Specifications and Lifecycle Management

A Commercial Drug Substance Manufacturing Site Perspective

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Agenda

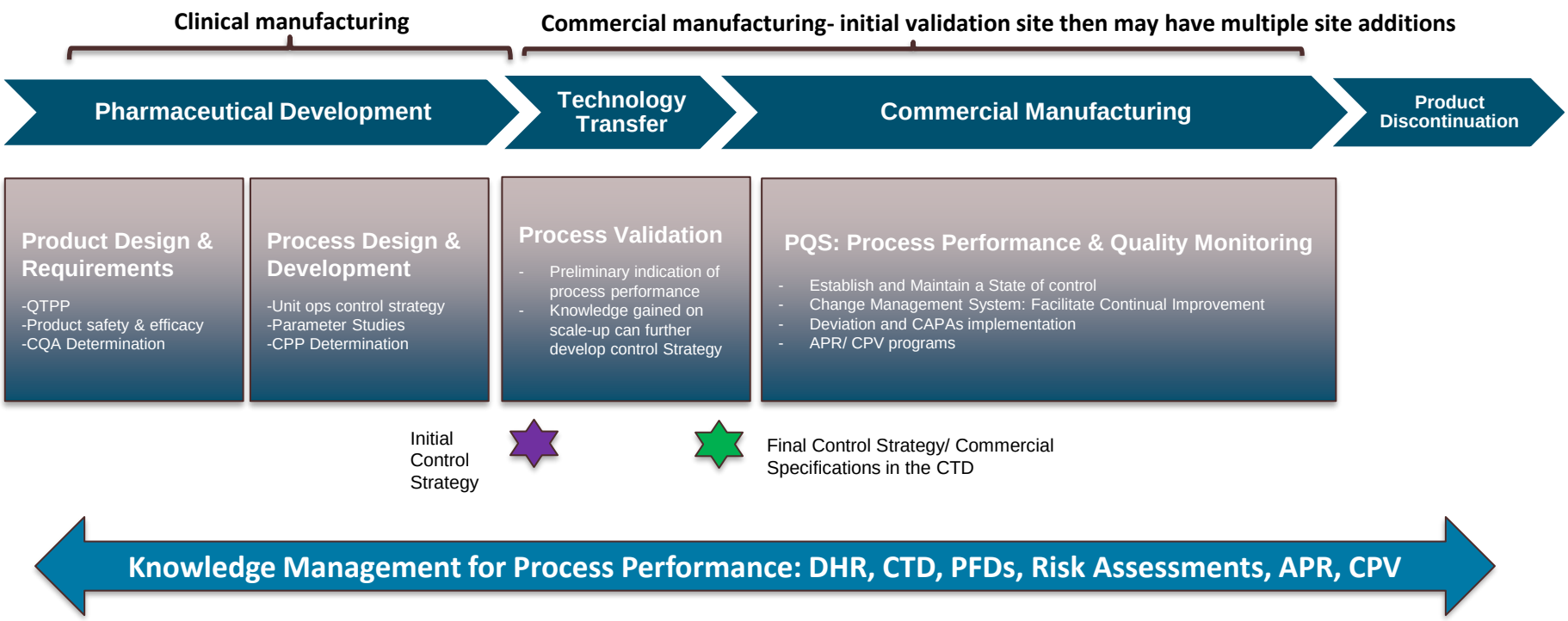
- Outline the use of a control strategy perspective in setting specifications
  - Narrow the scope of the problem of setting specifications to key attributes which can present challenges over the product lifecycle

- Present case study data on the justification of specifications from a recent regulatory submission
  - Outline the tools used to understand clinical experience and relevance
  - Developing acceptance criteria starting with the patient
  - Commercial risk considerations in setting specification acceptance criteria

- Present case study example for a legacy product where the specification was based on process capability

- Outline the program for monitoring process consistency during commercial manufacturing as part of the Continued Process Verification (CPV) program in the Pharmaceutical Quality System

Product Commercialization Lifecyle



Establishing a Control Strategy

ICH Q10: *A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.*

- Specifications are a **key component** of the control strategy in defining the range within an attribute range can vary with no impact to the established safety and efficacy of the product.
- The control strategy for a given product includes understanding the consequence, if certain **process parameters** are not controlled on the **impact to the CQAs**.
- The control strategy is developed after considering the impact the process has on the attribute (occurrence score) as well as the capability of the analytical tests (detectability).
- Understanding the control strategy and the **relationship** between **process** performance (leading indicators) and **analytical** performance (lagging indicators) is key during commercial manufacturing to ensure manufacturing consistency.

