Justification of specification & life-cycle management of relevant analytical methods

CMC Strategy Forum | China 2021

Dr. Ulli Backofen & Dr. Rico Lippmann

April 23rd-24th 2021

Boehringer Ingelheim

Agenda

Specifications of Biopharmaceuticals throughout Development (focus on mAB)

Critical Quality Attributes (CQA) and Control Strategy

Specifications during Early and Late Stage Development

Case Studies / **E**xamples

Method Life Cycle

Definition - Specifications

Definition

List of tests, references to analytical procedures

Appropriate acceptance criteria (numerical limits, ranges, or other criteria for the tests described)

Confirm quality rather than full characterization

Control

Confirm Quality & Ensure Safety and Efficacy

Set of criteria to consider DS/DP to be acceptable for intended use

Conformance to specification means DS/DP meet the acceptance criteria, if tested

Regulation

ICH **Q6B,** Specifications, ICH Topic **Q1A**, Stability testing of new drugs and products, ICH Topic **Q1E**, Evaluation of stability data, ICH **Q2(R1)** Validation of analytical procedures

Life Cycle linked to

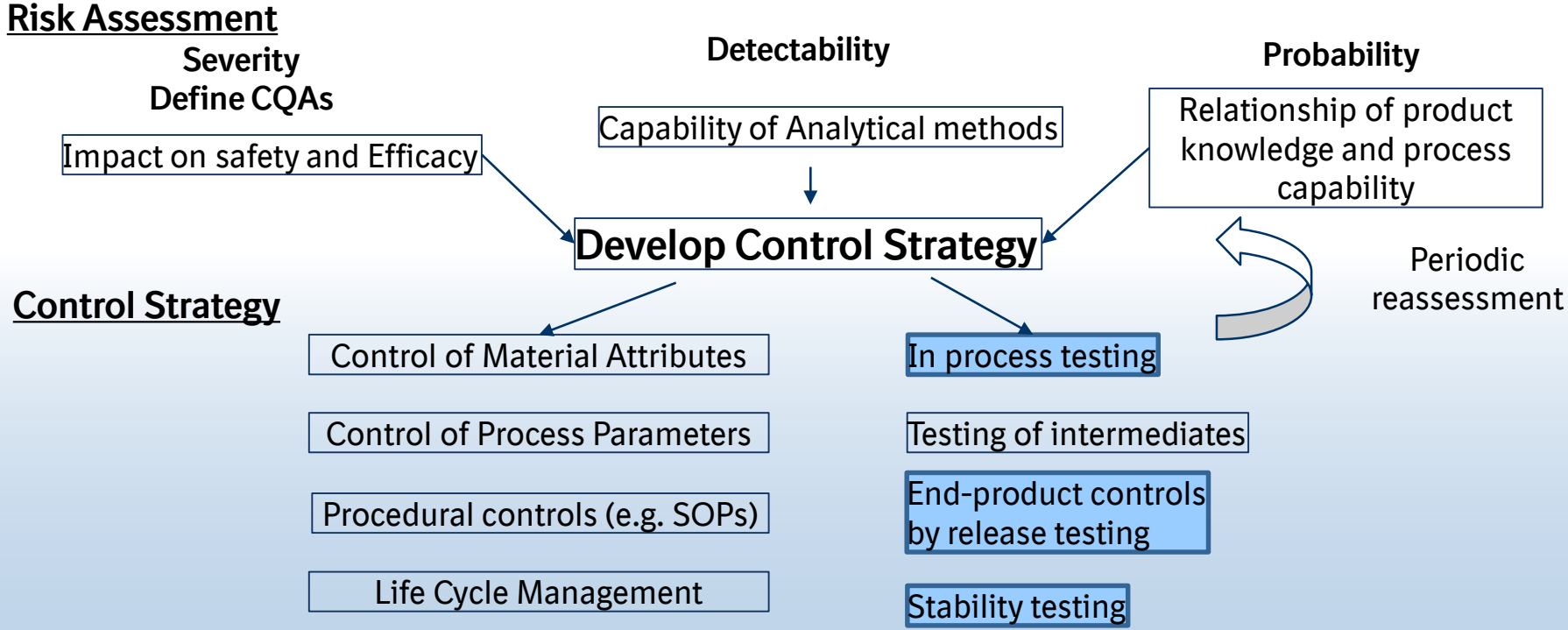
Manufacturing process

Preclinical and clinical studies

Analytical procedures

Stability of substance and product

Risk assessment model as applied to design of control strategy



„Reproduced“ from, Schenerman, MA, Axley, MJ, Oliver, CN, Ram, K, and Wasserman, GF (2009), Using a Risk Assessment Process to Determine Criticality of Product Quality Attributes. In: Rathore, AS, Mhatre, R, Quality by Design for Biopharmaceuticals: Perspectives and Case Studies. Wiley Interscience. pp. 53-84.

Specification: Inputs and Output

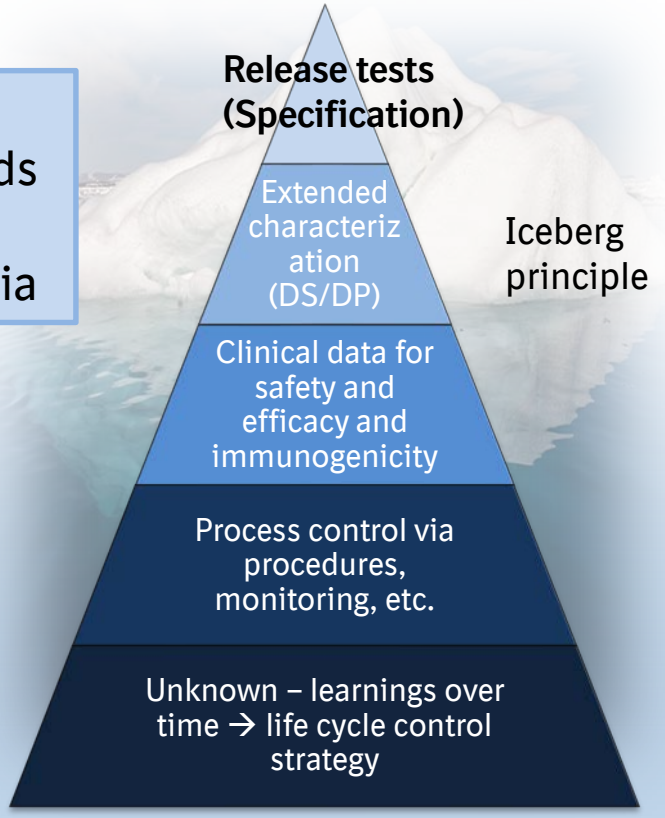
Input

- Process robustness
- DS/DP Stability
- Clinical data
- Pharmacopeia requirements
- CQA Understanding
- Development data
- Analytical methods
- Structure function of variants

Specification Setting

Output

List of
Analytical methods
&
Acceptance criteria



Iceberg principle

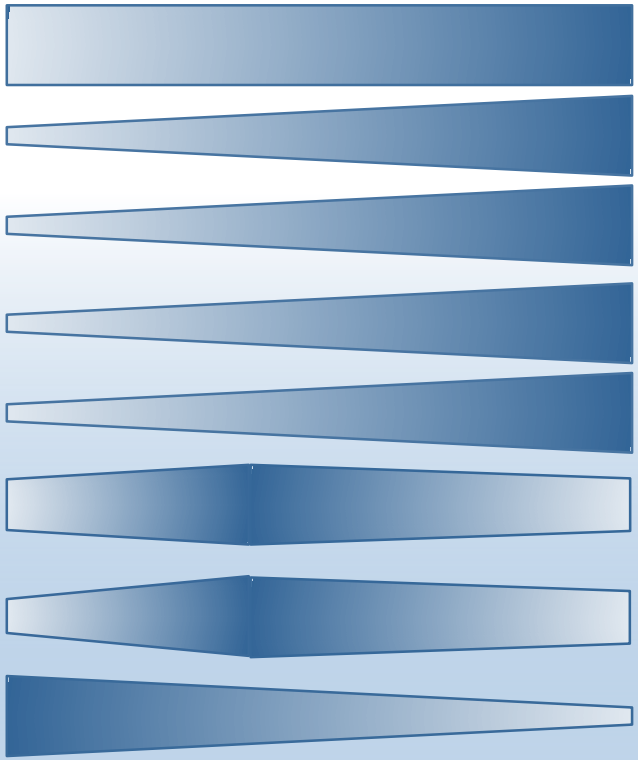
Specifications confirm the quality rather than to fully characterize

