Vol.	5 mLs + 0.3 mL	≥ 5.3 mL

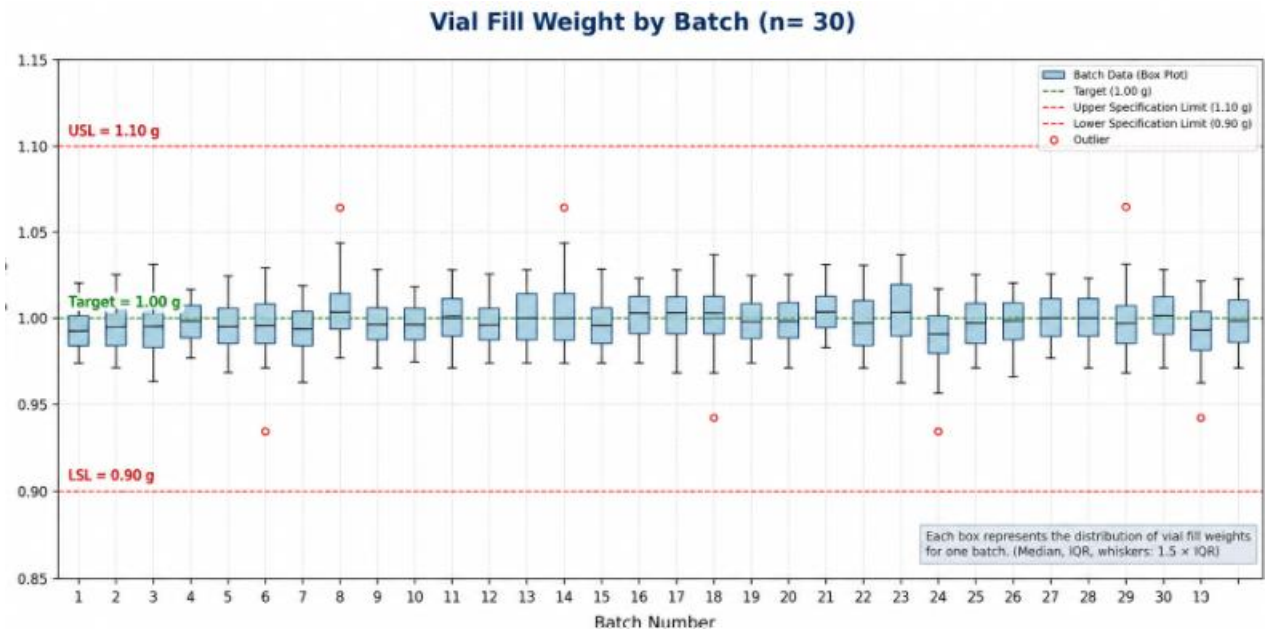
Labeled Content/ net container content	Recommended Excess Volume (<1151>)
5.0 mL	0.30 mL



Vial filling machine fill weight check IPC



100% IPC on every container




SAMSUNG BIOLOGICS
Thank you.

M4Q EWG



Sheila Inada

브라질 아스트라제네카 규제업무 총괄 매니저

AstraZeneca Brazil, Regulatory Affairs, Executive Regulatoy Manager

셰일라 이나다는 상파울루대학교(USP) 히베이랑프레투 약학대학에서 생화학약학 학위를 취득했으며, 제툴리우 바르가스 재단(FGV)에서 경영학 석사과정을 이수했습니다.셰일라는 규제업무 분야에서 18년의 경력을 보유하고 있으며, 존슨앤드존슨, 다이이찌산쿄, 사노피, 노바티스, 아스트라제네카 등 다국적 제약기업에서 전문성을 쌓았습니다. 지난 5년간 아스트라제네카 브라질의 규제업무팀에서 근무해 왔으며, 현재는 규제업무 총괄 매니저로 재직하고 있습니다.2019년부터 브라질 연구중심 제약산업협회인 Interfarma에서 CTD 워킹그룹을 총괄하고 있습니다. 또한 2021년부터 국제제약단체연합회(IFPMA)를 대표하여 ICH M4Q 가이드라인 개정인 M4Q(R2)를 담당하는 전문가 워킹그룹에 참여하고 있으며, 공통기술문서(CTD)의 품질 부문 현대화 및 국제 조화를 위한 논의에 기여하고 있습니다.

Sheila Inada holds a degree in Biochemical Pharmacy from the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (USP), and a postgraduate qualification in Business Administration from Fundação Getulio Vargas (FGV).Sheila has 18 years of experience in regulatory affairs, with expertise acquired at multinational pharmaceutical companies including Johnson & Johnson, Daiichi Sankyo, Sanofi, Novartis, and AstraZeneca. She has been part of AstraZeneca Brazil's Regulatory Affairs team for the past five years and currently serves as Executive Regulatory Affairs Manager.Since 2019, Sheila has coordinated the CTD Working Group at Interfarma, the Brazilian Association of the Pharmaceutical Research Industry. In 2021, she began representing the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) in the ICH Expert Working Group responsible for the revision of the M4Q guideline, M4Q(R2), contributing to international discussions on the modernization and harmonization of the quality section of the Common Technical Document.

Program

ICH M4Q(R2) – CMC 허가자료의 새로운 패러다임

ICH M4Q(R2) – a new paradigm for the CMC dossier

This presentation introduces ICH M4Q(R2), a proposed new paradigm for the organisation and assessment of pharmaceutical quality information in the Common Technical Document (CTD). The presentation explains how Module 2 would become the primary basis for regulatory assessment, providing a comprehensive overview of the product, its manufacturing process, pharmaceutical development, and Overall Control Strategy (OCS). It also describes how Module 3 would function as a structured repository of detailed supporting information and data. The proposed Module 2 structure includes the Introduction, Overall Control Strategy, Core Quality Information, Development Summary and Justification, Product Lifecycle Management, and, where appropriate, Product Quality Benefit-Risk considerations.The revised approach is intended to support risk-based regulatory decision-making, enhance communication between applicants and regulators, facilitate digitalisation and future structured pharmaceutical quality submissions, and accommodate innovation such as advanced manufacturing and advanced analytical tools.

