#2_Q12

Title	**Practical Implementation of ICH Q12** **ICH Q12 이행 사례**
Speaker	Frank Montgomery (Global Head Regulatory CMC, AstraZeneca)
Bio	Frank obtained his degree and PhD from Imperial College London and Post-Doc at Ohio State University USA in synthetic chemistry. He joined AstraZeneca in 1996 and spent 14 years in API and drug product development and manufacture before moving to Regulatory CMC in 2009. Frank is now Global Head Regulatory CMC at AstraZeneca and a member of Implementation Working Group (IWG) as EFPIA Expert for ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management since its initiation in 1994 and has been responsible for leading teams drafting several sections of the guideline. He has presented and organised several international conferences on implementation of QbD & ICH Q12 for DIA, ISPE, PDA, CASSS, facilitated training activities and workshops for regulatory agencies including EMA, FDA, NMPA, MFDS on topics such as implementation of ICH Q8-11 and training and implementation of ICH Q12.
Summary	The presentation will highlight the need for ICH Q12 to enable the vision for Q10 of continual improvement in Pharmaceutical drug quality. This will also illustrate some of the learning and experience from AstraZeneca as well as future challenges.

ICH Q12 – Practical Implementation
Now the Hard Work Starts

Dr. Frank Montgomery
Global Head Regulatory CMC, AstraZeneca

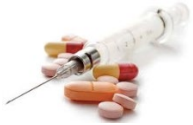
November 2020

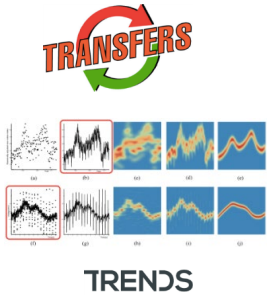
Introduction

- Do we need ICH Q12?
- Background to Q12
- How has AstraZeneca Implemented Q12
- Health Authority Implementation of Q12

The Life of a Product Is Dynamic

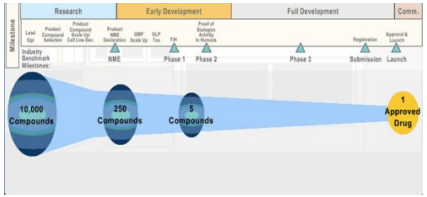
QTPP
CQAs
CPPs



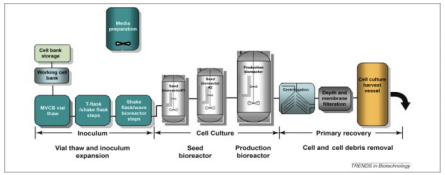


Evolution of Control Strategy

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation



Initial product & process knowledge

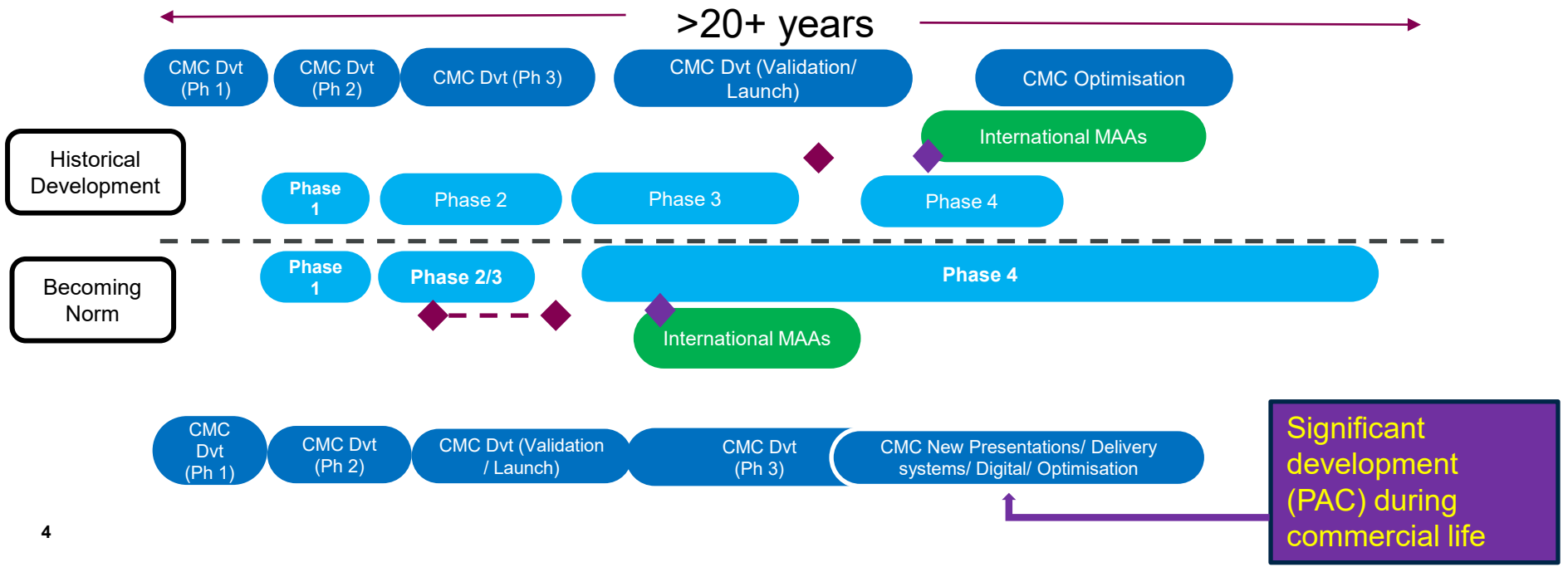


New product & process knowledge
(changes in CQAs & CPPs)

Acceleration Drug Development

Submission ◆
Approval ◆

- Clinical development is accelerating as targeted therapies and disease understanding grows
- Oncology business strategy is to design for registration off extended Ph1 or Ph 2 studies
- Huge number of additional Ph 4 clinical studies (240 One product) linked to common mechanism of action
- ***CMC development goes beyond submission; final supply chain or optimal device often introduced post-approval***



