Setting acceptance criteria for release specification based on limited batch data

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- It is often challenging to set appropriate acceptance criteria for release specifications when limited batch data on the commercial process are available.
- Regulatory expectations:
  - Acceptance criteria should be clinically justified
  - Reflect the process capability of the commercial manufacturing process
  - Ensure product consistency
  - Ideally the use of a SD above 3.0 should be avoided
- Industry limitations
  - Limited batch data may be available on the commercial process
  - The clinical process may have differences that may limit their suitability for setting criteria
  - Acceptance criteria that are set too tight may lead to costly batch rejections, which could also impact supply to patients

EMA PRIME Toolbox

- *"The justification of specification limits for CQAs should be linked to clinical performance rather than solely derived from statistical methods such as tolerance intervals.* ***Statistical analysis of a limited number of batches could result in specification limits which are too broad and cannot be justified clinically****."*

- The opposite is also frequently true - ***Statistical analysis of a limited number of batches could result in specification limits which are too narrow****.*

Case study

- Biological product with different main variants to the manufacturing process
- Changes between processes are relatively minor and comparability has been demonstrated for all changes
- Some changes to CQAs are observed with Process 2/2b – e.g. reduction in impurity levels
- Initial acceptance criteria were based on all available batches

Number	Process	Use	Notes
Dev	Development	Non-clinical studies	
1	Early clinical process	Phase 1, 2, 3	Initial clinical process
2	Late clinical process	Phase 2, 3	Optimized clinical process
2b	Commercial process	Phase 2, 3, PPQ	Minor modifications, highly similar to Process 2

Question Summary

- *Acceptance criteria for impurities and active substance :*
  - *Clinically justified*
  - *Reflect the process capability of the commercial process and the comparable late stage process*
  - *Ensure product consistency*
- *Impurity content was lower for the commercial process*
- *Avoid use of a SD above 3.0*

Problem statement

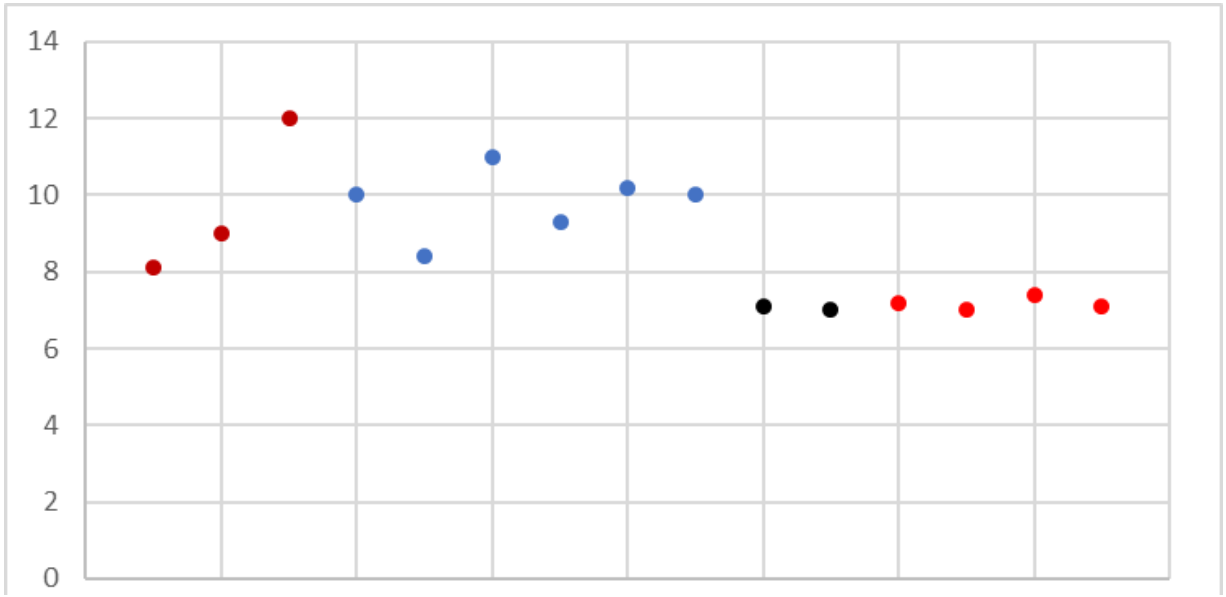
- The commercial process (2b) is highly similar to the optimized late clinical process (2) and comparability has been demonstrated. Both processes and 2b can be considered to be representative of the commercial process.
- Some batches have been manufactured using processes 2 and 2b
- There are some differences in CQA levels between the early clinical process (1) and late clinical (2) and commercial processes (2b) (e.g. reduced impurity levels)

- **Acceptance criteria should be based on the process capability of the commercial process, however, it is not appropriate to set acceptance criteria of 3.0 SD based on very limited batch data**
- Three standard deviations based on a limited number of lots would result in a higher reject rate, which is unreasonable given the clinical coverage for each of these parameters

Proposed solution

- In order to set limits that are both clinically justified and represent the commercial and late stage processes the data were analyzed in different ways:
  - Acceptance ranges based on three standard deviations (SD) from the mean impurity levels in the Phase 2 and/or Phase 3 clinical studies (clinical and commercial processes, n = >10)
  - Acceptance ranges derived from an upper or lower confidence limit of a one-sided 99% confidence interval (CI) with 99% population coverage probability based on all commercial DS batches (n = <10)
  - The proposed limits were chosen as the tighter value for each impurity between the two calculated limits
- Commitment to review limits after pre-determined number of batches have been manufactured

Example hypothetical batch data – Impurity 1



Hypothetical Test	Hypothetical Acceptance Limit		
	99% Confidence, 99% Coverage commercial process	3 SD based on DS Batches Used in Phase 2 and/or 3 Studies	Proposed Limits
Sample Size	n = <10	n = >10	
Impurity 1	8	13	≤ 8%
Impurity 2	4	4	≤ 4%
Impurity 3	5	7	≤ 5%

Conclusions

- Setting meaningful acceptance criteria based on limited batch data can be challenging
- A maximum limit of 3 SD is generally expected by regulatory authorities however this may not be statistically justified for small sample sizes and may result in unreasonable tight limits
- A hybrid approach was proposed where batch data were analysed in two ways:
  - 3 SD from the mean levels in batches used in late stage clinical studies
  - Acceptance ranges derived from an upper or lower confidence limit of a one-sided 99% confidence interval (CI) with 99% population coverage probability based on all commercial DS batches
- Acceptance criteria were based on the tighter value for each impurity between the two calculated limits

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