Case Studies for Patient-Centric Specification Setting for a Therapeutic Protein and IQ Readout on Endotoxin Acceptance Criteria

Katrina Kearns

Pfizer

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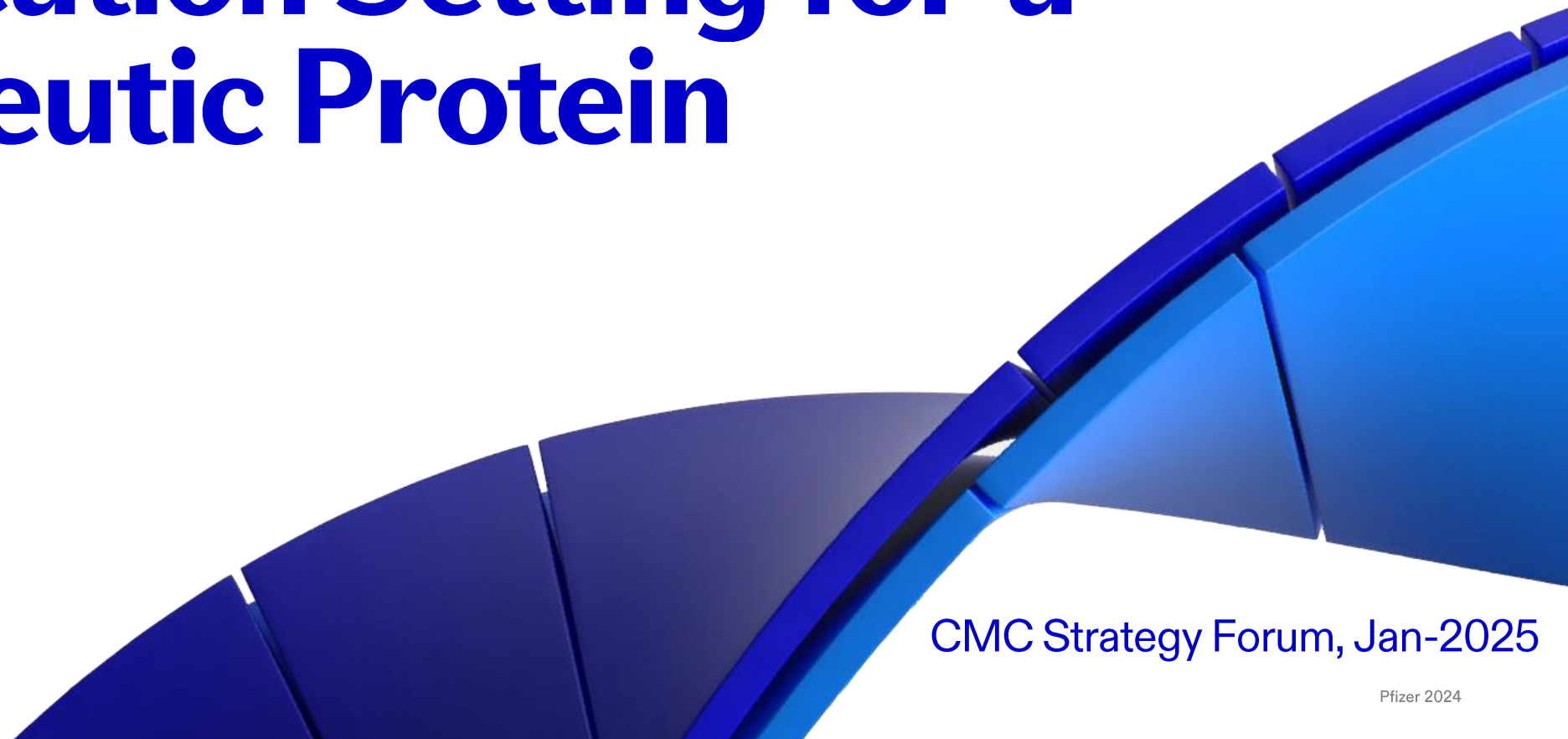
Part 1: Case Studies for Patient-Centric Specification Setting for a Therapeutic Protein