Diverse global regulatory environment for post-approval changes

Example of a single change: introduce a new filling site

Total expected approval lead time for a world wide approval

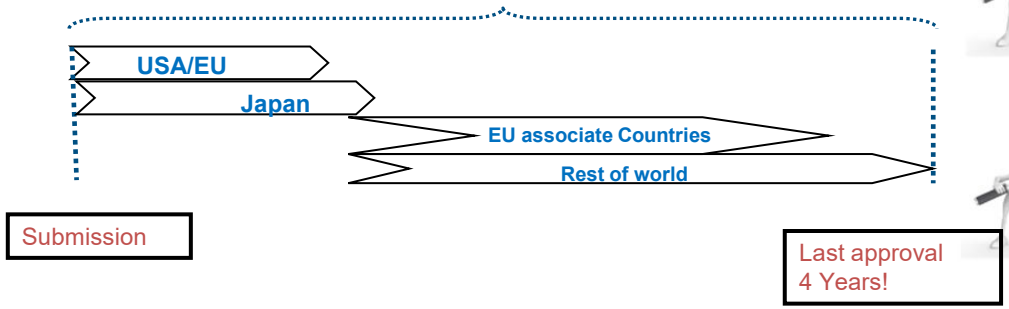
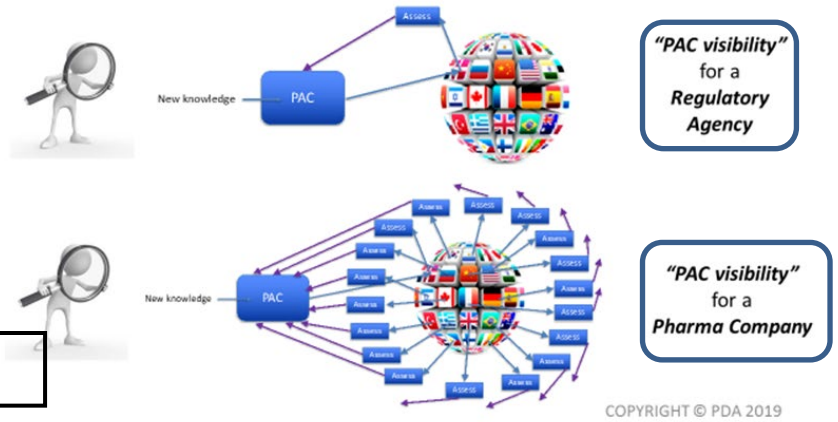


Figure 2: PAC Regulatory Complexity – Seen From Different Angles



A. Vinther and E. Ramnarine, PDA Journal of Pharmaceutical Science and Technology, 2019

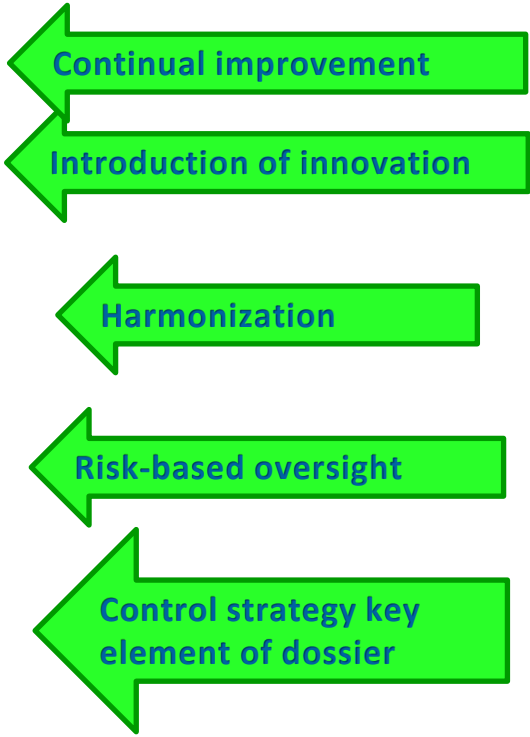
Result:

- For a new filling site, long and different approval time lines => some countries will have to be supplied from the old filling factory for four years.
- Company must be able to produce different variants of the same product

BACKGROUND TO Q12

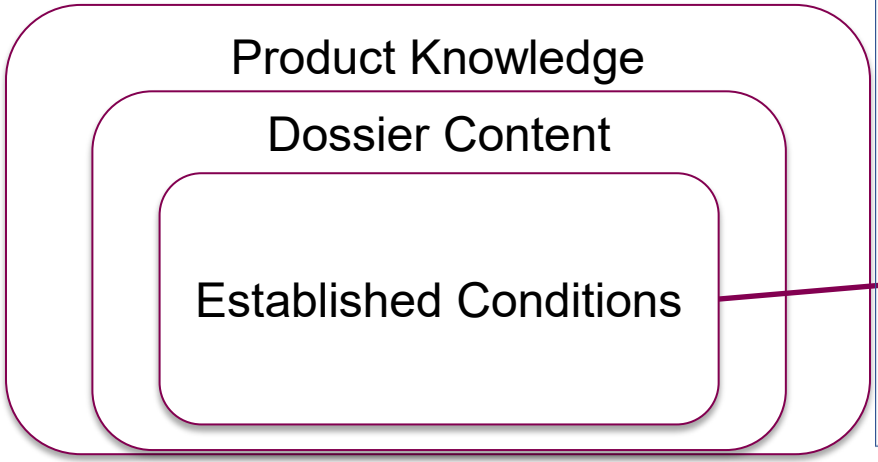
ICH Q12 a Great Opportunity For Patients and Industry

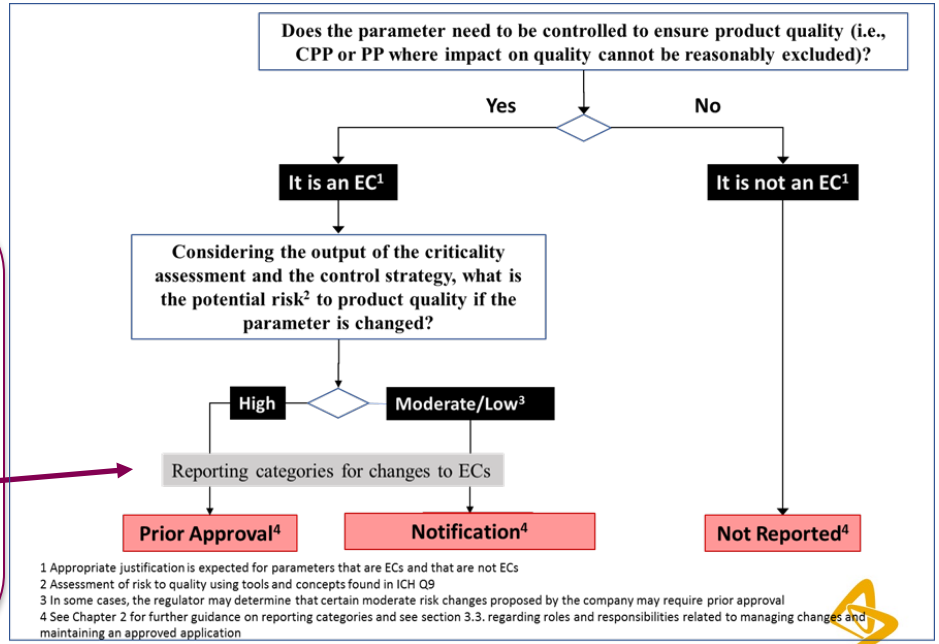
- Provides a **risk based framework** to facilitate the management of post-approval CMC changes in a more **predictable and efficient manner**
- Includes **harmonized** regulatory tools and enablers with associated guiding principles
- Outlines how increased **product and process knowledge** can contribute to understanding of **which post-approval changes** require regulatory **submission**
- Reiterates how an **effective pharmaceutical quality system** is essential in the management of **changes during the product lifecycle**