CQA Control Strategy- Control Points Matrix

The relationships identified between unit operations used in drug substance manufacturing and their potential impact to critical quality attributes are presented as the Control Points Matrix in 3.2.S.2.6 *Process Development*

Quality Attribute	Impact of Unit Operation on CQA											
	Flask Exp	Seed BR Exp	Prod Br	Prim Recov	ProA	LpH VI	COL 2	COL 3	VF	TFF	DS Fill	Testing Elements
Biological Activity												
Potency	–	–	O	–	–	–	–	–	–	–	–	LR
Molecular Heterogeneity												
Charge Heterogeneity	–	–	O	–	–	–	–	–	–	–	–	LR
Specific Charge Variants (oxidation, deamidation)	–	–	O	–	–	–	–	–	–	–	–	LR
Product-Related Impurities / Purity												
Total Aggregates	–	–	O	–	–	↓	–	↓	–	↑	–	IP, LR
Purity (Reduced) / Total Fragments	–	–	O	–	–	–	–	–	–	–	–	IP, LR
Purity (Non-Reduced) / Total Fragments	–	–	O	–	–	–	–	–	–	–	–	IP, LR
Process-Related Impurities												
Residual DNA	–	–	O	–	↓	↓	–	–	–	–	–	IP, LR
Residual HCP	–	–	O	–	↓	↓	–	↓	–	–	–	IP, LR
Residual Protein A	–	–	–	–	O	↓	–	↓	–	–	–	IP, LR
Microbiological Safety												
Bioburden	–	–	–	–	–	–	–	–	–	–	↓	IP, LR, UBH
Endotoxin	–	–	–	–	–	–	–	–	–	–	–	IP, LR
Viral	–	–	–	–	–	↓	↓	–	↓	–	–	UBH
Solution Properties												
Identity	O	–	–	–	–	–	–	–	–	–	–	LR
Description	–	–	–	–	–	–	–	–	–	O	–	LR
Quantity	–	–	–	–	–	–	–	–	–	O	–	IP, LR
pH	–	–	–	–	–	–	–	–	–	O	–	IP, LR
PS80 Concentration	–	–	–	–	–	–	–	–	–	-	O	LR

Typical Process Capability assessments during Commercial Manufacturing:


CpK >1.3


CpK 1.0 -1.3


CpK <1.0

Risk Assessment for Drug Substance Specification Acceptance Criteria- Low Risk CpK

CQA	Unit Operation Control Point	Parametric Controls	Drug Substance Analytical Control		
			Routine release	Stability	Comparability
Process-Related Impurities					
Residual DNA	Protein A	N/A	N/A	N/A	qPCR
	LpH VI	e.g. Depth filter load			
Residual HCP	LpH VI	e.g. Depth filter load	ELISA OR N/A	N/A	ELISA
	Column 2/3	e.g. Column Load			
Solution/ Formulation Properties					
Identity	Cell Culture	N/A	e.g. CEX, Cell-based Bioassay	N/A	e.g. CEX, Cell-based bioassay
Description	Tangential Flow Filtration	DF buffer make-up	Visual	Visual	Visual
Quantity	Tangential Flow Filtration	Final conc.	UV	UV	UV
Polysorbate 80	DS Fill	Surfactant addition qty	e.g. HPLC-UV	e.g. HPLC-UV	e.g. HPLC-UV

Solution Properties

- ✓ Potential to **indirectly impact the safety and efficacy** of the drug product, **quantitative acceptance criteria** are chosen to ensure the consistency and stability of the drug substance and drug product.
- ✓ These quality attributes are **well controlled** in the manufacturing process, and not subject to variability therefore, meeting the DS specifications is not of concern over the product lifecycle.

