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

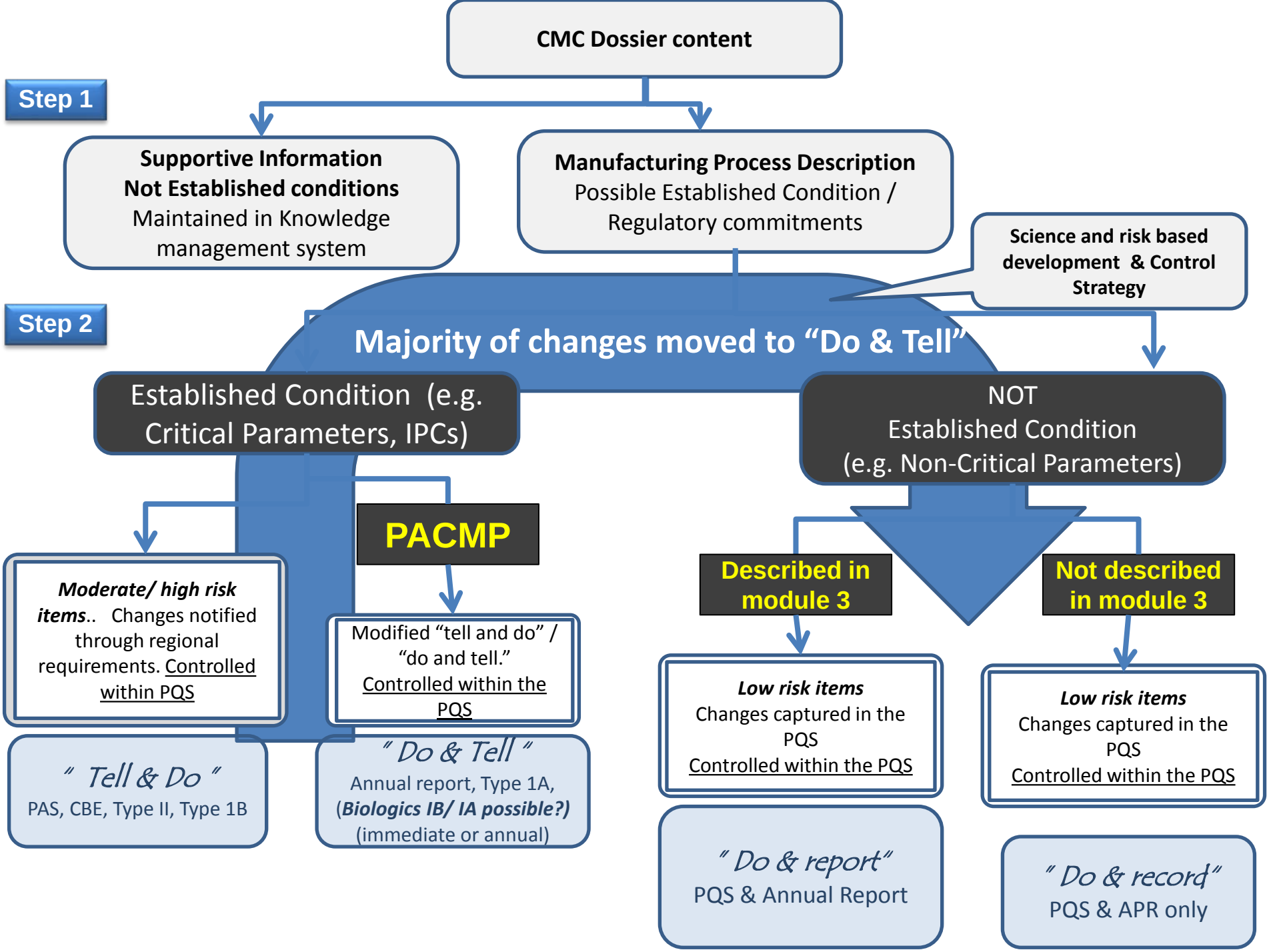
Case studies on Established Conditions

Established Conditions (EC)

- EC for Manufacture and Control are binding information or elements in the dossier concerning the manufacture and control of a pharmaceutical product
  - Description of the product, elements of the manufacturing process, facilities and certain equipment, specifications and other elements of the associated control strategy
- EC may vary in their level of detail based on a sponsor's product and/or process understanding, ease of characterization and/or risks tied to product quality and performance
  - E.g. Established Conditions, in certain cases, could simply be the method principle and the performance characteristics of a monitoring or testing method

Benefits

- Greater transparency within an organization and with regulatory authorities
- Greater focus on mitigation of high risk elements
- Opportunities to utilize more effective and efficient post-approval change management strategies
- Increased opportunities to provide supportive information
- Significant incentive to invest in the development of their pharmaceutical products and their pharmaceutical quality system (PQS)
- Facilitation of continual improvement and seeking out opportunities for technical advancement