Established Conditions

- **Established Conditions** are legally binding information necessary to assure product quality
- The change reporting categorization for ECs becomes a risk-based evaluation of the impact on product quality
- **Negotiated up-front with the agency**
- If **not an EC** changes are **only** managed within the PQS and available for inspection





Example of CTD sections that contains ECs or supportive information

APPENDIX 1: CTD SECTIONS THAT CONTAIN ECS

Notes:

- This table does not contain a complete list of ECs for a product. The intention of the table is to provide general guidance about the elements of manufacture and control that constitute ECs and their location within the CTD structure.
- White rows indicate CTD sections where ECs are generally located. Grey rows indicate CTD sections where supportive information is generally located.
- CTD sections containing ECs may also contain elements of supportive information.
- For information related to the drug delivery system for a drug-device combination product, the location or the relevant content within the CTD structure may vary depending on the design of the particular product and region.

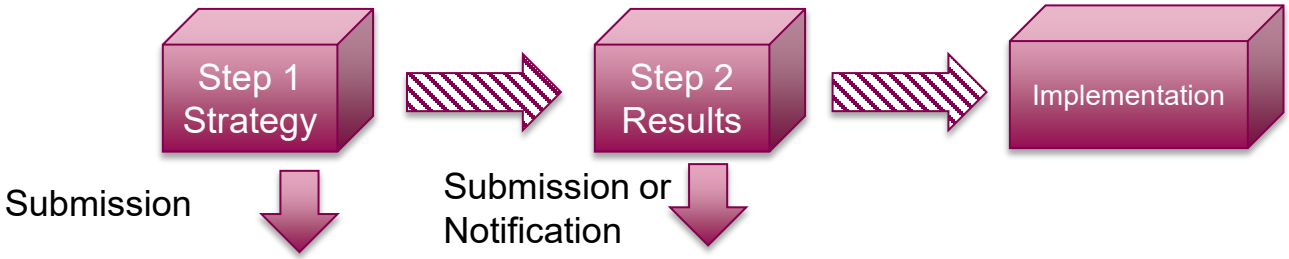
CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S	**DRUG SUBSTANCE**	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	Drug Substance Name, Structure.
3.2.S.1.2	Structure	
3.2.S.1.3	General properties	Supportive information
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacturer(s)	Drug Substance Manufacturing Site(s) (including testing)
3.2.S.2.2	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3, section 3.2.3.1 – *Identification of ECs for the Manufacturing Processes*
3.2.S.2.3	Control of Materials	Starting material specifications (test, elements of analytical procedure and acceptance criteria) Raw material/reagent/solvent critical controls

Sections where supportive information are generally located

Sections where EC are generally located

Post-Approval Change Management Protocol (PACMP)

- Need to expand the use of PACMPs
- Need to be able to be re-used over the product life
- Modification of a PACMP by **notification**
  - e.g for replacement or revision of a test, study or acceptance criterion, should provide the same or greater capability for product quality



Component	Step 1 contents (registration of protocol)	Step 2 contents (change implementation)
Overall Strategy Scope & Limitations	Defined scope and limitations	Demonstrate requirements of scope met, including process changes associated with transfer
QRM	Description of QRM program and approach to site transfer risk assessment	Documented risk control strategy and executed risk management report summary
Comparability & Stability	Comparability plan, real-time stability commitments and acceptance criteria (product-specific)	Data demonstrating that acceptance criteria are met
Process Validation	Overview of validation program	Summary of facility/equipment differences and applicable validation; validation summary data support the process, facility/equipment, and method transfer
Site risk	Description of site inspection risk assessment	Outcome of site inspection risk assessment defines actual change submission requirements

Annex I D: PACMP Example 1 –
Alternative manufacturing site for a small molecule drug substance

Outline for Step 1 Submission

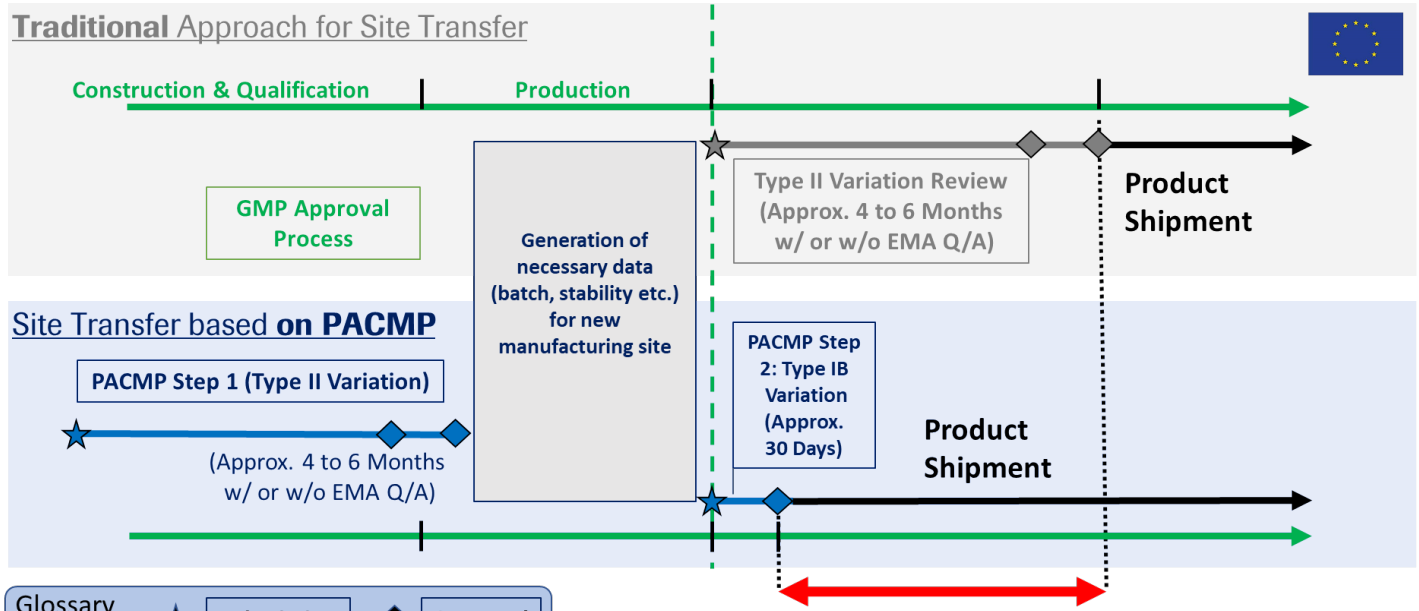
- 1. Introduction and Scope
  - PACMP for the addition of an alternative manufacturing site for manufacture, testing, and release of the drug substance for a small molecule solid oral drug product.
  - Implementation of this change (Step 2) proposed as lower reporting category or **shorter review timelines**
- 2. Quality Risk Management (QRM) Activities includes:
    - Identification and assessment of the potential risks associated with the proposed change, as well as the activities proposed to mitigate each risk;
    - Accounting for known elements of the process, such as robustness, existing controls, and potential impact on product quality;
    - Incorporating prior knowledge gained from development and commercial manufacturing experience.