Katrina Kearns



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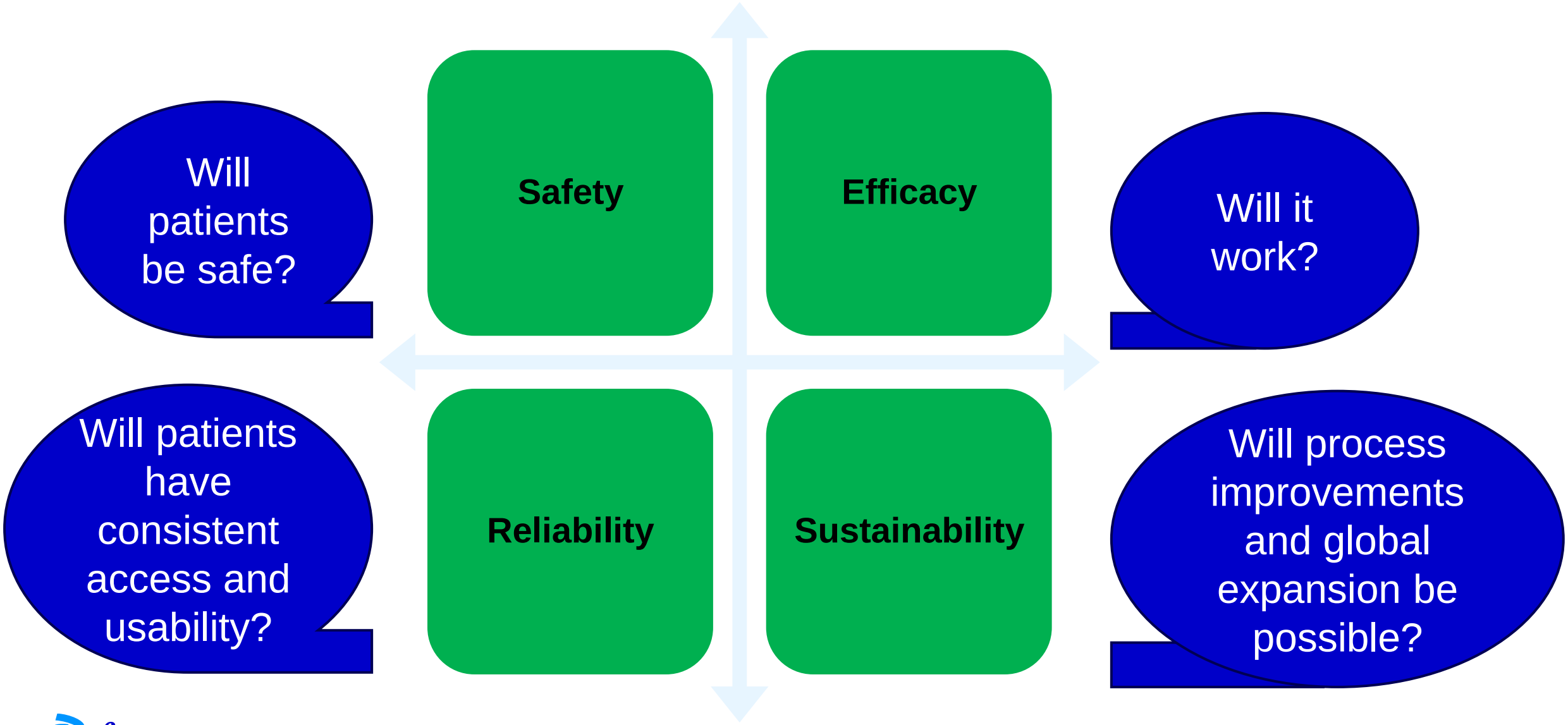
Considerations for Patient-Centric Specifications



Example 1 – Aggregates (SE-HPLC) Acceptance Criterion

Aggregates considered CQA due to potency and potential immunogenicity impact

Quality Attribute	Justification	Region 1 Proposed Strategy	Region 1 Final	Region 2 Proposed Strategy	Region 2 Final
		4 Markets		EU + Follow-on Markets	
Aggregates	Structure / function studies and clinical batch data	DS Tolerance Interval (2.8%)	DS Tolerance Interval (2.8%)	DS Tolerance Interval (2.8%)	3 SD (2.6%)

