Data Quality Expectations for Biosimilars with Case Studies

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Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.

Case studies may be hypothetical

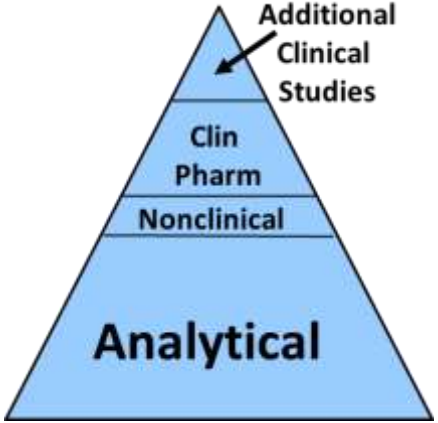
Learning Objectives

- Understand the need for a strong comparative analytical assessment
- Learn the key points for how to perform a strong comparative analytical assessment
- Learn about recent updates to an FDA Guidance for biosimilars
  - Most updates were included to clarify expectations, but do not introduce new expectations

The Foundation: Comparative Analytical Assessment

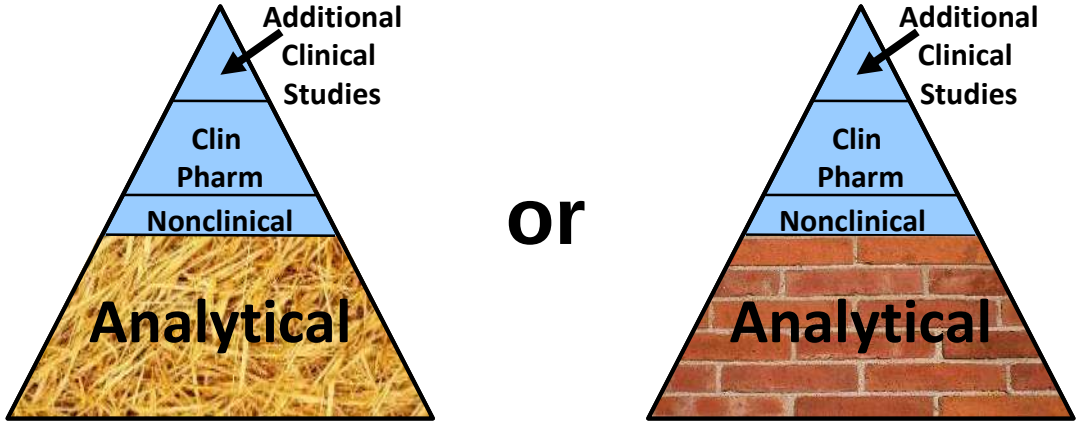
- Step-wise approach:
  Begins with extensive analytical characterization of the reference product and the proposed product

- Helps to shape and customize successive steps in the BP development program



Slide from Jee Chung

A Solid Foundation Requires Solid Data



- Can we rely on the comparative analytical data in the BLA to hold up the pyramid?

Slide from Jee Chung

How Do We Build a Strong Foundation?

- Understand the reference product and its critical quality attributes
- Lot selection:
  - Reference product: goal is to understand product variability
  - Proposed product: goal is to analyze investigational and commercial lots
- Method selection:
  - Include sufficient methods to adequately characterize the product
  - Use of orthogonal methods
  - Use of adequately qualified methods
- Adequate documentation and traceability

The Comparative Analytical Assessment

Structural

- Primary structure
- Higher order structure including aggregates
- Molecular weight
- Degree of heterogeneity (derived from enzymatic, unintended and intentional modifications)

Impurity profiles

- Product-related impurities
  - Inactive protein variants generated during manufacture or storage

Functional

- Biological activity (i.e. potency)
- Functional domain
- Enzyme kinetics
- Receptor binding
- Protein-target binding
- Fc effector function

Stability

- Degradation profiles under accelerated, stress (high temperature, freeze-thaw, light exposure, agitation), forced conditions

Slide from Maria-Teresa Gutierrez-Lugo

The Comparative Analytical Assessment

Collectively, these quality attributes can be used to define identity, purity, potency, and stability of the products, and if critical, they correlate with safety and efficacy

<u>Understanding the relationship</u> between quality attributes and the clinical safety & efficacy profile aids in the ability to determine **<u>residual uncertainty</u>** about biosimilarity.

- Inactive protein variants generated during manufacture or storage

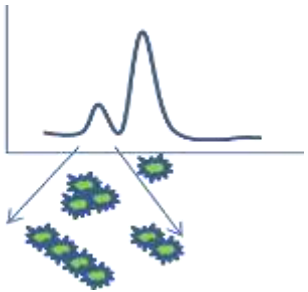
exposure, agitation), forced conditions

Slide from Maria-Teresa Gutierrez-Lugo

Analytical Method Development and Qualification Strategies

Begin with basic understanding of the method

- E.g. should you use SEC or AUC to detect aggregates?