Annex I D: PACMP Example 1 –
Alternative manufacturing site for a small molecule drug substance

Outline for Step 1 Submission

- 3. Acceptance criteria
  - Three consecutive batches of drug substance manufactured at the alternative manufacturing site should meet approved specification to demonstrate equivalence to batches manufactured at the currently approved site
- Other conditions to be met prior to implementation:
  - **Confirmatory Stability studies** will be initiated immediately on a suitable number of commercial scale batches of drug substance manufactured at the alternate manufacturing site and provided after implementation
  - **Alternative manufacturing site to have acceptable compliance status** last GMP inspection /valid GMP certificate, etc.
  - **Alternative manufacturing site to use similar manufacturing equipment**

Example - Manufacturing site transfer: Timelines PACMP Approach vs. ”Traditional“ Approach* (based on EU/EMA case, similar to US)



➢ Up to 5 months faster approval of the site change using a PACMP (time benefit similar in US)

Up to 6 Mo additional implementation benefit if confirmatory stability data provided after implementation **(US)**

**Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision*

Product Lifecycle Management (PLCM) Document

PLCM document connects the Q12 tools reported in submission across the lifecycle of the product.

The PLCM document outlines the specific plan for product lifecycle management and includes key elements:

Proposed ECs for the product

Reporting category (RC) for making changes to approved ECs

PACMPs to prospectively manage and implement one or more post-approval changes

Post-approval CMC commitments

Provides clarity between the MAH and Regulatory Authority

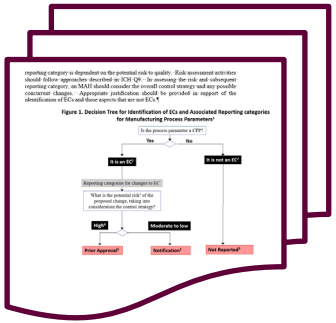
HOW HAS ASTRAZENECA IMPLEMENTED Q12

AZ FDA Pilot: What Product to choose?

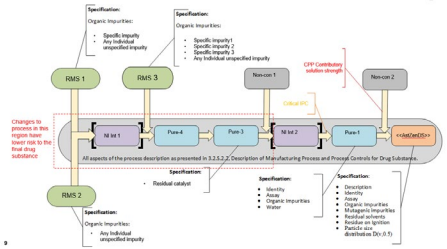
- AZ requested participation in FDA Established Conditions pilot and proposed: PAS on drug substance ECs in May this year with formal acceptance into the pilot programme by FDA at the beginning of July.
- **AZ DS** was selected because of clinical significance, recent development knowledge and low overall drug substance risk to patient. (Chemical, physiochemical and biopharmaceutical properies)
- In selecting **AZ DS** very careful consideration was given to ensure no risk the approved NDA or anticipated changes to supply chain.

Risk	Severity	Likelihood	Mitigation
There is a risk that submission of this PAS may trigger a re-review of the control strategy and the process controls approved previously, leading to a tightening of criteria beyond the capability of the process and difficulties in supply to patients.	High	Low	Should there be any questions coming back from FDA during review that appear to be assessing previously agreed elements of the process controls or control strategy, the filing will be withdrawn and a dialogue will be opened with FDA.
There is a risk that resource could be pulled into this submission, either at time of filing or during review, compromising functional work in other key areas.	Low/Mod	Moderate	This can never be mitigated fully. All parties involved have committed time to support this initiative, but there needs to be an ongoing dialogue to give people the opportunity to flag when resource might be constrained.
There is a risk that in filing this change, we adversely impact other major filings related to drug substance supply such that these are not brought to a conclusion within the agreed timelines.	High	Low	This file will have no impact on the content of Module 3 and therefore there is no impact on any ongoing or subsequent amendments filed to FDA for drug substance. At the time of writing, there are not major drug substance amendments tabled for submission in this time frame anyway.
The management of post-approval changes could be made more challenging by having different views on the implementation of this supplement, leading to confusion and delay in the implementation of future changes.	Moderate	Low	Even if this supplement is approved, there is no obligation on us to implement it immediately. We can make decide to delay implementation of this until we have secured agreements with Quality broadly and have the procedural infrastructure in place to fully manage Q12.
There is a risk that the reviewer could challenge the potential risk positioning criteria for our ECs and ask for more data to be provided that is not already in the existing file. This could be very difficult to provide and may impact our total package going forward.	Moderate	Low	If questions such as this arise during review, the proposal would be to capitulate on the assessment of criticality of the EC questioned and not to provide further information to try to support our position. The discussion could then be taken with the agency at a later date.

Proposed Format of EC Document



- Intro setting out how we made our assessment of the ECs
- Risk assessment criteria underpinning this.
- Showing AZ Drug Substance to be overall low risk in terms of Chemical, physiochemical and biopharmaceutical properties.