Only a small part of CQAs needs to be specified if comprehensive process knowledge and molecule specific data is available

(adapted S. Kozlowski & P. Swann, 2006)

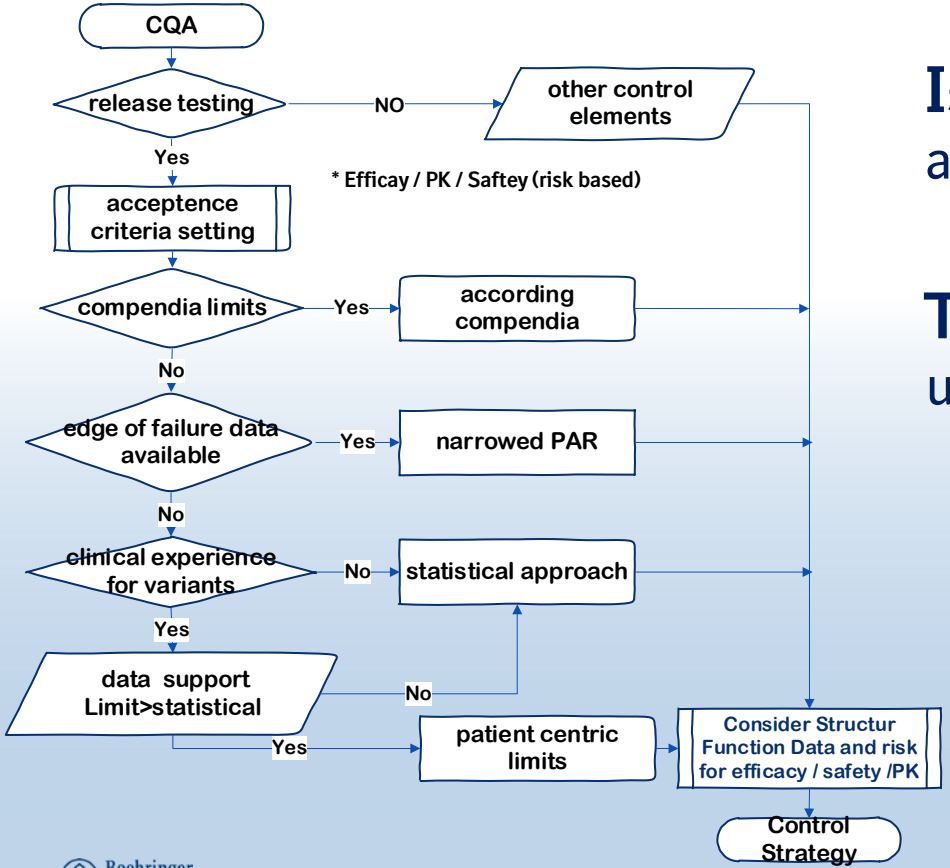
Specification evolve during development

Early ⟹ Late ⟹ MAA



CQA	Does not change as a result of risk management
Process knowledge	CQAs controlled via stable process instead of release specification
Clinical data	Incorporate knowledge from clinic to set acceptance criteria
Characterization	Improved understanding of probability/ detectability
Stability data	Definition of end of shelf-life acceptance criteria and degradation trends
# Analytical tests	Start with platform methods and develop to molecule specific methods
# Specifications release	Increase with clinical phases/may decrease with gained process knowledge
Tightness acceptance criteria	Starts with report result/platform specifications, tightened during development