Understand the method purpose to help design the qualification study

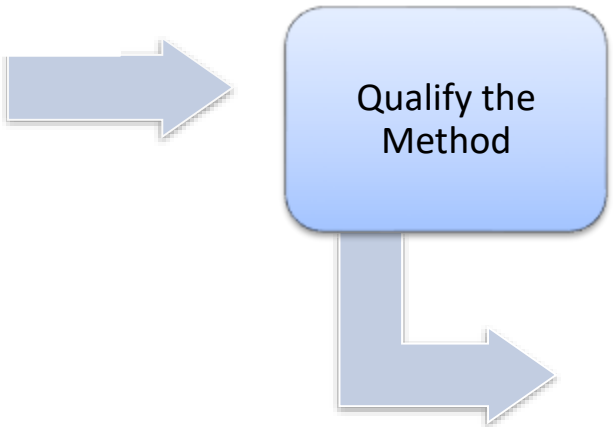
- What is the method going to be used for
  - To quantify a critical quality attribute?
  - To reduce residual uncertainty?
  - To confirm a result?

Evaluate method capabilities and limitations

- E.g. specificity, precision, accuracy, etc.
- How sensitive is the method to detect differences?
- How critical are reagents to method performance?

Adapted from Jee Chung

Analytical Method Development and Qualification Strategies



- Establish system suitability parameters to ensure adequate performance
- Document the qualification results

- Include sufficient detail to ensure consistent performance by trained analysts
- Document analyst training

Adapted from Jee Chung

Case Study 1: Method Qualification

Literature shows methionine oxidation of 10% (Met-ox) can impact binding

Peptide Mapping Data

Proposed Product	Reference Product
15% Met-ox	5% Met-ox

Peptide Mapping Method Qualification Data

Sample	% Met-ox
Positive Control	10.5 ± 2
Negative Control	8.7 ± 2
25% oxidized sample	11.5 ± 2
60% oxidized sample	13.0 ± 2

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Challenge Question: Based on the method qualification data, *can you make a conclusion?*

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Challenge Question: Based on the method qualification data, *can you make a conclusion?* **No. It is unclear if the method is not suitable or if the samples tested during method qualification were not suitable for the qualification exercise**

Adapted from Jee Chung

Principles of Data Integrity

- Defined in FDA guidance document as "…the completeness, consistency, and accuracy of data."
- Even if site of data generated is not cGMP, same type of principles should be considered

ALCOA	Meaning
Attributable	Data generated are traceable to an individual (the who and when)
Legible	Data should be readable and permanently recorded
Contemporaneous	Data documented at the time they occurred
Original/true copy	Not transcribed data, first capture data
Accurate	Data records should be free from errors, complete, and truthful; can be achieved by verification by a qualified 2nd person

FDA Guidance for Industry, "Data Integrity and Compliance With CGMP, Questions and Answers" (December 2018)

Slide from Jee Chung

Case Study 2: Traceability of Data

- A portion of analytical similarity data were derived from HPLC instrument X
- Sponsor purchased a new HPLC instrument
- HPLC-X was de-commissioned
- Sponsor failed to backup data from HPLC-X and raw data from HPLC-X could not be located
- Outcome: No way to verify the data in the submission

Adapted from Jee Chung

Challenge Question

What went wrong here?

a. Nothing, the data were acquired in a non-GMP lab

b. The firm should have backed-up the data to ensure that data are accurate, complete, and secure from inadvertent erasures or loss

Adapted from Jee Chung

Challenge Question

What went wrong here?

a. Nothing, the data were acquired in a non-GMP, research & development lab

b. The firm should have backed-up the data to ensure that data are accurate, complete, and secure from inadvertent erasures or loss

Adapted from Jee Chung

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sandra Benton, 301-796-1042, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

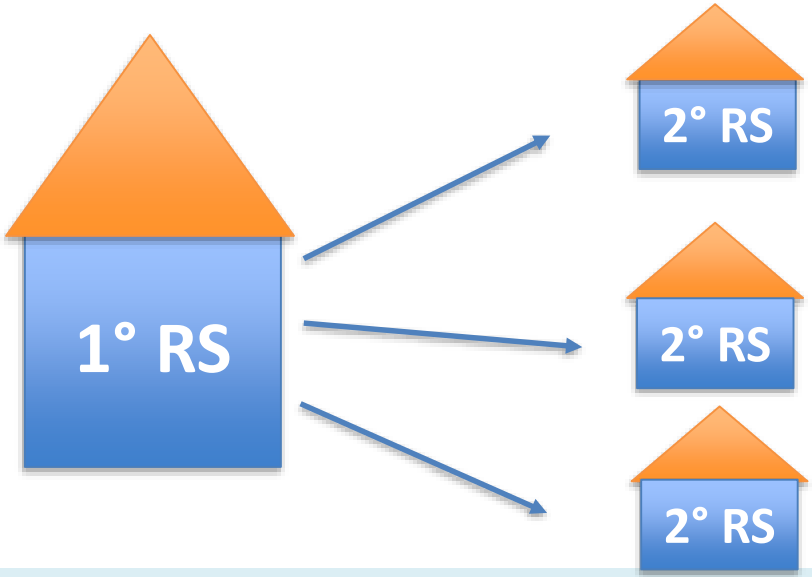
Updated Draft Guidance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

