Joint BWP/QWP/GMDP IWG – Industry
European Workshop on Lifecycle Management

Application of ICH Q12 Tools and Enablers

Lifecycle Strategy

AESGP

APIC Active Pharmaceutical Ingredients Committee

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

EGA Making Medicines Affordable

EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL

EuropaBio® The European Association for Bioindustries

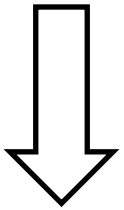
Vaccines Europe An industry for healthy lives

Outline

- **Introduction:** Lifecycle Strategy - a new concept
- **Lifecycle Management Plan (LCMP) - PDA Input to ICH Q12 Lifecycle Strategy** *(SanofiPasteur, presenter: Anders Vinther)*
- **Product Development & Lifecycle Strategy** *(GSK, presenter: David Tainsh)*
- **Established Conditions linked to PALM plan/ lifecycle strategy** *(Roche, presenter: Kowid Ho)*

Introduction

> The application file should contain a section summarizing the essential control strategy elements (at time of submission) learned from the science and risk-based pharmaceutical product development. In addition, for all new registration dossiers, this section should also include a subsection on lifecycle management strategy (future planned changes) derived from the information/data submitted in the original application file (dossier). This will enhance post-approval change management flexibility, contributing to continual improvement and reliable supply to patients.



- **Lifecycle Strategy** is a new concept presented in the current draft of Q12 and the following three examples should help to facilitate a common understanding & promote the concept

Example 1: SanofiPasteur/ PDA

- **Lifecycle Management Plan (LCMP) - PDA Input to ICH Q12 Lifecycle Strategy**
  (presenter: Anders Vinther)

Lifecycle Management (LCM) Plan

MAH

- Part of lifecycle strategy
- Submit with new application or for an existing product
- Describes planned changes, comparability approach & suggested reporting category

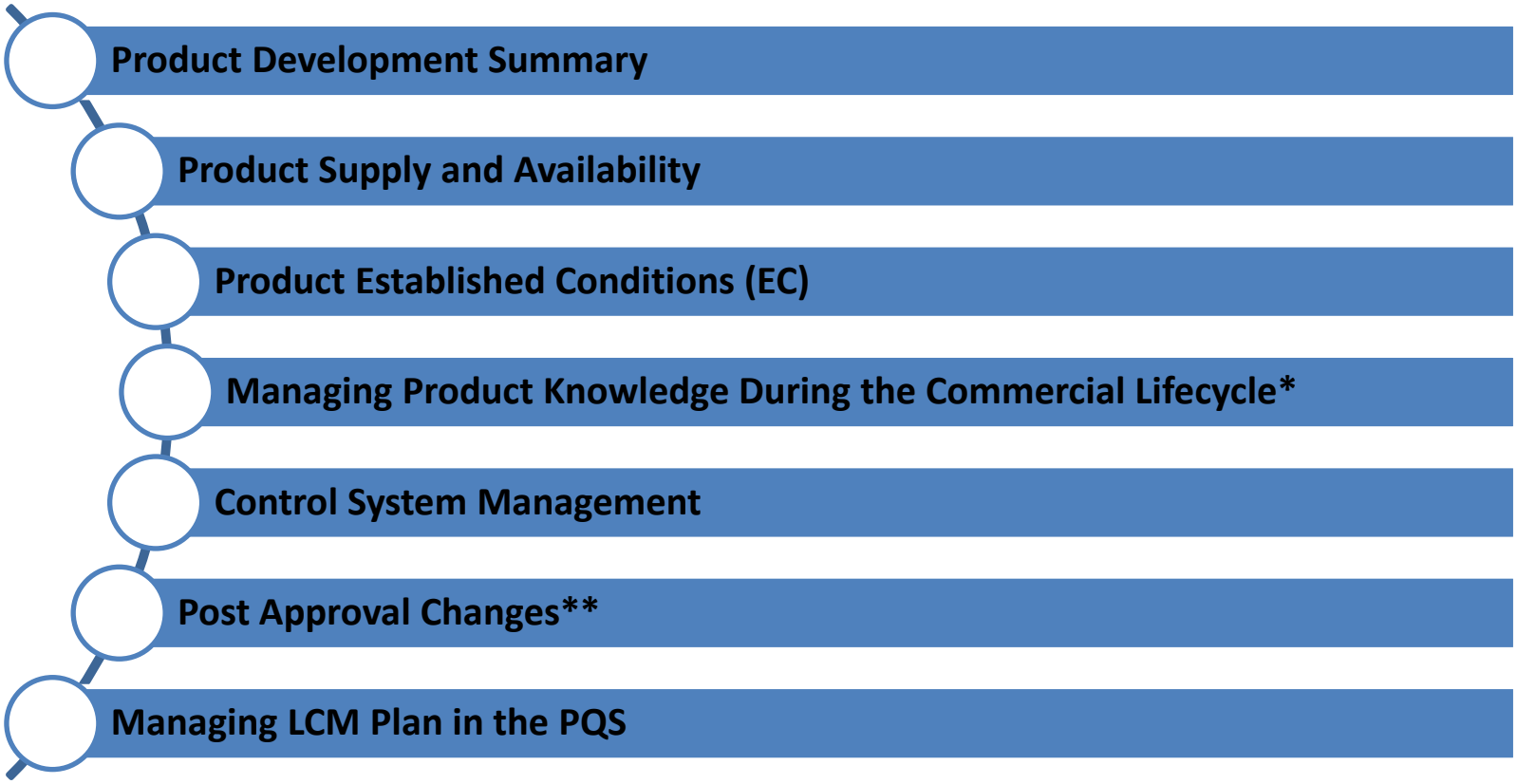
- Regulatory agreement between HA and MAH
- Early communication mechanism for prospective planning
- Enhanced transparency of planned changes

