ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Training Material
Module 3 – Established conditions (ECs)

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Established Conditions

Introduction and Rationale

- Established Conditions (ECs) are elements considered necessary to assure product quality
  - Elements can be: manufacturing process parameters, analytical parameters, acceptance criteria …
- Established Conditions are legally binding information
- As a consequence, any change to ECs necessitates a regulatory communication to the Regulatory authority

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Introduction and Rationale

- The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed
- All regulatory submissions contain a combination of ECs and supportive information
- Knowledge gained throughout the product lifecycle (including pharmaceutical development and characterisation of drug substance and drug product) is the basis for identifying the elements of CMC that are ECs and those elements which are supportive information

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Introduction and Rationale

- This guideline describes how ECs are identified as well as what information can be designated as supportive information that would not involve a regulatory communication, if changed. In addition, guidance is included for managing revisions of the ECs.
- Supportive information is not considered to be an EC
- Appendix 1 provides an overview of CTD sections that generally contain ECs

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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 is generally located

Sections where ECs are generally located

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- **CMC regulatory commitments** (e.g., stability, post-approval CMC commitment and other commitments)
  - Should not be confused with ECs
  - Considered supportive information
  - Changes to CMC commitments are managed according to existing regional regulations and guidance
  - If any, should be included in PLCM (see Chapter 5)

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ECs in a regulatory dossier:

- **MAH:**
  - Should consult regional legal frameworks, as they may define ECs with their reporting categories and/or the use of scientific risk-based approaches described in chapter 3
  - Should **clearly identify** the elements which they consider ECs and those which they consider to be supportive information
  - Supportive information is not considered to be ECs but is provided to share with regulators the development and manufacturing information at an appropriate level of detail
  - Should provide in the appropriate sections of CTD module 3 (see Appendix 1):
    - Rationales for the ECs, and, in certain cases, supportive information
    - Rationales for the associated reporting categories for changes to the ECs
- **Regulators:**
  - Assess and approve the ECs and associated reporting category, where appropriate

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Identification of ECs :

- Chapter outlines approaches to define ECs for manufacturing processes and analytical procedures
- Similar approach can be used to define other types of ECs (e.g., performance of the container closure system, device elements of drug-device combination products)
- Extent of ECs may vary based on:
  - The company's development approach
  - Product and process understanding
  - The potential risk to product quality

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ECs for manufacturing processes:

- Include individual unit operations and the sequence in the manufacturing process
- Comprise those **inputs** (e.g., process parameters, material attributes) and **outputs** (may include in-process controls) **necessary to assure product quality**
- Should consider the overall control strategy

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ECs for manufacturing processes (cont.):

- Process parameters (critical and others) that need to be controlled to ensure that a product of required quality will be produced should be considered ECs
- Identification of ECs draws upon:
  - An initial risk assessment
  - Prior knowledge
  - Application of knowledge gained from executed studies
  - A criticality assessment that determines the level of impact that a process parameter could have on product quality
    - Should account for severity of harm (ref ICH Q9) and whether the ranges studied sufficiently account for the expected variability in the EC

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Identification of ECs for manufacturing processes:

- Rationales for the ECs, and, in certain cases, elements that are not ECs should be provided, taking into account the development approach
- **Manufacturing processes can be divided in different approaches:**
  - **<u>Parameter-based approaches</u>, including:**
    - A **minimal approach,** with a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process tests)
    - An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate

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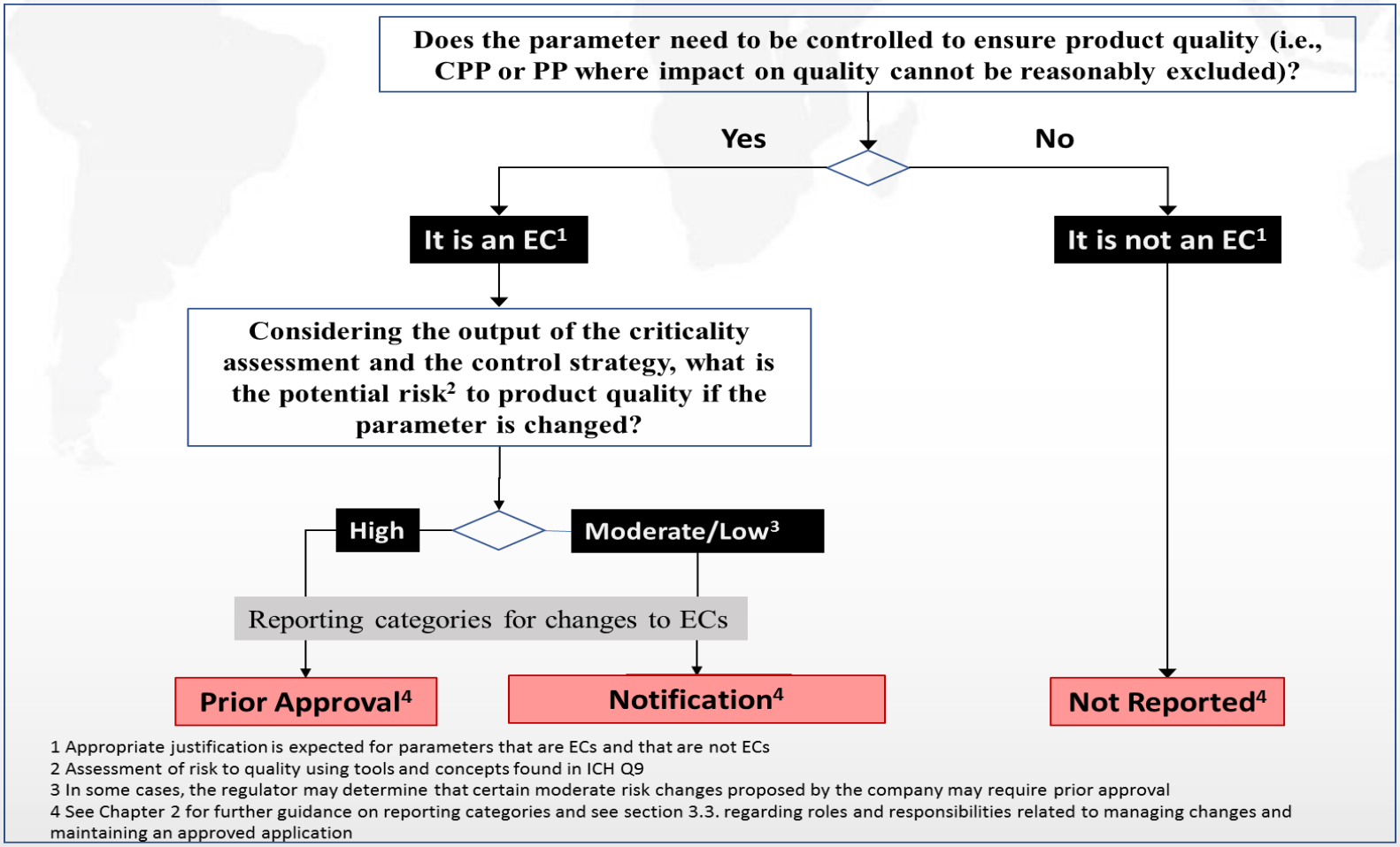
Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters following parameter-based approaches



1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 See Chapter 2 for further guidance on reporting categories and see section 3.3. regarding roles and responsibilities related to managing changes and maintaining an approved application

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Established Conditions

Identification of ECs for manufacturing processes:

- **Performance-based approach**, ECs could be primarily focused on control of process outputs (e.g., attributes, measurements, responses) rather than process inputs (e.g., process parameters and material attributes). This is enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., models, Process Analytical Technology (PAT)).

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Identification of ECs for <u>analytical procedures</u>

- Include elements which assure performance of the procedure
- Extent of ECs and reporting categories can vary based on the degree of understanding of the relationship between method parameters and method performance, method complexity, and control strategy
- Different approaches can be used to identify ECs:
  - When more limited development studies have been conducted this may result in a narrow operating window to ensure method performance. In such cases ECs may be more extensive with fixed and/or tight conditions.
  - Enhanced understanding can lead to a wider operating window that ensures method performance, where ECs can be reduced and focused on method performance (e.g., method parameters acceptable ranges rather than set points, performance criteria)

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Revision of ECs

- May be necessary to change approved ECs as a result of knowledge gained during the product lifecycle (e.g., manufacturing experience, introduction of new technologies, or changes in the control strategy)
- ECs may be revised through:
  - Appropriate post-approval regulatory submission describing and justifying the change
  - Submission of a PACMP, in the original MAA or as part of a post-approval submission, describing and justifying a revision to ECs
  - Use of an approved post-approval regulatory commitment, as appropriate

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Roles and responsibilities - Maintenance

- Management and maintenance of the approved marketing authorisation is the responsibility of the MAH
- There is a joint responsibility to share and utilise information between the MAH and any manufacturing organisations
- This includes any referenced submission (e.g., Type II Drug Master File, Active Substance Master File)

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ANNEX I: Illustrative Examples

- The examples provided are mock examples for illustrative purposes.
- They only suggest how the tools described in chapters 3, 4, and 5 could be applied, and should not be used as a template or the sole basis for a regulatory submission
- The reporting categories may differ across regions depending on regional legislation, the nature of the product, and the MAH's demonstrated understanding of the product, process, and analytical procedure