Emphasis on Reference Standards

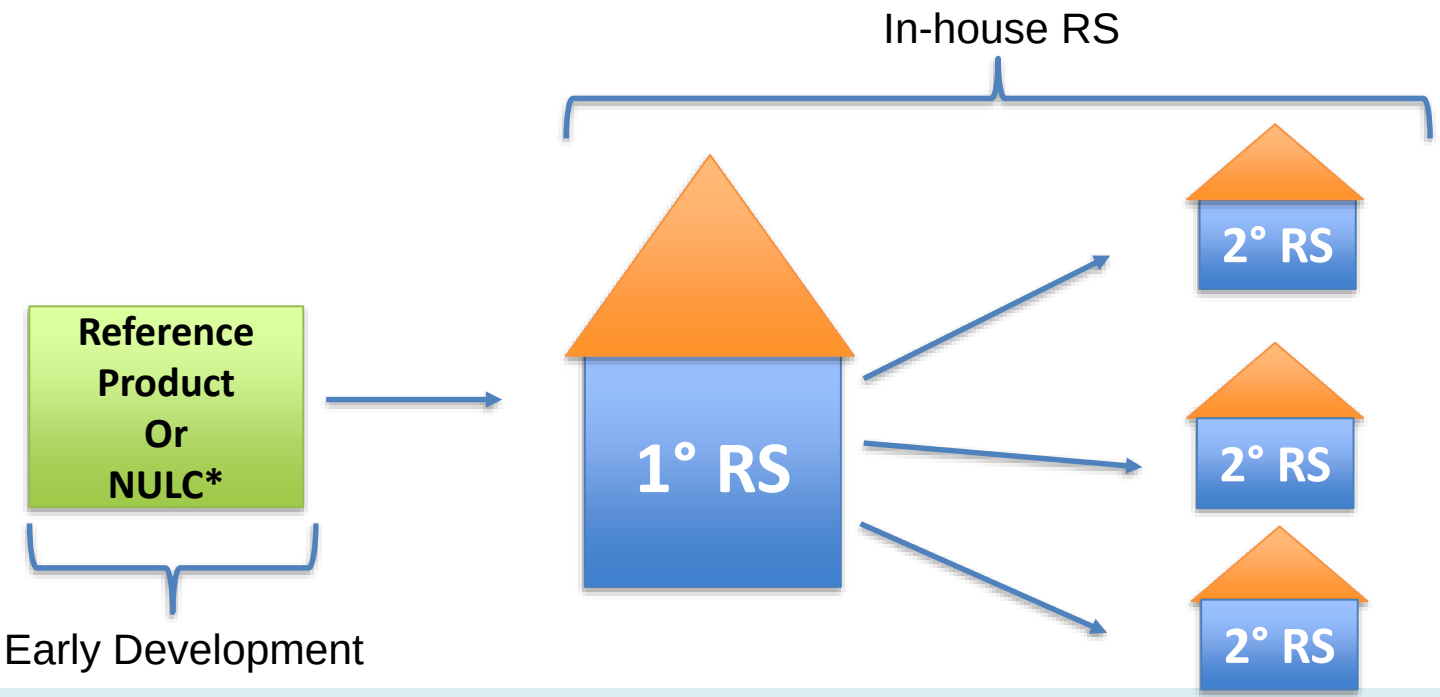
Use of in-house Reference Standard (RS)



FDA Draft Guidance for Industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019)

Emphasis on Reference Standards

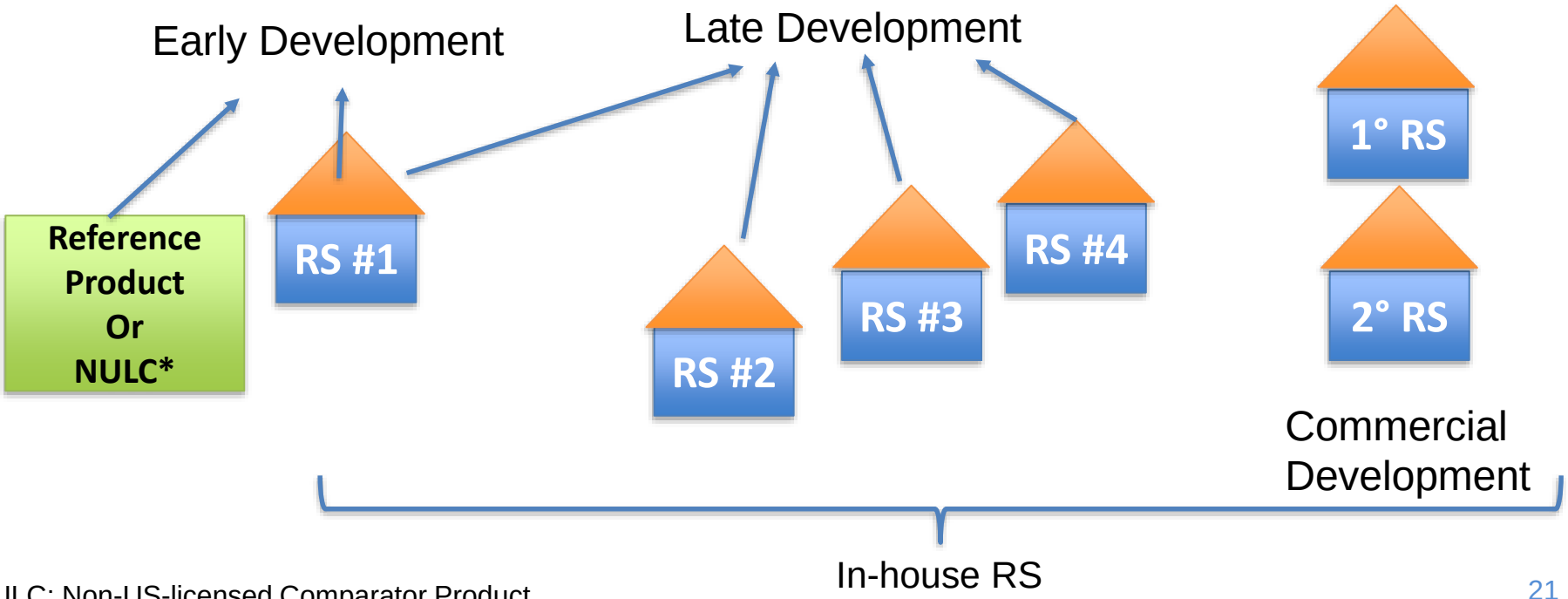
Use of reference product or NULC as a RS during early development



