Joint BWP / QWP workshop with stakeholders in relation to
prior knowledge and its use in regulatory applications

How to Use Prior Knowledge in Defining the Control Strategy

EMA, London; 23 November 2017

efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

EMA Prior Knowledge Workshop

Case Study: Prior Knowledge for Setting Acceptance Criteria

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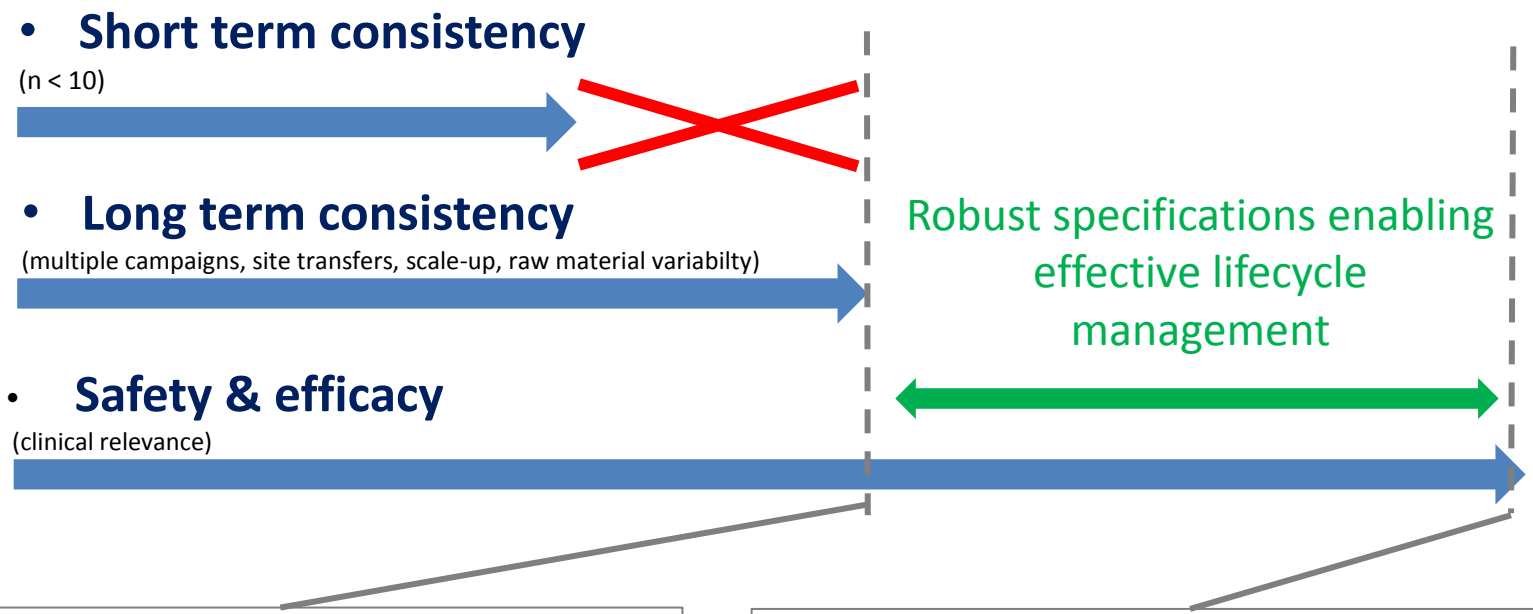
Nov 2017

Setting Specification Limits Based on...