ICH M4Q(R2) – a new paradigm for the CMC dossier

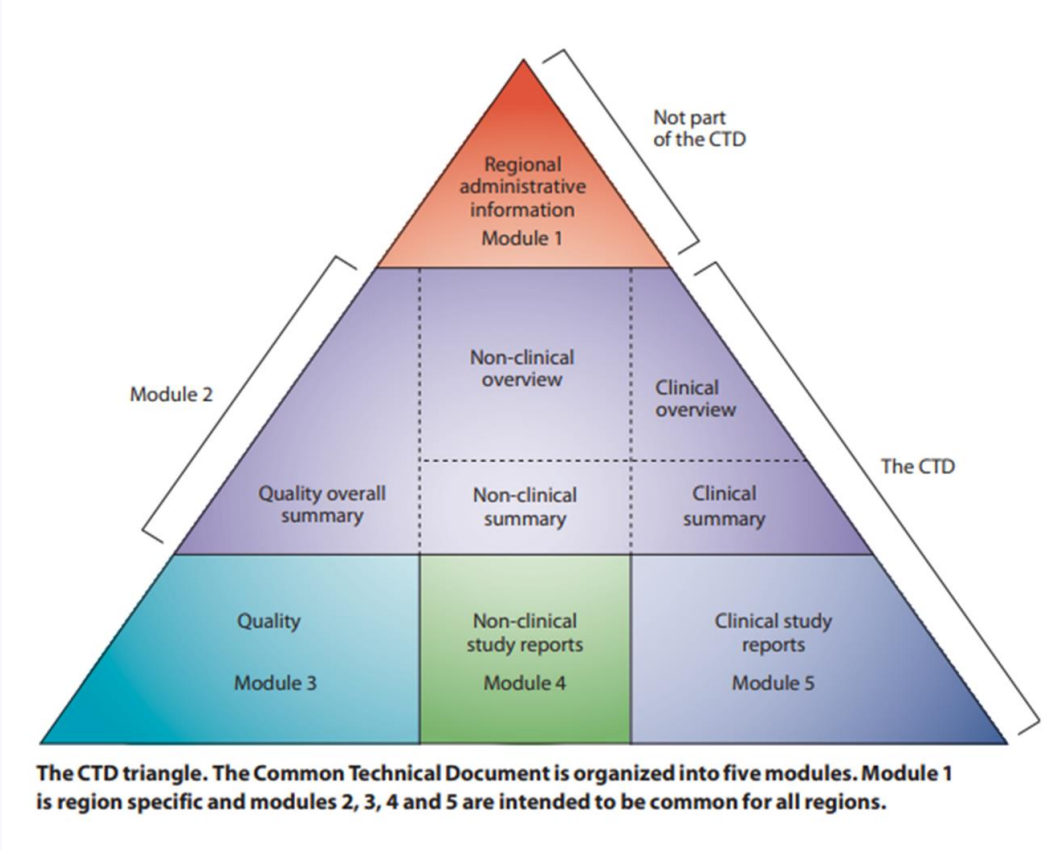
Sheila Inada,
Executive Regulatory Affairs Manager at AstraZeneca,
ICH M4Q(R2) Expert Working Group, Industry Member (IFPMA)

2026 ICH Guideline Training Program, 1 October 2026, South Korea

What was M4Q(R1) Designed to Do?

- Globally harmonized content and organization of quality information in Common Technical Document (CTD)/eCTD
  - **Module 2.3 Quality Overall Summary (QOS)**
  - **Module 3 Quality**

- M4Q(R1) was a substantial improvement compared to the prior state with regional submission formats



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q(R1) Quality overall Summary of Module 3, Module 3: Quality, September 2002

ICH’s Effort to Shape the Future

ICH M4Q(R2) defines the new structure of Module 2.3 and Module 3



SPQS (M16) will define Structured Product Quality Submissions

Cloud computing

Big data analytics

Knowledge management

Artificial Intelligence

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ICH M4Q(R2) Concept paper



ICH
harmonisation for better health

Concept Paper

M4Q(R2) Common Technical Document on Quality Guideline

Endorsed by the Management Committee on 15 November 2021

Type of Harmonisation Action Proposed

Revision of Existing Guideline

Statement of the Perceived Problem

Introduction of the Quality - M4Q(R1) guidelines on the Common Technical Document (CTD) in 2002 harmonized the format of quality information for registration of pharmaceuticals for human use and offered great benefits to industry, regulators, patients, and consumers. M4Q(R1) is now due for revision to further improve registration and lifecycle management efficiency, leverage digital technologies, and accelerate patient and consumer access to pharmaceuticals. The specific drivers for this revision include:

1. Several ICH regions have not fully implemented ICH M4Q(R1). The modernization will support and clarify global understanding of the CTD, enabling greater regulatory convergence and harmonization, and decrease redundancy.
2. The M4Q(R2) guideline should align with modern quality guidelines Q8-Q14, and other relevant ICH guidelines that have been developed or given greater focus since the

ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf

Objectives and Benefits

M4Q(R2) Objectives

Expand the scope of M4Q(R1) guideline to include all pharmaceutical drug substances and products (both chemical and biological)

Establish the role of M4Q(R2) as the main source of the structure and location of regulatory quality information.