HA

- Structured risk based regulatory oversight - reduces burden of PAC
- Globally harmonized approaches
- Opportunity for mutual reliance between HAs

- May be established at any point during the commercial life (new or legacy products)
  - ECs would need to be defined as an integral part of the LCM Plan
- Updates to LCM Plan when
  - changing EC to non-EC and vice versa, or
  - any changes to EC

Content of a Lifecycle Management Plan



*
- *Process and Product Monitoring*
- *Annual Product Review (APR)*
- *Post-marketing Surveillance and Phamacovigilance*

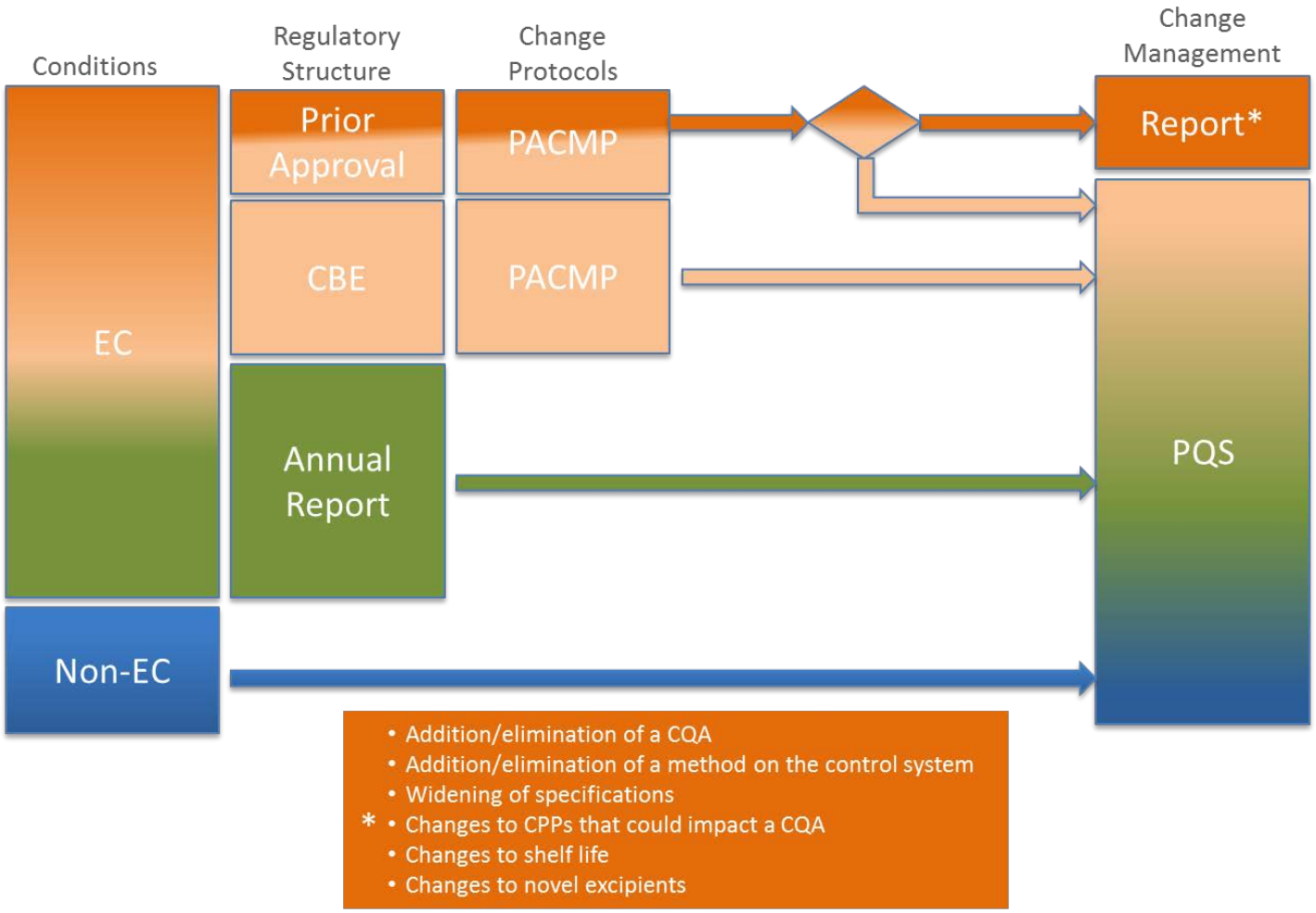
**
- *Comparability Protocols (CP)*
- *Global Change Protocols (gCPs)*
- *Change Management*