ICH Terminology	**Regional Terminology**
Prior Approval (PA)	PAS, Type II, PCA, etc.
Notification Moderate (NM)	CBE 30, Type IB, MCN, etc.
Notification Low (NL)	CBE 0, AR, Type IA, MCN, etc.
Not Reported (NR)	

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ANNEX IA/B: Identification of ECs for Manufacturing Process

- Illustrate how the development approaches could be applied
- MAAs could consist of a combination of these approaches
- These examples demonstrate that increased knowledge and understanding lead to reduction of uncertainty and improved management of risk. As a result, ECs could become less extensive and reporting categories more flexible

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ANNEX IA/B: Identification of EC for Manufacturing Process

- For example:
  - Enhanced knowledge may lead to a reduction in uncertainty, demonstrating that a material attribute or process parameter initially considered potentially critical in a minimal approach is not actually critical, i.e., does not have an impact on product quality and, therefore, is not an EC
  - Risk management activities could lead to different reporting categories e.g., a change from prior approval to a notification for a change to a CPP
  - Where the performance-based approach is used,
    - Some process parameters may not be classified as ECs due to assurance of quality being provided by online monitoring
    - In this circumstance, the typical operating conditions for process parameters are provided as supportive information. During manufacture, the process parameters may be adjusted to deliver the expected outcome
    - The risks related to the in-line PAT (Process Analytical Technology) tests, e.g., NIR, should be appropriately managed throughout the lifecycle. In-line PAT tests used for quality control are considered ECs

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Annex IA: Chemical Medicinal Product

- **Powder Blending Unit Operation**

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input Materials	API PSD	20-50 um Tighten (NL) Widen (PA)	5-200 um Tighten (NL) Widen (NM)	5-200 um Tighten (NL) Widen (NM)
	API Moisture	<1.0% (NM)	(NR)	(NR)
	Excipients #1-3 Specification	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial
Equipment and Parameters	Operating Principle	Diffusion Mixing (PA)	Diffusion Mixing (PA)	Diffusion Mixing (PA)
	Equipment type	V-blender (NM)	V-blender (NL)	(NR)
	Scale	200 kg Increase >10x (NM)	200 kg Increase >10x (NL)	200-600 kg Increase >10x (NL)
	Blend Speed	20 rpm CPP (NM)	Design Space consisting of Blend speed: 10-20 rpm Blend time 15-25 minutes CPP (NM)	15 rpm CPP (NR)
	Blend Time	20 minutes CPP (NM)		20 minutes CPP (NR)
Output Performance Measure	Homogeneity method principle	HPLC (NM)	Not Tested	NIR online analyser (PA)
	Homogeneity acceptance criteria	<5% RSD IPC (NM)	Not Tested	<5% RSD IPC (NM)

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The impact of PSD of API on blend homogeneity and dissolution was well understood. DoE studied PSD within 5-200 um. API PSD was confirmed as having no impact on dissolution. The proposed control range for PSD of 5-200 um maintained adequate homogeneity. Compared to the minimal approach, a wider PSD range is the EC.

It is assumed that a performance-based approach is developed on the basis of an enhanced approach. The same relationships between material attributes, equipment, process parameters, and product quality as outlined above for the enhanced parameter-based approach apply.

However, some of the ECs are different as a result of a performance-based control strategy.

The impact of particle size distribution (PSD) of API on blend homogeneity and dissolution could not be excluded during development. PSD was not studied outside the range of 20-50 um; this range is an EC.

...ding Unit Opera...n

	Parameter	Accep... ranges and reporting categories (White boxes... ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	**Enha...ced Parameter-Based Approach**	**Performanc...-Based Approach**
Input Materials	API PSD	20-50 um Tighten (NL) Widen (PA)	5-200 um Tighten (NL) Widen (NM)	5-200 um Tighten (NL) Widen (NM)
	API Moisture	...2.0% (NM)	(N...)	(NR)
	Excipients #1-3 Specification	Pharmacopoeial	P...acopoeial	Pharmacopoeial
...ers	Operating Principle	Diffusion Mixing (PA)	...on Mixing (PA)	Diffusion Mixing (PA)
			...NL)	(NR)
			...x (NL)	200-600 kg Increase >10x (NL)
			...nsisting of ...0-20 rpm ...5 minutes ...M)	15 rpm CPP (NR) 20 minutes CPP (NR)
			...ed	NIR online analyser (PA)
Pe...			...ed	<5% RSD IPC (NM)

The impact of a change outside this range on blend homogeneity and dissolution is unknown, and the risk to product quality is potentially high. As a result, any future change outside the range would be reported as PA, supported by appropriate studies and data. Changes to tighten the EC range based on knowledge gained during the commercial phase (e.g., better process control observed at tighter ranges) are considered low risk and reported as NL.