Organize product and manufacturing information in a suitable format for easy access, analysis, and knowledge management.

Incorporate concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines.



Better capture the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure.



Enhance the Quality Module 2 to facilitate the efficiency and effectiveness of regulatory submissions and assessments.



ICH M4Q-R2 Concept paper

ICH M4Q(R2) Benefits



Industry

- Clearer regulatory expectations
- Streamline submission preparation
- Support lifecycle management and post-approval changes

Patients

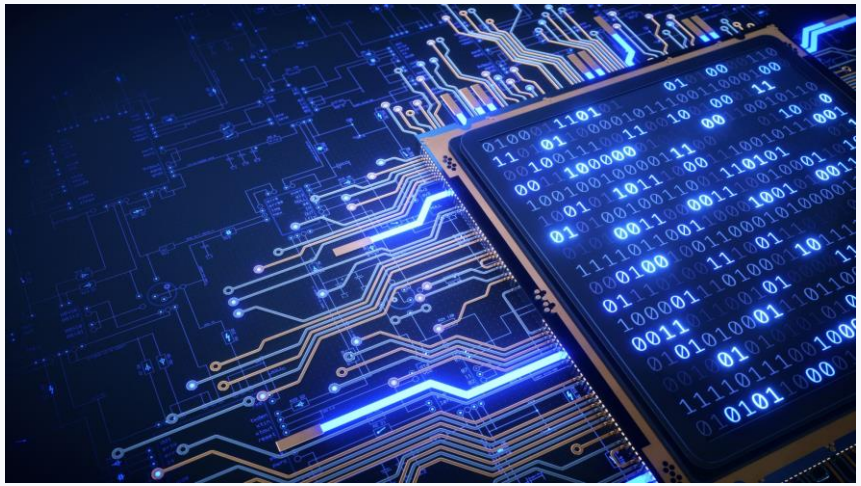
- Accelerated access to new medicines
- Improved lifecycle management reducing supply issues

Regulators

- Improve assessment efficiency
- Facilitate science- and risk-based assessment
- Support global reliance and work-sharing

M4Q(R2) shaping the future

- **Whenever possible, terms and logic aligned to ISO IDMP to facilitate future move to SPQS**
- Both M2 and M3 should **facilitate inclusion of information supporting emerging concepts**, such as advanced manufacturing, IT/software components, digitalization, data management, artificial intelligence/machine learning, and advanced analytical tools, to support regulatory assessment.
- M16 - **Structure Product Quality Submission (SPQS)**



M4Q(R2) Design

M4Q(R2) Establishes Module 2 as the Basis for Regulatory Assessment, Supported by Module 3



MODULE 2

- Basis for regulatory assessment, Risk-based approach
- Comprehensive overview of the product and its components
- Product and manufacturing process understanding and overall control strategy
- Lifecycle management

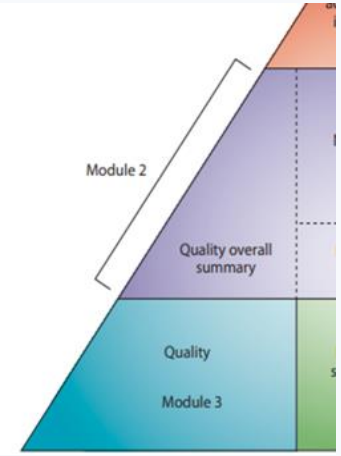
INTER-LINKING

MODULE 3

- Information and data repository incl. reports, data, protocols, descriptions
- Prepared for SPQS
- Supporting emerging concepts



M4Q(R2) Structure Overview



Module 2

2.3.1 General Information
- Essential product details, optionally supported by a schematic

2.3.2 Overall Development and Overall Control Strategy
- High level summary of the development and overall control strategy, including the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and how control elements ensure consistent quality

2.3.3 Core Quality Information (CQI)
- Information needed to support a science- and risk-based review for product approval and ongoing lifecycle management

2.3.4 Development Summary and Justification (DSJ)
- Scientific and risk-based rationale for development, including justifications for specifications and control strategies

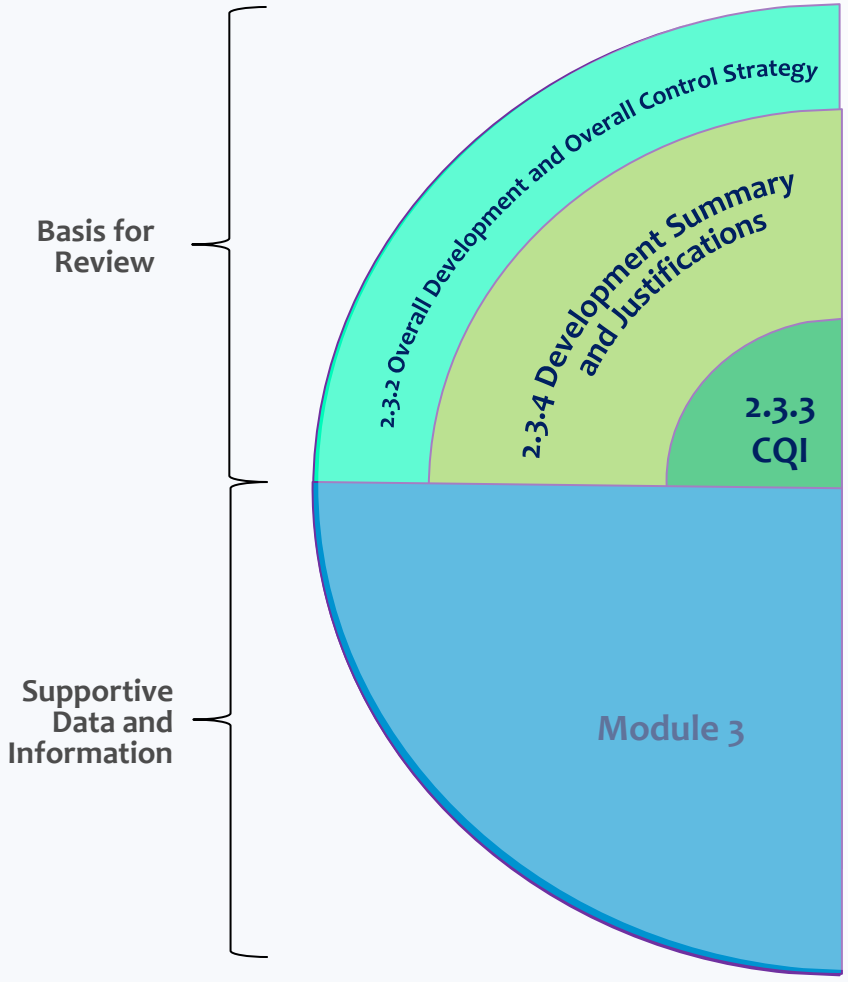
2.3.5 Product Lifecycle Management (PLCM)
- Strategy for managing post-approval changes, including a summary of changes, the PLCM, and any associated protocols or commitments