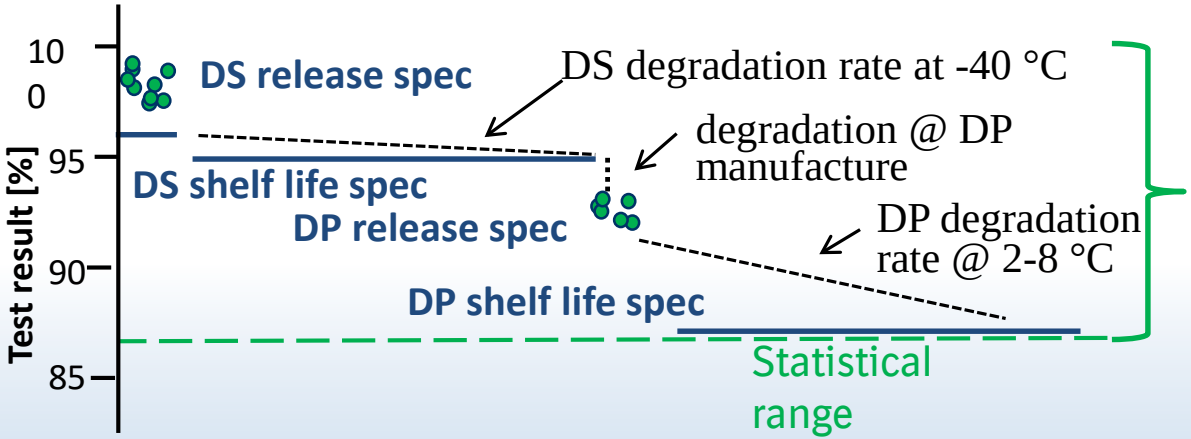
Simplified Flow of Specification Setting



Is rather a combination of described approaches than a yes/no decision

Typically, more than one information is used to finally justify the specification

Statistical approach for release and end of shelf-life criteria



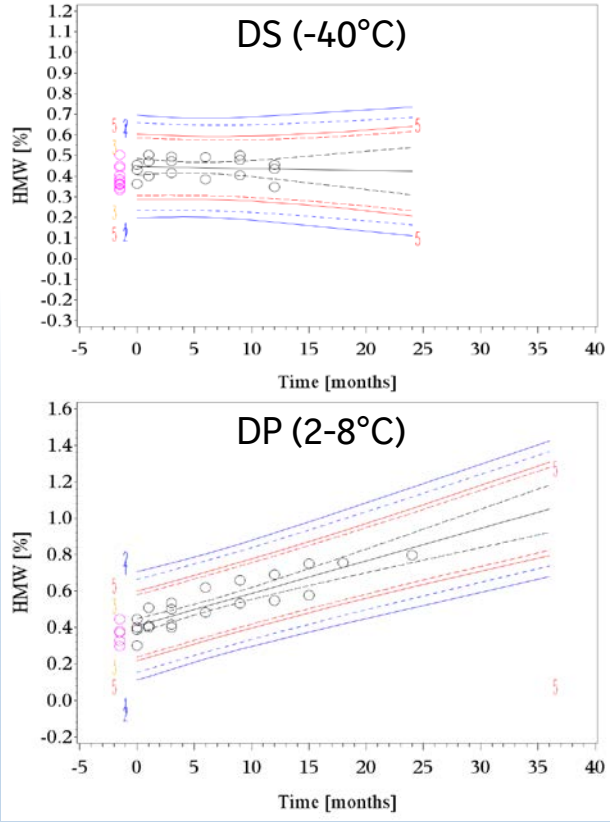
Statistical calculation
(tolerance intervals or mean ± 3/5 SD)
considering batch data and to assess the ranges a process can deliver

Weaknesses:

If batch data is limited / no sources of potential random process variation
→ estimate of variation not representative of true process variability

Even large data set may be derived from very few raw materials or process intermediate lots, and therefore underestimate expected sources of random process variability.