Process-Related Impurities

- ✓ When it is possible to **demonstrate excess clearance capability** within the manufacturing process through challenge study data presented in 3.2.S.2.6, a DS specification may not be required/requested.
- ✓ These quality attributes are **well controlled** in the manufacturing process, and typically not subject to variability.

Risk Assessment for Drug Substance Specification Acceptance Criteria- Med/ High Risk CpK

CQA	Unit Operation Control Point	Parametric Controls	Drug Substance Analytical Control		
			Routine release	Stability	Comparability
Biological Activity					
Potency	Production Bioreactor	N/A	Cell-based bioassay	Cell-based bioassay	Cell-based bioassay
Product related Impurities/ Substances					
Aggregation	Production Bioreactor	e.g. pH, feed qty	SEC	SEC	SEC
	LpH VI	pH, temp, time			
	Column 2/3	e.g. Column Load			
	DS Fill	PS 80 conc			
Fragmentation	Production Bioreactor	e.g. pH, feed qty	CE-SDS	CE-SDS	CE-SDS
Molecular Heterogeneity					
Multiple Charge Variants (e.g., oxidation, deamidation)	Production Bioreactor	culture duration, pH, temp	CEX, iCIEF or variant specific assay (as required)	CEX, iCIEF or variant specific assay (as required)	CEX, iCIEF, LC-MS or variant specific assay (as required)

- For CQAs that have the potential to **directly impact the safety and efficacy** of the drug product (including potency, aggregation, fragmentation), the proposed release and end of shelf-life acceptance criteria are based on a **risk assessment of the potential patient impact** in addition to clinical experience. Charge heterogeneity is treated in a similar manner.

- Typical issues experienced:
  - **Potency** inherent property of the molecule- **susceptible to analytical variability**, unlikely to gain a wide range of material quality in clinic
  - **Aggregation and fragmentation** are **well controlled** in the process, this would lead to tight specifications if set based on process variability
  - **Charge heterogeneity** complex in nature, most susceptible to **process variability** from changes such as scale-up and media vendor changes through the product lifecycle

Setting Commercial Specifications

- Setting Commercial Specifications and the Justification of Specifications within the regulatory dossier has been a journey for most companies; moving from **capability** to **clinical experience** to clinically relevant/ **patient centric** approach.

- In preparation for setting commercial specifications, begin with an assessment of the risk to the patient for each CQA to understand the **clinically relevant space**.

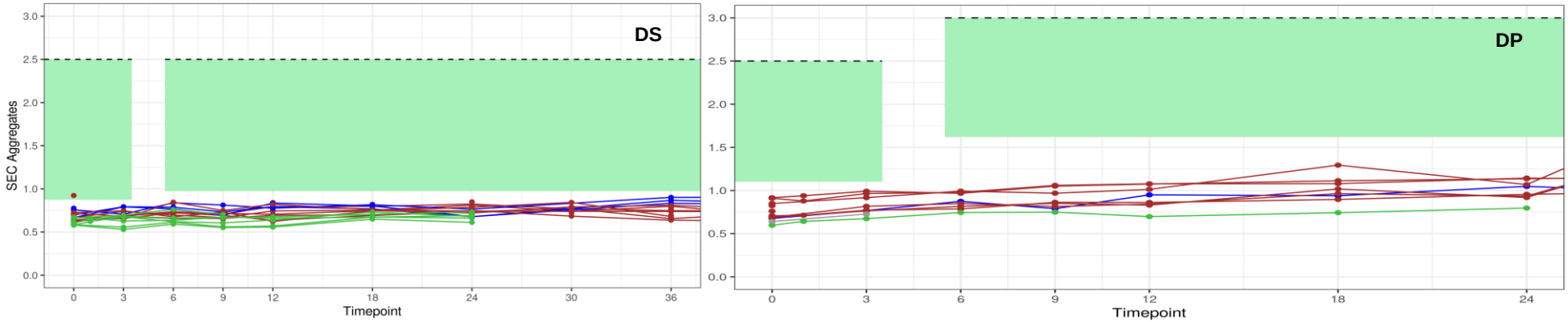
- Characterize batch quality in clinical trials.
  - Evaluate the quality at release, change on stability and patient in-use.

