Approaches to Setting Specification Acceptance Criteria

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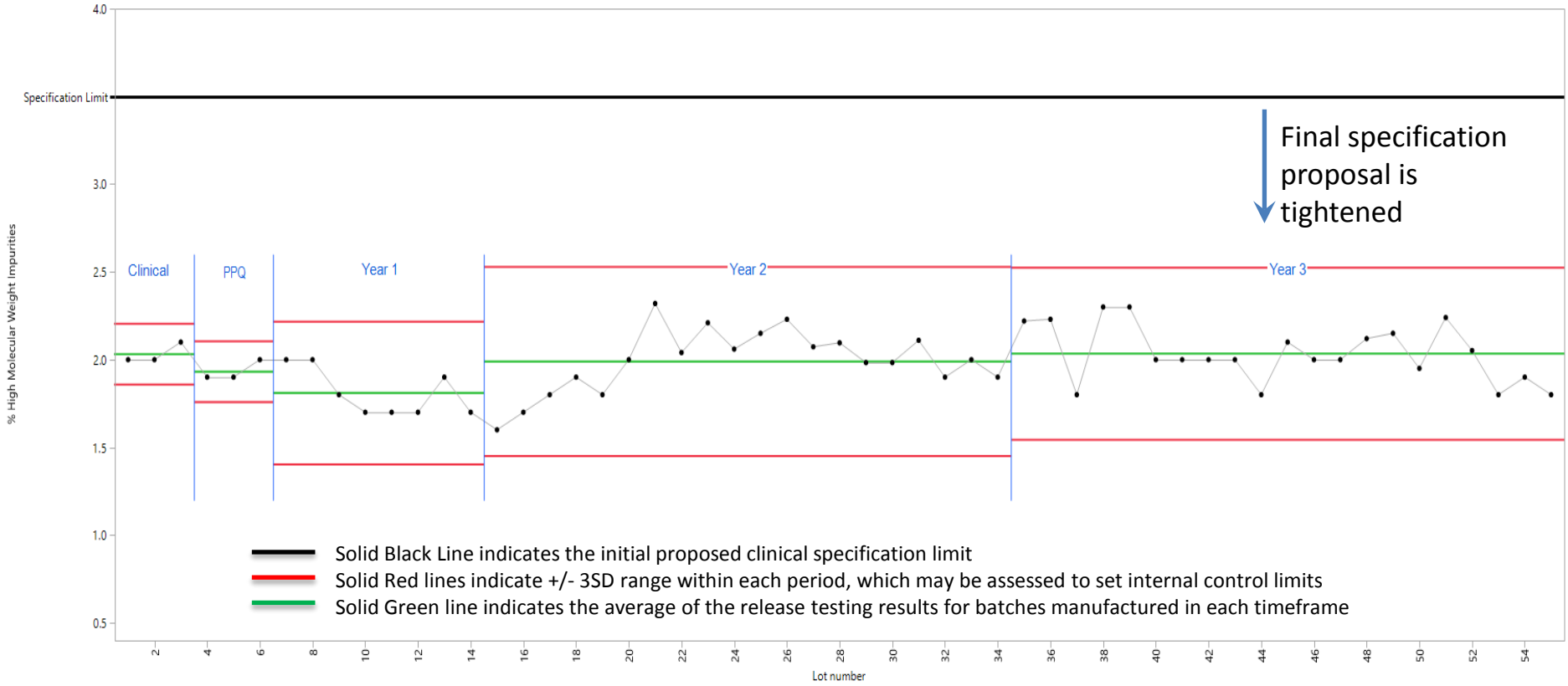
Problem Statement

- Acceptance criteria for specifications are often set strictly based on the range of values observed in clinical batches
- Products developed through accelerated routes are likely to have a limited number of batches at the time of approval
- Acceptance criteria rigidly set based on very limited numbers of batches are not likely to reflect the attribute acceptable range and future process capability
- This is likely to lead to failure of lots with acceptable product quality, shorter expiry periods and issues with continued global supply of these critical products

Case Study

- In the next three slides, consider two key product quality attributes: High Molecular Weight Impurities by SEC and Purity by CE-SDS
- Initially, the batch data available from manufacturing, release and stability testing may be minimal for a product being developed through an accelerated pathway
- Over time as additional experience is gained, manufacturing and analytical variability is expected to be observed
- Routine process monitoring as applied via continuous process verification leads to identification of atypical batches, allows for investigation of root cause and furthers product knowledge
- Stability trends in key product quality attributes become more clear and may confirm clinical lot stability trends
- Over time, post approval, the ongoing stability program adds additional lot data to the stability data set