Case Study – Statistical approach for high molecular weight species (HMWs)



DS Release **0.657 %**

No significant degradation (+/- Δ 24m DS) for DS @ -40°C
DS release = DS stability specification (usual case)

DS Stability **0.657 %**

DS stability limit + Δ DS/DP release
Δ DS/DP = Potential degradation DP manufacture

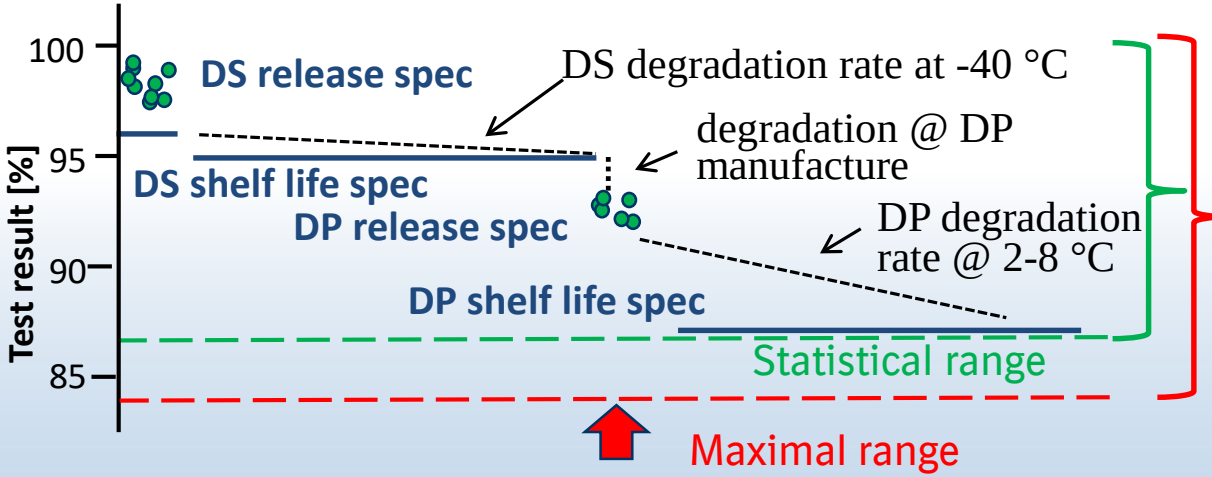
DP Release **0.752 %**

DS stability limit + Δ DS/DP release + Δ 36m DP stability + Δ Ci + (Δ 0.5m 25°C)
DP release ≠ DP stability specification (usual case)

DP Stability **1.236 %**

Patient centric specifications

Specifications based on risk to clinical performance, not what can be achieved by the process



Established clinical range and/or justified by *in-vitro* studies

Acceptance criteria wider than the limits calculated statistically is justified when there is a low risk of impact to patient safety and efficacy

Advantage: Patient-centric specifications enable appropriate control over higher risk CQAs to ensure product quality for the patient, and flexibility for lower risk PQAs for a sustainable supply chain.

Case Study - Patient centric: high molecular weight species exposure

Request from Health Authority: *...the specification for aggregates should be tightened in line with batch data only or it should be justified that the proposed specification is clinically qualified.*

HMW (%)
Release
2.85
2.81
1.83
1.98
2.25
Stability (24 months, 5°C)
3.24
3.41
2.83

Highest level used in clinic was at 3.4% HMW at 24 months

Drug product close to end of shelf-life had no impact on ADA incidence or ADA titers