- Develop specification acceptance criteria that are **within** the **clinically relevant space** and are **consistent** with the **clinical experience**.
  - Quantify the manufacturing capability of meeting a proposed commercial specification.

- Final commercial specs are a matter of agreement between the sponsor and individual regulatory agencies.
  - Often results in global **divergence** of specifications. Within the Lilly commercial manufacturing site, the **most stringent** specification acceptance criteria are applied within the DS manufacturing site specification.

mAb Case Study-

Establishing an Acceptable Attribute Range for Total Aggregates



Clinical Dataset

- The maximum result for Total Aggregates was 1.9% in early Phase 2 clinical trial drug product batches.
- Tighter DP release criterion proposed to account for change on stability for DP. DS release and end of shelf life aligned with DP release criterion.

Biological Activity (potency) – low risk of impact

- Highly aggregated material with Total Aggregates levels of 5.1% showed no change in potency.

Safety (immunogenicity/PK) –low risk of impact

- The aggregate has been demonstrated to be predominantly non-covalent, dimeric species. These species have demonstrated lower risk to immunogenicity than larger protein multimers and oligomers.
- Additionally, higher dosing studies (3x) demonstrated favorable safety profile.

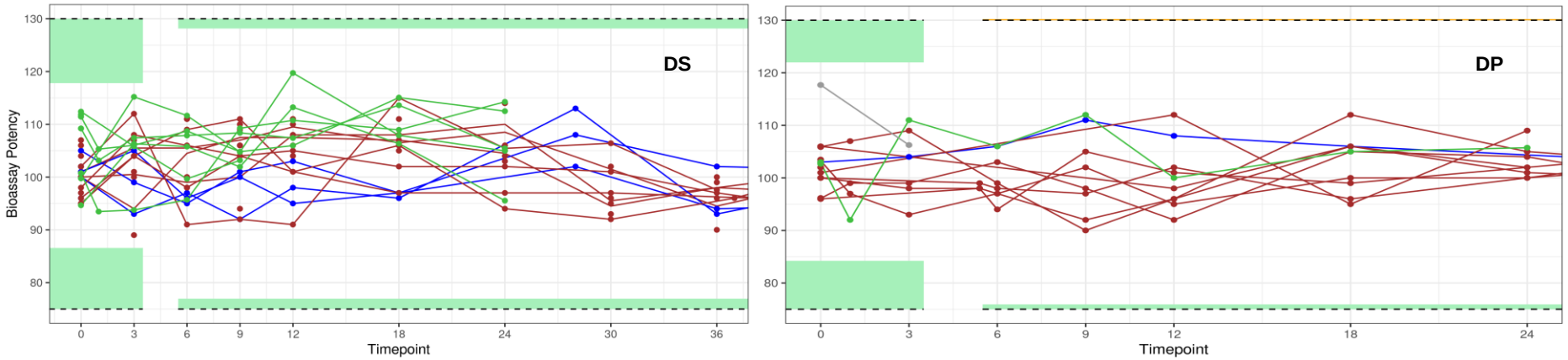
✓ **Ideal Scenario- same specification accepted across agencies based on a patient centric justification.**

For prior submissions, regulatory feedback received *"the proposed range is significantly wider than values observed for batches used during clinical studies"*

	Drug Substance		Drug Product	
	Release	Stability	Release	Stability
Proposed	NMT 2.5	NMT 2.5	NMT 2.5	NMT 3.0
Market 1	NMT 2.5	NMT 2.5	NMT 2.5	NMT 3.0
Market 2	NMT 2.5	NMT 2.5	NMT 2.5	NMT 3.0
Most stringent	**NMT 2.5**	**NMT 2.5**	**NMT 2.5**	**NMT 3.0**

mAb Case Study-

Establishing an Acceptable Attribute Range for Potency



Clinical Dataset

- During early phase and Phase 3 clinical trials, DS and DP potency results encompassed a range of 74-116%.
- Predominant source of observed variability in potency results is analytical variability, DS release and end of shelf-life aligned with DP release and end of shelf-life criteria.