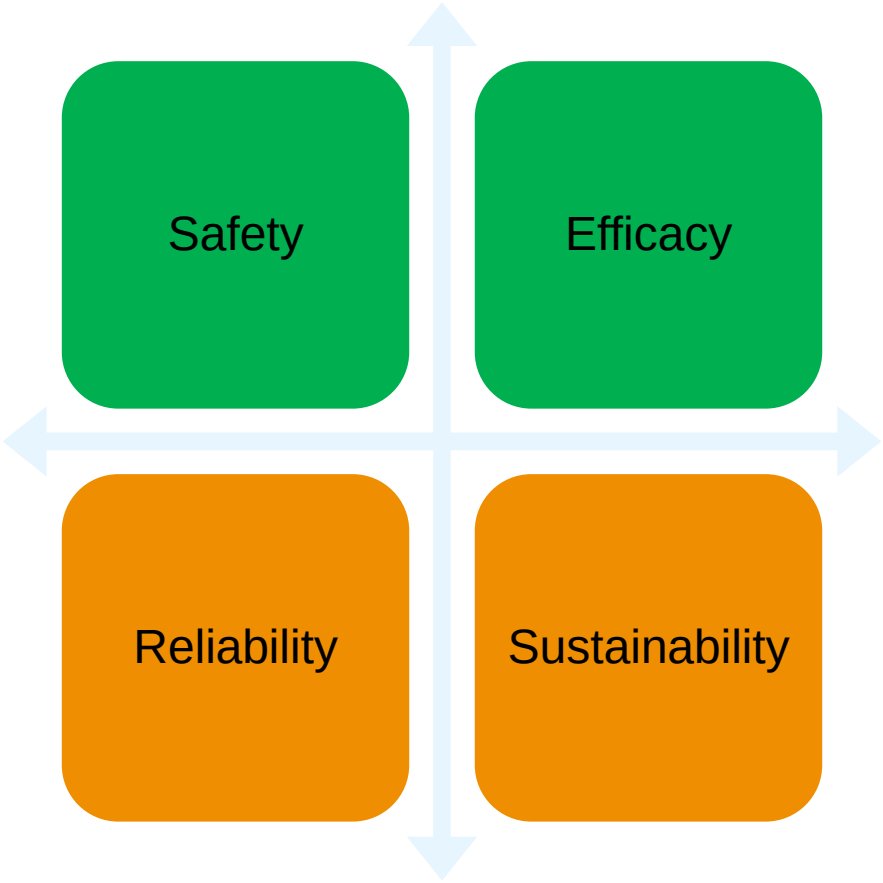
Manufacturer's Justification:

- Clinical experience: Material with 4.1% aggregates dosed in Phase 1 and Phase 2 clinical studies with no immunogenicity concerns identified
- Structure/Function: Material containing 7% aggregates maintained full potency

Reviewer Feedback

- One rapporteur agreed the tolerance interval proposal was "clinically qualified"; however, requested to tighten acceptance criteria based on pivotal batch history

Example 1 – Aggregates Acceptance Criterion



Aspects of Patient Centricity Applied to Review

- ✓ Safety – The reviewer requested a tightening of the limit well within safe exposures.
- ✓ Efficacy – The reviewer's request did not adversely impact the delivered dose to the patient.
- ✗ Reliability – The manufacturer determined the risk of failing the new limit was high and could put supply at risk.
- ✗ Sustainability – Future process improvements (scale-ups to enable global supply, changes to decrease environmental concerns) put at risk by tight acceptance criterion.