LCM Plan - Benefits

- Science and risk based approach to facilitate ICH Q10 objectives
  - Product realization (availability of quality products)
  - Continual improvement (technology innovation)
- Provides transparency and assurance to regulators maintaining state of control for a product during its commercial lifecycle
- Expedites reviews and implementation of planned post approval changes (PAC)
- Potentially reduces reporting category and regulatory burden for changes to EC (including effective use of gCP and PQS)
- Enhances predictability, certainty and transparency of studies to implement a change
- Facilitates proactive internal communication and planning of changes by MAH

Managing Post Approval Changes

Reducing regulatory burden; effectively leveraging gCPs & PQS



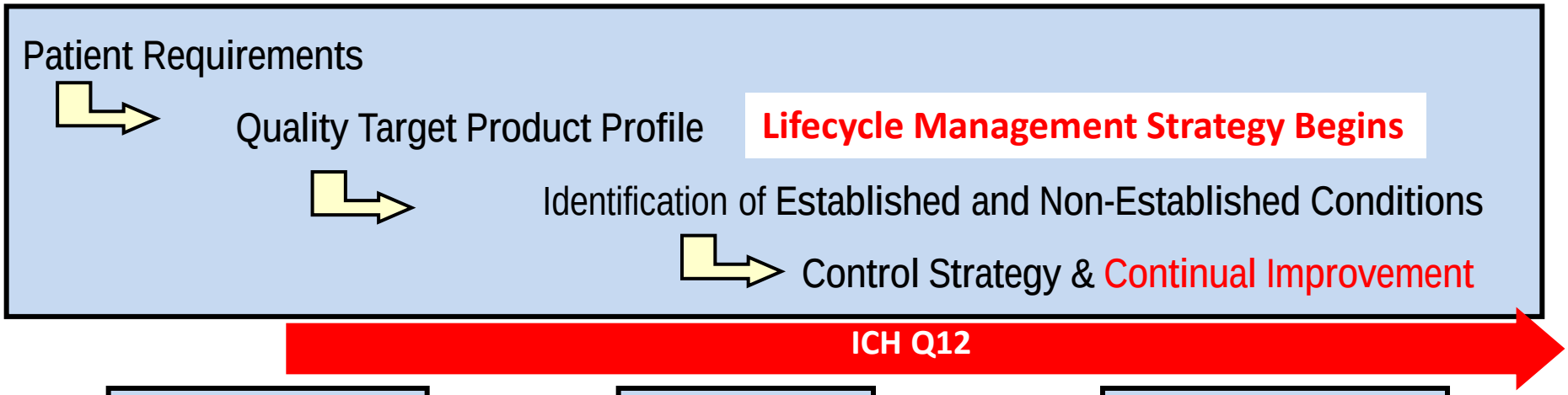
Example 2: GSK

- **Product Development & Lifecycle Strategy**
  (presenter: David Tainsh)

