Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Product and Process Characterization – The Data Sources for an Adequate Control Strategy

www.pei.de

Session 2: Antibody and Recombinant Protein Product

CMC Strategy Forum China 2021

23-24 April 2021

Steffen Gross,
Head Section monoclonal - and polyclonal Antibodies
Paul-Ehrlich-Institut
Germany

Outline

- ICH Q8-Q14, the new framework for product/process development
- QbD/Designs Space (Process and Testing)
- CQA identification
- Process validation (biological active substance)
- Control Strategy and RTRT

The view expressed in the following is the ones of the presenter and does not necessary express the view of either the CHMP, BWP, EDQM or the Paul-Ehrlich-Institute.

Aim of QbD

- Desired State
  - *“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight” 1*
  - *“…is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors“ 2*

1 US Food and Drug Administration (August 2002). *Pharmaceutical cGMPs for the 21st century: A risk-based approach*
2 ICH Q8R2

Definitions

Continuous process verification
An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).

Control strategy
A planned set of controls, (ICH Q10).

Concurrent validation
Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches (GMP Annex 15).

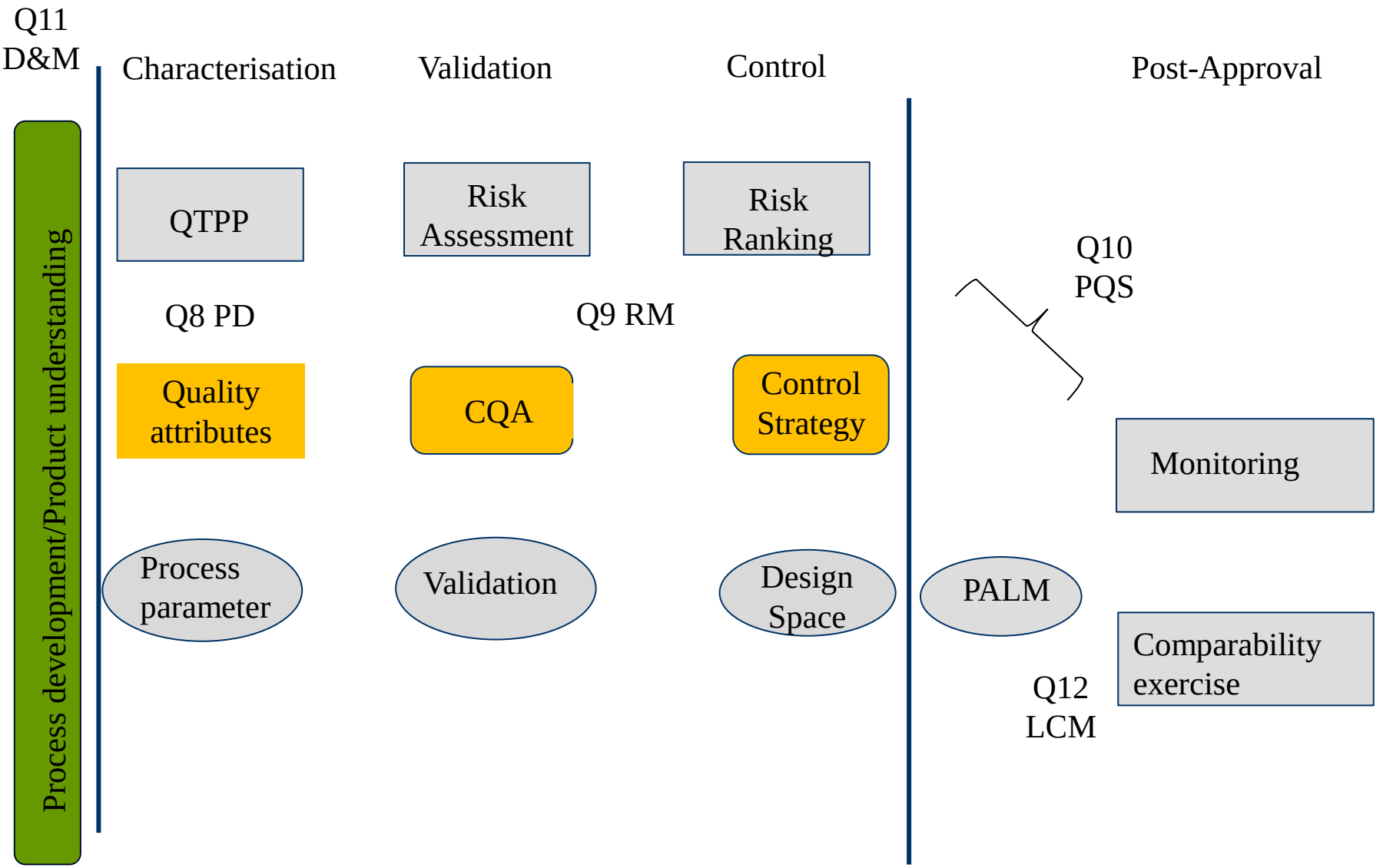
Enhanced approach to process development
In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the active substance which may include the establishment of design space(s) (ICH Q11).