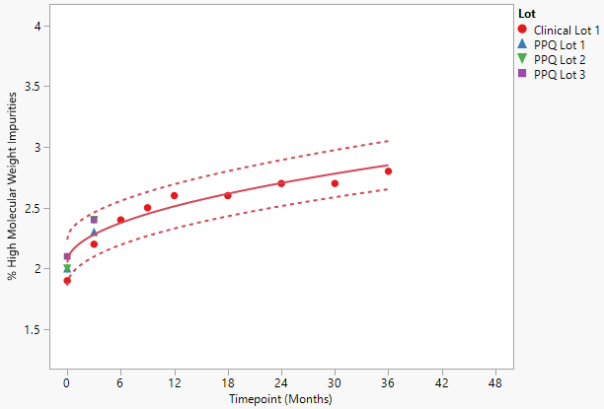
Case Study: Evaluation of HMW Impurities Acceptance Criteria



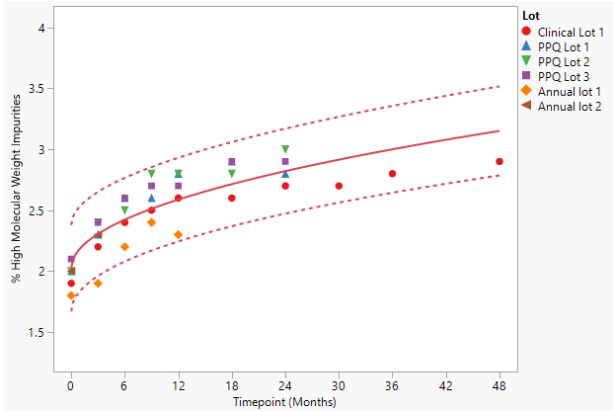
- **Continued process verification is implemented and the process is well-controlled for this attribute**
- **Final specification limit is tightened with strong confidence in future process capability that >95% of future batches will meet specification**
- **This specification justification is filed with the agency to meet the Post-Approval Commitment**