*NULC: Non-US-licensed Comparator Product

FDA Draft Guidance for Industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019)

Case Study 3: RS Qualification



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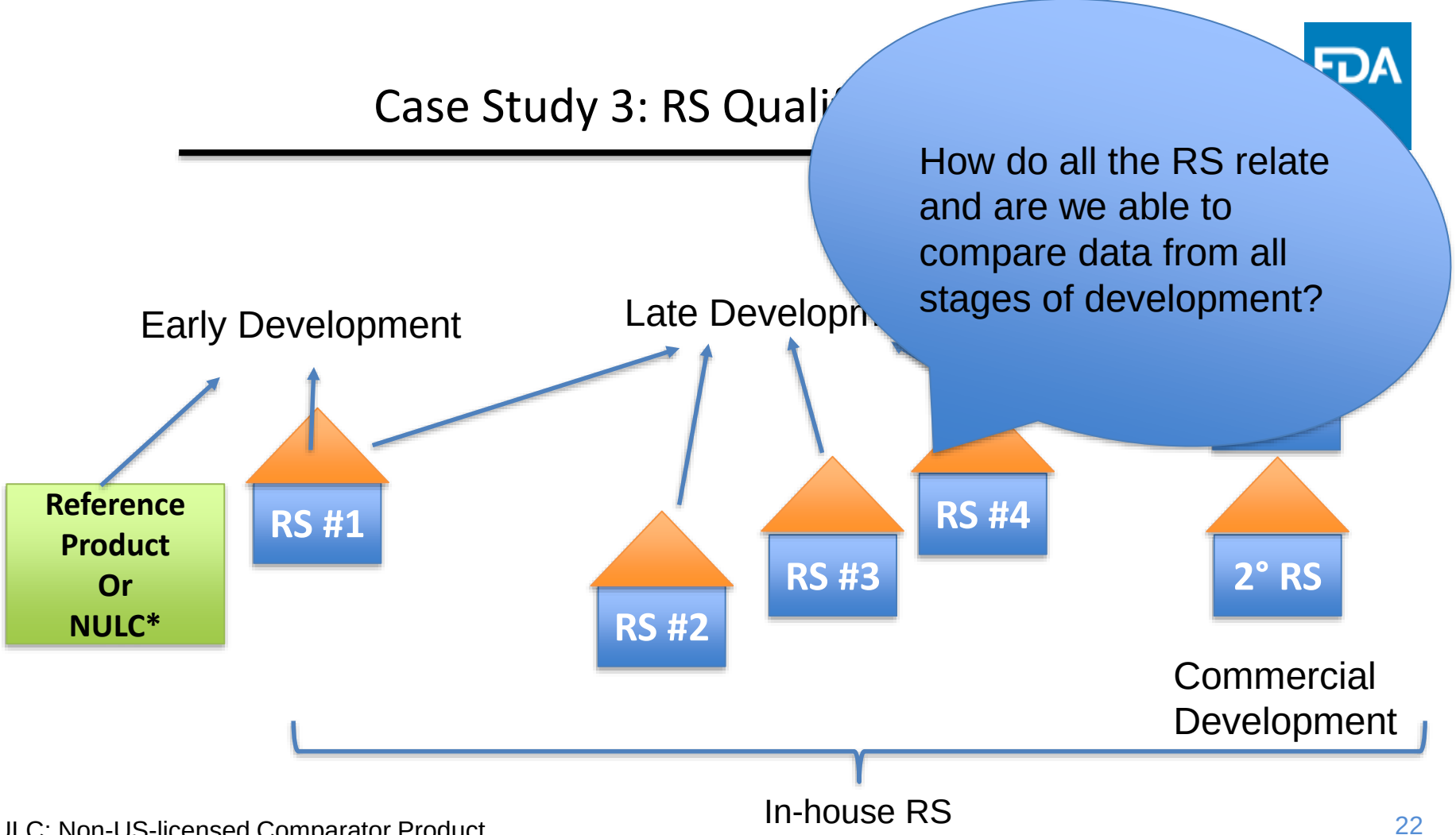
Case Study 3: RS Quali