Ongoing process verification (also known as continued process verification)
Documented evidence that the process remains in a state of control during commercial manufacture.

Performance indicator
Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system (ICH Q10).

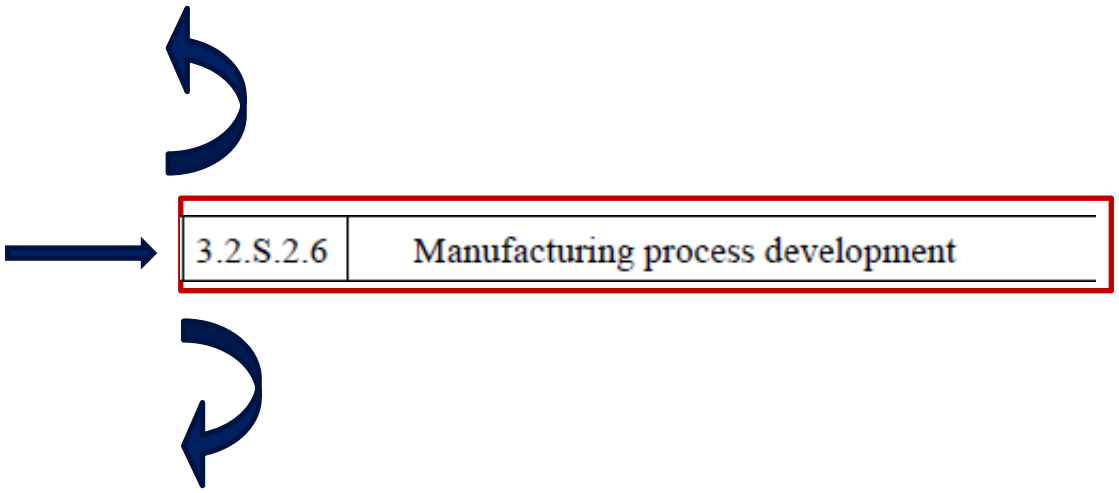
Proven Acceptable Range (PAR)
A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (ICH Q8).