Biological Activity (potency) – low risk of impact

- Steady state pharmacologic properties and the range of clinical experience demonstrate that potency values within the proposed acceptance criteria would not impact the DP efficacy.

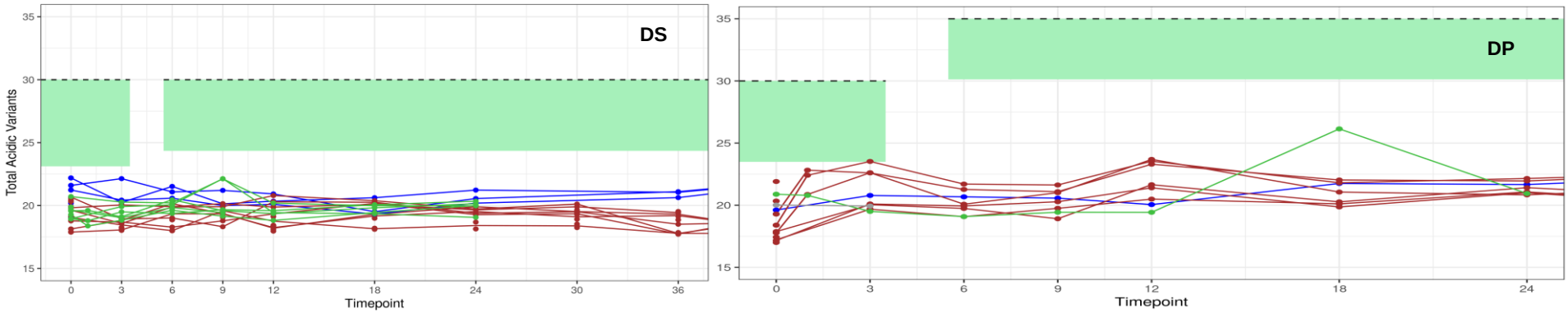
❖ **Typical Scenario, different specifications proposed by individual agencies.**

Potency Challenge: Based on DS & DP release results only, can look capable of meeting more stringent specification. However, the inclusion of the stability data provides a better representation of common cause analytical variability.

	Drug Substance		Drug Product	
	Release	Stability	Release	Stability
Proposed	70- 130	70- 130	70- 130	70- 130
Market 1	80-130	80-130	80-130	80-130
Market 2	70-130	70-130	70- 130	70- 130
Most stringent	**80-130**	**80-130**	**80-130**	**80-130**

mAb Case Study-

Establishing an Acceptable Attribute Range for Total Acidic Variants



Clinical Dataset

- During early phase clinical trials, total acidic variants up to 38% were observed
- Tighter DP release criterion to account for change on stability for DP. DS release and end of shelf life aligned with DP release criterion

Biological Activity (potency) – low risk of impact

- During clinical trials, the total acidic variants were as high as 38% for early phase and 24% for Phase 3

Safety (immunogenicity/PK) –low risk of impact

- The acidic variants have been well characterized and determined to be predominantly Fc deamidated and oxidized species.
- These modifications have no known impact to the safety or efficacy of the product

✓ **Ideal Scenario- same specification accepted across agencies based on a patient centric justification.**

Charge Heterogeneity Challenge: often asked to set the specification based on process variability.