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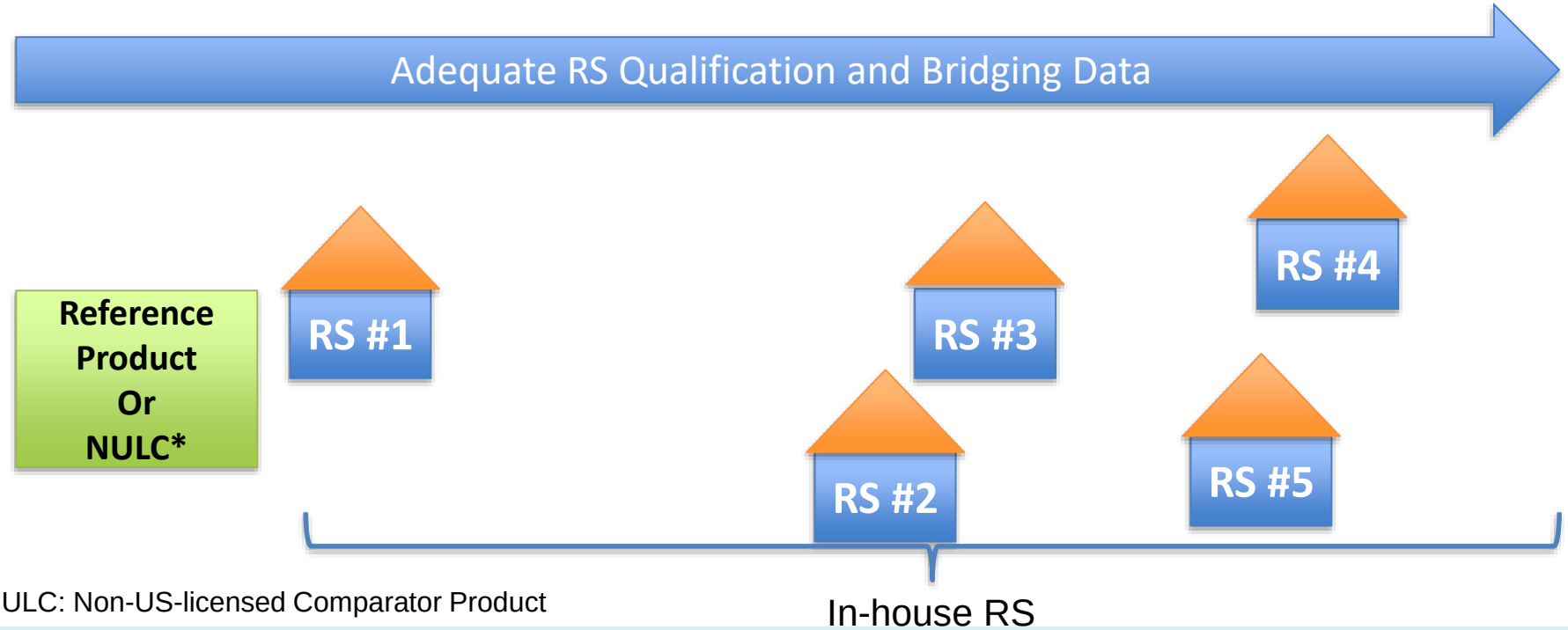

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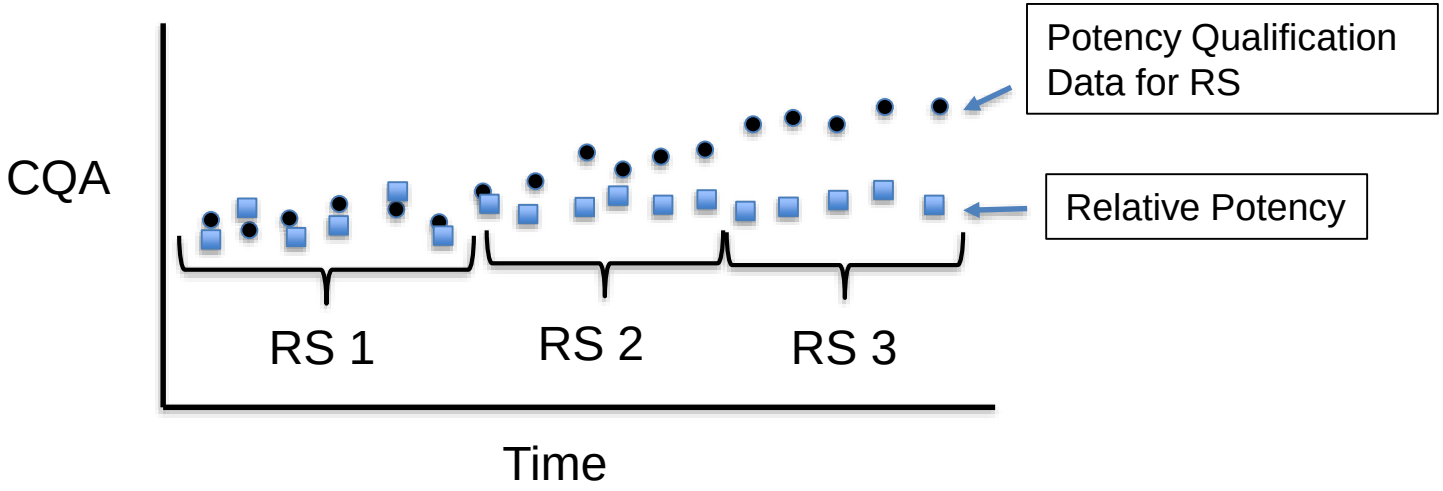
Adequately Qualified RS Prevents Drift