Implementing QbD

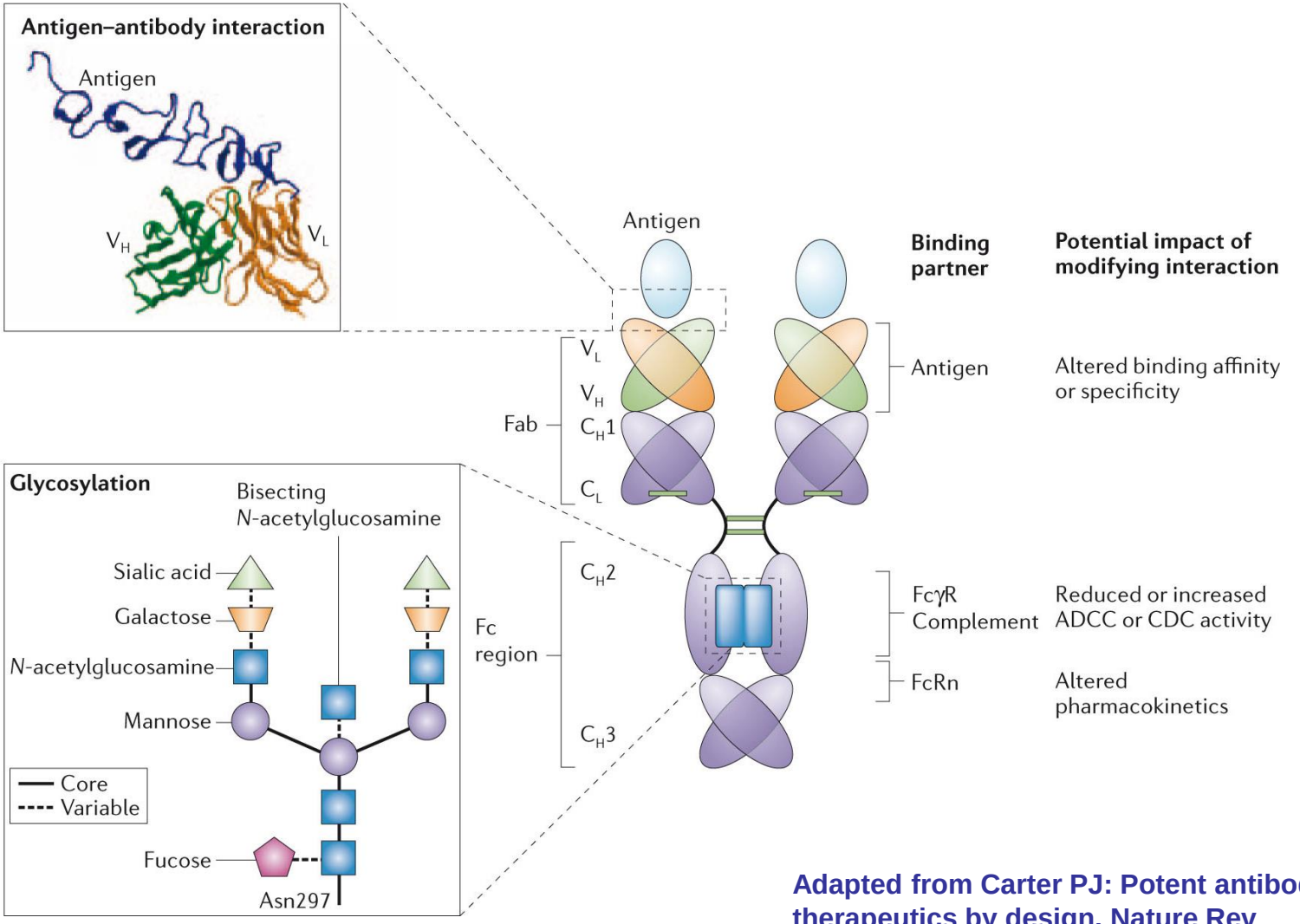


Volume 2B
Notice to Applicants

3.2	BODY OF DATA
3.2.S	DRUG SUBSTANCE
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.3	Control of materials
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation and/or evaluation
3.2.S.2.6	Manufacturing process development
3.2.S.3	Characterisation
3.2.S.3.1	Elucidation of structure and other characteristics
3.2.S.3.2	Impurities
3.2.S.4	Control of drug substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability



Characterisation is the basis for QTPP



Adapted from Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunology 6, 343 (2006)

Process characterisation Methodology

Prior knowledge evaluation

- Knowledge from similar processes
- Manufacturing experience

Risk assessments and process characterization planning

- CQA risk assessment
- Process risk assessments
  - Identification of process parameters requiring further study

Process characterization studies

- Scale-down model qualification
- Process characterization studies

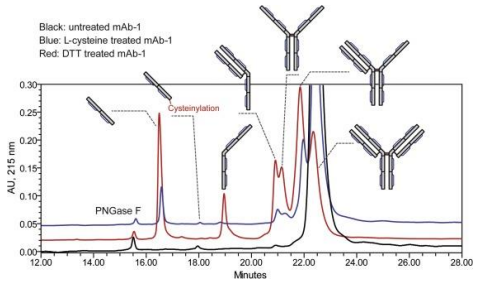
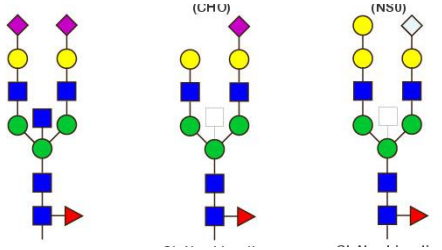
Establishment of parameter criticality and associate ranges

- Evaluation of DoE Study Results
- Evaluation of linkage Study Results

Control strategy

- Process validation
- Process Description
- In-process controls
- Integrated Control Strategy