	Drug Substance		Drug Product	
	Release	Stability	Release	Stability
Proposed	NMT 30	NMT 30	NMT 30	NMT 35
Market 1	NMT 30	NMT 30	NMT 30	NMT 35
Market 2	NMT 30	NMT 30	NMT 30	NMT 35
Most stringent	**NMT 30**	**NMT 30**	**NMT 30**	**NMT 35**

CQA Monitoring during Commercial Manufacturing- PQS

Product quality data analyses for Commercial Manufacturing governed by:

- **Annual Product Review**
  - **Annual** holistic review of process data, analytical data including stability, deviations and changes to **assess** the state of **process control and capability**
  - **Appropriateness** of the process **controls**, internal limits, control limits etc
  - Conclusion on the state of validation

- **Continued Process Verification (CPV)**
  - **Ongoing** monitoring program to analyze product and process data to assure state of **control** of the process.
  - Evaluation of the performance of the process to analyze and **respond to trends** in process and analytical data as part of the assessment of the overall control strategy and take appropriate action.

✓ The programs are reviewed as part of a site inspection.

✓ 3.2.S.2.5 *Process Validation* includes the commitment to have the Continued Process Verification (CPV) monitoring plan to ensure that the manufacturing process remains in a state of control during commercial production and demonstrates the robustness of the control strategy. Any changes to the validated process will be governed by the internal quality change management system.

CQA Monitoring during Commercial Manufacturing- Limits

Product quality data analyses in the PQS is performed against several ranges/ limits:

- **Registered** specifications that provide assurance of a safe and efficacious product
  - Release & End of Shelf-life acceptance criteria that the DS and DP is required to meet at the time of release and throughout the expiration period, respectively. Most stringent specifications from all markets applied.

- **Internal Manufacturing Control Limits** used during commercial production within the GMP quality system
  - Control Limits are determined after a sufficient (typically >20) number of commercial batches are manufactured.
  - Control Limits are used to monitor and confirm **consistency** during processing and help distinguish between two types of variation in a process; common cause and special cause variation.
  - Data from the review period are assessed against the control limits to **assess** for atypical results, **trends**/ patterns in the data set, changes in the spread of the data and investigated appropriately.
  - Control Limits are reviewed annually as part of the APR process and revised as appropriate.

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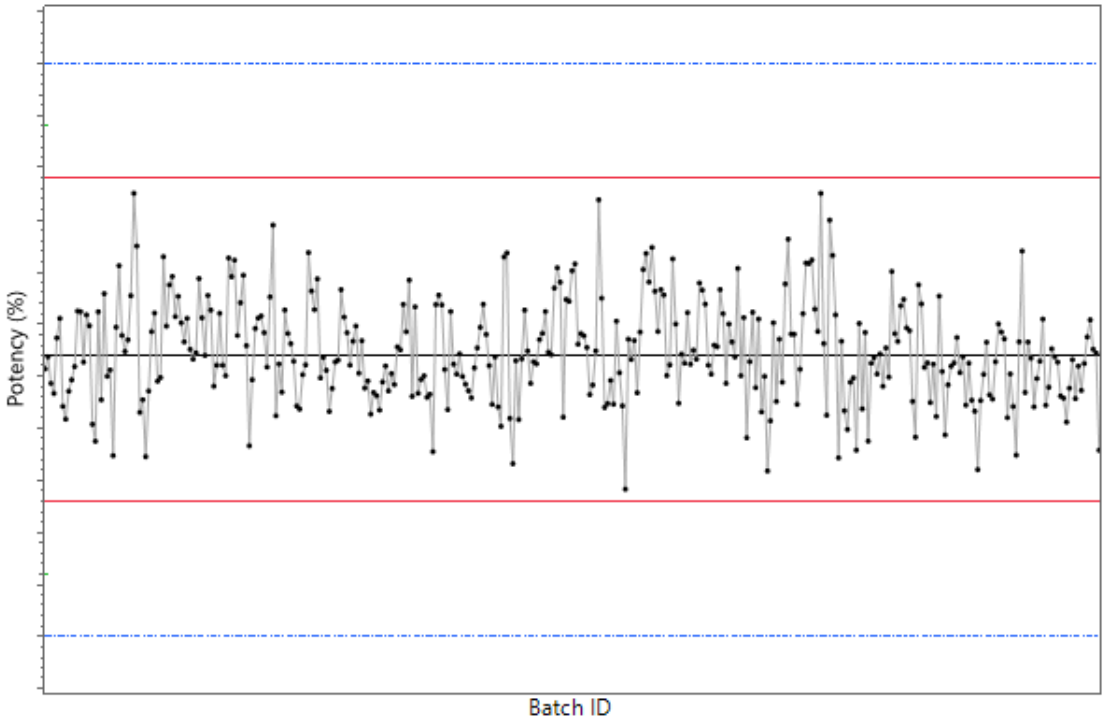
CQA Monitoring through Product Lifecyle- Potency