Enhanced knowledge gained from studying a wider range led to a reduction in uncertainty regarding the impact of changing the EC and a better understanding of the risk related to homogeneity. A change to increase the range beyond that studied is considered a moderate risk and reported as NM. Changes to tighten the EC range based on knowledge gained during the commercial phase (e.g., better process control observed at tighter ranges) are considered low risk and reported as NL.

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Product

The impact of API moisture content on blend flowability, which impacts content uniformity, could not be reasonably excluded during development and has not been further studied in detail. The set point value is based on a limited amount of development and manufacturing data. API moisture content is therefore considered an EC.

API Moisture has been studied in detail and demonstrated to have no impact on flowability and content uniformity within the ranges explored. API moisture content is not an EC.

A change in this EC is considered moderate risk since downstream processing involves a power-assisted feeder in the tablet press which mitigates the risk of content uniformity failure. The change is reported as NM.

		(W…	…le ranges and reporting categories …are ECs and grey boxes are not ECs.)	
		Minimal Parameter-Based Approach	**…anced Parameter-Based Approach**	**Performance-Based Approach**
Input Materials	API PSD	20-50 um Tighten (NL) Widen (PA)	5-200 um Tighten (NL) Widen (NM)	5-200 um Tighten (NL) Widen (NM)
	API Moisture	<1.0% (NM)	(NR)	(NR)
	Excipients #1-3 Specification	…rmacopoeial	…Pharmacopoeial	Pharmacopoeial
…ers	Operating Principle	Diffusion Mixing (PA)	Diffusion Mixing (PA)	Diffusion Mixing (PA)
		V-blender (NM)	V-blender (NL)	(NR)
		200 kg Increase >10x (NM)	200 kg Increase >10x (NL)	200-600 kg Increase >10x (NL)
		20 rpm CPP (NM)	Design Space consisting of Blend speed: 10-20 rpm Blend time 15-25 minutes CPP (NM)	15 rpm CPP (NR)
E…	Blend Time	20 minutes CPP (NM)		20 minutes CPP (NR)
Output Performance Measure	Homogeneity method principle	HPLC (NM)	Not Tested	NIR online analyser (PA)
	Homogeneity acceptance criteria	<5% RSD IPC (NM)	Not Tested	<5% RSD IPC (NM)

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Annex IA: Chemical Medicinal Product

- **Powder Blendi**

The impact of different equipment types within the same operating principle on blend quality was studied and no significant impact was observed. Due to this enhanced knowledge, the EC is focused on blending principle, rather than specific type of equipment.

Only one type of blending equipment (V-blender) was considered in development. Due to the limited knowledge, blender type is considered an EC.

A change in this EC is considered moderate risk and therefore is reported as NM.

Enhanced understanding regarding the impact of different blending equipment reduced uncertainty regarding the impact of changing blender type on blend homogeneity. A change is considered low risk and is reported as NL.

	Parameter		and reporting categories nd grey boxes are not ECs.)	
			arameter-Based proach	**Performance-Based Approach**
		20-50 um Tighten (NL) Widen (PA)	5-200 um Tighten (NL) Widen (NM)	5-200 um Tighten (NL) Widen (NM)
		<1.0% (NM)	(NR)	(NR)
	Excipients #1-3 Sp	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial
ent and Parameters	Operating Principle	Diffusion Mixing (PA)	iffusion Mixing (PA)	Diffusion Mixing (PA)
	Equipment type	V-blender (NM)	V-blender (NL)	(NR)
	Scale	Increase >10x (NM)	>10x (NL)	200-600 kg Increase >10x (NL)
	Blend Speed	20 rpm	ace consisting of -20 rpm minutes	15 rpm CPP (NR)
				20 minutes CPP (NR)
Output Performanc Measure	Homogeneity method principle		d	NIR online analyser (PA)
	Homogeneity acceptance criteria		d	<5% RSD IPC (NM)

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Enhanced understanding of blending parameter variability on homogeneity allows ranges for blend speed and blend time (i.e., design space established across these two parameters) that maintain adequate product quality and offer more operational flexibility than setpoints. The ranges studied for both parameters are considered to be ECs. The EC for blend homogeneity testing seen in the minimal approach is not an EC in this approach as a result of enhanced knowledge about the risk of blend segregation gained through homogeneity assessment and stratified sampling during development.