Quality by Design and Lifecycle Management Strategy

Traditional Approach to Registered Manufacturing Processes

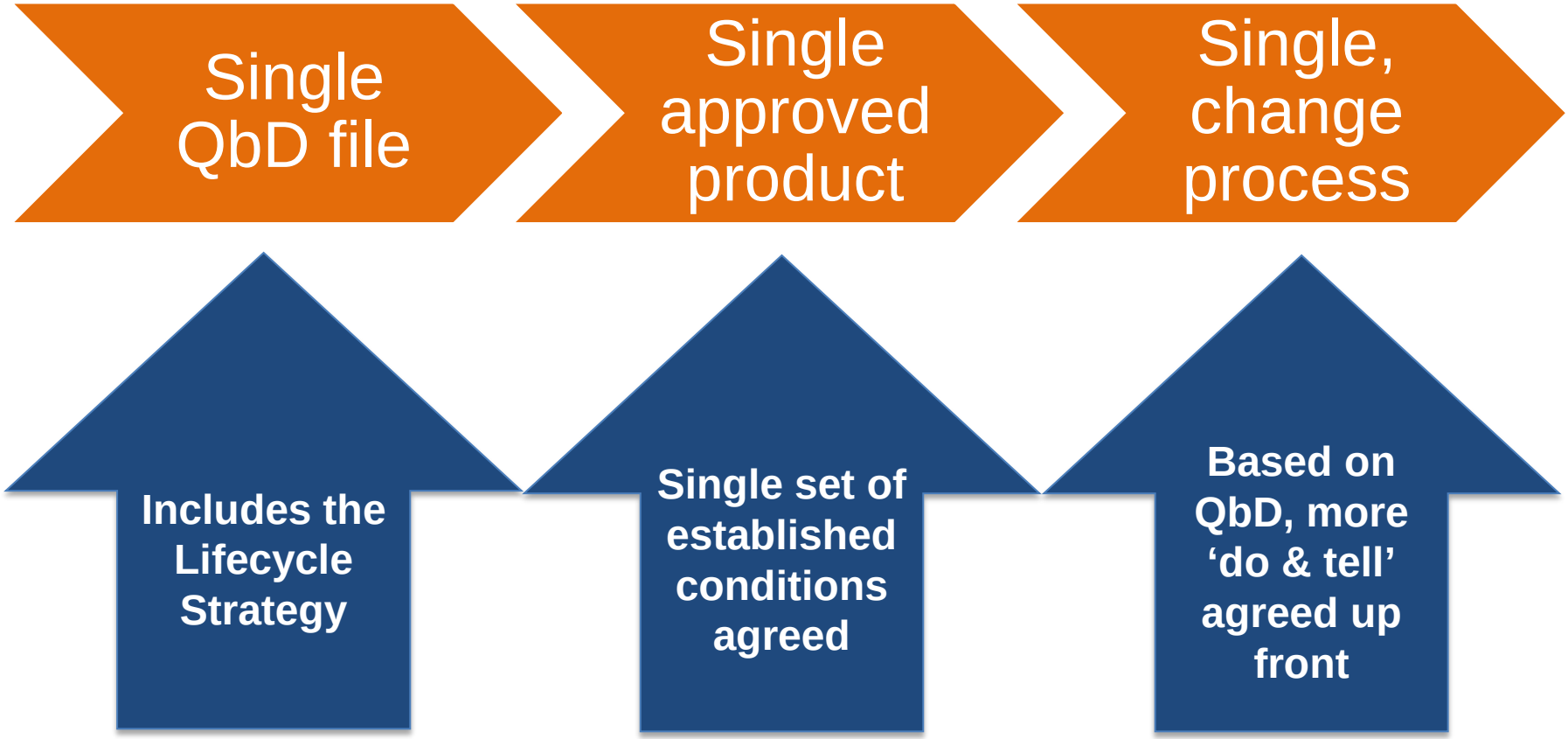
ICH Q8, Q9, Q10 & Q11 Enhanced Approach



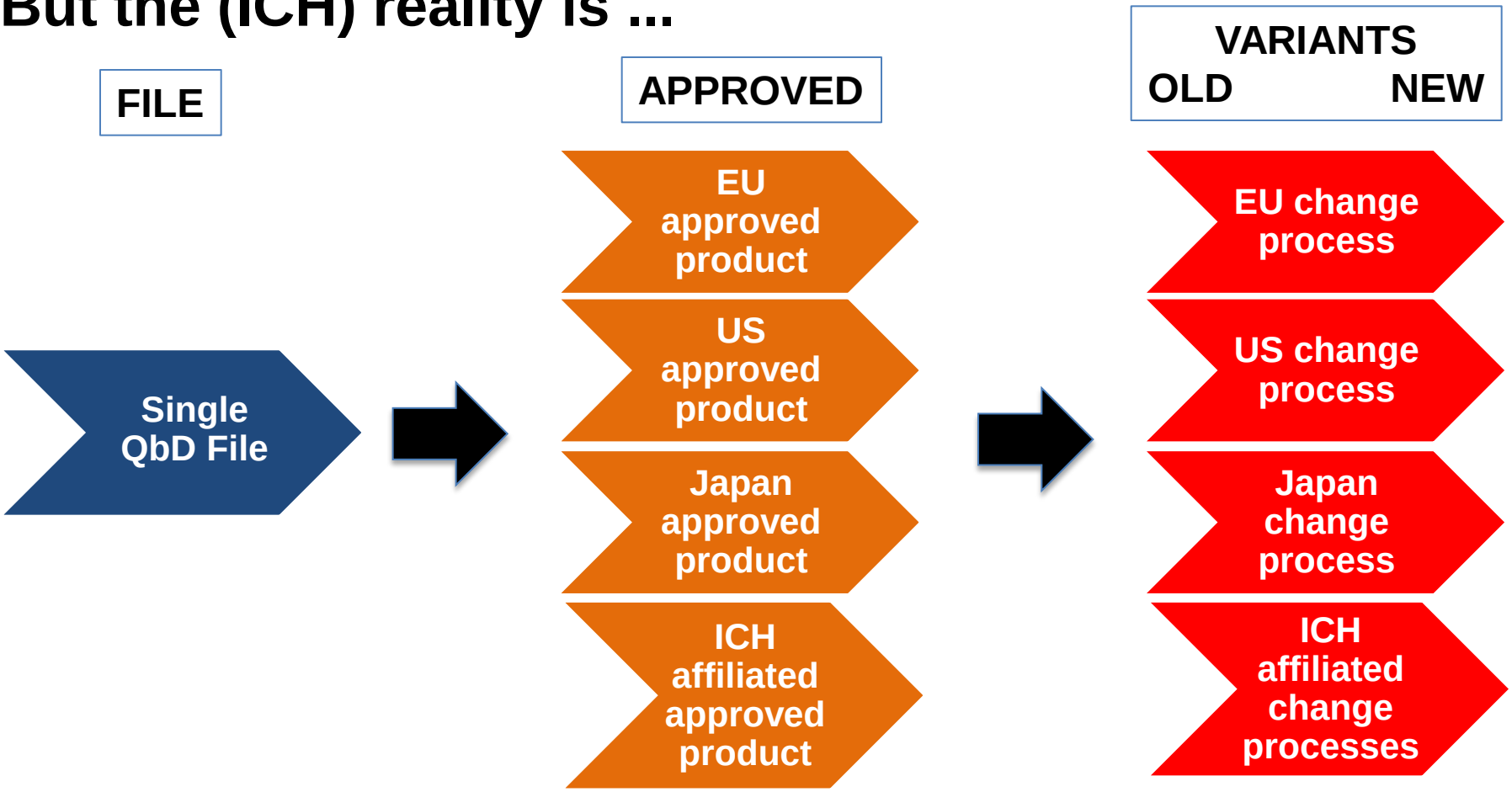
ICH Q12 is just as relevant to the Initial File as to the Post Approval Plan