Example 2 – Related Forms (RP-HPLC) Acceptance Criteria

- Multi-use autoinjector with weekly dosing at home for a maximum of 28 days
- Temperature-sensitive attribute

Quality Attribute	Justification	Proposed Strategy	Approved Strategy	Post-Marketing Update Strategy
Related Forms (Deamidation, Oxidation, Isomerization, etc.)	Structure / function studies, literature supporting safety and efficacy at high levels, and clinical batch data	**DP Release:** DS Tolerance Interval + Change During DP Manufacture **DP Stability:** DP Release + Change During Stability	**DP Release:** DS 3x SD + Change During DP Manufacture **DP Long-Term Stability:** DP Release + Change During Stability **DP In-Use Stability:** DP Long-Term Stability + Projected Change During In-Use Stability	**DP Release:** DS 3x SD + Change During DP Manufacture **DP Long-Term Stability:** DP Release + Change During Stability **DP In-Use Stability:** DP Long-Term Stability + Change During In-Use Stability

Example 2: Related Forms (RP-HPLC) – Initial Proposal Based on Release and Long-Term Stability Data Only

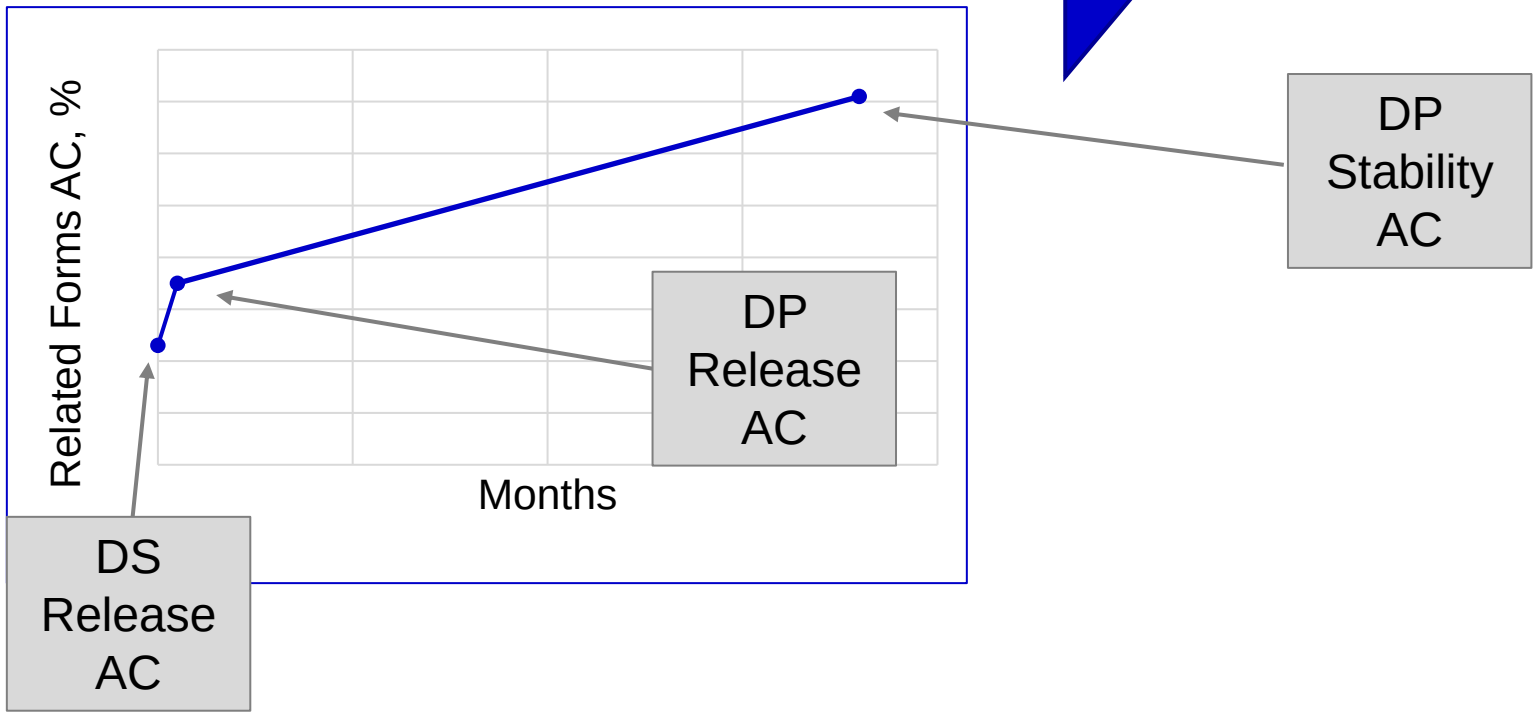
DS Release AC (Tolerance Interval)