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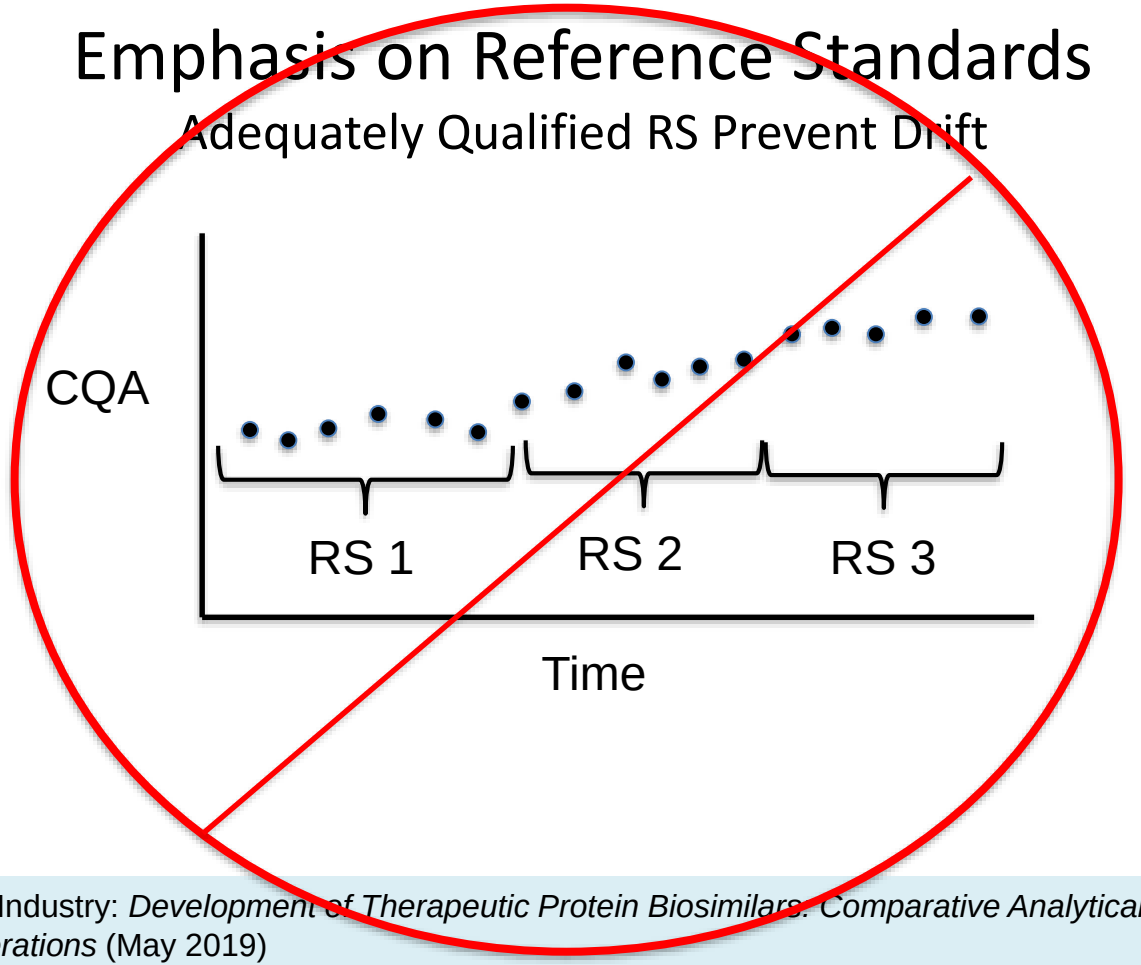