- Summary of ECs

Risk Classification	EC Change Reporting Category	Potential Impact on Product Quality	Stability Considerations
High risk	Prior approval supplement	Potential for increased level of known impurities above drug substance control limit or new impurity above defined ICH limits for residual solvents, elemental impurities and the identification threshold for related organic impurities. Control of CQAs is typically provided at only one point during the synthesis.	Drug substance stability data from an appropriately designed and scientifically justified accelerated stability study/ies to reconfirm the retest period. These data will be provided in the PAS. Commitment for formal ICH stability study for drug substance to be reported in Annual Report.
Moderate risk	Notification via CBE 30	Impact is limited by capacity of process to purge impurities Control of CQAs is typically provided at multiple points during the synthesis but with higher risk to fail final control point limit.	Confirmatory stability studies to be conducted post-implementation of change.
Moderate to Low	Notification via CBE 0	Impact is limited by capacity of multiple process steps to purge impurities Control of CQAs is typically provided at two or more points during the synthesis with low risk to fail final control point limit ICH classification of solvent is unchanged. Supported by process understanding and commercial-scale manufacture experience	No additional stability required other than as defined by GMP requirements.
Low risk	Notification via annual report	Impact is limited by capacity of multiple process steps to purge impurities Control of CQAs is typically provided at multiple points during the synthesis	No additional stability required other than as defined by GMP requirements.

- Summary of Stability considerations

Process element	Potentially Impacted CQAs	Reporting Category	Assessment
Manufacturing Site	Active substance and impurities	CBE 0	Control strategy is unchanged for new manufacturing site ensuring all known criticality is controlled and quality of <<AstZenDS>> maintained. Risk to quality of drug product is considered to be moderate to low. (Dependent on the quality system of the new site being subjected to successful audit by FDA, else this change will follow regional guidance)
Synthetic Sequence, including named starting materials, intermediates.	Active substance and impurities	Prior Approval Supplement	The synthetic route is critical to production of the correct active substance. Changes may result in new impurities and therefore changes to the route will have a high risk to impact <<AstZenDS>> and drug product quality.
Upper limit of the CPP <<contributory solution>> above X.0% w/w	Specific Impurity A	CBE 30	The upper limit of strength of the <<contributory solution>> was identified as critical process parameter in development studies which showed the parameter to be critical in the purge of Impurity A in the <<AstZenDS>> synthetic step. However additional controls are also provided by the control of the <<AstZenDS>> specific impurity in Late Stage, which is a precursor to Specific Impurity A, process capability to purge Specific Impurity A in the Pure-1 step and control in the <<AstZenDS>> specification. Risk to quality of <<AstZenDS>> and drug product is considered to be moderate due to increase in risk to fail the final control point.

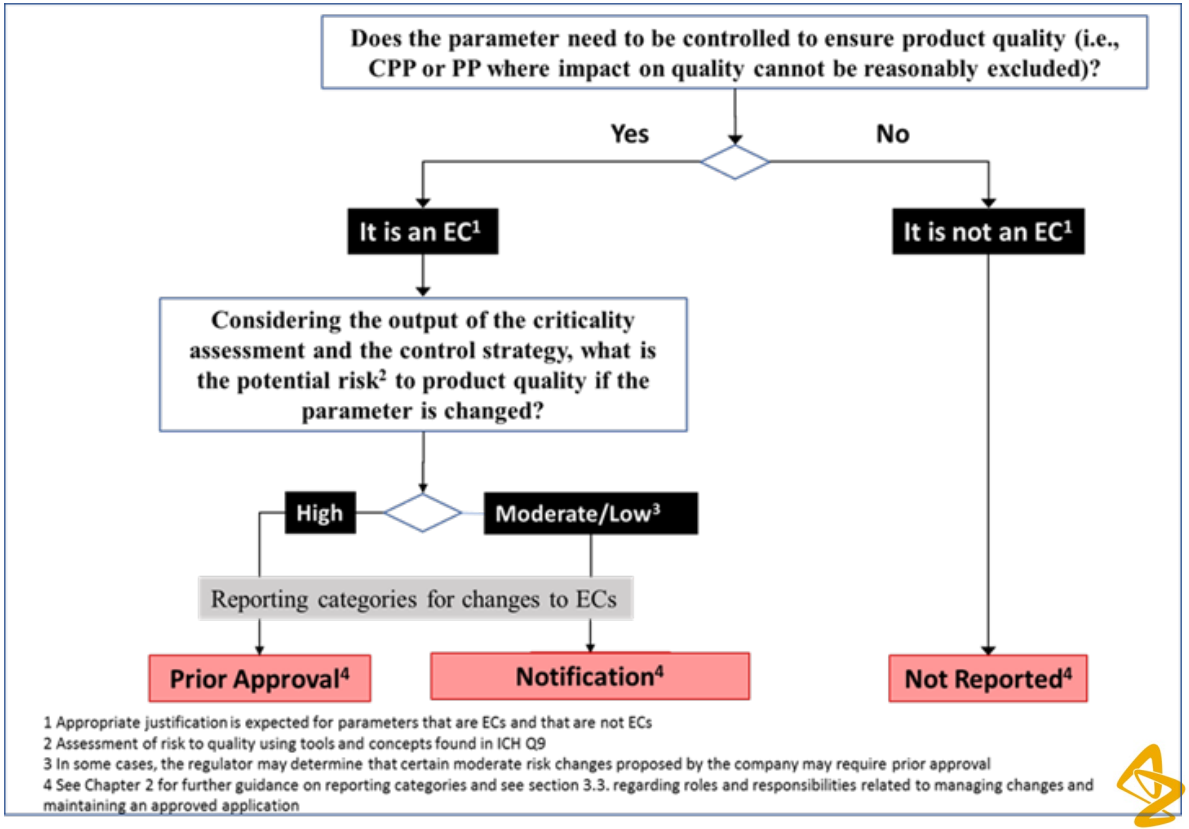
- Tabular format with more exposition on classification of the ECs according to Risk and with reporting category
- Links also to sections of module 3 containing the necessary scientific background supporting the assessment

Product Risk Considerations

- Potential impact to patient was assessed through looking at several factors
- From this it was clear that
  - The drug substance process has been shown to produce well controlled drug substance
  - The stability of the drug substance is excellent
  - The biopharmaceutical risk and impact to the drug product were low
  - Capability of the process to purge impurities was high
- Established conditions were, therefore, weighted towards
  - Ensuring that the synthetic route including starting materials and intermediates, are maintained to ensure drug substance is manufactured consistently
  - Ensuring that impurities with potential to persist to drug substance are controlled adequately