Critical Quality Attributes Evaluated in Process Characterization Study

CQA	Process Steps Evaluated
LMW Species 	Production culture (N) Media preparation and storage Cell culture harvest Protein A chromatography Virus inactivation low pH CEX AEX
Glycosylation Pattern 	Subculture Production culture Media preparation and storage

Failure Modes and Effects Analysis (FMEA)

- The Failure Modes and Effects Analysis (FMEA) methodology to evaluate risks by assessing severity, occurrence and detectability of potential process parameter failure modes.
- A risk priority number RPN is calculated for each process parameter (RPN = S × O × D).
- RPN scores are compared to a pre-determined threshold. Those classified as high risk will be studied further in process characterization.

RPN	Class	Actions
1 - 3	Low	No measures or study required
4 - 6	Mid	Team decision; risk reduction measures or study may be required
7 - 27	High	Risk reduction measures or study are required

DoE and Small scale studies/linkage studies

- Knowledge of process performance when operated under worst-case conditions for each CQA.
  - Small scale studies are considered essential in order to address multivariate parameters
  - Provide scientific rationale for worst case
  - Moving outside of worst-case conditions

- The Design Space is limited by the multivariate ranges for all critical process parameters (CPPs).

Experiment	pH	Conc	Temp	pH	Conc	Temp
				Factor levels		
1	6.5	1.8	22	0	0	0
2	6.2	2.1	22	-1	1	0
3	6.8	1.4	22	1	-1	0
4	6.8	2.1	22	1	1	0
5	6.2	1.4	22	-1	-1	0
6	6.5	1.8	22	0	0	0
7	6.2	1.4	20	-1	-1	-1
8	6.8	1.8	24	1	0	1
9	6.5	1.8	20	0	0	-1
10	6.5	1.8	24	0	0	1
11	6.2	1.4	22	-1	-1	0
12	6.2	1.4	20	-1	-1	-1
13	6.8	2.1	24	1	1	1
14	6.5	1.8	25	0	0	1.5
15	6.5	1.8	19	0	0	-1.5
16	6.5	1.8	22	0	0	0

Presentation of Results
prediction models, contour plots…

Figure 5 Model Prediction Affinity Chromatography (CHOP)

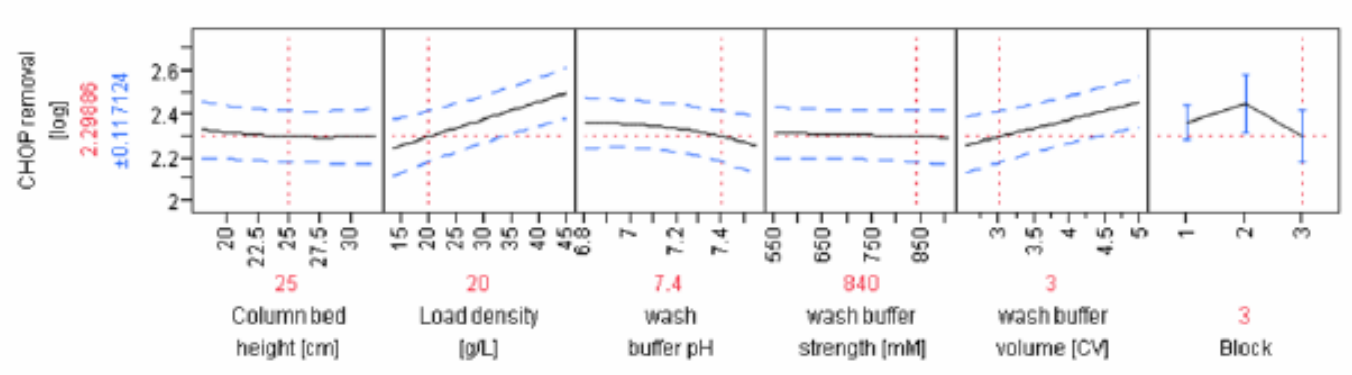
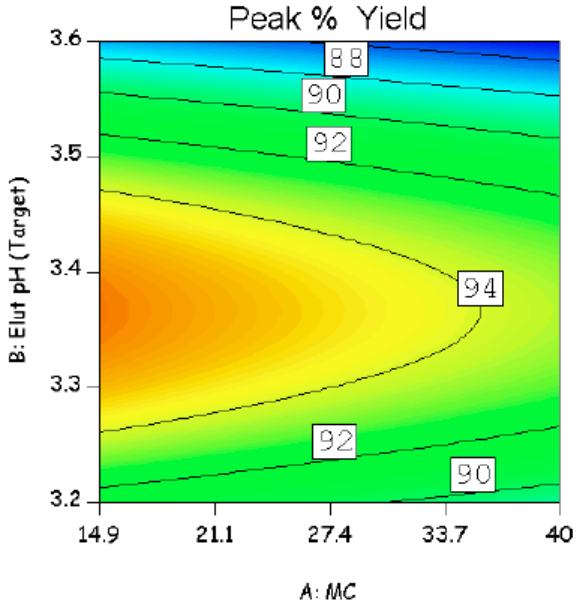
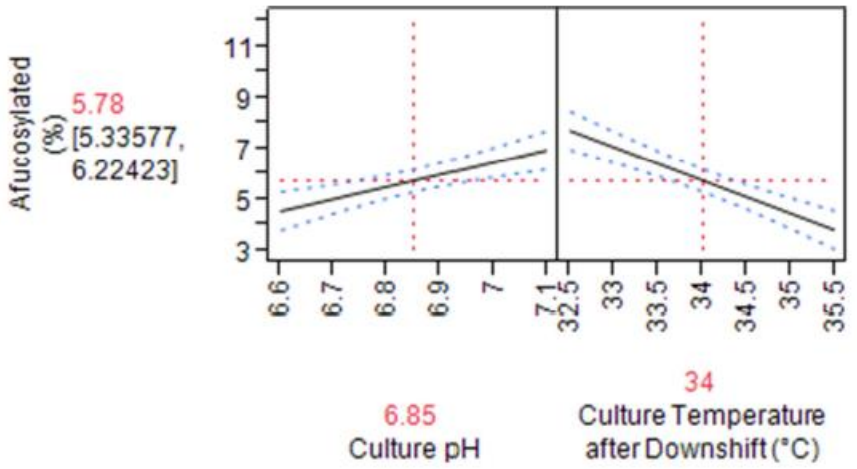