2.3.6 Product Quality Benefit Risk (Optional)
- Optional summary of how quality-related risks are mitigated and justified in the context of the product's therapeutic benefits, especially relevant for expedited review pathways

Module 3

3.2 Body of Data
- Detailed descriptions of methods, data, and other relevant quality information that supports Module 2.3

M4Q(R2) – How Sections Work Together

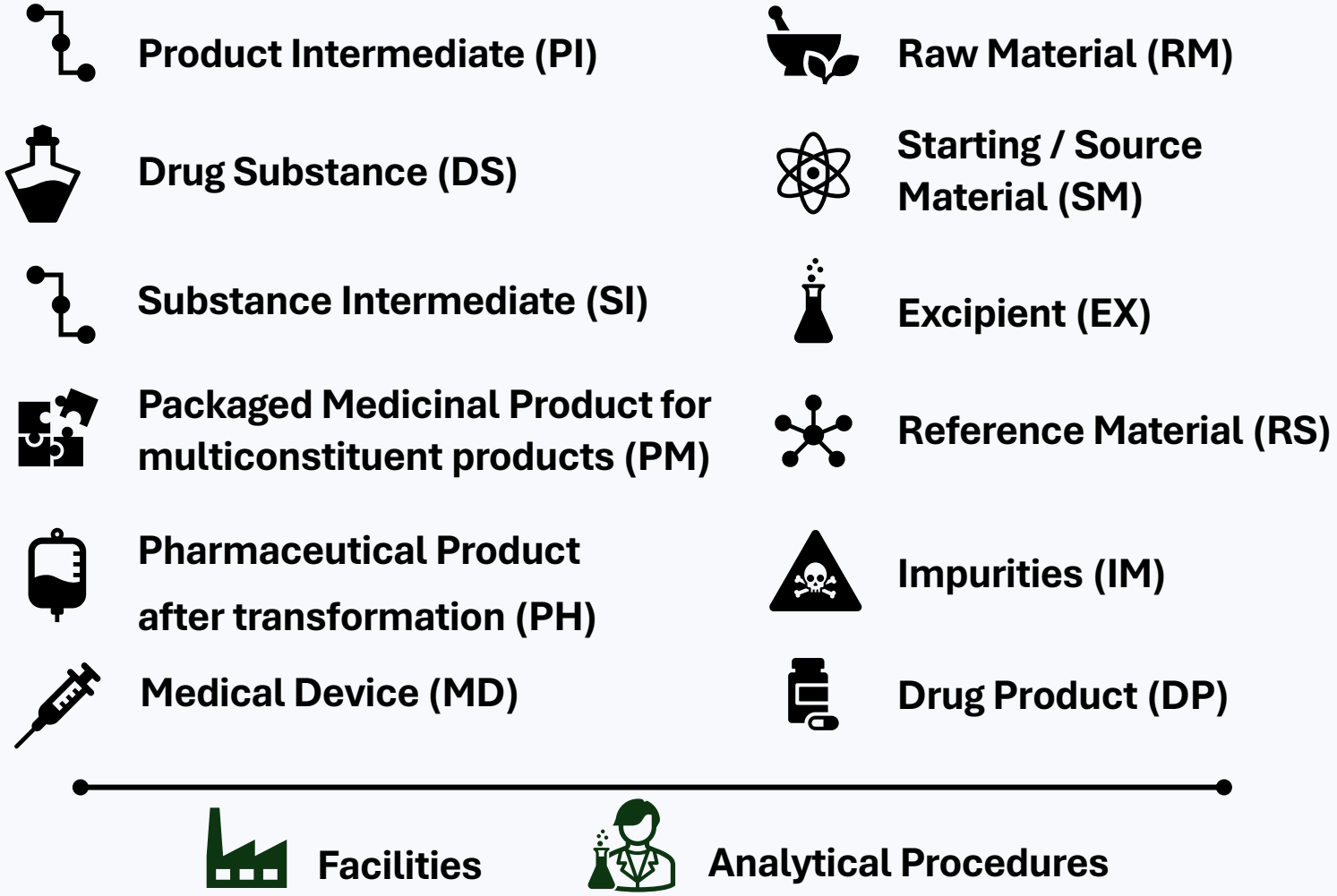


	Function During Initial Marketing Authorisation	Function During Lifecycle Management
Basis for Review	Facilitates overall understanding and supports an efficient assessment	The integrated Module 2.3 sections and Development Summary and Justifications are supportive and may be supplemented or amended due to a Post-approval change
Basis for Review	Describes how the product and manufacturing process were developed, including science- and risk-based justifications	
Basis for Review	Information considered necessary to support a science- and risk-based regulatory assessment	The content of Core Quality Information (CQI) should be maintained throughout the product lifecycle to ensure that product quality information remains current.
Supportive Data and Information	Repository for detailed descriptions of methods, data, and other assessment-relevant quality information	The M3 content is supportive and may be supplemented or amended due to a Post-approval change