Establishing needs and requirements from a manufacturing perspective

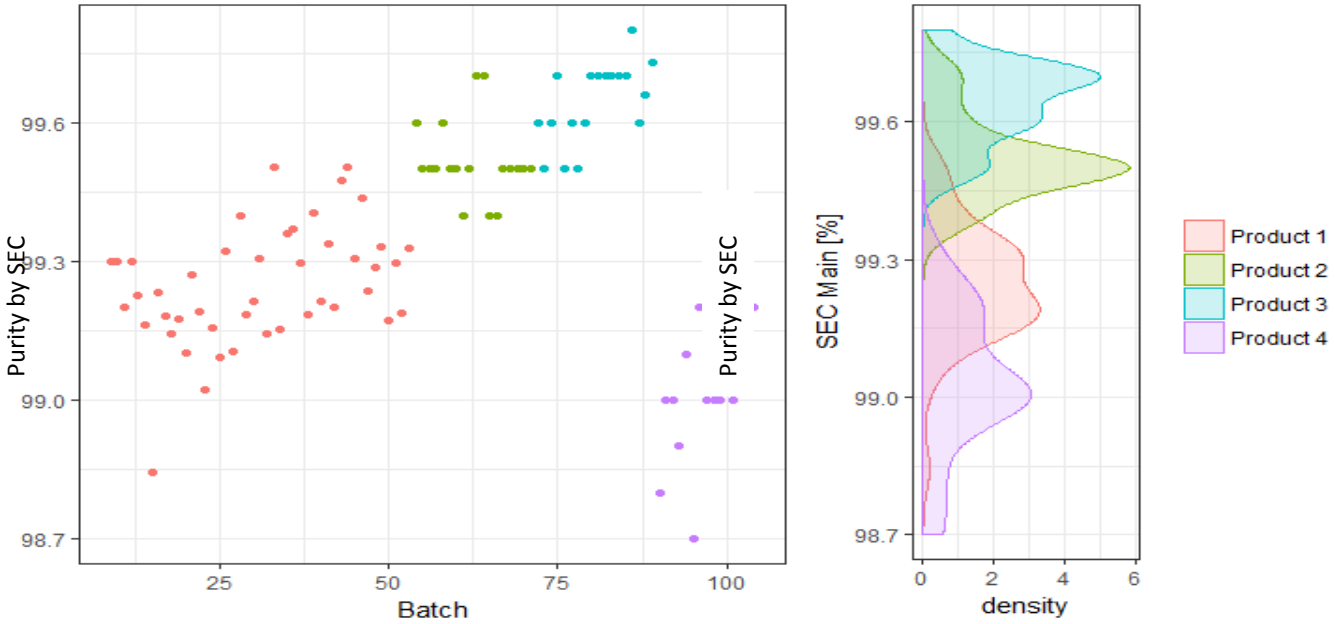
- Account for uncertainty in estimation of variability
- Capable process
- Process Characterization
- **Prior knowledge: Considering known long-term variability from related processes / molecules**

Justification of proposed limits with respect to safety and efficacy

- Batches used on preclincial and clinical studies
- Product Understanding / CQA / QSAR
- **Prior Knowledge**
  - **Platform knowledge for process-related impurities**
  - **Biosimilar's reference product**
  - **Literature and guidances (WHO, ICH,...)**

Establishing Needs and Requirements From a Manufacturing Perspective

Platform knowledge: Considering known long-term variability from related processes / molecules

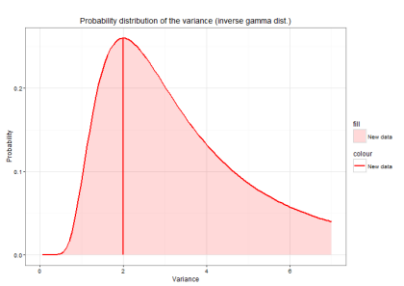


- Applicable also for other quality attributes, such a glycosylation or charge variants
- How to argue with platform variabilities?
  - Supportive evidence in a narrative justification?
  - Mathematically combining platform variability with product-specific data?

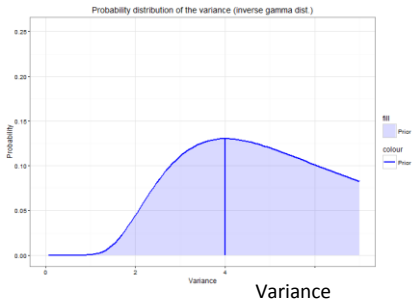
Statistical Approach for Combining Prior Knowledge with New Data

Product-specific evidence

Probability distribution for the variance based on **process-specific data** (during development, typically only few data points)

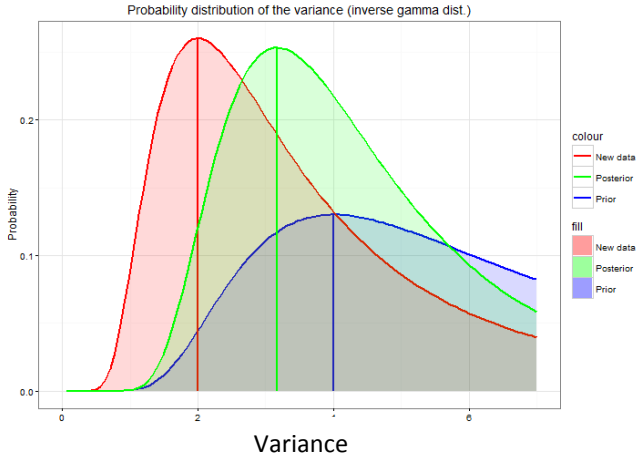


Variance



Variance

Bayesian estimation of posterior probability



Prior Knowledge

Probability distribution of the variance based on **platform knowledge** (aggregated knowledge from several processes, more data points)