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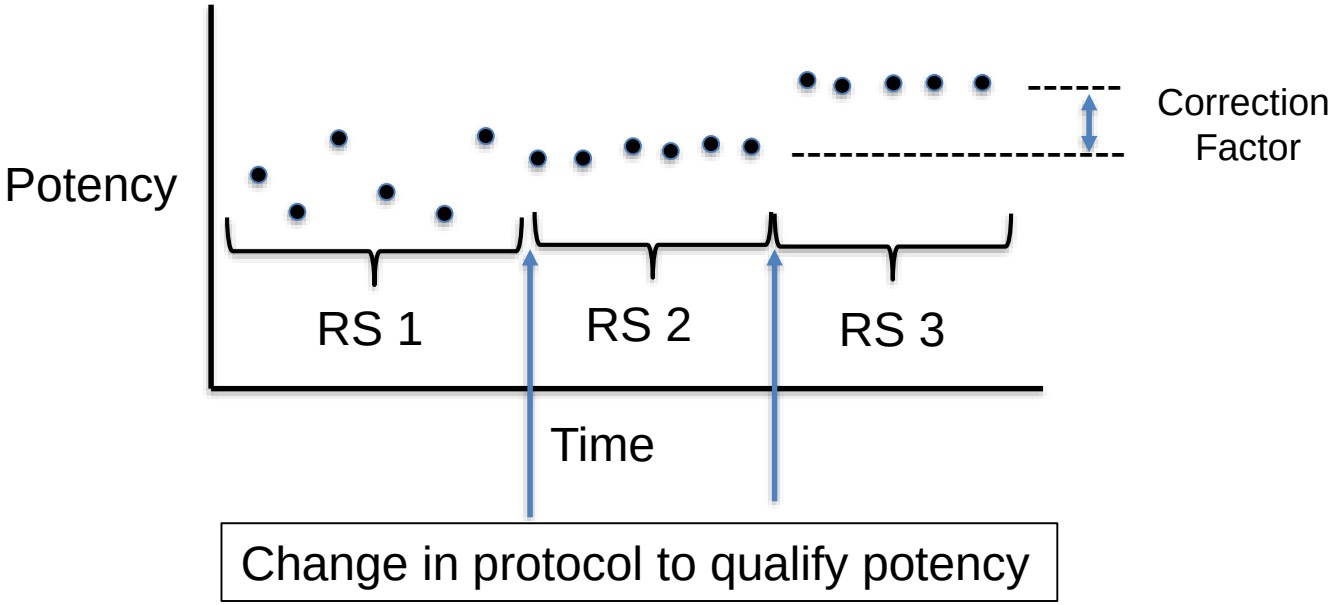

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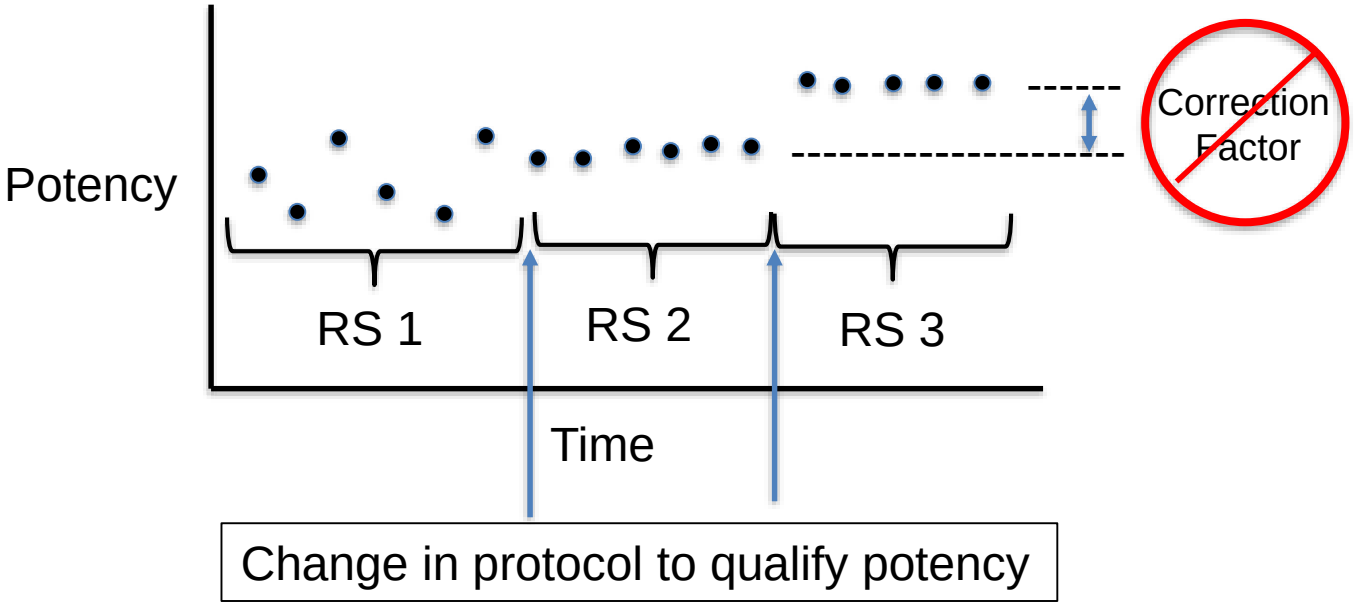

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Use of inadequately qualified RS may raise concerns regarding the comparative analytical assessment.

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Consider storing lots of the proposed product, Reference Product, non-US-licensed comparator product, RS, as applicable at appropriate conditions to allow for reevaluation, if needed

https://www.pri.org/stories

FDA Draft Guidance for Industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019)

New Section
VI. Comparative Analytical Assessment

Considerations for Reference and Biosimilar Products:

- Understand the reference product and the observed lot-to-lot variability
  - Sufficient number of lots to inform on variability:
    - At least 10 reference product lots
    - At least 6-10 representative, independent lots of proposed product

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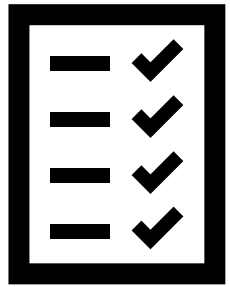
  - Justify the inclusion/exclusion
  - Dates of analytical testing and product expiration date (or age of proposed product)