Figure 3.2.S.2.6-3. The Effect of Elution pH and Load Challenge on Protein A Step Yield (%)





Validation GL for biotech active substance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 April 2016
EMA/CHMP/BWP/187338/2014
Committee for Medicinal Products for Human Use (CHMP)

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

Draft Agreed by Biologics Working Party	April 2014
Adoption by CHMP for release for consultation	25 April 2014
Start of public consultation	1 May 2014
End of consultation (deadline for comments)	31 October 2014
BWP Drafting Group review of comments	November 2014 - January 2016
Agreed by BWP	February 2016
Adoption by CHMP	28 April 2016
Date for coming into effect	1 November 2016

Keywords	***active substance, biologics, process validation, process evaluation, process verification, lifecycle***

Introduction

- Process characterization (4) is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records.
  - Process development (4.1)
  - Process evaluation (4.2)

- Process verification (5) should confirm that the final manufacturing process as established based on the process evaluation studies performs effectively in routine manufacture

- Process characterisation and verification studies should normally be completed and included in the marketing authorisation application or a variation application as appropriate.

4.1 Process development

For further information, please refer to ICH Q11 guideline.

Manufacturing process development should identify which inputs (e.g. material attributes, process parameters) and outputs (e.g. quality attributes, process indicators) for each process step/unit operation should be further evaluated during process validation studies.

Documented prior knowledge and risk assessment can help identify and justify the material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters with the potential for having an effect on drug substance CQAs and/or process performance.

Process development information should usually be submitted in Section 3.2.S.2.6 of the CTD

4.2. Process evaluation

- Successful process evaluation demonstrates that the design of the manufacturing process, with the preliminary definition of operational ranges along with its control strategy is appropriate for commercial manufacturing.

  - selected inputs and outputs according to their potential criticality
  - operating within the proposed input ranges, the output meets relevant quality criteria supports the proven acceptable ranges (PAR)
  - evaluation of selected step(s) operating in worst case and/or non-standard conditions
  - Small scale models are important tools in the development and evaluation of biopharmaceutical manufacturing processes.
  - certain raw materials: impact of these materials should be addressed.

5. Process verification Section 3.2.S.2.5 of the CTD

- A prospective process validation, as defined in ICH Q7, is expected for biotechnology-derived active substances.