Estimation of expectable variance

- → combines prior knowledge and new observations
- → Provides a compromise between both, which is weighted by the number of observations

Bayesian estimation incorporates process-specific data as well es platform knowledge to calculate a reasonable estimation of expectable variance

Justification of Proposed Limits with Respect to Safety and Efficacy

Prior Knowledge for process-related impurities

- not related to the mode of action → Prior Knowledge easier tranferable

Examples: DNA, raw materials, elemental impurities

Prior Knowledge typically easily transferable if basic pre-conditions are met

- **Prior Knowledge sources:** Tox assessments, regulatory guidances (e.g. ICH Q3D, WHO,...), internal batch data, literature
- **Considerations:** dosing, route of administration, expression system (DNA)

HCP – may require more justification of Prior Knowledge transferability

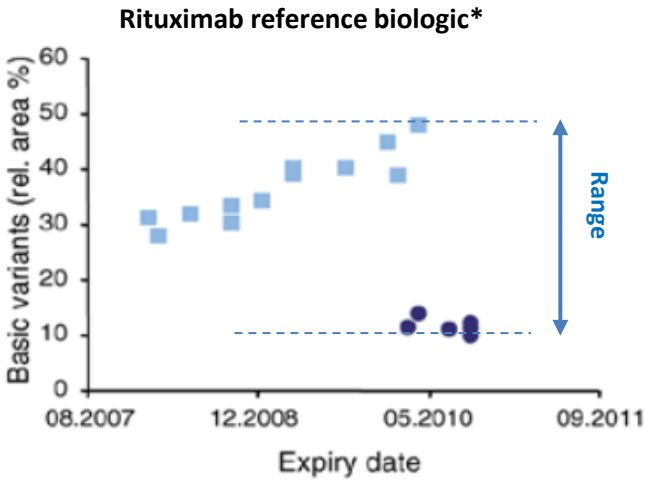
- **Prior Knowledge sources:** Internal batch data of related processes, literature, generally acceptable levels (typically < 100 ppm)
- **Considerations:** assay, expression system, overall risk profile (incl. indication, immunogenicity risk, HCP identity)

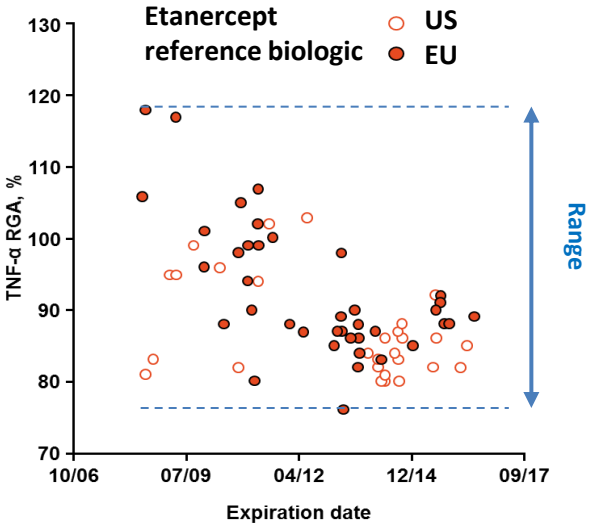
Justification of proposed limits with respect to safety and efficacy

Prior Knowledge for CQAs (incl. product variants)

- may be related to the mode of action → higher requirements to justify Prior Knowledge transferability
  Enabler: same active substance, highly similar, biosimilar

Examples:





- **Safety and efficacy within this variability have been demonstrated in clinical studies and by real-life experience with the referenced product**

* Schiestl et al. Nature Biotechnology 2011

Towards a common understanding for the use of Prior Knowledge in the setting of specifications

- Specifications are set and justified by industry and approved by regulators
- Over time a common understanding about acceptable justifications including the use of prior knowledge grows
  - prior knowledge for establishing needs and requirements from a manufacturing perspective
  - prior knowledge for the justification of proposed limits with respect to safety and efficacy
- It would be useful if this common understanding can be reflected in regulatory guidance (e.g. Q&A, Guideline, published examples and case studies)
- Over time also knowledge on classes of biotherapeutic products grows.
- It would be useful if generally accepted knowledge about these classes could be published (e.g. in the European Pharmacopoeia)

THANK YOU