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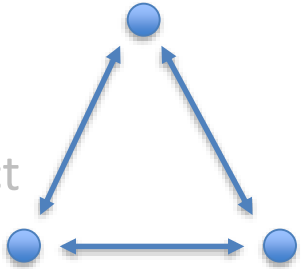
  - Dates of analytical testing and product expiration date (or age of proposed product)
- If using a non-US-licensed comparator in certain studies:
  - Comparative analytical data for all pairwise comparisons
  - Combining data from the reference product and non-US-comparator product to perform the comparative analytical assessment is not acceptable



FDA Draft Guidance for Industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019)

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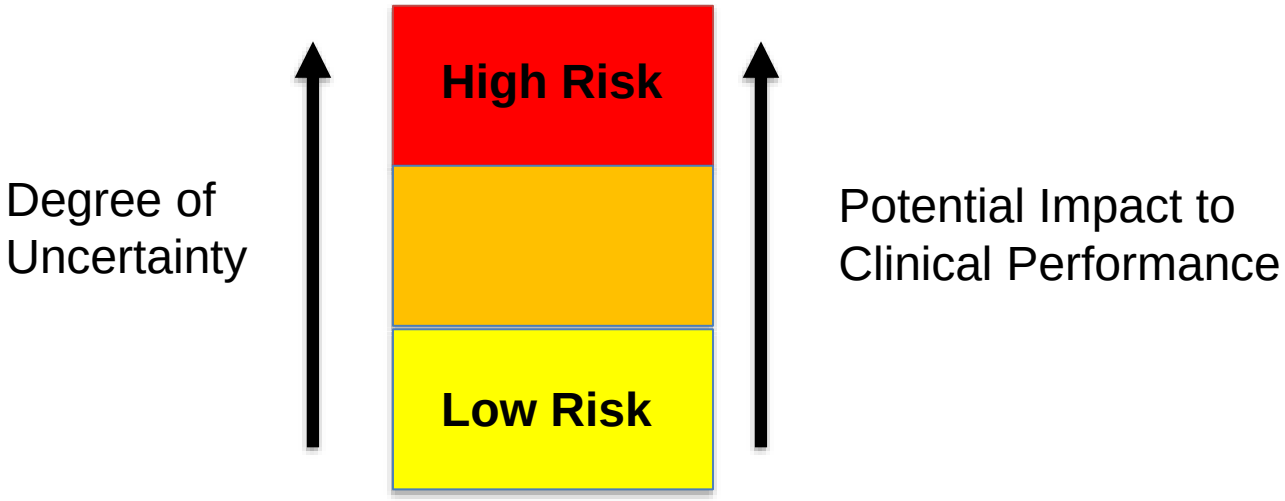
Considerations for Data Analysis:

- Identify quality attributes (QAs) and rank them according to risk



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VI. Comparative Analytical Assessment

Considerations for Data Analysis:

- Identify quality attributes (QAs) and rank them according to risk
- Evaluate the QAs (see guidance for factors to consider when determining the type of analysis to apply to each QA or assay)
  - Quantitative analysis:
  - Qualitative analysis:

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    - One approach: Quality Ranges (QR) for high to moderate risk QAs
    - FDA recommends narrower QR acceptance criteria for higher risk QAs
    - Tolerance intervals not recommended
    - Equivalence testing no longer recommended *new*

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  - Qualitative analysis:
    - Use of raw data/graphical comparisons for QAs with lowest risk ranking or those that cannot be quantitatively measured
    - Present data side-by-side to facilitate review

Acknowledgements

- Maria-Teresa Gutierrez-Lugo
- Susan Kirshner
- Jee Chung
- Emanuela Lacana
- Other FDA colleagues

U.S. FOOD & DRUG ADMINISTRATION

Clarification on CMC Expectations for Biosimilar BLAs

Complete Application

- Ensure a well-organized, complete application:
  - Provide the data and supporting information in the appropriate section (ICH M4Q)
  - Provide narrative describing relevance of data, reports
    - Generic reports
  - Use eCTD format, working hyperlinks, English translations, etc.
- This will:
  - Help ensure an application is fileable
  - Make the review process more efficient
  - Reduce the number of information requests
  - Reduce submission of major amendments

Slide from Maria-Teresa Gutierrez-Lugo

Pre-License Inspection (PLI)

- Critical aspect of application review
- PLI is the same for the 351k:
  - All facilities should be ready for inspection at the time of submission (form FDA 356h) – Filing requirement.
  - The product should be manufactured during the inspection to allow for a meaningful inspection (21 CFR 600.21)
  - Production schedule for all locations should be available at time of BLA submission.
- Scope: Traditional PLI topics as well as similarity data
  - Provide in the 3.2.R, Regional section, a listing of all sites where the analytical similarity assessment was conducted and identify the testing site(s) for each method.
  - In instances that similarity site is non a registered GMP facility, a “site visit” may be arranged.

Slide from Maria-Teresa Gutierrez-Lugo

Information Requests

- Address the request with data and justification
- Request clarification when needed
- Respond in a timely manner
  - Prevent submission of a major amendment late in the review cycle

Slide from Maria-Teresa Gutierrez-Lugo