Using a performance-based approach (online NIR analyser) in the control strategy allows homogeneity confirmation in real-time. Use of the NIR analyser with feedback to blending operating parameters minimizes the need to rely on blend speed and time to ensure blend homogeneity. Therefore, these CPPs are not ECs. The NIR method and blend homogeneity specification are ECs. Enhanced understanding of blending and output measurement allows for a l operating conditions for blend speed and time described in Module 3.2 is supportive information and monitored to assure performance.

Blend speeds and times utilised have not been studied in detail beyond the set points described. The set point values are based on a limited amount of development and manufacturing data. Therefore, the set points and the homogeneity specification are considered ECs.

		Pharmacopoeial	Pharmacopoeial	Pha al
Equipment and Parameters	Operating Principle	Diffusion Mixing (PA)	Diffusion Mixing (PA)	Diffus g (PA)
	Equipment type	V-blender (NM)	V-blender (NL)	R)
	Scale	200 kg crease >10x (NM)	200 kg Inc ease >10x (NL)	0-600 kg Inc ase >10x (NL)
	Blend Speed	20 rpm CPP (NM)	Design Space consisting of Blend speed: 10-20 rpm Blend time 15-25 minutes CPP (NM)	15 rpm CPP (NR)
	Blend Time	20 minutes CPP (NM)		20 minutes CPP (NR)
Output Performance Measure	Homogeneity method principle	HPLC (NM)	Not Tested	NIR online analyser (PA)
	Homogeneity acceptance criteria	<5% RSD IPC (NM)	t Tested	<5% RSD IPC (NM)

When assessing the risk of changing set points for these parameters, it was demonstrated that detection mechanisms are sufficient to capture disturbances in homogeneity. Therefore, changes in these process parameters and specification are reported as NM.

Changes outside of the design space established for blend speed and time are considered moderate risk and reported as NM.

ICH Q12 – Module 3

ANNEX IB – Production Culture

Unit Operation	Input/Output	Acceptable ranges and reporting categories (White boxes are ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	Enhanced Parameter-Based Approach	Performance-Based Approach
Input	Inoculum Cell Density	4.0-6.0 x10^5 cells/mL PP (NM)	2.0-8.0 x10^5 cells/mL PP (NR)	Controlled by MSPC PP (NR)
	Temperature	37.0 – 38.0°C CPP (PA)	36.0 – 39.0°C CPP (NM)	Controlled by MSPC CPP (NR)
	Input Y	### CPP (PA)	### CPP (PA)	Controlled by MSPC CPP (NR)
Output	Viability at harvest	≥ 70% IPC (NM)	≥ 50% (Monitored) (NR)	≥ 50% IPC in-line automatic counting (NM)
	Titre	≥ 4.0 g/L IPC (NM)	≥ 4.0 g/L Predicted through process model (NR)	≥ 4.0 g/L IPC in-line HPLC (NM)
	G0-F oligosaccharide (CQA)	Included in release specification	Included in release specification	2.0-5.0% IPC in-line UPLC UV/MS (CQA not included in specification) (PA)
	Bioburden	## CFU/mL IPC (PA)	## CFU/mL IPC (PA)	## CFU/mL IPC (PA)

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ANNEX IB – oduction Culture

Process development is minimal. Due to the lack of supporting justification, most parameters are considered ECs and ranges are narrow.

A change of inoculum cell density is medium risk taking into account that control of viability and titre takes place for this step. The change is reported as NM.

Considering that the impact of temperature and Input Y was not studied, and that literature suggests potential impact of these parameters on CQA, changes to these parameters are considered high risk. These changes are reported as PA.

The bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.
A change in the bioburden test or results is considered high risk considering the severity of microbial contamination at that stage. The change is reported as PA.

		Acceptable ranges and reporting categories (White boxes are ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	Enhanced Parameter-Based Approach	Performance-Based Approach
Input	Inoculum Cell Density	4.0-6.0 x10^5 cells/mL PP (NM)	2.0-8.0 x10^5 cells/mL PP	Controlled by MSPC PP NR)
Input	Temperature	37.0 – 38.0°C CPP (PA)		d by MSPC PP NR)
Input	Input Y	### CPP (PA)	(PA)	d by MSPC PP (NR)
Output	Viability at harvest	≥ 70% IPC (NM)	≥ 50% (Monitored) (NR)	≥ 50% IPC in-line automatic counting (NM)
Output	Titre	≥ 4.0 g/L IPC (NM)	≥ 4.0 g/L Pre	≥ 4.0 g/L ine HPLC M)
Output	G0-F oligosaccharide (CQA)	Included in release specification	Includ	5.0% UPLC UV/MS ed in specification) PA)
Output	Bioburden	## CFU/mL IPC (PA)	(PA)	FU/mL PC (PA)