So What Could This Aspirational ICH Paradigm Represent?

... We would always be making & registering one product.



But the (ICH) reality is ...



- Results in multiple product variants & change processes for the company to manage.
- QbD file is not utilised to facilitate 'Do & Tell'

A Complex Case Study… and this is just API!

USA

API spec modified for heavy metals & micro

API intermediate specs modified

Significantly more process detail and PPs in S.2.2

Revised commitment on how to handle changes to CPPs and PPs

EU

API spec unchanged

API intermediate specs modified; different to USA

Solvent spec modified

Significantly more process detail and PPs in S.2.2

More detail on validation of analytical methods

Japan

API spec modified for heavy metals

Residual solvent spec modified

Additional process details added

IMPACTS:

Approved Files differ in tri-partite countries but also differ in countries taking the same QbD File e.g. Switzerland, South Africa, Australia, NewZealand, Canada, Turkey etc

A Complex Case Study S2.2 PPs

USA

Stage 1
5 non-CPPs

Stage 2
7 non-CPPs, 2 CPPs

Stage 3
7 non-CPPs, 6 CPPs

Stage 4
6 non-CPPs, 2 CPPs

Stage 5
3 non-CPPs, 2 CPPs

Micronization
3 non-CPPs

EU

Stage 1
No Change

Stage 2
12 non-CPPs*, 2 CPPs

Stage 3
8 non-CPPs**, 6 CPPs

Stage 4
No Change

Stage 5
No Change

Micronization
No Change

Japan

Same parameters as NDA, non-CPPs classed as minor change items in square brackets.

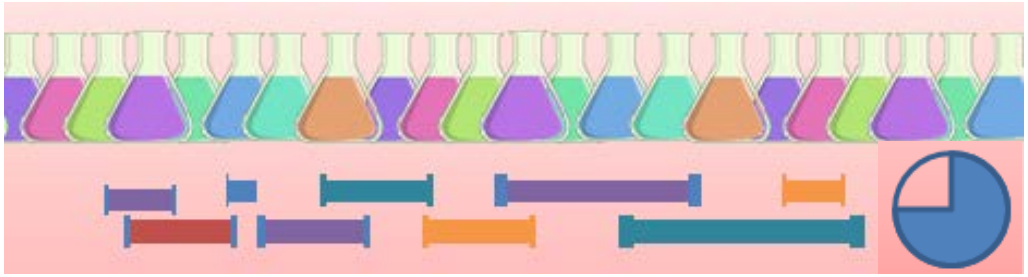
- Multiple and different PPs.
- Different approaches to change control across ICH regions

*1 Stir speed, 2 reaction times, 2 reaction temperatures added to Stage 2
**1 Stir speed added to Stage 3

Magnitude of the Challenge : An Analytical Example

- Our central stability testing laboratory tests a wide range of different products which contain 20 different actives and would benefit tremendously from being able to run these using a single “always on” method.