ECs for All DS Manufacturing Processes & Controls

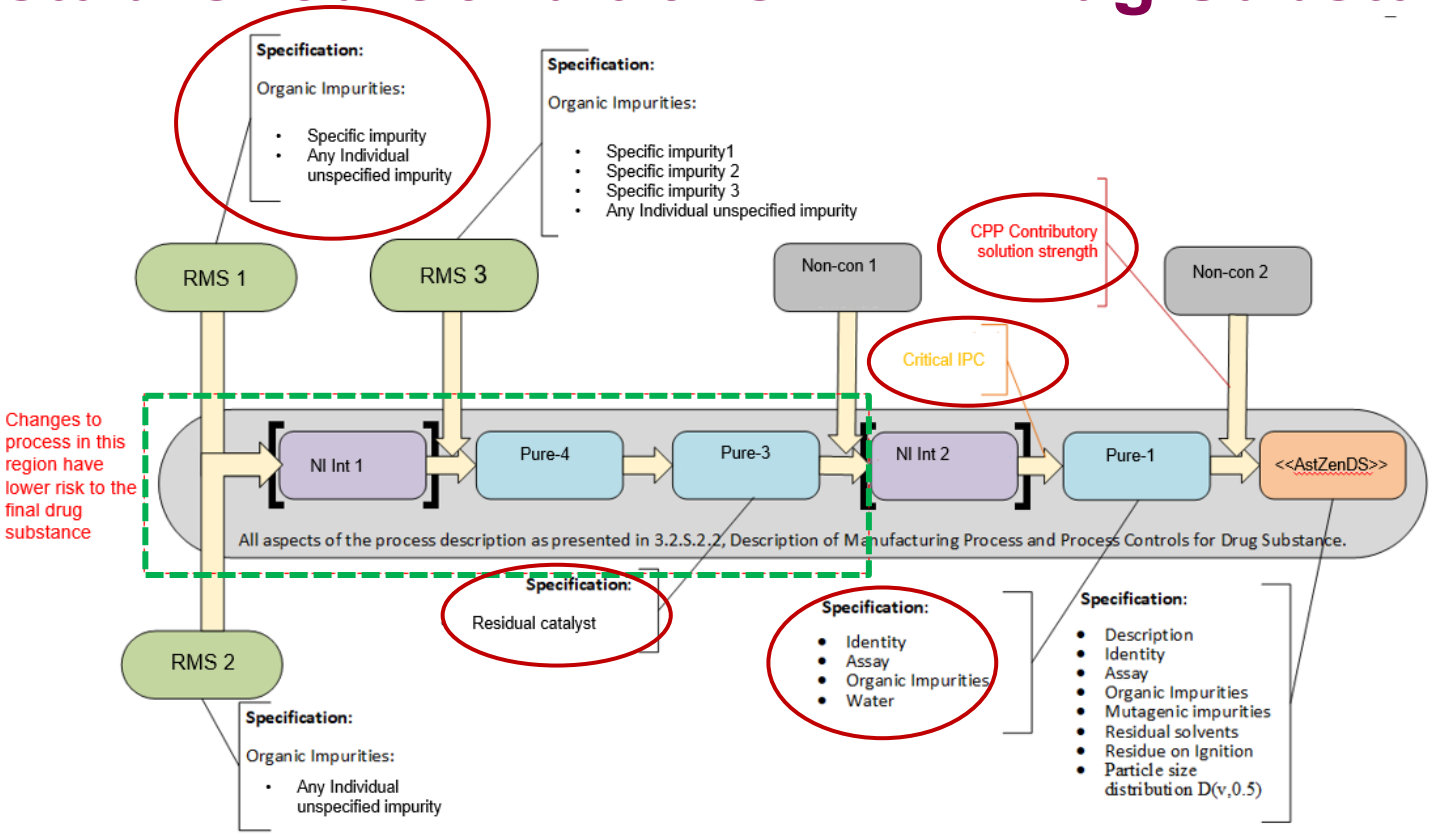
- Decision tree specifies process parameters
- BUT **principles** are intended to be used for all aspects of defining ECs for process and controls
- AZ used this concept to consider all ECs for Drug Substance



Risk Considerations

Established Conditions	Risk	Rationale
Synthetic route	High	Changes to the route have the potential to significantly impact the DS
Synthetic process upstream (close to API)	Moderate	Process changes have the potential to impact DS due to limited number of control points and potential for purge
Synthetic process downstream (Early stages)	Low	Impact of process changes are significantly reduced due to multiple control points in later stages and capability of the process to purge impurities
Input material attributes	Moderate to Low	In each case individual impurities with the potential to track to DS are considered moderate risk, all else is low.
Intermediate material attributes		
In-process controls	Low	Existence of multiple other control points means that the majority of IPCs are low risk and exist to support manufacturability and reduce waste

Established Conditions – AZ Drug Substance



Established Conditions – Reporting Category & Discussion

Process element	Potentially Impacted CQAs	Reporting Category	Assessment
Manufacturing Site	Active substance and impurities	**CBE 30**	Control strategy is unchanged for new manufacturing site ensuring all known criticality is controlled and quality of **AZ DS** maintained. Risk to quality of drug product is considered to be moderate to low. (Dependent on the quality system of the new site being subjected to successful audit by FDA, else this change will follow regional guidance)
Synthetic Sequence, including named starting materials, intermediates.	Active substance and impurities	Prior Approval Supplement	The synthetic route is critical to production of the correct active substance. Changes may result in new impurities and therefore changes to the route will have a high risk to impact <<AstZenDS>> and drug product quality.
Upper limit of the CPP <<contributory solution>> above X.0% w/w	Specific Impurity A	CBE 30	The upper limit of strength of the <<contributory solution>> was identified as critical process parameter in development studies which showed the parameter to be critical in the purge of Impurity A in the **AZ DS** synthetic step. However additional controls are also provided by the control of the **AZ DS** specific impurity in Late Stage, which is a precursor to Specific Impurity A, process capability to purge Specific Impurity A in the Pure-1 step and control in the **AZ DS** specification. Risk to quality of **AZ DS** and drug product is considered to be moderate due to increase in risk to fail the final control point.
Other Process Parameters and description of the process(es) text for the Pure -1 & **AZ DS** step	Impurities	CBE 30	The impact of change to the process parameters and description of the process description text have been determined moderate risk for the later process steps Pure -1 and **AZ DS** given their proximity to formation of **AZ DS** and importance re control of impurities, particularly Pure -1 which provides control for multiple named impurities some of which have limited purge in the **AZ DS** step.