ICH Q12 – Module 3

ANNEX IB – Production Culture

Unit Operation	Input/Output	Minimal Parameter-Based Approach	Enhanced Parameter-Based Approach	
		Acceptable ranges and report		
Input	Inoculum Cell Density	4.0-6.0 x10^5 cells/mL PP (NM)	2.0-8.0 x10^5 cells/mL PP (NR)	(NR)
Input	Temperature	37.0 – 38.0°C CPP (PA)	36.0 – 39.0°C CPP (NM)	Controlled by MSPC
Input	Input Y	### CPP (PA)	### CPP (PA)	
Output	Viability at harvest		≥ 50% (Monitored) (NR)	
Output	Titre	IPC (NM)	≥ 4.0 g/L Predicted through process model (NR)	(NM)
Output	G0-F oligosaccharide (CQA)	Included in release specification	Included in release specificatio	
Output	Bioburden	## CFU/mL IPC (PA)	## CFU/mL IPC (PA)	

Inoculum cell density does not impact CQAs and is not considered an EC.

CQAs have been identified and DoE studies for selected CQAs show that: Temperature and Input Y can impact the CQA G0-F at different magnitude (high impact for Input Y and low to moderate impact for temperature); these are considered ECs.

A change in temperature is considered moderate risk given the low to moderate impact on G0-F. The change is reported as NM.
A change to Input Y is considered high risk because Input Y has been shown to have a high impact on G0-F. The change is reported as PA.

Titre is predicted through a process model. With this knowledge, cell viability at harvest and titre are not considered ECs.

Linkage studies demonstrate the lack of impact of viability at harvest on CQAs when reduced to 50%. Process characterisation studies demonstrate that viability at harvest is maintained above 70% when the CPPs (temperature and Input Y) are maintained within the proposed ranges. Viability at harvest is not considered an EC.

Bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.
A change in bioburden test or limit is considered high risk given the severity of microbial contamination at that stage. The change is reported as PA.

ICH Q12 – Module 3

ANNEX IB – Prod

Unit Operation	Input/Output			egories e not ECs)
		Minim		Performance-Based Approach
Input	Inoculum Cell Density			Controlled by MSPC PP (NR)
	Temperature	CPP (PA)	CPP (NM)	Controlled by MSPC CPP (NR)
	Input Y	###	###	Controlled by MSPC CPP (NR)
Output	Viability at harvest			≥ 50% IPC in-line automatic counting (NM)
	Titre	≥ 4.0 g/L IPC (NM)	Predicted through process model (NR)	≥ 4.0 g/L IPC in-line HPLC (NM)
	G0-F oligosaccharide (CQA)	Inc	n	2.0-5.0% IPC in-line UPLC UV/MS (CQA not included in specification) (PA)
	Bioburden			## CFU/mL IPC (PA)

In-line tests are used to control outputs in real time. In-line tests are considered to be ECs.
Relevant inputs are monitored through Multivariate Statistical Process Control (MSPC) defining a process signature that is not considered an EC.
Inputs are adjusted in real time based on a model accounting for the in-line measurements of outputs.
Inputs are not considered ECs as the outputs of the step (titre and G0-F level) are assured by in-line testing.

Changes of viability and titre tests are assessed as moderate risk since CQAs are not directly impacted. These changes are reported as NM.
A change to G0-F test or ranges is assessed as high risk because this attribute is not tested in the drug substance specification. The change is reported as PA.

The bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.
A change in the bioburden test or results is considered high risk given the severity of microbial contamination at that stage. The change is reported as PA.

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ANNEX IB – Anion Exchange Chromatography

Unit Operation	Input/Output	Acceptable ranges and reporting categories (White boxes are ECs and **grey boxes are not ECs**.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input	Feedstock Conductivity	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(NR)**
	Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA >5.5)** **(NM <4.5)**	4.0-6.0 CPP **(NR)**
	Resin age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**	≤ 100 cycles, ≤ 3 yrs PP **(NL)**	≤ 100 cycles, ≤ 3 yrs PP **(NR)**
	Input Z	CPP **(PA)**	CPP **(NM)**	CPP **(NR)**
Output	Bioburden	≤ 10 CFU/10 mL IPC **(NL)**	≤ 10 CFU/10 mL (Monitored) **(NR)**	≤ 10 CFU/10 mL (Monitored) **(NR)**
	Endotoxin	≤ 5 EU/mL IPC **(NL)**	≤ 5 EU/mL (Monitored) **(NR)**	≤ 5 EU/mL (Monitored) **(NR)**
	HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC in-line UPLC UV/MS **(PA)**
	CQA X	*Tested in DS specification*	*Predicted through process model*	In-line IPC **(PA)**

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ANNEX IB – Anion Exchan

Process development is minimal. The impact of inputs on CQAs has not been studied. Due to the lack of knowledge, all inputs are considered to be ECs as they can potentially have impact on CQAs.
Considering the lack of understanding of the impact of inputs (feedstock conductivity and pH, resin age, and Input Z) on CQAs, changes to these inputs are considered high risk. These changes are reported as PA.