From: 22 mobile phases / 9 columns / Average Run Time : 45 mins



To: 2 mobile phases / 1 column / Average Run Time : 3 mins

- These products are sold in 174 different countries
- **This involves changing 6364 licenses!**

Potential Types of Lifecycle Management Change Categories

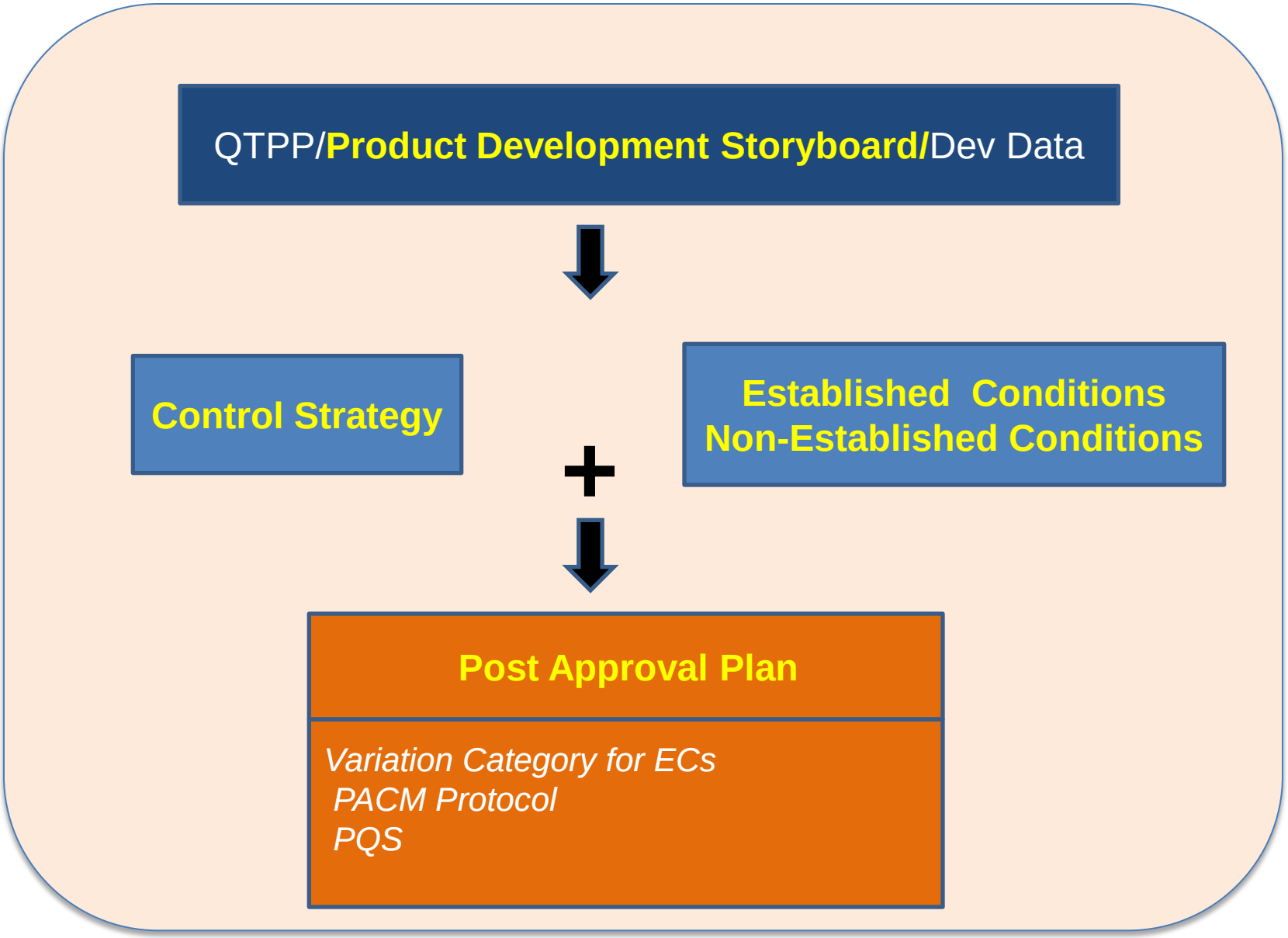
- Predictable – Plan to do
  - Scale up, additional site, new suppliers...
  - Expected changes at point of file
  - Enforced but unexpected changes e.g. from existing supplier
- Continual Improvement – Should do & Must do
  - Based on experience and trending – variability reduction – modifications to process parameters & analytical methods
  - Introduction of PAT, RTR, New route, etc
- Implementing new technologies – Could do
  - Continuous, Green Chemistry, Biotransformation
  - Can be very complex change across a commercial asset portfolio e.g. API impact on inhaled, intranasal and topical products ... So how can this be simplified?

Critical Questions Raised

- How can we move towards a more unified starting position for an ICH registered product?
- How can we reflect enhanced development through a simplified set of established conditions?
- How can concerns over lifecycle management of changes ensure that:
  - The same commitments/details of the control strategy are applied globally?
  - Post approval processes for managing changes are harmonised?