CMC Dossier content
Step 1
Supportive Information
Not Established conditions
Maintained in Knowledge management system
Manufacturing Process Description
Possible Established Condition / Regulatory commitments
Science and risk based development & Control Strategy
Step 2
Majority of changes moved to "Do & Tell"
Established Condition (e.g. Critical Parameters, IPCs)
NOT Established Condition (e.g. Non-Critical Parameters)
PACMP
Moderate/ high risk items.. Changes notified through regional requirements. Controlled within PQS
Modified "tell and do" / "do and tell." Controlled within the PQS
Described in module 3
Not described in module 3
Low risk items
Changes captured in the PQS
Controlled within the PQS
Low risk items
Changes captured in the PQS
Controlled within the PQS
" Tell & Do "
PAS, CBE, Type II, Type 1B
" Do & Tell "
Annual report, Type 1A, (Biologics IB/ IA possible?)
(immediate or annual)
" Do & report"
PQS & Annual Report
" Do & record"
PQS & APR only

Topic Areas

- Overview of established conditions vs. non-established conditions
  - Specific examples
  - Reporting mechanism for changes established and non-established conditions
    - How would this be different
- What benefits would it bring (less focus on minor issues for Reg & Industry, allow improvements, stock outs reduced and clearer compliance commitment, optional aspects)
  - Is the level of detail in the dossier too high causing unnecessary change (too many Type IAs)?
  - Does the level of detail need to be less or simplify administration significantly?
- Practicalities of dossier management
  - How do we get a workable way to represent ECs and Module 3 that is consistent across ICH
  - Consistency for Module 3 to be used globally
- Issues within EU & International
  - Reference country approval (Type IA is ok?)
- Keep RoW in mind for broader harmonisation

Background

- Many “details” are provided in regulatory dossier to enhance understanding of the manufacturing process and/or control strategy. Maintenance of those “details” is a burden.
- Examples of a recent variations for a drug substance (small molecule):
  - Change in starting material quantity: from 200-235 kg’ to ‘195-235kg’
  - Use of lower concentration of NaOH leading to higher volume loaded into the reaction (stoichiometry respected)
  - Lower amount of class 2 solvent used (from ‘2200-5650 kg’ to ‘2000-5650 kg’)
  - Stirring time changed from ‘approximately 2 hours’ to ‘at least 1 hour’ based on process experience (completion of reaction)

- Agreement on established conditions (EC) (to be maintained proactively) and non-established conditions (non-EC) should help to focus on change(s) with a potential quality impact. Non-EC would not be subject to proactive reporting to Health Authorities (HA) as stand alone.
- Similar principle applies to clinical trial applications as described in Directive 2001/20/EC.

Implementation of ICH Q12 in current EU regulatory framework

- EU variation regulation does not allow to waive reporting for indefinite period.

Update of Classification Guideline (Article 5 notification if appropriate)

- Recommendation for changes in non-EC parameters to submit at the next CTD module update (similar principle to 'editorial change').

  - Voluntary reporting may be desirable as non-EC changes may be required to be submitted in non ICH regions and ICH country submission/approval may be considered as reference.

- General Type IA without condition to facilitate dossier update, allowing grouping of all non-EC changes into one single submission.

  - List with relevant updated sections of dossier
  - Multiple submissions may still be required depending on the implementation of each individual non-EC parameters
  - Precise scope to be defined to avoid maintenance of all non-EC (for instance P83)

- Simplify Type IA for easy grouping and/ or update following EC modification
- Broaden the usage of Type IA to support more usage of this variation category beyond administrative

EC considerations

- Clear and unambiguous identification of established conditions (EC) and non-established conditions (non-EC) in the dossier is critical.

- ICH Q12 should provide guidance and multiple examples on how to identify and present the EC/non-EC in the dossier.

- Separate annex is proposed as an example based on draft FDA guidance (Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products).

- Location: part of CTD Module 2 and/or 3 (tbd, e.g. QOS or 3.2.A), as all ICH regions should apply the same rules. This is critical for Industry to have as much as possible one single set of EC and non-EC in all ICH regions.

- For the majority of modules, identification of EC/non-EC should not be problematic. Difficulties are mainly expected for S.2.2, S.2.3-S.4.2, P.3.3-P.5.2 or 3.2.A.1.