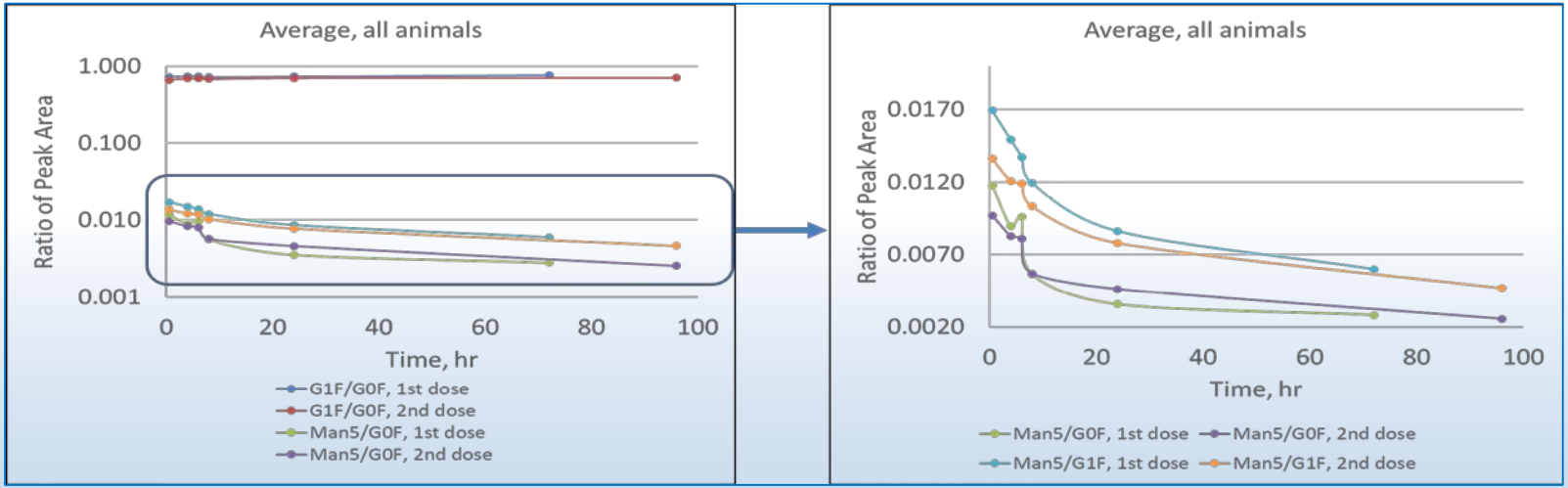
Highest dose in clinic for same indication 15% higher than proposed commercial dose, i.e. up to 3.9 % HMWs could be justified

3.9% HMW proposed as commercial stability specification for DP

ADA, anti-drug antibodies; DP, drug product; UP-SEC, ultra-high-performance size-exclusion chromatography

Case Study - CQA high mannose controlled via process and product knowledge I/II

I. Critical Quality Attribute (CQA) Understanding



Structure-function studies of variants

No Impact on Efficacy

Increased clearance (PK; in house data)

Literature data (e.g. 10% no impact on PK - Goetze et al 2011)

Case Study - CQA high mannose controlled via process and product knowledge II/II

II. Development

Upstream process characterization study (PCS) increase process knowledge

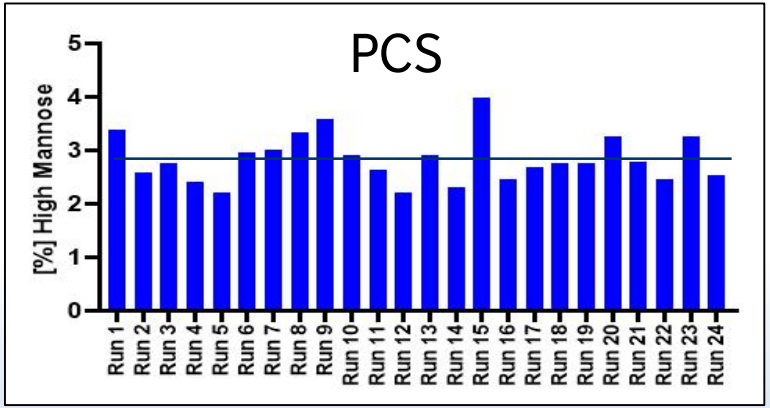
Seeding cell density, temperature and feeding influence high mannose content

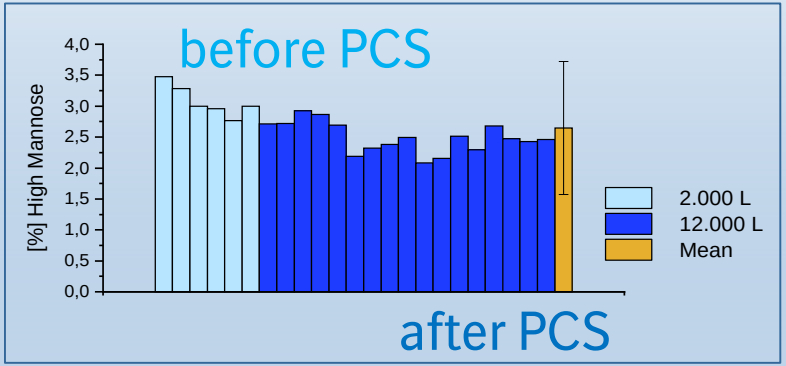
To control high mannose the PAR seeding, temperature and feeding was tighten