- The key to delivering on the above is to leverage the science and risk identified during development

Lifecycle Strategy



Post Approval Plan

Description of Change	Rationale/ Supporting development data	Established Conditions	Variation category	Reference to PACM protocol	PQS commitments
Can be predicted, continual improvement or future innovation	Provide rationale to support change and link to relevant CTD sections or additional supporting data, if appropriate	Description of relevant established conditions	Linked to complexity, development approach and risk described in the file	If required	Relevant elements of change management, continuous verification , knowledge management etc

Lifecycle Management Strategy Benefits

- Lifecycle Management Strategy provides a single holistic framework that provides a big picture view for every Regulator that :
  - links the realisation of the QTPP through the Control Strategy, the definition of Established Conditions (Compliance and variation reporting), Non-Established Conditions (For Information and no updating) and a plan for Post Approval Continual Improvement
  - facilitates more commonality in review across ICH regions, promotes achievement of a single approved file and a single agreement on a post-approval change control process founded on a science and risk based regulatory oversight
  - positively supports innovation and continual improvement, and builds trust and openness between Industry and Regulator

- **Lifecycle is a strategy that impacts both the Initial File as well as Post Approval Change and is facilitated by enhanced development**
- **It is NOT an add-on to a set of regulatory tools solely to manage Post Approval Change**

Example 3: Roche

- **Established Conditions linked to PALM* plan/ lifecycle strategy** *(presenter: Kowid Ho)*

** PALM Plan = post-approval lifecycle management plan; concept equivalent to LCMP*

Principles included in post-approval lifecycle management (PALM) plan

<table>
<tr><th rowspan="2">Risk Level</th><th rowspan="2">PQS</th><th rowspan="2">Reporting category</th><th colspan="2">PALM PLAN</th></tr>
<tr><th>Change in EC</th><th>Change in non-EC</th></tr>
<tr><td>0</td><td>Yes</td><td>None (managed within quality system only)</td><td rowspan="2"></td><td rowspan="2">Reporting managed through PALM plan</td></tr>
<tr><td>1</td><td>Yes</td><td>Reported at next module update or via a consolidated sequence</td></tr>
<tr><td>2</td><td>Yes</td><td>“Do and Tell”
Type IA / Annual report
or IA IN / immediate notification</td><td rowspan="3">IN ACCORDANCE WITH VARIATION REGULATIONS

Level 3 and 4 could be downgraded in accordance to APPROVED PROTOCOL or DESIGN SPACE</td><td></td></tr>
<tr><td>3</td><td>Yes</td><td>“Tell and Do”:
Type IB/CBE-30</td><td rowspan="2"></td></tr>
<tr><td>4</td><td>Yes</td><td>Type II/PAS</td></tr>
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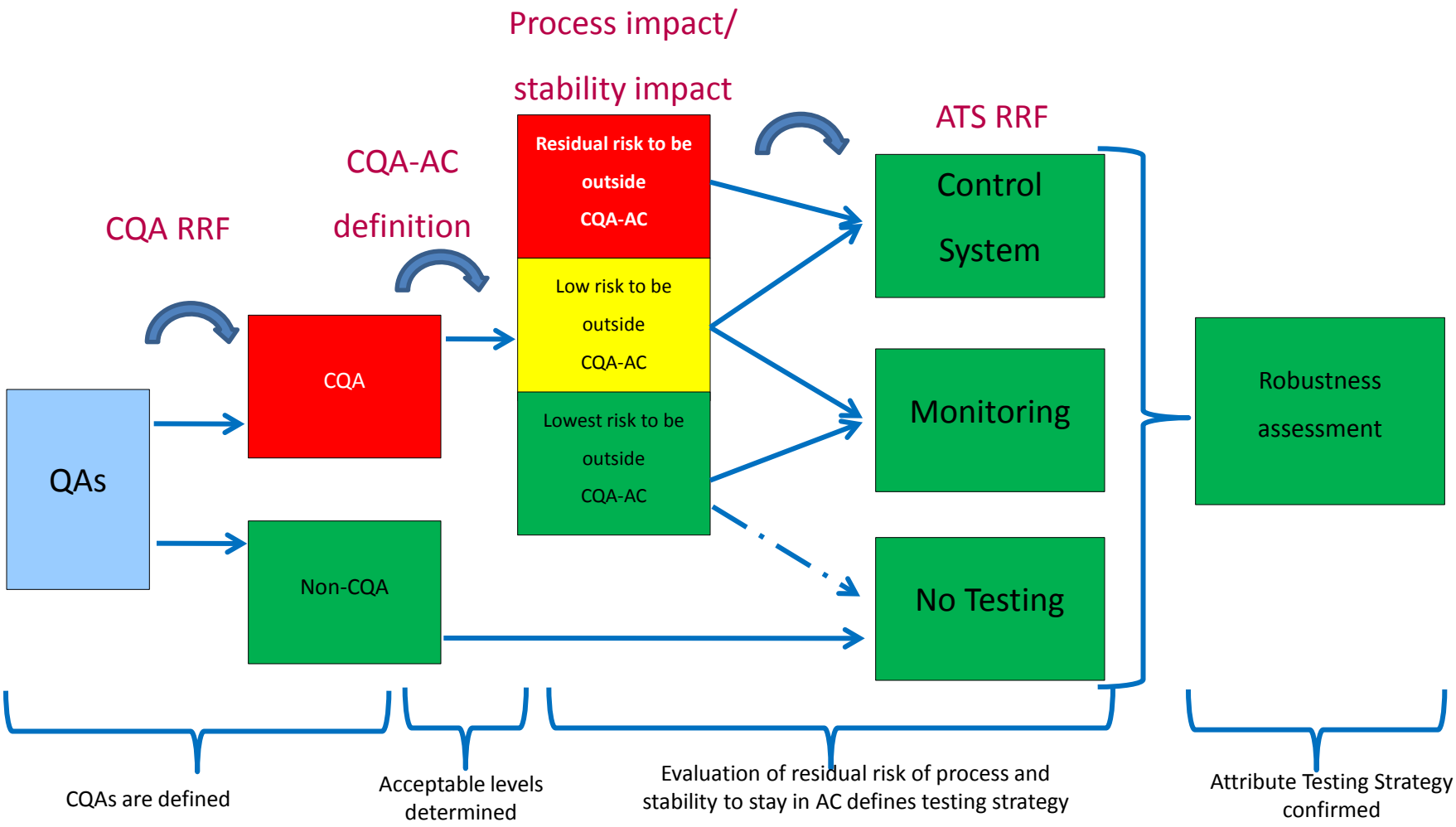
Attribute Testing Strategy (ATS) – A Major Component of the Overall Control Strategy