- Process verification studies should confirm that the final manufacturing process (i.e. full scale commercial process) performs effectively.
  - suitability of the small scale model could reduce data requirements for process verification

- Such studies are generally performed in accordance with normal set points (NOR) for operating conditions and process parameters.

Critical Step (Unit operation)	Critical Process Parameter	Acceptable Operating Range
Production in 3000 L bioreactor	Temperature	35–38°C
	Seeding density[a]	1.6E6–6.1E6 viable cells/mL

2.4E6	2.0E6	2.0E6

- Process verification data should normally be completed and presented in the regulatory submission on an appropriate number of consecutive batches produced with the commercial process and scale
  - (1) the complexity of the process being validated
  - (2) the level of process variability;
  - (3) the amount of experimental data and/or process knowledge
  - (4) the frequency and cause(s) of deviations and batch failure

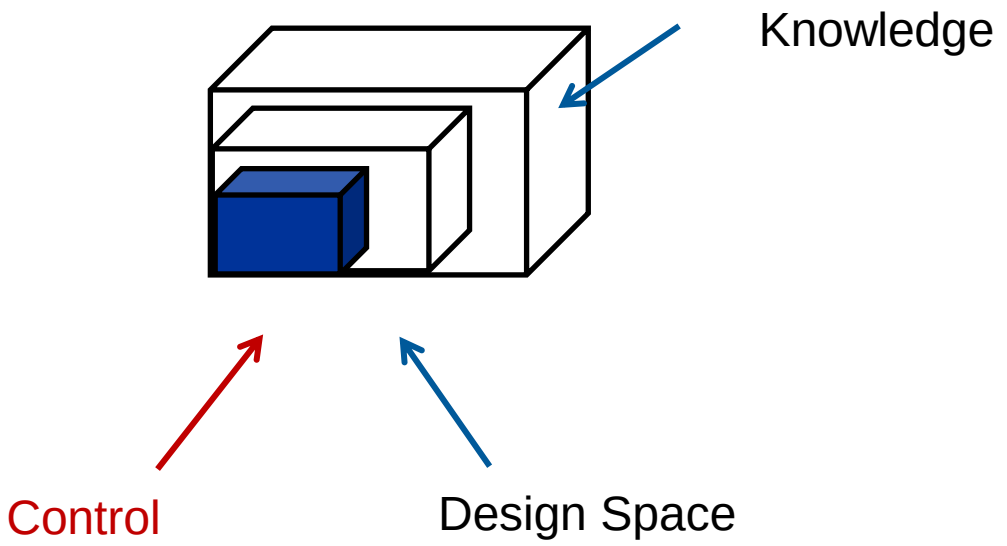
Overall control strategy

- Description of the manufacturing process and process controls
- Control of critical steps and intermediates
- IPC/RTR
- Specifications (release and stability)
- Monitoring (PQS)

Control Strategy

ICH Q8 (R2)

- *Enhanced understanding of product performance* ***can justify the use of alternative approaches to determine that the material is meeting its quality attributes. The use of such alternatives could support real time release testing.***



Real Time Release Testing

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 March 2012
EMA/CHMP/QWP/811210/2009-Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Final

Draft Agreed by CHMP / CVMP Quality Working Party
Adopted by CHMP for release for consultation
End of consultation (deadline for comments)
Agreed by Quality Working Party
Adopted by CHMP
Date for coming into effect

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Medicinal Products – Quality, Safety and Efficacy

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for Good Manufacturing Practice
for Medicinal Products for Human and Veterinary Use

Annex 17: Real Time Release Testing and Parametric Release

Deadline for coming into operation: 26 December 2018 (6 months after publication]

RTRT as part of a Control Strategy

3.1 A combination of in-process monitoring and controls may provide, when authorized, substitute for end-product testing as part of the batch release decision.

3.2 When designing the RTRT strategy, the following minimum criteria are expected

(i) ***Real time measurement and control of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.***

(ii) ***The valid combination of relevant assessed material attributes and process controls to replace finished product attributes should be established with scientific evidence based on material, product and process knowledge.***

(iii) ***The combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process should provide a robust foundation for RTRT and the batch release decision.***

3.3 A RTRT strategy should be integrated and controlled through the PQS

3.4 Change control program is an important part of the real time release

3.5 maintain a state of control and ensure that a product of the required quality will be consistently produced.