M4Q(R2) introduces specific subsections for materials/components

- Facilitates re-use of information/ minimises duplication
- Alignment with ISO IDMP standards
- Information organised in defined substructure (DMCS)

- Information on analytical procedures and facilities applies across materials and is presented in dedicated sections with separate substructure



M4Q(R2) Organization – Standard Subsections

Most subsections of M4Q(R2) follow a standardized Description, Manufacture, Control, Storage (DMCS) model for information about materials, such as substances and products

D	Description	Identifies the material and its key characteristics
M	Manufacture	Outlines the production process
C	Control	Describes quality control measures such as specifications
S	Storage	Provides stability, container closure information, and retest period/shelf-life

This DMCS model applies across the main dossier sections to support efficient information management and retrieval

Example of DMCS Model for Drug Product

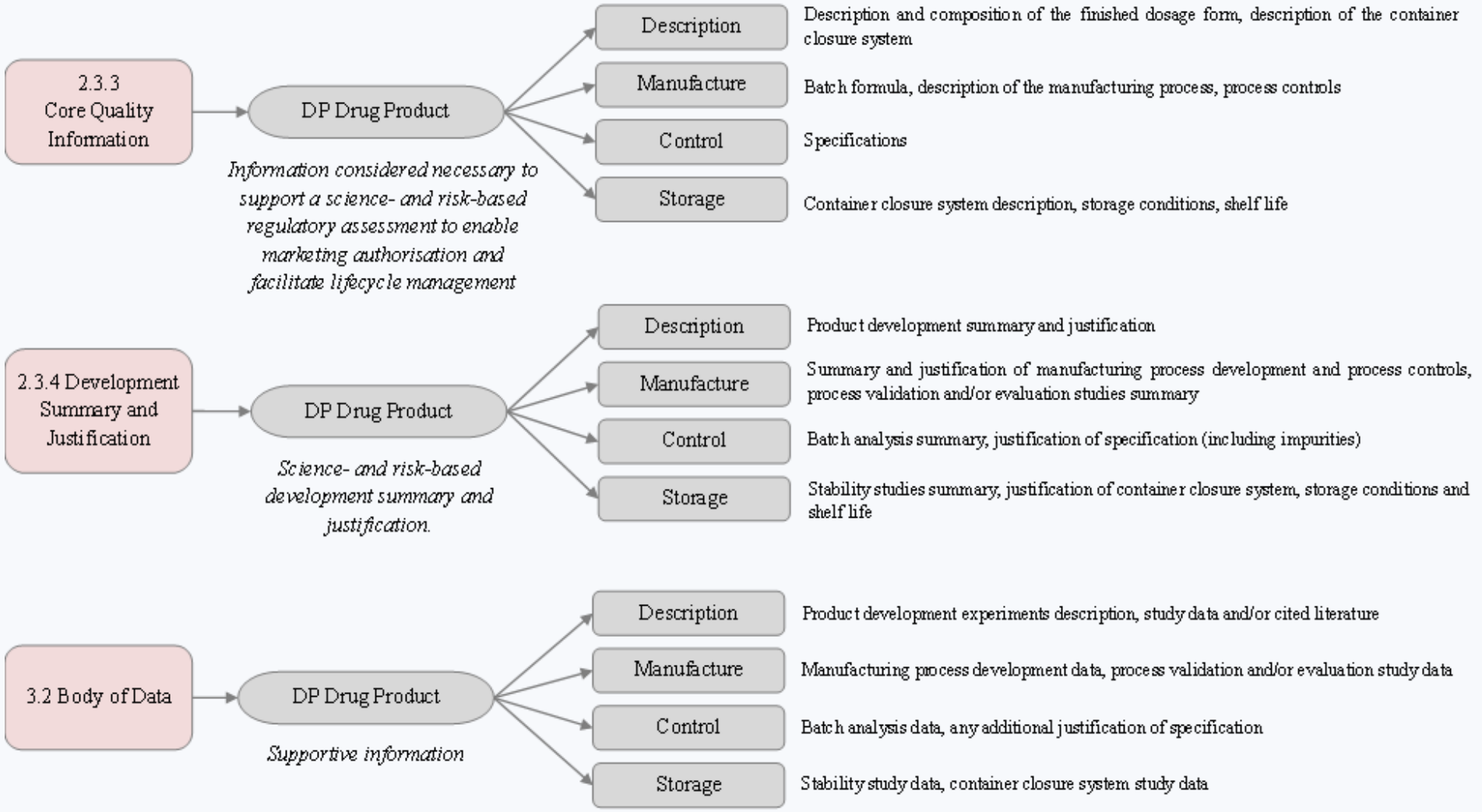


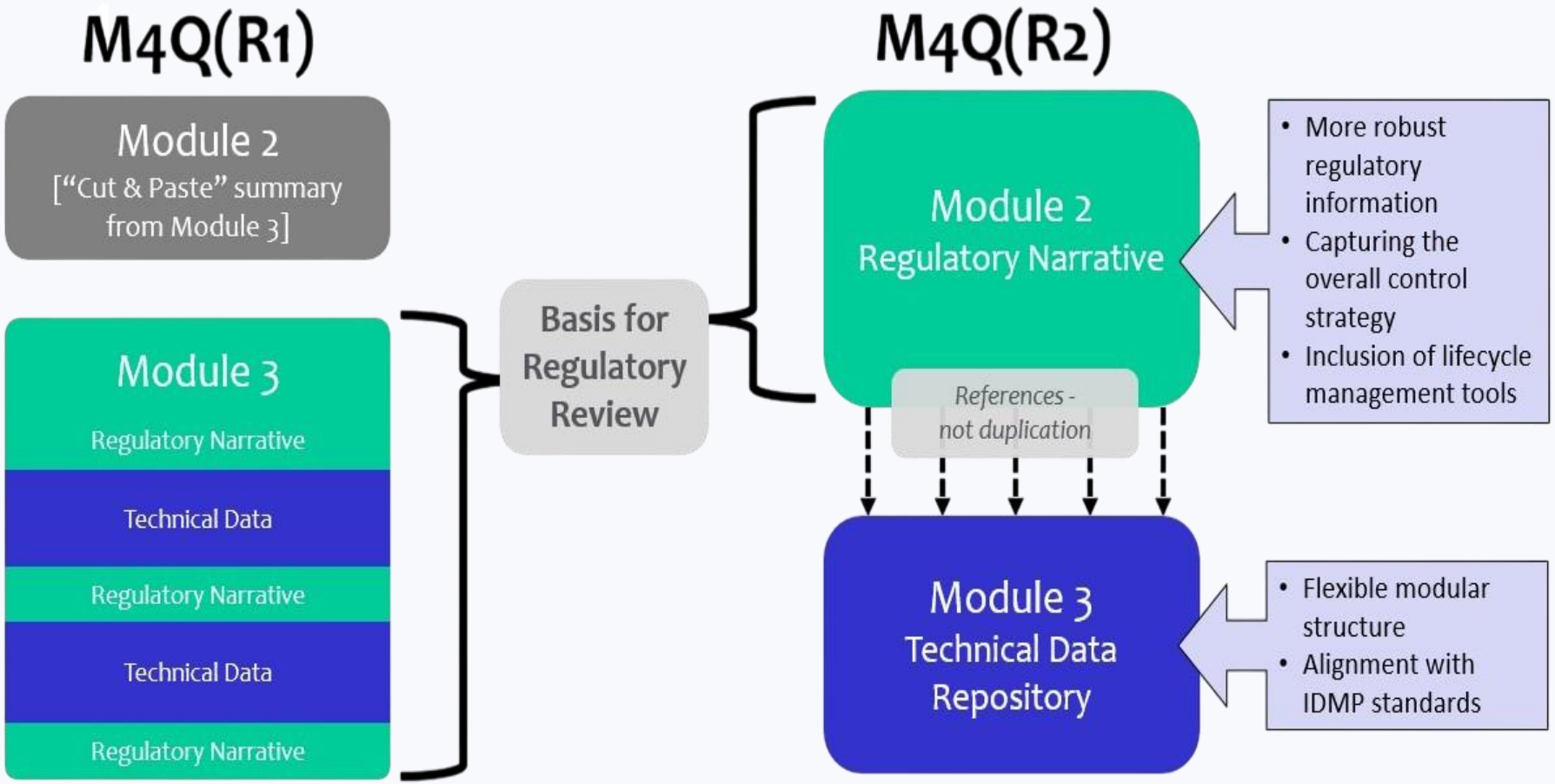
Figure 1: Illustration of the relationship between section 2.3.3 (Core Quality Information), 2.3.4 (Development Summary and Justifications), and Module 3.2 (Body of Data) under the DMCS Model for materials, using the Drug Product as an example

Regional Information

- M4Q(R2) aims to foster harmonization/convergence of the Quality dossier content, ideally enabling the submission of a single dossier across ICH member countries