1st Example

Case Study: Drug Product Manufacturing

Focus on:

- Small molecule / Simple DP pharmaceutical form
- CTD module 3.2.P.3 with focus on 3.2.P.3.3
- Use of cross references to identify EC

Option of how EC could be presented

Identification of Established Conditions using hyperlinks:

- When hyperlinks are used, EC should be clearly identifiable in the module (link to a specific table or complete specific section).
- Applicant should ensure that hyperlinks are maintained throughout complete lifecycle (e-CTD filing).
- No risk of divergent information between the module 3 and EC annex

Example of 3.2.P.3 section from EC annex

3.2.P.3	**Manufacture**	
3.2.P.3.1	Manufacturer(s)	EC are described in table 1, [hyperlink to table 1] **Alternative:** Manufacturers including name, address and responsibility(ies)
3.2.P.3.2	Batch Formula	Batch size range and batch formulae described in table 1-1 [hyperlink to table]
3.2.P.3.3	Description of Manufacturing Process and Process Controls	EC are described in the flow chart [hyperlink to flow chart] **Alternative:** Detailed of the EC are provided in a separate table in this annex [hyperlink to separate table provided in this annex]
3.2.P.3.4	Controls of Critical Steps and Intermediates	Complete module
3.2.P.3.5	Process Validation and/or Evaluation	None

1.2 Manufacturing process description

1.2.1 Mixing / screening

1. Mix the drug substance, lactose, cellulose and crospovidone together in a diffusion mixer.
2. Sieve the mixture from step 1 in a screening mill.
3. Mix again in a diffusion mixer.
4. Sieve the magnesium stearate using a hand sieve.
5. Add the sieved magnesium stearate to the mixture from step 3 and mix in a diffusion mixer.

1.2.2 Compaction / compression

6. Press the tableting mixture obtained in step 4 into tablets using a power assisted tablet press.

1.3 Assembly process

Tablets are packaged in double-sided aluminum blister packs. Blisters are assembled in a cardboard based pack.

2 Manufacturing Process parameters

2.1 Process parameters

Process step	Equipment	Parameter	Target value/range
1 Mixing	Mixer	Rotations	100-150 rpm
2 Sieving	Screening mill	Sieve size	1.5 mm
3 Mixing	Diffusion mixer	Rotations	200-250 rpm for minimum 15 min
4 Sieving	Screening mill	Sieve size	1.5-2.0 mm
5 Mixing	Diffusion mixer	Rotations	40-60 rpm for minimum of 30 min
6 Compression	Tablet press	Compressing strength	350-400 N
		Dwell time	10-20 ms