3.6 Personnel should be given specific training on RTRT technologies

3.7 Validation and qualification policy

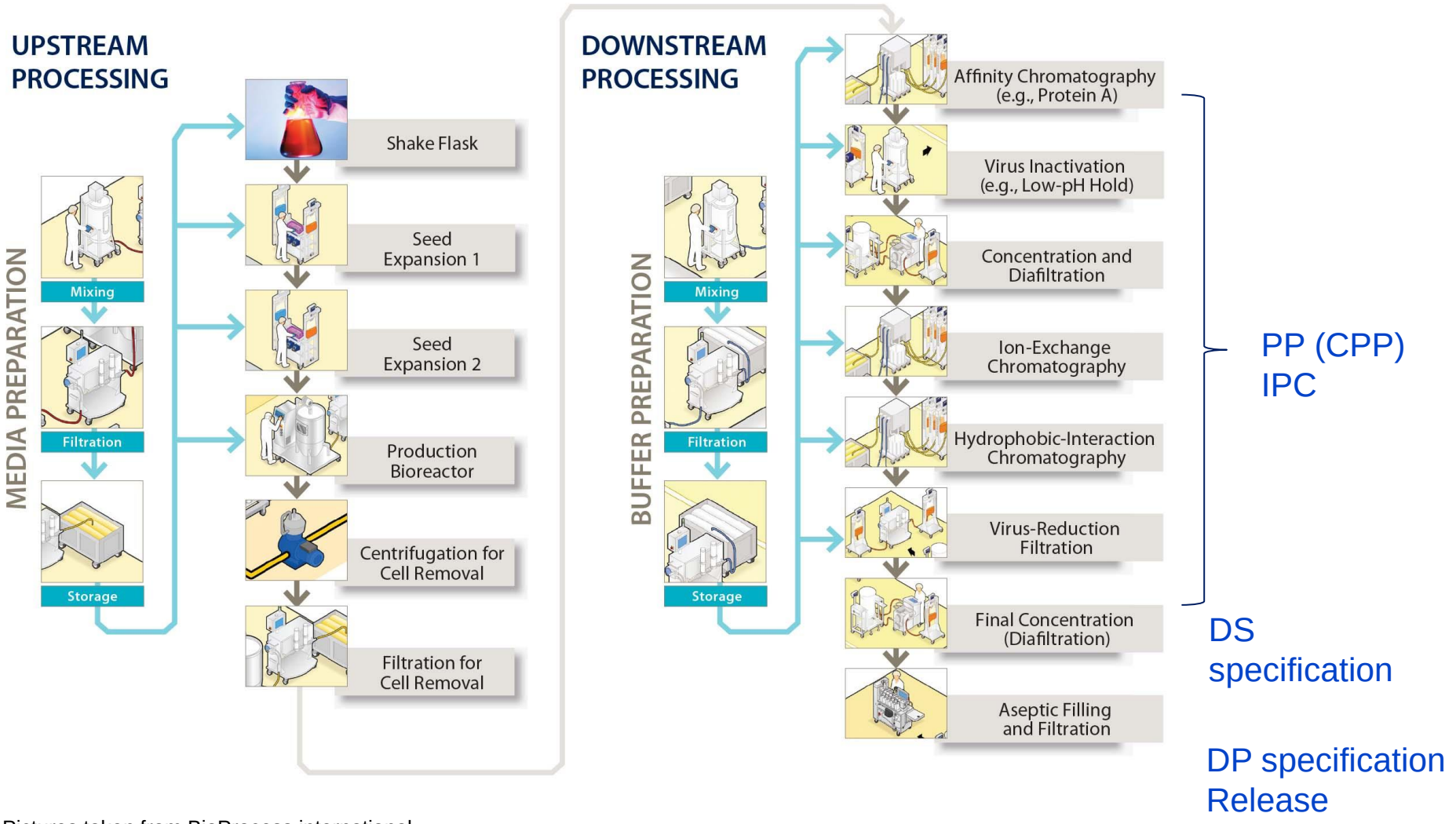
3.8 any deviation or process failure should be thoroughly investigated