PLCM content

Established Conditions – Reporting Category & Discussion

Process element	Potentially Impacted CQAs	Reporting Category	Assessment
Other Process Parameters and description of the process(es) text for the Pure-3 and Pure-4 steps	Impurities	Annual Report	The impact of change to manufacturing process parameters and the process description text have been determined to be of low risk for the ealier steps as there are multiple control points within the downstream Pure-1 and **AZ DS** manufacturing steps both in terms of the capability of the process to purge impurities and controls provided by Pure-1 and **AZ DS** specifications.
Particle size reduction process manufacturing method (and equipment)	Particle size distribution D(v,0.5)	Annual Report	**AZ DS** is considered to carry low biopharmaceutical risk. <<Detailed discussion of the biopharmaceutical risk>>
Particle size reduction manufacturing step (potential to remove this step)	Particle size distribution D(v,0.5)	Annual Report	
Lower **AZ DS** yield limit	Potentially Assay, Impurities	Annual report	Lower yields would not be preferred from an environmental or commercial perspective but provided quality of **AZ DS** is not impacted by losses during manufacture then risk to quality of **AZ DS** and drug product is considered to be low.

PLCM content

Stability Risk Assessment & Commitments

Risk Classification	EC Change Reporting Category	Potential Impact on Product Quality	Stability Considerations
High risk	PAS	Potential for increased level of known impurities above drug substance control limit or new impurity above defined ICH limits for residual solvents, elemental impurities and the identification threshold for related organic impurities. Control of CQAs is typically provided at only one point during the synthesis.	Scientifically designed DS accelerated stability study(s) to reconfirm the retest period. Data provided in the PAS. ICH stability study for DS in AR
Moderate risk	Notification (CBE 30)	Impact is limited by capacity of process to purge impurities Control of CQAs is typically provided at multiple points during the synthesis but with higher risk to fail final control point limit.	Confirmatory stability studies to be conducted post-implementation of change.
Moderate to Low	Notification (CBE 0)	Impact is limited by capacity of multiple process steps to purge impurities Control of CQAs is typically provided at two or more points during the synthesis with low risk to fail final control point limit ICH classification of solvent is unchanged. Supported by process understanding and commercial scale manufacture experience	No additional stability required other than as defined by GMP requirements.
Low risk	Notification (AR)	Impact is limited by capacity of multiple process steps to purge impurities Control of CQAs is typically provided at multiple points during the synthesis with very low risk to fail final control point limit ICH classification of solvent is unchanged. Supported by process understanding and commercial scale manufacture experience	No additional stability required other than as defined by GMP requirements.

FDA Pilot Program Experience to Date

- Three rounds of questions, plus one telecon
- FDA focused on how does the PQS support change?
- Agency were very interested in change management
  - if you do x, how will we know? How do you know doing x doesn't result in something unexpected
  - Are your analytical methods capable of picking up changes you haven't foreseen?
  - Lots of reference back to PQS
- Q12 Watershed: No request yet to document PQS aspects in the actual dossier.
  - Crossing the boundary between inspection and Module 3?
- Agreed to almost all AZ proposals
  - Site change for API proposed CBE0 agreed to CBE30
  - To enable FDA to conduct site risk assessment
- Final approval received 20th December with no Post Marketing Commitments

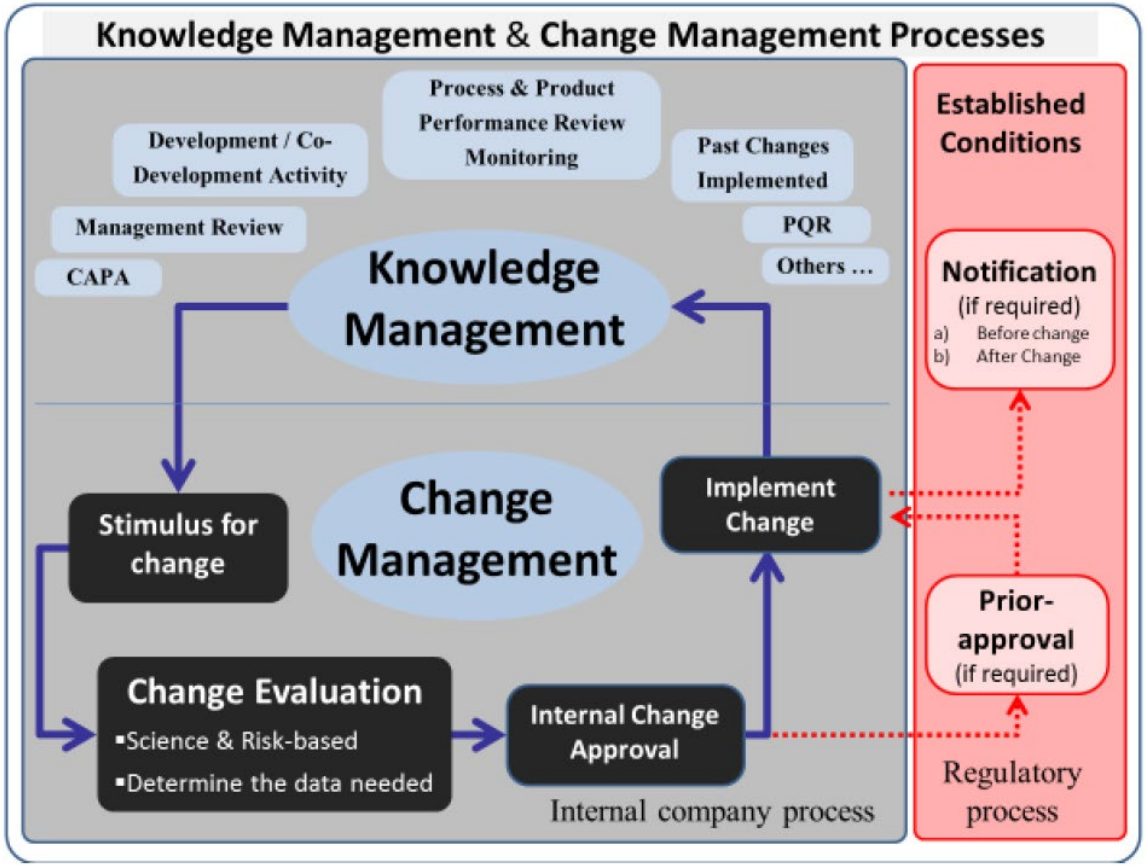
ICH Q12 Pilot Submission – How has it helped?