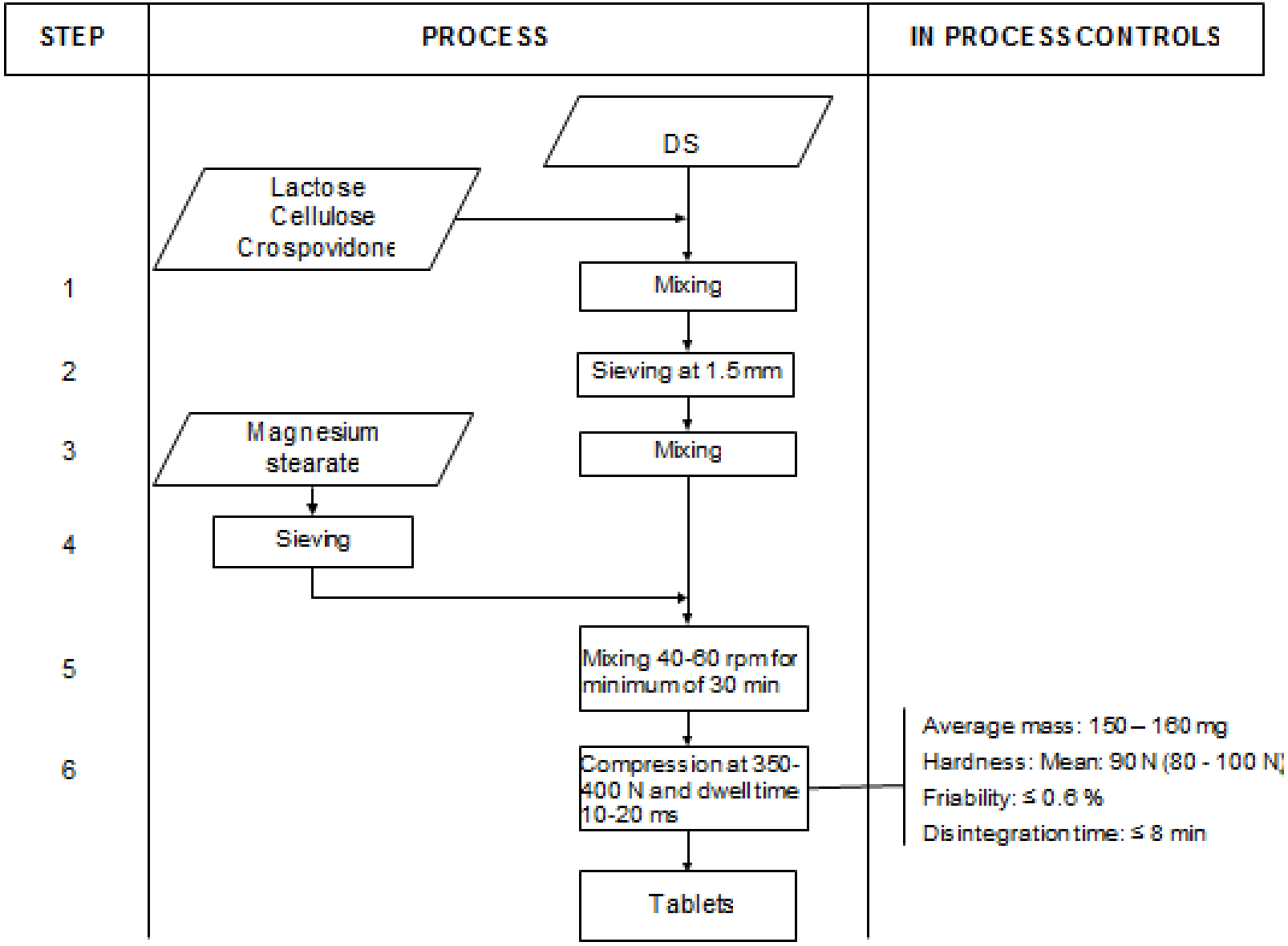
2.2 Process controls

The in-process controls are described in the table below.

Table 2-1 In-process controls for the manufacture of "Brand 100mg tablets"

Process step	Parameter	Target value/range
Compression	Appearance	White tablet
	Average mass	Mean: 150 – 160 mg Deviation ± 7.5 %
	Hardness	Mean: 90 N (80 - 100 N)
	Friability	≤ 0.6 %
	Disintegration time	≤ 8 min

1.1 Flow diagram



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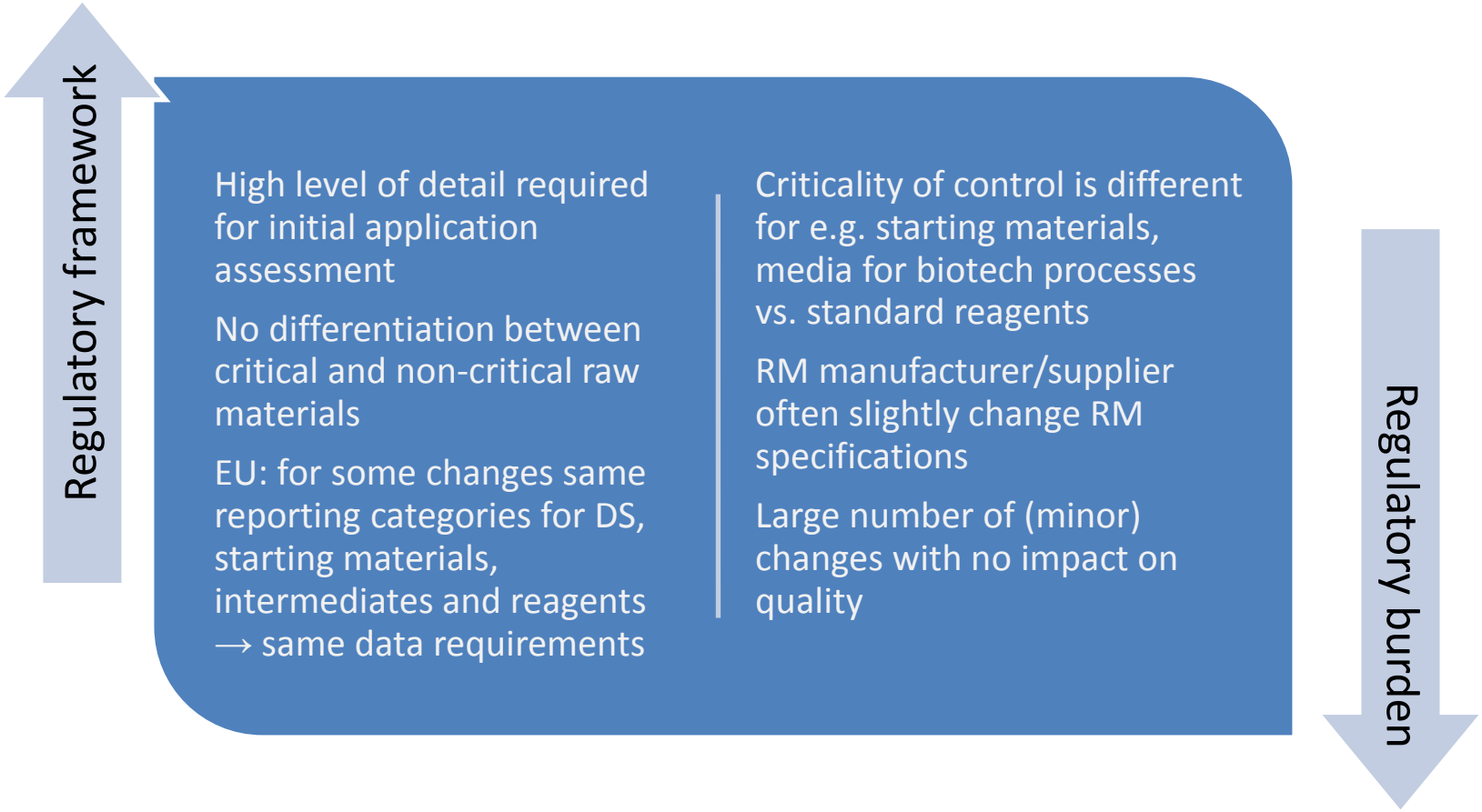
2nd Example