CQA and IPC testing

	Test principle	Equipment, reagent, SST or operational conditions	Limit	Change test				Change limit	
				Delete or change method principle	Add test	Add testing site	SST or operational conditions	widen	tighten
Control system	**EC**	Non-EC	**EC (acceptance criteria)**	**4**	**2***	**3**	**2***	**4**	***2^***
Monitoring	**EC**	Non-EC	Non-EC (action limits)	**3**	**1***	**2**	**1***	**2***	***0*^***
No testing	Non-EC	Non-EC	Non-EC	**0**	**0**	**0**	**0**	**0**	**0**

** Upgraded if biological assay*

^ Upgraded if due to unforeseen quality event

Risk Level	Reporting category
0	None (managed within quality system only)
1	Reported at next module update or via a consolidated sequence
2	"Do and Tell" **Type IA / Annual report or IA IN / immediate notification**
3	"Tell and Do": **Type IB/CBE-30**
4	**Type II/PAS**

Examples

Example of Changes	Current submission in EU	Submission in accordance to PALM plan	Comments
Method substantial change or replacement in specification	**II**	**4**	Same for control system (e.g. spec, IPC)
		3	Decreased for monitoring
Minor change to approved test procedure (e.g. column length, temperature)	**IA**	**2**	Same for control system (e.g. spec, IPC)
		1	Decreased for monitoring
Other changes to approved test procedure (e.g. SST)	**IB**	**2***	Same for bioassay in control system; Decreased for others
		1*	Decreased for monitoring
Widening limits	**II**	**4**	Same for control system (e.g. spec, IPC)
		2*	Decreased for monitoring, except bioassay
Tightening limits	**IA**	**2^**	Same for control system (e.g. spec, IPC)
		0*^	Decreased for monitoring, except bioassay and unforeseen event

** Upgraded if biological assay*

^ Upgraded if due to unforeseen quality event

Changes to CPP and non-CPP

			Change Input		Change limit	
	Input	Limit	Delete or replace	Add	widen	tighten
CPP	**EC**	**EC**	**4**	**3**	**4**	**2**
Non-CPP	**EC**	Non-EC	**3**	**2**	***2****	**1**

** Depending on magnitude of change, risk level may be upgraded, and may be downgraded through planned design space verification activity and/or linkage study*

Risk Level	Reporting category
0	None (managed within quality system only)
1	Reported at next module update or via a consolidated sequence
2	"Do and Tell" **Type IA / Annual report or IA IN / immediate notification**
3	"Tell and Do": **Type IB/CBE-30**
4	**Type II/PAS**

Summary

- **Established conditions:**
  - Identified and justified in QOS
  - Further supported by Module 3 data
- **Change in EC:**
  - Reported in accordance to variation classification guideline
  - Unforeseen changes managed in accordance with post-approval lifecycle management (PALM) plan
- **Change in non-EC:**
  - Managed through PALM plan
  - Follow risk based approach defining reporting category (i.e. no reporting, bundled in subsequent dossier updates or IA)