Release Specification

Control Limit

Control Limit

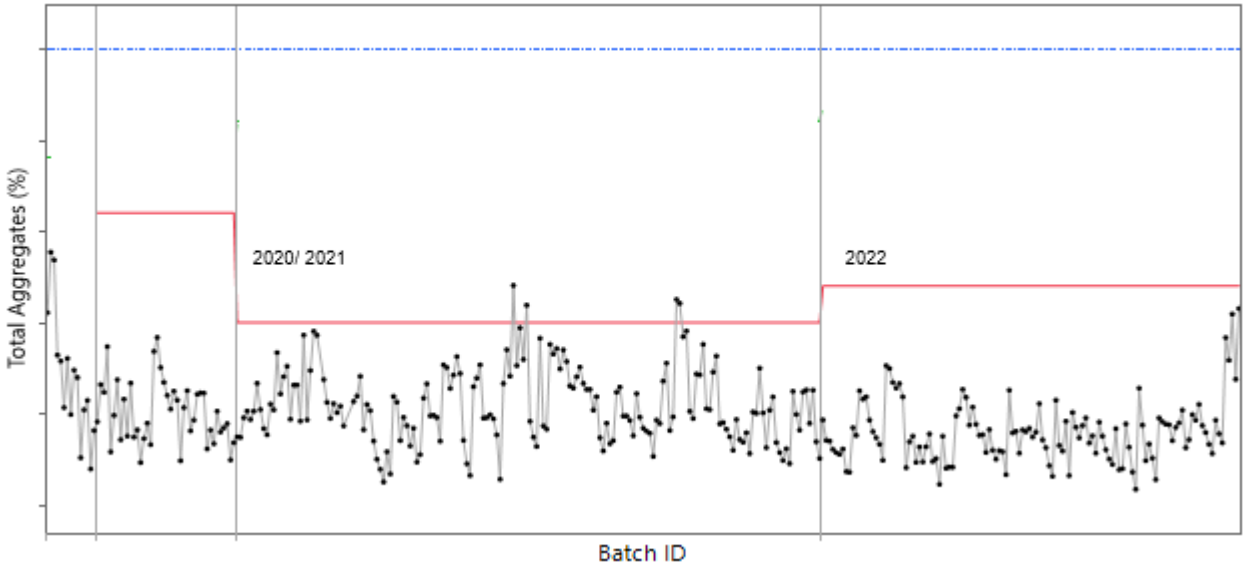
Release Specification

Review of the dataset in the APR/ CPV Program:

All drug substance results are within the control limit, and regulatory specification. The data set shows that the process is **stable** and predictable, and the control limits are appropriate for the process to monitor process consistency. A Cpk 1.3 was achieved in the review period which demonstrates that the process is **capable** with respect to the tightest release specification.

mAb Case Study-

CQA Monitoring through Product Lifecyle- Total Aggregates



Release Specification

Control Limit

Review of the dataset in the APR/ CPV Program:

- Prior to the 2020 campaign, the Control Limit was tightened with the availability of more representative data at commercial scale and a **tighter estimate** of expected **variability** applied. Several batches during the 2021 period exceeded the control limits, this was investigated and captured in the PQS- no special cause was identified.
- From the 2021 APR, it was recommended to **recalculate** the **control limits** and centre line to reflect the current operating space of the process and incorporate the additional **common cause variability**. (Note if the data was special cause event, this would not be included in the calculation of the Control Limits).