Case Study: Raw Materials

- CTD Module section 3.2.S.2.3
- Applicable to chemical entities as well as biologics
- Regulatory challenges

Current Challenges

Case Study: Raw Materials



- High administrative burden for HAs and MAHs due to submission of every (minor) change in the control of raw materials

Potential Resolution

Definition of “Established Conditions”

- By applying the tools of ICH Q12 regulatory binding information will be defined more clearly in the quality part of the dossier

Established Condition

Quality control of „critical“ raw materials

Definition based on risk assessment, process and product understanding

Regulatory binding

Change management via established reporting categoried or pre-approved PALMP

Non-Established Condition

Additional, supportive information

Quality control control of „non-critical“ raw materials

Definition based on risk assessment, process and product understanding

Not regulatory binding

Change management within PQS

No proactive reporting - update of dossier at e.g. next change in Established Condition

➢ Overall less regulatory burden for low impact changes in raw material controls

Changes in Specification for Raw Materials Defined as “Non-critical” → “Non-established Condition”

Change	Classification acc. to applied ICH Q12 tools	EU classification acc. to current procedure	US classification acc. to current procedure	Canadian classification acc. to current procedure	JP classification acc. to current procedure
1-Octanol Refractive index n 20/D 1.4291 – 1.4300 to 1.4285 – 1.4303 (slightly widened limit)	Managed within PQS	Type IB by default B.I.b.1 z) Change in specification parameters and/or limits of a reagent	Annual report	Notifiable change submission (annual report only if change within approved limits)	PAA
2-Butanol Deletion of test parameter „Odor – alcoholic, irritating“	Managed within PQS	Type IA B.I.b.1 d) Deletion of a non-significant specification parameter	Annual report	Annual report	PAA
2- Butanol Residue on evaporation NMT 10 mg to NMT 9 mg (tightening of limit)	Managed within PQS	Type IA B.I.b.1 b) Tightening of specification limits	Annual report	Annual report	Minor change notification

Changes in Specification for Raw Materials Defined as "Critical" → "Established Condition"

Change	Classification acc. to applied ICH Q12 tools	EU classification acc. to current procedure	US classification acc. to current procedure	Canadian classification acc. to current procedure	JP classification acc. to current procedure
Soy peptone Residue on ignition (sulfated ash) NMT 15% to NMT 14%	No change to current reporting categories	Type IA B.I.b.1 b) Tightening of specification limits	Annual report	Annual report	Minor change notification
Soy peptone Nitrogen content NLT 8.5% to NLT 8.0%	No change to current reporting categories	Type II B.I.b.1 g) Widening of approved specification limits for starting materials /intermediates which may have a significant impact in the overall quality *or* Type IB by default B.I.b.1 z) Change in specification parameters and/or limits of a reagent	CBE30 (in case animal derived)	Notifiable change submission (annual report only if change within approved limits)	PAA

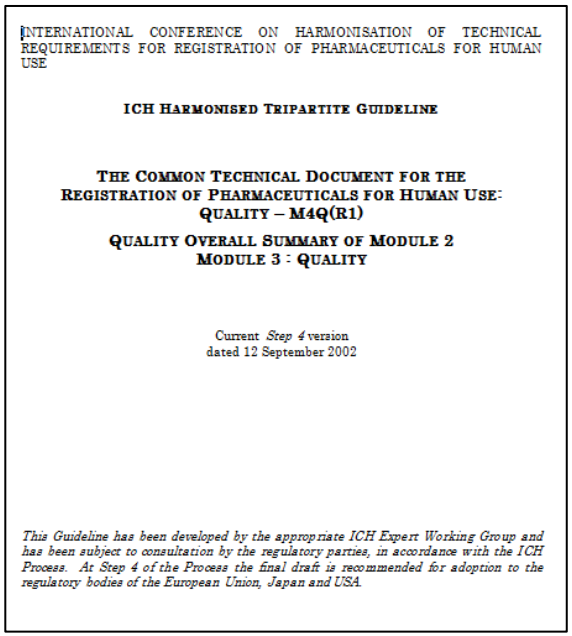
3rd Example

Case Study: Biological Drug Substance

- Established conditions:
  - identified and justified in QOS
  - Further supported by Module 3 data
- Change in EC:
  - Reported in accordance to variation classification guideline
- Change in non-EC:
  - Managed through lifecycle strategy, following risk based approach