- When legally obligated, the applicant should provide any additional information specific to the region directly in the relevant section in a separate document as an addendum to the harmonized core document used across ICH regions
- As an example, batch records should be provided in section 3.2.DP.M.1 when required as per regional regulations, as they would be considered as supportive information related to the description of manufacturing process

Comparison of M4Q(R2) and M4Q(R1)

CHANGES TO THE LOCATION OF INFORMATION
REGULATORY EXPECTATIONS ARE NOT CHANGING



M4Q(R1)

MODULE 2 : COMMON TECHNICAL DOCUMENT SUMMARIES 1
2.3 : QUALITY OVERALL SUMMARY (QOS) 1
INTRODUCTION 1
2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER) 1
2.
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2.3.P
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2.
2.
2.
2.3.A
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2.
2.
2.3.R
3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER) 5
3.2.S.1 General Information (name, manufacturer) 5
3.2.S.1.1 Nomenclature (name, manufacturer) 5
3.2.S.1.2
3.2.S.1.3
3.2.S.2
3.2.S.2.1
3.2.S.2.2
3.2.S.2.3
3.2.S.2.4
3.2.S.2.5
3.2.S.2.6
3.2.S.3
3.2.S.3.1
3.2.S.3.2
3.2.S.4
3.2.S.4.1
3.2.S.4.2
3.2.S.4.3
3.2.S.4.4
3.2.S.4.5
3.2.S.5
3.2.S.6
3.2.S.7
3.2.S.7.1
3.2.S.7.2
3.2.S.7.3
3.2.P DRUG PRODUCT (NAME, DOSAGE FORM) 11
3.2.P.1 Description and Composition of the Drug Product (name, dosage form) 11