III. Process Robustness

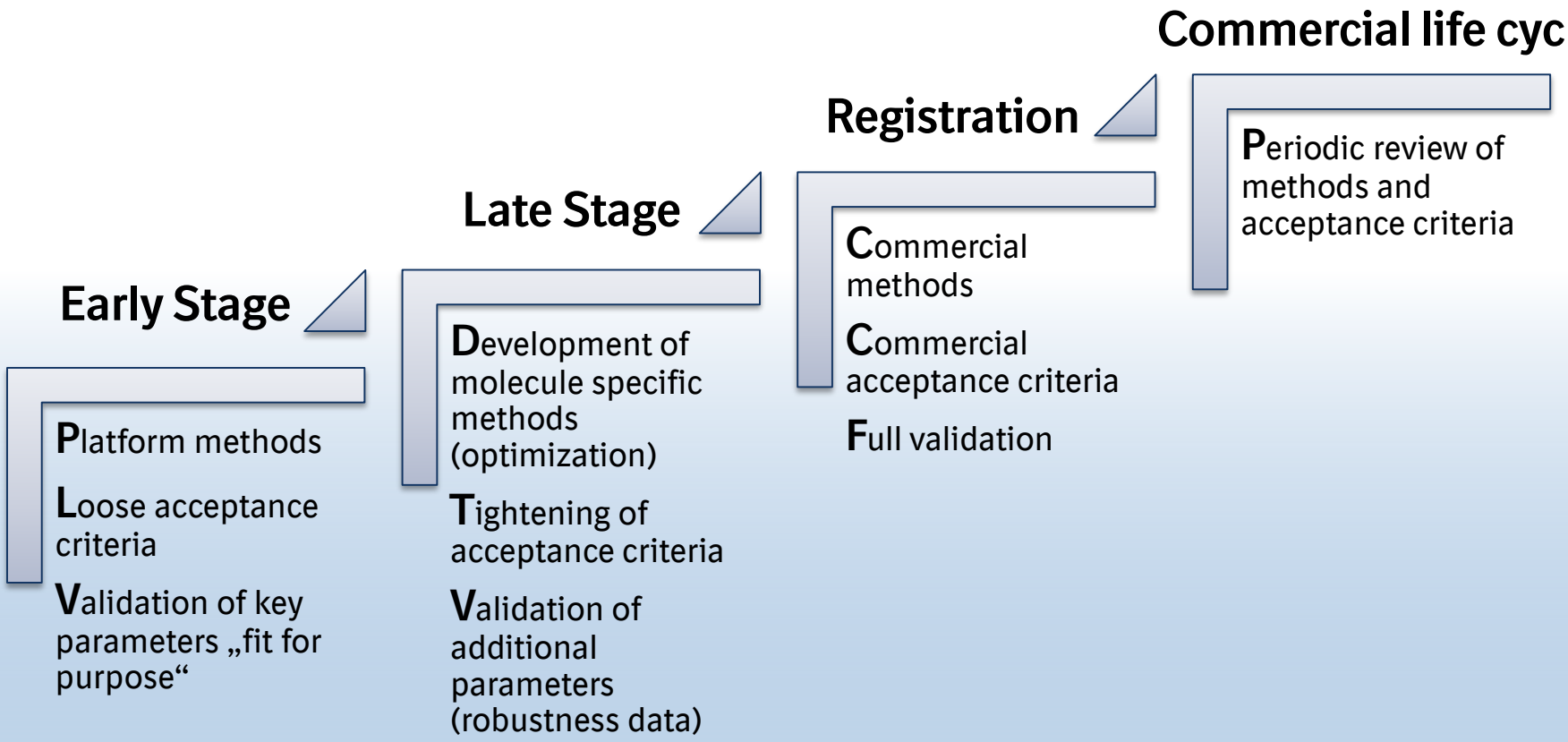
Presence of high mannose structures robust at all scales

2-4 % across all scales an batches





Method life cycle



Summary and Conclusion

Specification setting is a complex undertaking requiring profound understanding of the molecule and its manufacturing process

Responsible specification setting ensures safety, efficacy and quality and takes accountability to minimizes the risk of „false“ rejection of batches (supply risk)

There is not a single approach for setting specifications

Specification setting is a continuous/continued process

The Last Slide

Thank you for your attention!