+ Expected Change During DP Manufacture

DP Release AC (DS Release + Manf Change)

+ Expected Change During Long-Term Stability

Stability AC (DP Release + Stability Change)



Example 2 – Proposal Approved at Time of Marketing Submission Approval
Based on Release and Long-Term Stability Data Only
Post-Marketing Commitment Proposed

DS Release AC (Tolerance Interval)

+ Expected Change During DP Manufacture

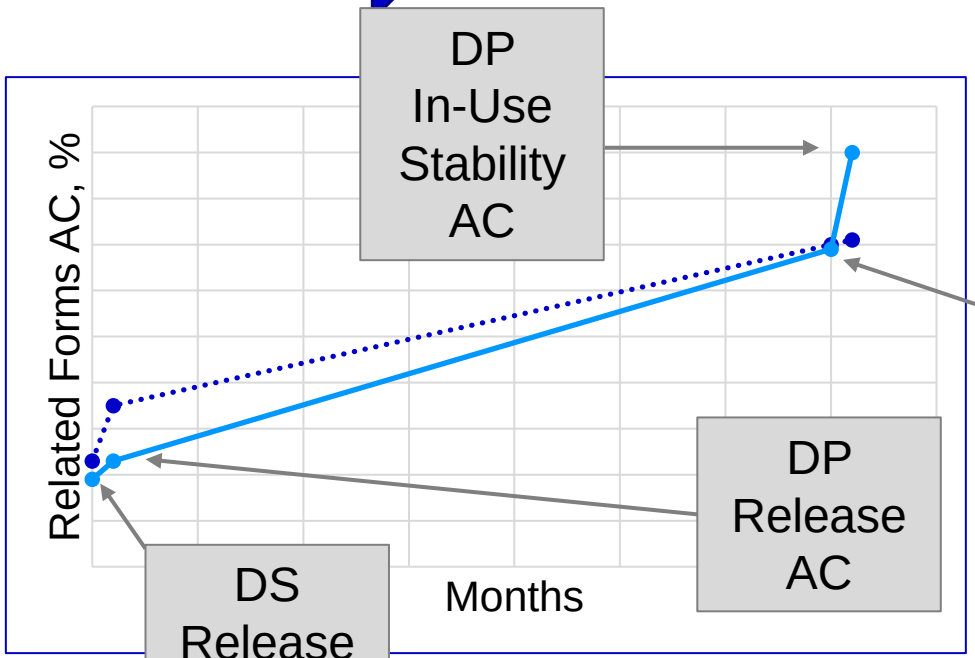
DP Release AC (DS Release + Manf Change)

+ Expected Change During Long-Term Stability

Long-Term Stability AC (DP Release + Stability Change)

+ Expected Change During In-Use Stability

In-Use Stability AC (Long-Term Stability + Projected In-Use Stability Change)



Example 2 – Post-Marketing Commitment AC Adjustment
In-Use Stability AC Tightened After Study Completion

DS Release AC (Tolerance Interval)