Option on how to describe EC

CTD format



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY – M4Q(R1)

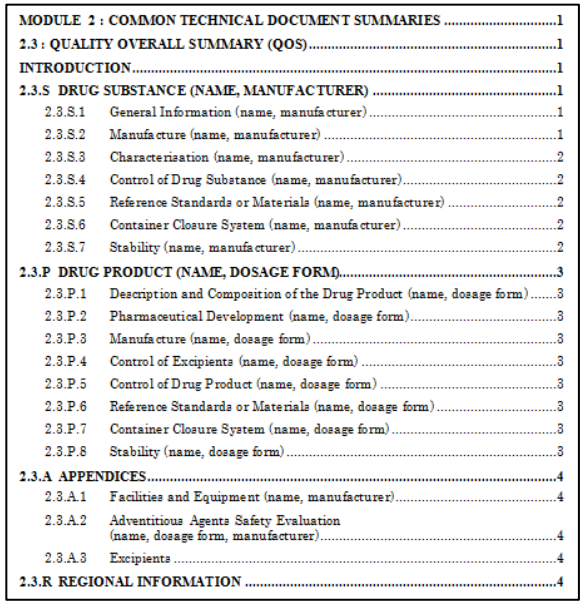
QUALITY OVERALL SUMMARY OF MODULE 2 MODULE 3 : QUALITY

Current *Step 4* version
dated 12 September 2002

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Module 2

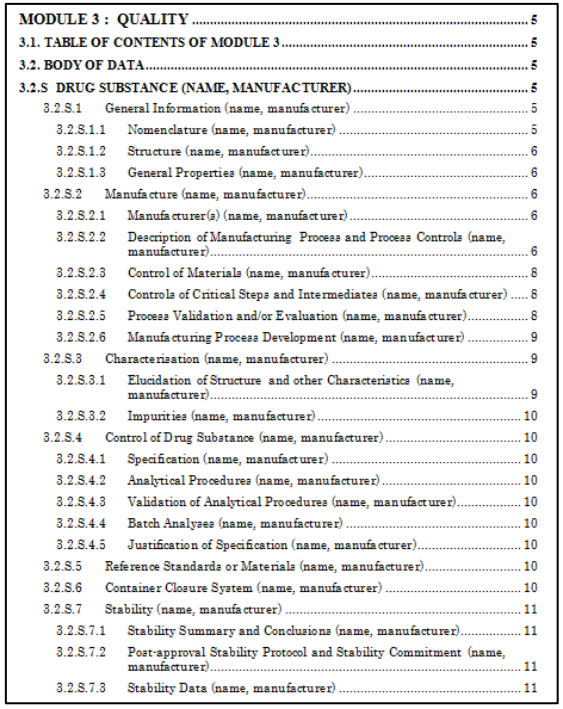
Describe and justify EC

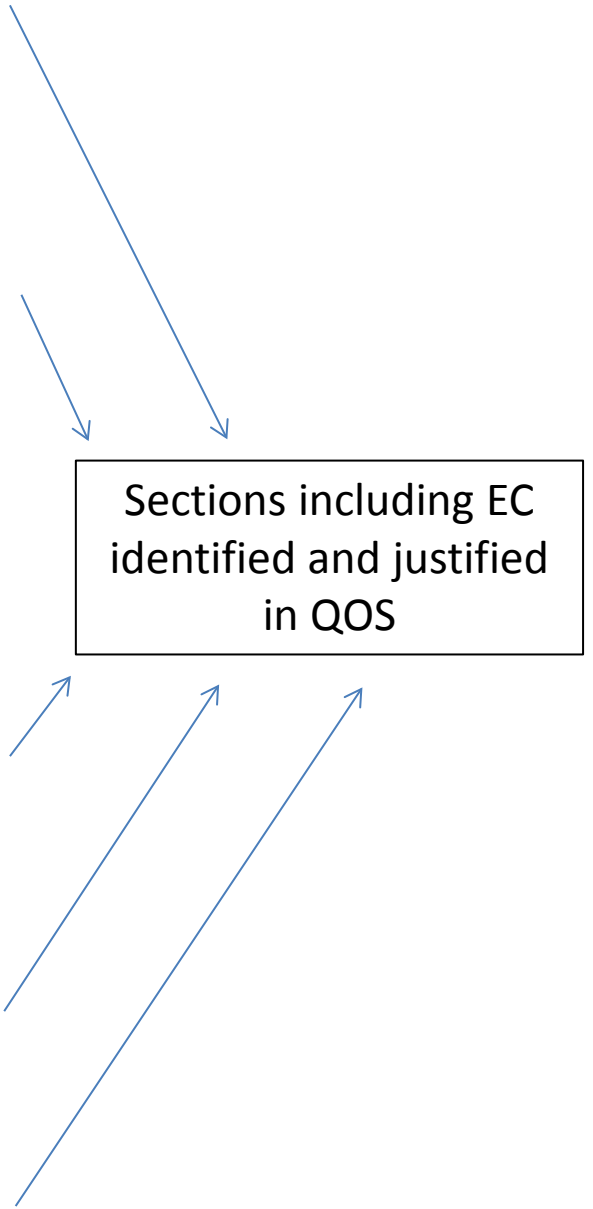


Module 3

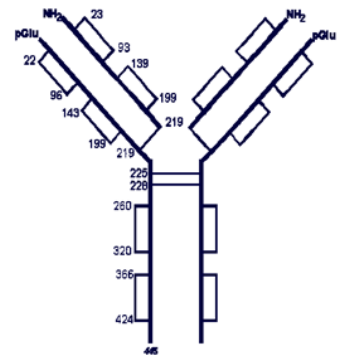
Detailed information

Consolidated EC & lifecycle strategy in R section

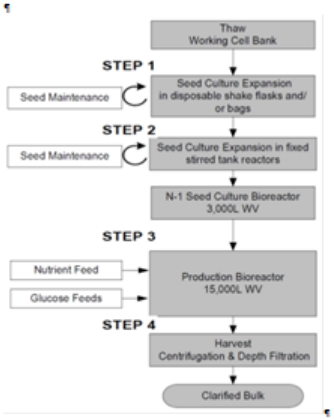




Consolidated list of Established Conditions in QOS appendix and 3.R

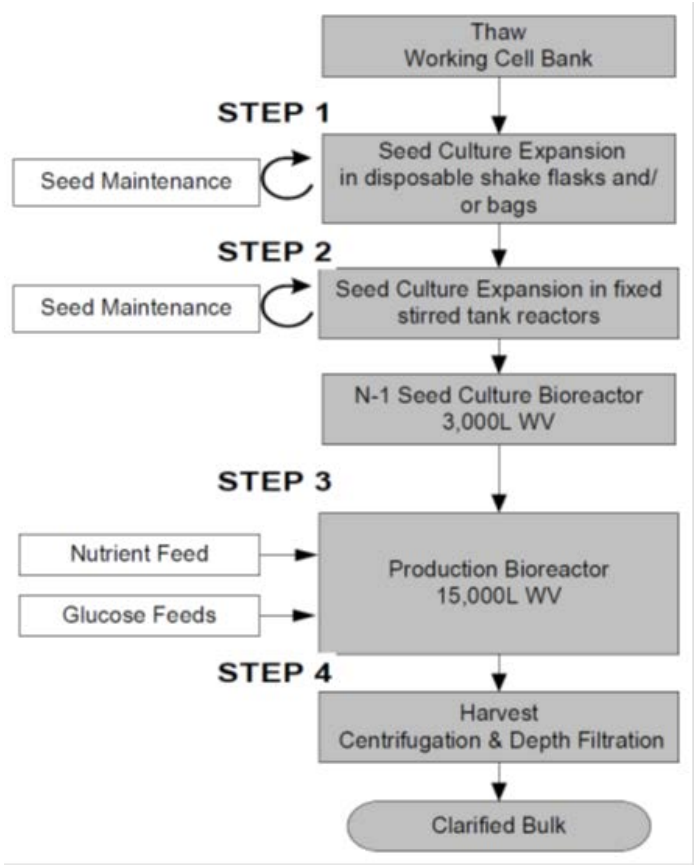
CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS
3.2.S	DRUG SUBSTANCE	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	Product Name: Pending International Nonproprietary Name (INN): mockestuzumab United States Adopted Name (USAN): Pending British Approved Name (BAN): Pending Japanese Accepted Name (JAN): Pending World Health Organization (WHO) Reference Number: Pending
3.2.S.1.2	Structure	**heavy chain** QVQLQESGPG LVRPSQTLSL TCTVSGFTFS DYYMSWVRQP PGRGLEVIGV 50 IDPENDDVQY APKFQGRVTM LVDTSKNQFS LRLSSVTAAD TAVYFCNSWG 100 SDFDHWGQGT TVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150 EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200 VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250 MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300 VVSVLTVLHQ DWLNGKEYMC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350 PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400 GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK 446 **light chain** DIQLTQSPSS LSASVGDRVT ITCRSSQTLV HTDGNTYLEW YQQKPGKAPK 50 LLIYKVSNRF SGVPSRFSGS GSGTDFTFTI SSLQPEDIAT YYCFQGSHLP 100 RTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150 VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200 VTHQGLSSPV TKSFNRGEC 219  http://www.abrf.org/jbt/articles/jbt0002/jbt0002.html