Case Study: Evaluation of HMW Impurities Acceptance Criteria

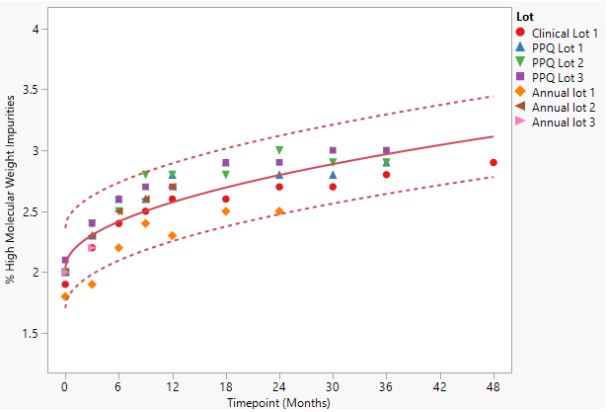
Initial Filing



2 years post approval

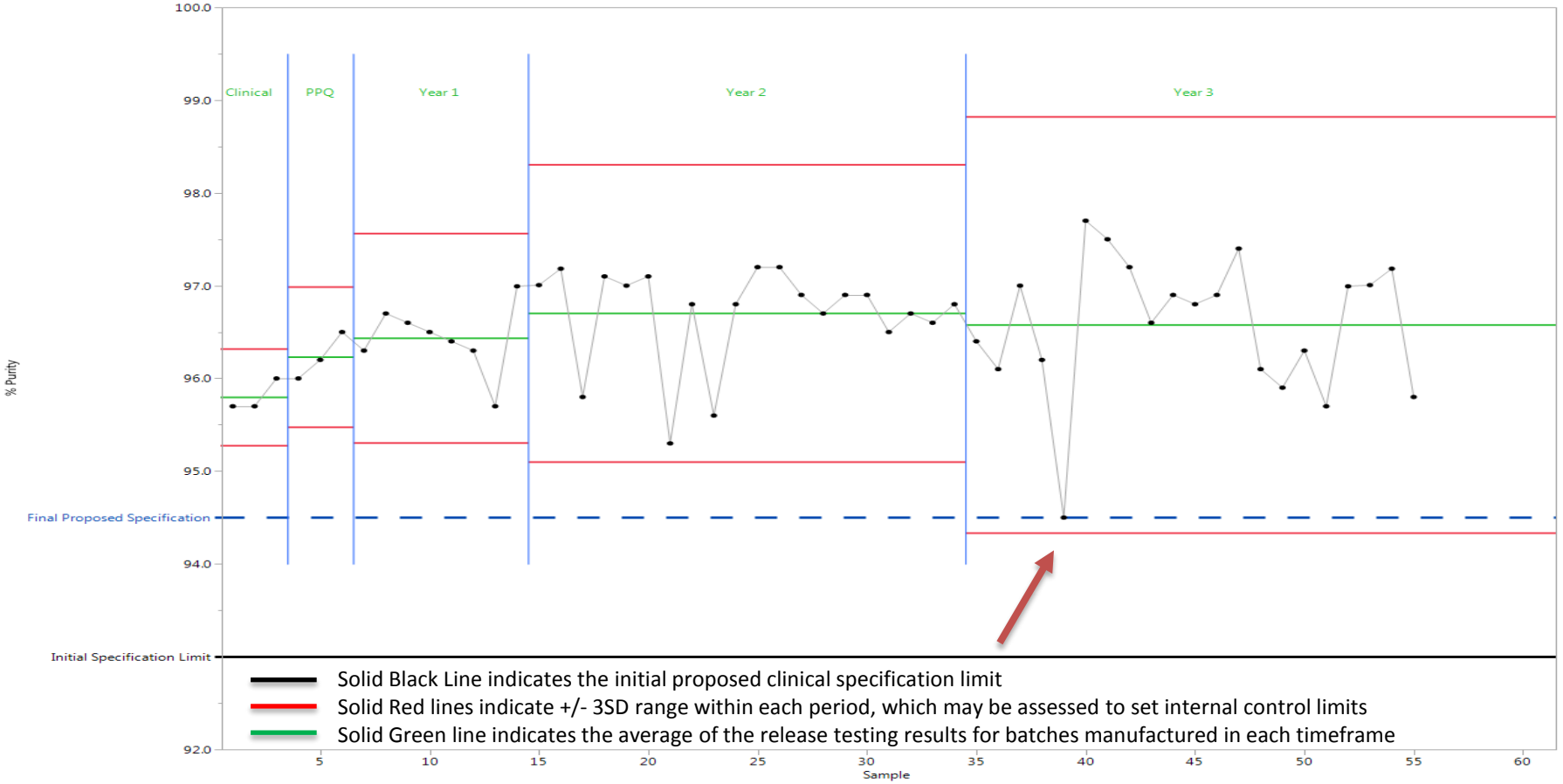


3 years post approval



- **Ongoing stability monitoring confirms the bi-phasic trend in this attribute demonstrated initially by the long-term trend of the clinical batches**
- **Final specification limit is tightened with strong confidence that the stability trends will meet specification through shelf-life**
- **This specification justification is filed with the agency to meet the Post-Approval Commitment**

Case Study: Evaluation of Purity Acceptance Criteria



- **Consider Purity by Nonreducing CE-SDS, note atypical batch is identified as the result is below the statistical control limit established by the prior periods**
- **Batch is investigated and found no correlated manufacturing root cause, root cause identified related to possible analytical issue**
- **Batch conforms to all specifications and no impact to product quality, released**
- **Final specification limit is tightened from ≥ 93.0% to ≥ 94.5% and filed with the agency**

Considerations of attribute knowledge

- In vitro and relevant in vivo bioanalytical methods/models used to evaluate the risk that a change in an attribute level will impact the established safety/efficacy profile
  - Enables assessment of purified or enriched attribute pools, or degraded samples
  - Ability to investigate wider attribute range compared to clinical experience
- Immunogenicity risk assessment
  - Is the attribute present on naturally occurring molecule?
  - Does attribute increase under physiologic conditions (eg, serum, pH 7.0/37^{o}C) indicating levels higher than observed at release or stability would have been encountered by patient?
  - Is there evidence of immunogenicity in relevant in vitro and in vivo animal models? Lack of impact at higher levels than allowed by acceptance criteria would suggest there is a low risk of clinical impact
  - Is relevant clinical data available from other products that informs on the potential of the attribute to be immunogenic at allowable levels
- Other relevant internal knowledge or information available in the literature that informs on the potential of the attribute to impact safety and efficacy at the allowable levels

Proposal

- Acceptance criteria for appropriate parameters approved through accelerated routes to be primarily set based on:
  - clinical phase specifications
  - documented risk assessments
  - prior knowledge
- Confidence in these acceptance criteria will be enhanced by strategies such as:
  - post-approval commitments to re-evaluate acceptance criteria when sufficient knowledge is available
  - post-approval commitments to provide a high level summary of trending data to the agency on an annual basis for the first 2-3 years post-approval (this easily leverages the APR/YBPR/Annual Report process)
  - Strong Quality Management System and fully implemented continuous process verification

Conclusions

- The ultimate goal is to establish acceptance criteria appropriate to the level of available knowledge with a high level of confidence that will be no impact to safety and efficacy within the allowable range.
- This approach is feasible using current Regulatory framework but would require the context of establishment of acceptance criteria to be more broadly considered.
- This approach would require closer interactions between the MAH and Assessor/Agency post-approval to ensure continued monitoring is appropriate and product quality expectations are being met.
- Ranges for product quality attributes are generally well controlled for biotechnology products and the impact of these attributes on safety and efficacy is better understood.
- Acceptance of this approach allows for rapid development of high quality medicines and continued supply globally to meet unmet medical needs.

Acknowledgements

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Supplemental Slides

BPOG, 2014, Continued Process Verification: An Industry Position Paper with Example Plan 2014, ©BPOG Biophorum Operations Group