Output (i.e., bioburden and endotoxin) are considered ECs as they have potential impact on product quality.
HCP and CQA X are part of DS specifications, and are not tested at this stage. HCP and CQA X are not considered ECs for this step.
Changes to bioburden and endotoxin limits are considered low risk as these are further tested in subsequent steps. These changes are reported as NL.

Unit Operation	Input/Output	Acceptable ranges an… gories (White boxes are ECs… s are not ECs.)		
		Minimal Parameter-Based Approach	**Enhan… eter-Based Approach**	**Performance-Based Approach**
Input	Feedstock Conductivity	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(NR)**
	Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA** >5.5**)**	4.0-6.0
	Resin age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**		
	Input Z	CPP **(PA)**		
Output	Bioburden	≤ 10 CFU/10 mL IPC **(NL)**	…/10 mL (Monitored) **(NR)**	≤ 10 CFU/10 mL (Monitored) **(NR)**
	Endotoxin	≤ 5 EU/mL IPC **(NL)**	≤ 5 EU/mL (Monitored) **(NR)**	≤ 5 EU/mL (Monitored) **(NR)**
	HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC in-line UPLC UV/MS **(PA)**
	CQA X	*Tested in DS specification*	*Predicted through process model*	In-line IPC **(PA)**

ICH Q12 – Module 3

ANNEX IB – Anion Exchange Chrom

Resin age has been studied up to 100 cycles and up to 3 years, and did not show any impact on CQAs. Impact on CQAs cannot be excluded when the range is further extended. Resin age is considered an EC.
Extension of resin age is considered low risk taking into account the ongoing validation protocol which includes time points beyond the claim of 100 cycles/3 years. This change is reported as NL.

Studies on scale-down models demonstrate that feedstock conductivity and pH, and Input Z can impact CQAs (HCP and CQA X) and are considered CPPs.
Change to feedstock conductivity is considered high risk because it can impact HCP and CQA X. This change is reported as PA.
Change to feedstock pH is considered high risk when increased beyond 5.5, and is reported as PA. This change is considered moderate risk below 4.5, and is reported as NM.

Bioburden and endotoxin are not considered ECs for this step, taking into consideration testing of the attributes in several of the following process steps, but are monitored.

HCP and CQA X are not considered ECs as multivariate studies demonstrated that they remain within their acceptance criteria when feedstock conductivity and pH, and Input Z are maintained within the studied ranges.
A change in Input Z has a moderate impact on HCP and CQA X. This change is reported as NM.

Unit Operation	Input/Output	eptable ranges and reporting catego boxes are ECs and **grey boxes are no**	Enhanced Parameter-Based Appr	
Input	Feedstock Conductivity		6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(NR)**
	Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA >5.5)** **(NM <4.5)**	4.0-6.0 CPP **(NR)**
	Resin age		≤ 100 cycles, ≤ 3 yrs PP **(NL)**	
	Input Z		CPP **(NM)**	
Output	Bioburden	≤ 10 CFU/10 m IPC **(NL)**	≤ 10 CFU/10 mL (Monitored) **(NR)**	
	Endotoxin	≤ 5 EU/mL IPC **(NL)**	≤ 5 EU/mL (Monitored) **(NR)**	(Monitored) **(NR)**
	HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC in-line UPLC UV/MS **(PA)**
	CQA X	*Tested in DS specification*	*Predicted through process model*	In-line IPC **(PA)**

ICH Q12 – Module 3

ANNEX IB – Anion Exchange Chromatography

Unit Operation	Input/Output	Acceptable ranges and reporting categories (White boxes are ECs and **grey boxes are not ECs**.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input	Feedstock Conductivity	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(NR)**
	Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA >5.5)** **(NM <4.5)**	4.0-6.0 CPP **(NR)**
	Resin age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**	≤ 100 cycles, ≤ 3 yrs	≤ 100 cycles, ≤ 3 yrs PP **(NR)**
	Input Z			CPP **(NR)**
Output	Bioburden			≤ 10 CFU/10 mL (Monitored) **(NR)**
	Endotoxin			≤ 5 EU/mL (Monitored) **(NR)**
	HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC in-line UPLC UV/MS **(PA)**
	CQA X	*Tested in DS specification*	*Predicted through process model*	In-line IPC **(PA)**

In-line tests are used to control outputs (i.e., HCP and CQA X) in real time. Inputs are adjusted in real time based on a model accounting for the in-line measurements of outputs. In-line tests are considered ECs.