- Site change for drug substance enabled in US by agreement of established conditions AND agreement on necessary supporting stability
  - **Confirmatory stability data provided rather than in application**
- Several process changes progressed without immediate reporting as agreed in PLCM
- Potential to simplify process via PQS as a result of agreement of ECs in PLCM
- Potential simplification of addition of RSM manufacturers as a result of agreement of ECs in PLCM

Knowledge Management & Change Management is critical

- **Ch 6** Change management process (ICH Q10) is critical to effective implementation of Q12
- Every change related to the manufacturing process for a product is managed through the company PQS and available for Inspection
  - Every change **<u>should not</u>** be communicated or subject to review!

- **Ch 7** Critical that reviewers understand the role of PQS and Inspectors role in surveillance of the "Effectiveness" of the PQS



HEALTH AUTHORITY IMPLEMENTATION OF Q12

EU Regulator and Industry Dialogue on Revisions to Regulatory Framework & Implementation Q12

- Joint Industry meeting and European Commission (EC) Jan 2020
  - Scope: Follow-up to meeting in Mar 2019 and opportunity to expand on industry responses to EC questions on Industry White Papers.
  - Outcome:
    - Generally positive. EC to discuss with EMA and define next steps
    - Overall, understand the rationale and need for revision of Regulation 1234/2008 and Guideline 2013/C 223/01.
    - Recognise the areas identified for improvement
    - Support for implementation of Q12

Global Implementation of ICH Q12?

- Project was initiated by EFPIA International Regulatory Expert Group (IREG) to understand further the **barriers and challenges to implement Q12**
  - IREG has a series of Regulatory Networks covering different countries/regions containing experts from Industry

- We surveyed the relevant Networks using a questionnaire to evaluate:
  - Barriers to post-approval changes and implementation of Q12
  - Adoption of Q8-11 (key guidelines that underpin ICH Q12)
  - Adoption of: Established Conditions (EC) and Post-Approval Change Management Protocols (PACMP)*

- Data presented compares ICH Member countries with ICH Observers

Group	Countries
ICH Members#	Brazil, China, Chinese Taipei, Republic of Korea, Turkey, Singapore
ICH Observers	Colombia, Mexico, Argentina, Cuba, EAEU (covering Russia/Kazakhstan), Malaysia, Saudi Arabia

Comparator to the group of ICH Members. Reflects a cross-section of countries, reflecting the information received from respondents in the EFPIA networks

*Also looked at adoption of product lifecycle management document (results not shown); similar to EC results
#Note-excluded the original members of ICH from the evaluation.

Important Factors Hindering Post-Approval Change (PAC) Systems

Members

Observers

	Members	Observers
Important Factors in the PAC system (top three)*	1. Capability/Capacity 2. Long/unpredictable timelines 3= Clarity on requirements *and* Additional local requirements *and* Limited/no classification	1. Capability/Capacity 2. Long/unpredictable timelines 3. Clarity on requirements
Barriers to Q12 Implementation (top three)*	1. Maturation of regulatory system 2. Inclusion of Q12 principles in framework 3. Training of regulators/industry	1. Inclusion of Q12 principles in framework 2= Maturation of regulatory system *and* Insufficient capacity/organization *and* Barriers to reliance
Is Q8-11 Implemented?#	**Partial** >*Yes*>*No* **No** >*Partial*>*Yes*	
If No/partial, when implemented?	**Near** >*Long* = *No Plan* **No Plan**	

*Respondents were asked to provide the top 3 barriers which were then grouped. The three most popular across the groups are shown.
#The most popular answer is shown followed in order by the other responses.

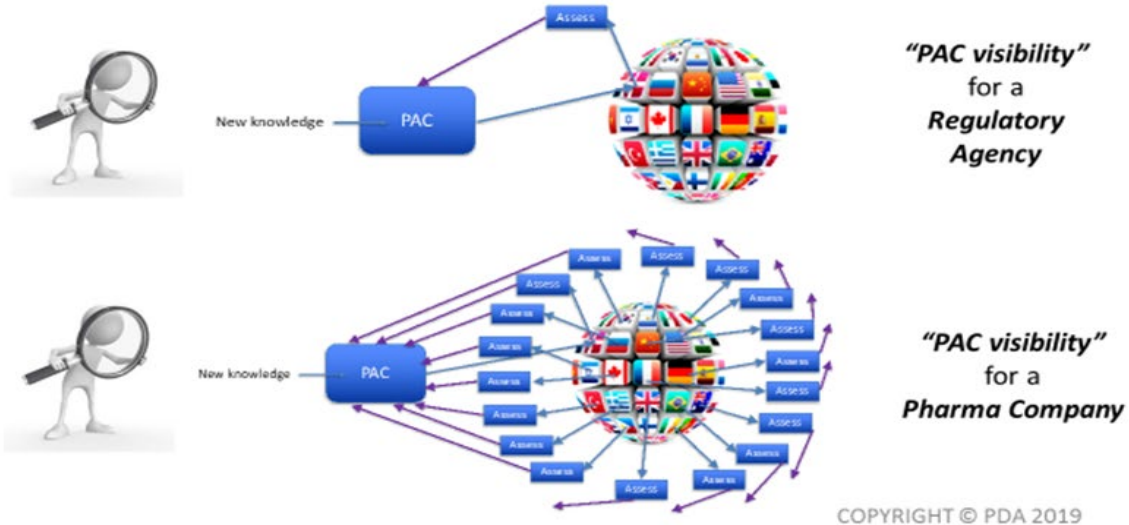
Conclusions

- Reflects an INDUSTRY view only – Regulators may have a different perspective
- The results show challenges to implement Q12…particularly in non-ICH Members
  - ICH 8 – 11 is lacking as is the plan to implement EC, PACMPs + PLCM
- New ICH Members show intent to implement but some fundamental challenges:
  - Some lacked basic categorization for changes
  - Laws, regulations or guidelines may be needed to bring in ECs, PACMP or PLCM
- Capacity building was also highlighted – clearly training is important
    - Industry role in supporting training
- Note that implementation also ongoing in original ICH Members
  - EC Pilot by US FDA

Is Q12 Sufficient to Resolve the Problem?

Real-Time Post Approval Changes (PAC)…..
…How Do We Get From YEARS to WEEKS for PACs?

Figure 2: PAC Regulatory Complexity – Seen From Different Angles



A. Vinther and E. Ramnarine, PDA Journal of Pharmaceutical Science and Technology, 2019

RA ↔ RA

- Reliance
- Recognition
- Follow WHO guidelines
- FDA/HPRA White Paper ICMRA

RA: Regulatory Agency; IN: Industry

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Questions?