3.2.P.2 Pharmaceutical Development (name, dosage form) 12
3.2.P.2.1 Components of the Drug Product (name, dosage form) 12
3.2.P.2.1.1 Drug Substance (name, dosage form) 12
3.2.P.2.1.2 Excipients (name, dosage form) 12
3.2.P.2.2 Drug Product (name, dosage form) 12
3.2.P.2.2.1 Formulation Development (name, dosage form) 12
3.2.P.2.2.2 Overages (name, dosage form) 12
3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form) 12
3.2.P.2.3 Manufacturing Process Development (name, dosage form) 12
3.2.P.2.4 Container Closure System (name, dosage form) 13
3.2.P.2.5 Microbiological Attributes (name, dosage form) 13
3.2.P.2.6 Compatibility (name, dosage form) 13
3.2.P.3 Manufacture (name, dosage form) 13
3.2.P.3.1 Manufacturer(s) (name, dosage form) 13
3.2.P.3.2 Batch Formula (name, dosage form) 13
3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form) 13
3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form) 14
3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form) 14

M4Q(R2)

Module 2

2 backlinks

- 2.3.1 Introduction
- 2.3.2 Overall Control Strategy
- 2.3.3 Core Quality Information
- 2.3.4 Development Summary and Justifications
- 2.3.5 Product Lifecycle Management
- 2.3.6 Product Quality Benefit Risk

Basis for review

Module 3

6 backlinks

- 3.2.DS Drug Substance(s)
- 3.2.SI Substance Intermediate(s)
- 3.2.SM Starting Material(s)
- 3.2.RM Raw Material(s)
- 3.2.EX Excipient(s)
- 3.2.IM Impuritie(s)
- 3.2.RS Reference Standard(s)/Material(s)
- 3.2.DP Drug Product(s)
- 3.2.AP Analytical Procedures
- 3.2.FA Facilities

Supportive

EWG recommendations for implementation of M4Q(R2)

- **Global Coordination**:
  - Establish plans for implementation of eCTD 4.0, if not yet
  - Align adoption timelines across ICH regions; allow optional early adoption
- **Adequate Transition Period**: Ensure sufficient time post-Step 4 for adapting systems, processes, and vendor-supported tools without disrupting regulatory operations
- **Balanced Approach**: Aim to support digital advancement while minimizing disruption for industry and regulators

Case Study

Sakurabloom Mock-up

- The Sakurabloom mock-up has been prepared by EWG is accessible using the public link SakuraBloom R2 (PhRMA - APIC)
- Other mock-up materials are in preparation and will be delivered over time
- Having a look at the mock-up is highly recommended to understand the guideline but please keep in mind
  - The content is illustrative and should not be interpreted as a formal position from EWG or regulators on the expected level of detail
  - While some examples of regional requirements are included, the mock-up is not intending to cover all regional requirements

The complementary sections create context, integration, rationale and evidence

THE THREE INFORMATION LAYERS

2.3.3 Core Quality Information — WHAT is essential and controlled?

2.3.4 Development Summary & Justification — WHY is the approach scientifically appropriate?

3.2 Body of Data — WHAT EVIDENCE supports the conclusions?

EXAMPLE 1

Module 2.3 Quality Overview

- 2.3.1 General information
- 2.3.2 Overall Development and Overall Control Strategy
- 2.3.3 Core Quality Information
- 2.3.4 Development Summary and Justifications
- 2.3.5 Product Lifecycle Management

2.3.3 Core Quality Information

- 2.3.3.DS Drug Substances
- 2.3.3.SI Substance Intermediates
- 2.3.3.SM Starting Material(s)
- 2.3.3.RM Raw Materials
- 2.3.3.EX Excipient(s)
- 2.3.3.RS Reference Standards and/or Materials
- 2.3.3.DP Drug Product → DP Shelf life
- 2.3.3.AP Analytical Procedures
- 2.3.3.FA Facilities

Module 3.2 Body of Data

- 3.2.DS Drug Substances
- 3.2.SI Substance Intermediates
- 3.2.SM Starting Materials
- 3.2.RM Raw Materials
- 3.2.EX Excipients
- 3.2.IM Impurities
- 3.2.RS Reference Standards and/or Materials
- 3.2.DP Drug Product → Relevant stability data and studies that support the shelf life
- 3.2.AP Analytical Procedures
- 3.2.FA Facilities

2.3.4 Development Summary and Justifications

- 2.3.4.DS Drug Substance(s)
- 2.3.4.SM Starting/Source Materials
- 2.3.4.EX Excipients
- 2.3.4 RS Reference Standards and/or Materials
- 2.3.4.DP Drug Product(s) → Summary and discussion of the stability data that supports the shelf life
- 2.3.4.AP Analytical Procedure(s)

EXAMPLE 2

Module 2.3 Quality Overview

- 2.3.1 General information
- 2.3.2 Overall Development and Overall Control Strategy
- 2.3.3 Core Quality Information
- 2.3.4 Development Summary and Justifications
- 2.3.5 Product Lifecycle Management

2.3.3 Core Quality Information

- 2.3.3.DS Drug Substances
- 2.3.3.SI Substance Intermediates
- 2.3.3.SM Starting Material(s)
- 2.3.3.RM Raw Materials
- 2.3.3.EX Excipient(s)
- 2.3.3.RS Reference Standards and/or Materials
- 2.3.3.DP Drug Product → DP release and stability specifications
- 2.3.3.AP Analytical Procedures
- 2.3.3.FA Facilities