The control strategy relies on the in-line tests to ensure that HCP and CQA X remain within acceptable ranges. Changes to these in-line tests or ranges are assessed as high risk and are reported as PA.

ICH Q12 – Module 3

Annex IC: Identification of Established Conditions for Analytical Procedures

- The following is an example to illustrate how ECs could be presented for an analytical procedure, acceptance criteria, and testing facility, along with their suggested reporting categories
- This example considers an analytical procedure (capillary electrophoresis) for a biological drug substance (non-glycosylated recombinant protein) referred to as *Illustropin*, using a minimal development approach validated in accordance with ICH Q2
- To better illustrate the example, the change categories, conditions, and data requirements are according to the WHO Guidelines on procedures for changes to approved biotherapeutic products. The actual reporting categories and data requirements may differ for a particular product and by region

Annex IC: Identification of Established Conditions for Analytical Procedures

- The information summarized in the table below provides guidance on:
  - The conditions to be fulfilled for a given change to be classified as moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is assessed and if appropriate the next higher reporting category may be used– for example, if any conditions recommended for a low-quality change are not fulfilled, the change may be considered a moderate quality change)
  - Adequate scientific data and justification should be provided to support a given change

	All information listed are ECs	Reporting (as example referring to WHO)
Method	Measurement of Purity: Determination of charged variants of active substance by capillary electrophoresis (Non-reduced) and corrected relative area %.	**NM** *Conditions: None* *Supporting Data:1-5*
Test Solutions	Illustropin Reference Standard: Concentration of test solutions and reference standards: 1 mg/ml Illustropin in water	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
Equipment	Suitable Capillary Electrophoresis system and Suitable spectrophotometric detector. Capillary: Material: uncoated fused silica capillary diameter Ø = 50 µm. Size: effective length = at least 70 cm	
Condition	**- Chemicals (Pharmacopoeial quality):** Separation buffer (CZE): 13.2 g/l solution of ammonium phosphate adjusted to pH 6.0 with phosphoric acid filtered; Rinsing Agents: 1M sodium Hydroxide, water, 0.1M sodium Hydroxide **- Instrument parameters:** Detection: 200 nm (UV); Electric Field Strength: 217 V/cm; Temperature: 30 °C **- Sample Analysis:** Injection test solution (a) and the reference solution; injection for at least 3 s then CZE buffer injection for 1 s. Separation: Separation buffer at both ends of the capillary; Sample storage at 4 °C during analysis. **- System conditioning:** Preconditioning: At least 20 min 1M Sodium Hydroxide; At least 10 min water; At least 20 min separation buffer Between-run rinsing: 0.1M Sodium hydroxide at least 2 min; Separation buffer at least 6 min	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
System Suitability	Specificity: the electropherogram obtained is similar to the electropherogram of Illustropin supplied with Illustropin reference; 2 peaks (I1, I2) eluting prior to the principal peak and at least 2 peaks (I3, I4) eluting after the principal peak are clearly visible.	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
Acceptance Criteria	Deamidated forms: maximum 5.0 per cent; Any other impurity: for each impurity, maximum 2.0 per cent; Total: maximum 10.0 per cent.	Widening: **NM** *Conditions: None* *Supporting Data:1, 5, 6* Narrowing: **NL** *Conditions: 2, 7* *Supporting Data:1*
Site Transfer		**NM** *Conditions None* *Supporting Data: 7 & 8* **NL** *Conditions 4-6* *Supporting Data: 7 & 8*

ICH Q12 – Module 3

Conditions and Supporting Data

Conditions that must be met in order to implement the change at the corresponding reporting category:
1. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability. 2. The method of analysis is the same and is based on the same analytical technique or principle (for example, change in column length or temperature, but not a different type of column or method) and no new impurities are detected 3. The modified analytical procedure maintains or improves performance parameters of the method 4. The change does not concern potency-testing 5. No changes made to the test method 6. The transfer is within a facility approved in the current marketing authorization for performance of other tests 7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits)
Supporting Data (Documentation to be submitted):
1. Updated drug substance specifications. 2. Copies or summaries of analytical procedures if new analytical procedures are used. 3. Validation/qualification results if new analytical procedures are used. 4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent. 5. Justification for the proposed drug substance specification (for example, tests, acceptance criteria or analytical procedures). 6. Documented evidence that consistency of quality is maintained. 7. Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 8. Evidence that the new company/facility is GMP-compliant.