One size doesn't fit all

Why it should be different guidances

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Unified statistical methodologies ?

Unified set of recommendations about statistical methodologies for three different questions:

• Comparability of processes after a change	Small	Large
• Biosimilar product	------	Large
• Generic product	Small	-----

What makes them different or common?

- Process
- Large molecule
- Specifications know
- Long history
  - Same assays
  - Few assays
  - Clinical data available

- Product
- Small molecule
- Specifications unknown
- Short history
  - New assays
  - Many assays
  - No clinical data available

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1 - Process or Product ?

When dealing with CMC and **Quality Attributes:**

- Is the central question about comparing processes or comparing products ?
- Patients receive individual batches
- Individual batches will be released to patients in the future
- The lots are the experimental units and central to the question
  - By contrast, in a clinical trial the patients are the experimental units used to estimate the efficacy/safety of a product.
  - In this setting the mean or the variance represents the process mean/variance only.
- The same applies to large molecules and small molecules formulation processes

1 - Process or Product ?

When dealing with CMC and **Quality Attributes:**

- Should the “acceptance limits” apply
  - to the Process and **individual** units ?
  - to the Product and the **means** and/or the **variances**?
- How to justify clinically defendable limits for mean or variance of process?
- Should the decision be made on current (past) batches or on future “capability” to produce lots within “acceptance limits” given observations.
- The range of the batches is important for the patient safety and efficacy.

2- Small and large molecules

- For small molecules, there are unambiguous ways to assess they are structurally the same. Consistency and adequacy of the formulation process is then central.
- For large molecules, there is no unambiguous ways to assess the products are the same
  - The reason the word “similarity” is used
- For large molecules, subtle changes in process may have important consequences
- The number of Quality Attributes
  - Small for small molecules
  - Large for large molecules, often highly correlated

3- Specifications and acceptance limits

- In pre/post manufacturing change
  - the specifications are known and constant values.
- For biosimilars
  - specifications are (by definition) unknown
  - should be established and justified and therefore are random variables.
- In pre/post manufacturing change
  - specifications are about individual batches.
  - Why should it be different for biosimilars
- How to map from specifications on individual batches to acceptance limits on parameters such as mean?
- For small molecules, there are already several “good practices” fixed limits defined (“80%-125%” rule, CU, 98%-102%, ….)

4 – Long history vs limited history

- In pre/post manufacturing changes
  - Reduced list of Quality Attributes
  - Many “reference” batches available and few “test” batches usually envisaged
  - Number of “test” batches not really a matter of debate
- In Biosimilars
  - Large list of Quality Attributes
  - Several “reference” and several “test” batches are required
  - Sample size computation of probability of success is a matter of debate
- When Biosimilar company evaluates Reference products
  - not always sure about the independency of batches, age, etc…

5- Same assays or new assays

- In pre/post manufacturing changes
  - the assays used are the same and therefore consistency of results is assumed
  - Assay variance wrt process variance is “known”
  - The format of the reportable results is (should) be appropriate
- In biosimilars
  - New assays need to be developed and validated
  - Head to head assays should be envisaged
  - What is the contribution of assay component and format
- For generics
  - Mostly physico-chemical procedures whose overall performance are less an issue

6 – Many QAs or limited number of QAs

- In pre/post manufacturing changes
  - the number of Quality Attributes to be evaluated is reduced
  - The list is less prone to debate given history
  - The multiplicity issue is limited
- In Biosimilars
  - The number of Quality Attributes to be evaluated is large
  - The list is a matter of debate and agreement
  - The multiplicity issue is rather important
- Generics
  - Same as in pre/post manufacturing changes

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7 – Clinical data available

- If a “reference” product is on the market
  - it is within specifications
  - It is clinically acceptable
- The range of values obtained for “reference” batches
  - Are by definition clinically acceptable values and justified
  - Do applies to the individual batches and are natural “acceptance limits”
  - How to figure out the real range of values patients are exposed to ?
- How can “acceptance limits” be built for the mean or variance based on range of individual batches ?
  - Another arbitrary constant such as 1.5 or 1/8 should then be invoked for biosimilars
  - For generics, there are already criteria established since a long time (eg 80%125%) that have a proven relevance

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Conclusions

Pre/post change manufacturing

- Specifications known
- Reduced list of QAs – limited multiplicity issues
- Many “reference” and few “test” batches
- Same assays with overall contribution appropriate
- Acceptance limits available

Biosimilars

- Specifications unknown
- large list of QAs – non-ignorable multiplicity issue
- Many “reference” and many “test” batches
- New assays with overall contribution unknown
- Acceptance limits to justify

Generics

- Specifications defined
- Reduced list of QAs– limited multiplicity issues
- Few “reference” and few “test” batches
- Physico-chemical assays with overall contribution appropriate
- Acceptance limits available

Is it possible to find a unified statistical methodology given those differences ?

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Conclusions

- Three guidances
  - Easy to have a lean guidance by domain
  - Easy to implement for the industry
- Two guidances
  - One for biologics, one for small molecules
  - Then pre/post change manufacturing and Biosimilars are handled the same way
- One guidance
  - Might be too complicated
  - Some areas will remain subjected to interpretation