mAb Case Study-

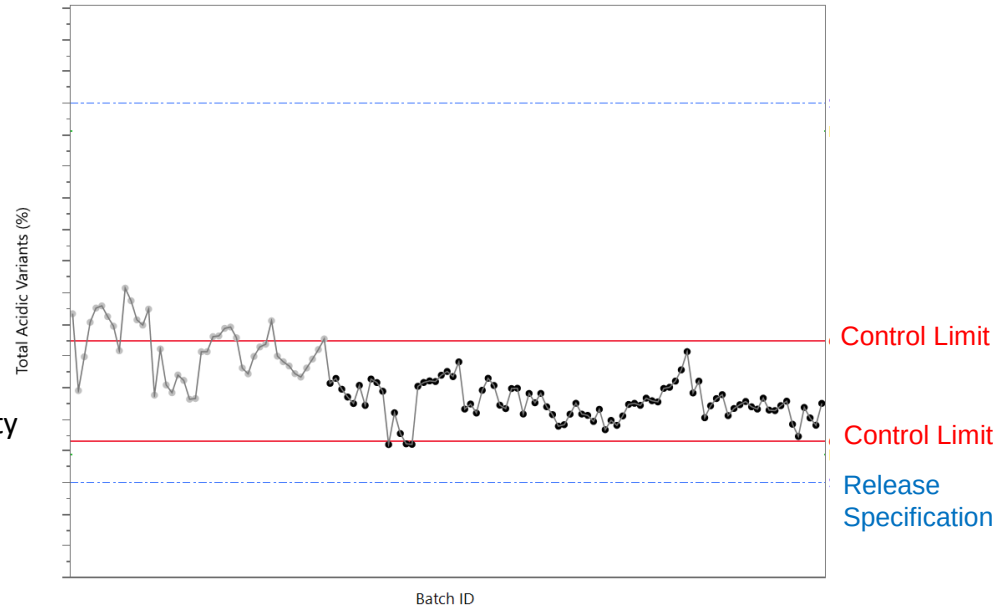
CQA Monitoring through Product Lifecyle- Charge Heterogeneity TAV

Background:

- The commercial DS specification (first submission 2016) was established based upon clinical experience, with limited manufacturing experience, analytical method variability and stability data.

Review of the dataset in the APR/ CPV Program:

- There was shift upwards in %MP and %TBV with additional commercial manufacturing experience with an associated **downward shift in TAV** attributable to improvements in the manufacturing process and a reduction in analytical variability over time.
- Several batches were **outside** the TAV **Control Limits** in the APR/CPV monitoring program, which was captured and investigated in the PQS where several CAPAs were implemented within the allowable operating space.



Regulatory Action taken to ensure long-term Robust Commercial Supply:

- A Prior Approval Supplement (PAS) was used to revise the DS and DP specification to reflect commercial manufacturing experience, with an increase in %MP & %TBV proposed and associated decrease in %TAV.
- To support the proposed revision, the shift in charge heterogeneity was characterized and the impact on patient safety assessed; 3.2.S.4.5 Justification of Specifications.
- Prior knowledge demonstrated that the charge variants were biologically active, an assessment of the cell-based bioassay of the more recent batches confirmed no impact to the biological activity as a result of the shift.
- The revision to the DS specification was accepted.

Key Takeaways

- The Problem Statement on setting specifications may be narrowed using a Control Strategy Methodology.

- Specification acceptance criteria should
  - ✓ Be based on the risk to clinical performance
  - ✓ Provide consistency of the commercial material back to the clinical experience
  - ✓ Not be based on the capability of the manufacturing process
  - ✓ Not hinder process improvements/ site additions which may have an adverse impact on reliable supply.

- Monitoring process consistency during commercial manufacturing through the use of internal control limits is a key component of the CPV and APR programs in the Pharmaceutical Quality System, which are extensively reviewed during site inspections.

- *Further discussion required on how to provide assurance that product consistency monitoring and reaction to trends is a key requirement in the PQS*
  - *Is greater collaboration between the reviewer and inspector required or is there a need to include more detail on the monitoring program in the dossier, perhaps Section 3.2.S.2.5 Process Validation?*

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