QUESTIONS?

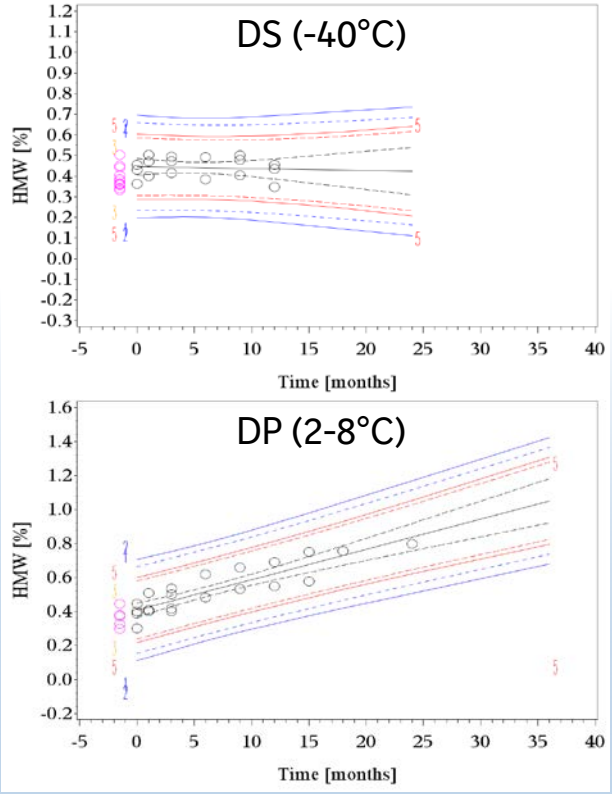
Additional Information

Boehringer Ingelheim

Abbreviations

Abbreviation	Meaning
CMC	Chemistry, Manufacturing, and Control
CQA	Critical Quality Attribute
CPP	Critical process parameter
DS	Drug Substance
DP	Drug Product
EoS	End of shelf-life
HMW	High molecular weight species
ICH	International Conference on Harmonization
PCS	Process characterization study
PK	Pharmacokinetics
PQA	Product quality attribute
3 (5) SD	3 (5) Standard deviation
SEC	Size exclusion chromatography

Legend for Case Study – Statistical approach (SEC- HMWs)



Release data
Stability data
Prediction from regression (stability)
Two-sided tolerance interval from regression (stability)
One-sided tolerance interval from regression (stability)
2 2 2 Two-sided tolerance interval (release)
1 1 1 One-sided tolerance interval (release)
3 3 3 3-sigma limit (release and end of shelf-life)
5 5 5 5-sigma limit (release and end of shelf-life)
Two-sided prediction interval from regression (stability)
One-sided prediction interval from regression (stability)
Confidence interval from regression (stability)

Literature

High-mannose glycans on the Fc region of therapeutic IgG antibodies increase serum clearance in humans
Andrew M Goetze, Y Diana Liu, Zhongqi Zhang, Bhavana Shah, Edward Lee, Pavel V Bondarenko, Gregory C Flynn
Glycobiology, Volume 21, Issue 7, July 2011, Pages 949–959

Strategies for Setting Patient-Centric Commercial Specifications for Biotherapeutic Products Margaret N.Ruescha, Luca Benettib, Eileen Berkayc, David J.Cirellia, Neha Frantzd, Martin H.Gastense, Wayne P.Kelleyf, Juliana Kretsingerg, Mike Lewisc, Shawn Novickh, Barbara Rellahani, Laura Packj, Corné J.M.Stroopk, AnnSubashil, PingYinmMingZengn, JohnStults
Journal of Pharmaceutical Sciences, Volume 110, Issue 2, February 2021, Pages 771-784

Current and future issues in the manufacturing and development of monoclonal antibodies
Steven Kozlowskia & PatrickSwann
Advanced Drug Delivery Reviews Volume 58, Issues 5–6, 7 August 2006, Pages 707-722