3.9 Continuous learning through data collection and analysis over the life cycle

3.10 When RTRT has been approved, this approach should be routinely used for batch release.

3.11 Attributes that are indirectly controlled by approved RTRT should still appear in the "Certificate of analysis".

Where to place the controls



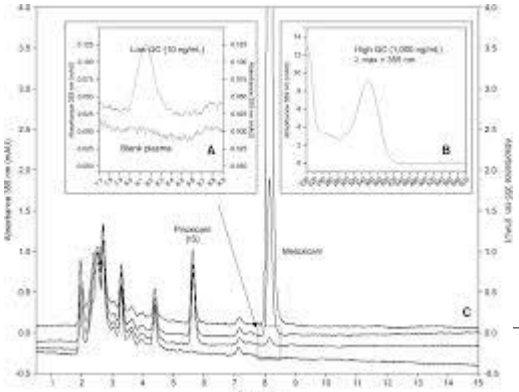
Pictures taken from BioProcess international

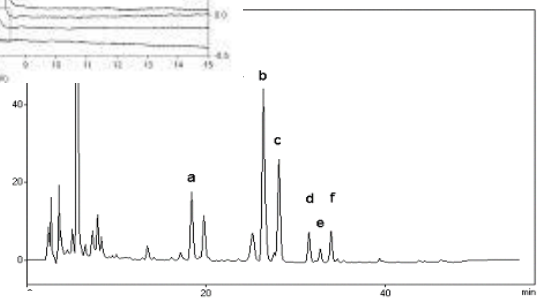
Specifications

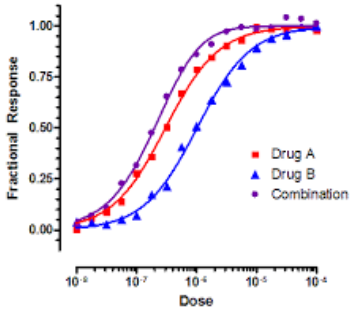
Pharmacopoeia: Monoclonal antibodies for human use, 01/2012:2031

Tests

Appearance
Solubility
pH
Osmolality
Extractable Volume
Total Protein
Molecular-size distribution
Molecular identity and structural integrity
Purity
Stabiliser
Water
Sterility
Endotoxins
Tests applied to modified antibodies
Assay: carry out a suitable biological assay







ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

ICH Consensus Guideline

TABLE OF CONTENTS

12.12.2008 EN Official Journal of the European Union L 334/7

COMMISSION REGULATION (EC) No 1234/2008

of 24 November 2008

concerning the examination of variations to the terms of mar products for human use and veterinary me

(Text with EEA relevance)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 London, 16 February 2012
2 EMA/CHMP/BWP/729106/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on the use of starting materials and
5 intermediates collected from different sources in the
6 manufacturing of biological medicinal products
7 Draft

Draft Agreed by Biologics Working Party	Dec 2011
Adoption by Committee for medicinal products for human use for release for consultation	16th February 2012
End of consultation (deadline for comments)	31st August 2012
Agreed by Biologics Working Party	<Month YYYY>
Adoption by Committee for medicinal products for human use	<DD Month YYYY>
Date for coming into effect	<DD Month YYYY>

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 30 June 2010
2 EMA/CHMP/BWP/422351/2010

3 Reflection paper on the respective role of inspectors and
4 assessors in relation to changes to a manufacturing
cess including implementation of ICH Q8, Q9 and Q10
Draft

Agreed by BWP	<Month YYYY>
tion by CHMP	
ords	

Directorate-General for Health & Consumers

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 March 2012
EMA/CHMP/BWP/534898/2008
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Draft Agreed by Biologic Working Party	January 2010
Adoption by Committee for Medicinal Products for Human Use for release for consultation	18 February 2010
Start of public consultation	28 February 2010
End of consultation (deadline for comments)	31 August 2010
Agreed by Biologic Working Party	7 March 2012
Adoption by Committee for Medicinal Products for Human Use	15 March 2012
Date for coming into effect	15 April 2012

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 19 May 2011
2 EMA/CHMP/BWP/25360/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on the need for a guideline on proces
5 validation of medicinal products containing biotechnology
6 derived proteins as active substance
7
8 **DRAFT**
9

Agreed by Biologics Working Party	
Adoption by CHMP	19 May 2011
End of consultation (deadline for comments)	31 August 2011

10
11 Comments should be provided using this template. The completed comments form should be sent to BWPSecretariat@ema.europa.eu

12

Keywords	*Process validation, biological active substance*