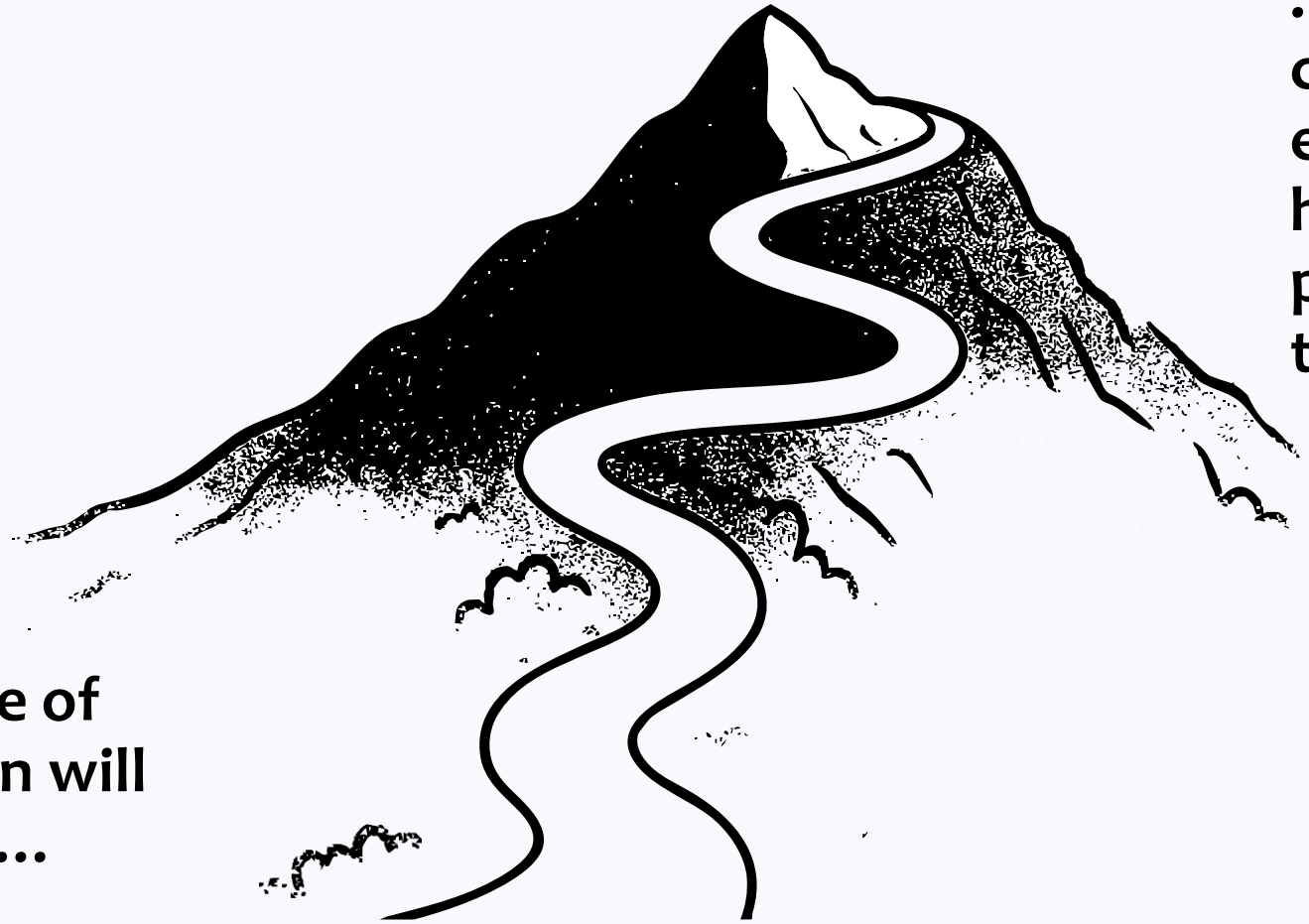
Module 3.2 Body of Data

- 3.2.DS Drug Substances
- 3.2.SI Substance Intermediates
- 3.2.SM Starting Materials
- 3.2.RM Raw Materials
- 3.2.EX Excipients
- 3.2.IM Impurities
- 3.2.RS Reference Standards and/or Materials
- 3.2.DP Drug Product → Any relevant supportive information and the results of batch analysis or CoAs for relevant batches
- 3.2.AP Analytical Procedures
- 3.2.FA Facilities

2.3.4 Development Summary and Justifications

- 2.3.4.DS Drug Substance(s)
- 2.3.4.SM Starting/Source Materials
- 2.3.4.EX Excipients
- 2.3.4 RS Reference Standards and/or Materials
- 2.3.4.DP Drug Product(s) → Impurities assessment summary , tabulated overview of batch analyses and the justification of specifications
- 2.3.4.AP Analytical Procedure(s)

ICH M4Q(R2): A path towards Greater Efficiency and Patient Access



The uphill stage of implementation will be challenging…

…M4Q(R2) will combine innovation, efficiency, and global harmonization to help patients receive treatments faster.

Useful Links

ICH M4Q(R2) Concept Paper:

https://database.ich.org/sites/default/files/ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf

ICH M4Q(R2) Draft Guideline:

https://database.ich.org/sites/default/files/ICH%20M4Q%28R2%29_Draft_Guideline_2025_0514.docx

ICH M4Q(R2) Step 2 Presentation:

https://database.ich.org/sites/default/files/M4Q%28R2%29_Step%202_Slides%20to%20Accompany%20Consultation_2025_0624_SEC.pdf

ICH M4Q(R2) Business Plan:

https://database.ich.org/sites/default/files/ICH_M4Q-R2_BusinessPlan_Endorsed_2021_1115.pdf

ICH M4Q(R2) Work Plan:

https://database.ich.org/sites/default/files/ICH52_M4QR2_EWG_WorkPlan_2026_0318.pdf

ICH M4Q(R2) Mapping Document:

https://database.ich.org/sites/default/files/ICH_M4Q%28R2%29_MappingDocument_2026_0112.pdf

ICH M4Q(R2) Mock-Up:

https://ich.org/page/ich-m4qr2-mock-ups

Thank you!