+ Expected Change During DP Manufacture

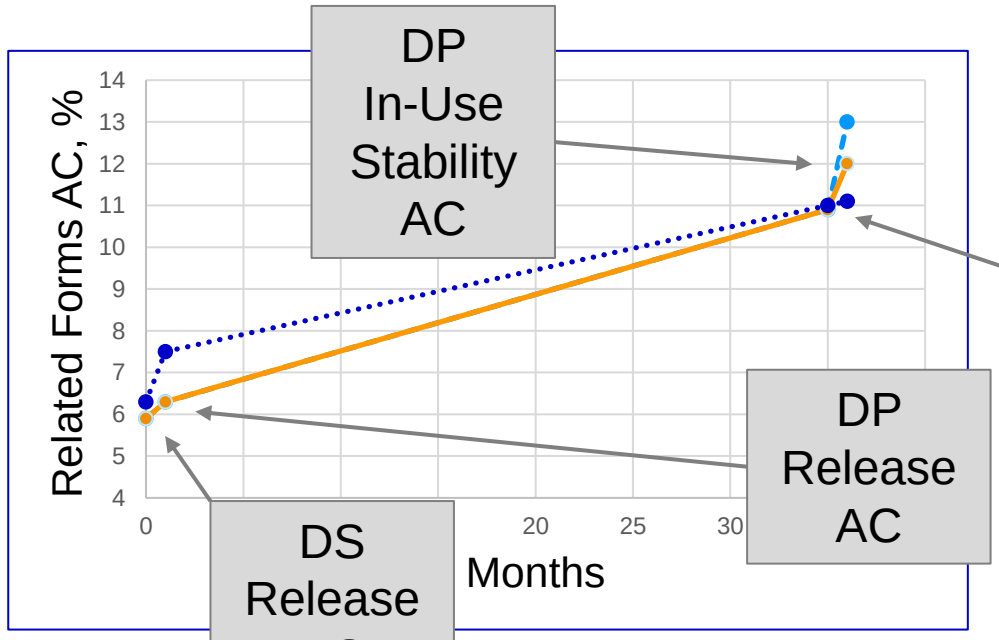
DP Release AC (DS Release + Manf Change)

+ Expected Change During Long-Term Stability

Long-Term Stability AC (DP Release + Stability Change)

+ Expected Change During In-Use Stability

In-Use Stability AC (Long-Term Stability + In-Use Stability Change)



DP In-Use Stability AC

DP Long-Term Stability AC

DP Release AC

DS Release AC

Example 2 – Related Forms Acceptance Criteria Review

Aspects of Patient Centricity Applied to Review

- ✓ Safety – The reviewer requested a tightening of the limits and enabled addition of an in-use criterion, all within safe exposure levels.
- ✓ Efficacy – The reviewer's request did not adversely impact the delivered dose to the patient.
- ✓ Reliability – The final limits enabled consistent supply and user-friendly label conditions.
- ✓ Sustainability – Future process improvements (scale-ups to enable global supply, expansion to Zone IV global markets) were enabled by wider in-use acceptance criteria.

In-Use and Thermal Cycling Considerations

Excessively tight specifications place a patient's ability to have consistent, usable supply at risk

Overly restrictive label and/or temperature excursion requirements can result in destruction of material that was safe and efficacious and can prevent certain markets from access

In-use and thermal cycling data should be considered for specifications in addition to release and long-term stability data

Patients are less likely to be compliant with dosing instructions if label instructions are too restrictive

Goal → Enable patients to have consistent access to life-changing, safe and efficacious medicines with in-use instructions that fit into their environments and lives

Example 3 – Endotoxin Acceptance Criterion

Product is a subcutaneous injection with no reconstitution or dilution at point of use.

Quality Attribute	Justification	Region 1 Proposed Strategy	Region 1 Final	Region 2 Proposed Strategy	Region 2 Final
		5 Markets		3 Major Markets + Follow-on Markets	
Endotoxin	Compendial limit of 5 EU/kg/hr	2-fold Safety Factor (50 & 125 EU/mL, equivalent to 2.5 EU/kg/hr)	2-fold Safety Factor (50 & 125 EU/mL, equivalent to 2.5 EU/kg/hr)	2-fold Safety Factor (50 & 125 EU/mL, equivalent to 2.5 EU/kg/hr)	2x Worst-Case LOQ (10 EU/mL, equivalent to 0.5 & 0.2 EU/kg/hr)

Manufacturer's Justification:

- The manufacturer provided a safety-based justification for a 2-fold safety factor compared to compendial guidance

Reviewer Feedback

- Reviewers insisted that limits needed to be based on batch data alone

Example 3 – Endotoxin Acceptance Criterion Review

Aspects of Patient Centricity Applied to Review

✓ Safety – The reviewer requested a tightening further within the demonstrated safe levels.

✓ Efficacy – The reviewer's request did not impact the delivered dose.

? Reliability – Based on the 11 batches of data available, it is likely the tightened limit would not impact reliability of supply *in the short-term*.

x Sustainability – Longer term process improvement options could be hindered by the unnecessary tightening of the endotoxin limit.

Acknowledgements (Part 1)

- Tom Lerch
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Thank You!!!