3.2.S.2.2	Description of Manufacturing Process and Process Controls	**CELL CULTURE PROCESS:** The A-MAb cell culture process uses a proprietary, chemically defined, basal medium formulation. The medium is essentially protein free as recombinant human insulin (1 mg/mL) is the only protein component that is added. The growth medium also contains 1 g/L Pluronic and 50 nM methotrexate, which is added up to the N-2 seed bioreactor. The N-1 and production bioreactor steps do not contain the methotrexate. In the seed expansion steps (Steps 1 and 2) one container of Working Cell Bank (WCB) is expanded to a volume of culture that contains enough cells to meet the target initial cell density of the production bioreactor (Step 3). For this, the seed cultures are expanded through multiple passages by increasing the volume and/or number of disposable culture vessels in Step 1 and by increasing the bioreactor volumes in Step 2. To provide flexibility in the manufacturing schedule, the seed cultures can be maintained for additional culture passages or used to generate additional inoculum trains. The production bioreactor (Step 3) is inoculated to achieve a range of initial Viable Cell Concentration (iVCC) and cultivated at controlled conditions for temperature, pH, and dissolved oxygen (DO). A bolus addition of nutrient feed, NF-1, is added at a defined time post inoculation and multiple discrete glucose feeds are used to maintain the glucose concentration at > 1.0 g/L. Antifoam C solution is added as required for foam control up to a maximum of 100 PPM. Viable cell concentration (VCC), culture viability and residual glucose concentration are monitored periodically starting at the day of inoculation.



Process Step	Analytical Procedure	Type of Limit	Limit
Step 1 and 2	Cell viability[a]	Action limit	
	Temperature	Action limit	
	pH	Action limit	
	Dissolved oxygen	Action limit	
	Inoculation density	Action limit	
	Culture duration	Action limit	
Step 3	Temperature	Acceptance criterion	32.0–39.0°C
	Nutriment feed	Action limit	
	pH	Acceptance criterion	6.5–7.5
	Culture duration	Acceptance criterion	14–21 days
	Dissolved oxygen	Acceptance criterion	15–80%
	Cell age at harvest	Acceptance criterion	210 PDL
	Bioburden (pre-filtration)	Acceptance criterion	≤ 10 CFU/10 mL
	Mycoplasma	Acceptance criterion	None detected
	General Viral Screening Assay Preharvest Cell Culture Fluids	Acceptance criterion	None detected
	Rodent Parvovirus of Cell Culture Fluids	Acceptance criterion	Negative
	Bioburden (post-filtration)	Action limit	
	Endotoxins	Action limit[c]	
	Endotoxins	Action limit[c]	
Step 4	Hold duration	Acceptance criterion	<120 hours at 2–8°C
	Endotoxins	Action limit[c]	
	Bioburden	Action limit[c]	

Control of CQA, IPC, CPP and non-CPP : EC



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	Hold duration	Acceptance criterion	<120hours at 2-8°C
	Endotoxins	Action limit	
	Bioburden	Action limit	

Non-CPP limits : Non-EC (limits presented in QOS and Module 3, but not included in consolidated EC table)

CPP limit: EC

CQA or IPC tested with acceptance limit (EC) at appropriate step

CQA or IPC tested with action limit (non-EC) at appropriate step

Principles included in lifecycle strategy

<table>
<tr><th rowspan="2">Risk Level</th><th rowspan="2">PQS</th><th rowspan="2">Reporting category</th><th colspan="2">Post-Approval Lifecycle Management (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>
</table>

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

Benefits

- Greater transparency within an organization and with regulatory authorities
- Greater focus on mitigation of high risk elements
- Opportunities to utilize more effective and efficient post-approval change management strategies
- Increased opportunities to provide supportive information
- Significant incentive to invest in the development of their pharmaceutical products and their pharmaceutical quality system (PQS)
- Facilitation of continual improvement and seeking out opportunities for technical advancement

Discussion Points

- An update to classification guide may be needed
  - To allow more use of Type IA (change of non-EC)
  - Simplify reporting of multiple non-EC changes within one Type IA (listing of changes)
- Are we currently adding too much detail in Module 3?
  - Is this an issue if we simplify and reduce administrative burden to report?
- How to increase consistency of EC across regions?
  - How much guidance within ICH Q12 possible?
  - More examples, lists, Q&As...?
  - Clarity in Risk Assessment for EC/non-EC cutoff?
- Introduction of EC concept could complicate dossier management?
  - Maintenance of non-ECs, transparency of EC/non-ECs in CTD
  - What is an acceptable time point for updating non-EC information, at next EC change vs. annual reporting?
- Grey zone between assessment and inspection
  - More change management oversight by Inspectors