US FDA Perspectives on Biosimilars and Biological Products *focused on analytics*

2015 Biomanufacturing Technology Summit

IBBR June 25th Rockville, MD

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OPQ/CDER/FDA

Purpose Statement

This talk informs academic and other stakeholders about regulatory expectations and challenges to facilitate the development of useful analytical technologies

Disclaimers

1) It may not work
2) Please consider actual text in statute, regulations and/or guidance

§ 262. Regulation of biological products

(a)(2)(C) The Secretary shall approve a biologics license application—

(i) on the basis of a demonstration that—

(I) [redacted] is the subject of the application is **safe, pure, and potent**; and

(II) the facility in which the biological product is **manufactured**, processed, packed, or held meets **standards** designed to ensure that the biological product **continues to be safe, pure, and potent**;

SAFETY & EFFICACY

QUALITY

Pharmaceutical Quality

- Dr. Janet Woodcock, defined high quality drug products as those that,
  - 1) consistently and reliably deliver the clinical performance and other characteristics stated on the label,
  - 2) are free from contamination, and
  - 3) are available .

Woodcock, J. 2004. The Concept of Pharmaceutical Quality. Am. Pharm. Rev. 47(6): 1-3.

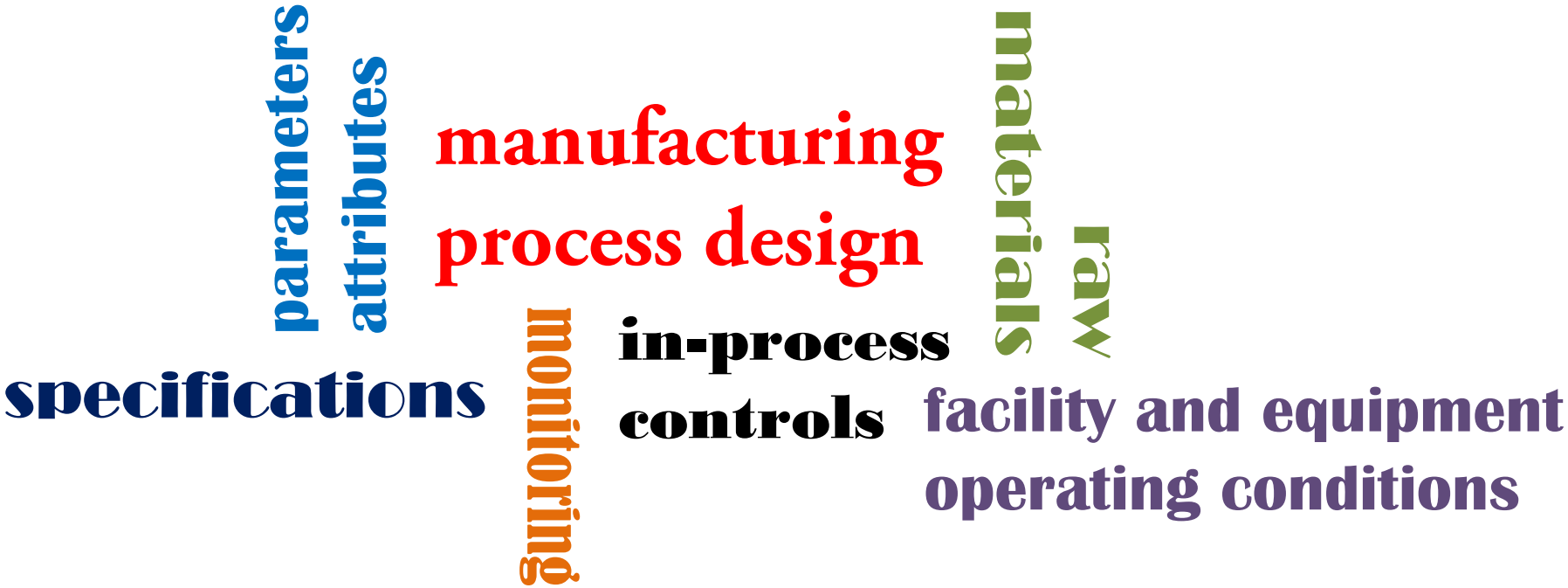
Continues to be Safe, Pure, and Potent

consistently and reliably deliver the clinical performance….

- Manufacturing process approved at licensure
  - Control Strategy
- Changed/Different manufacturing process
  - Comparability (same sponsor)
  - Biosmilarity (different sponsor)

Control Strategy is defined as

- A planned set of controls
  - derived from current product and process understanding
  - that assures process performance and product quality

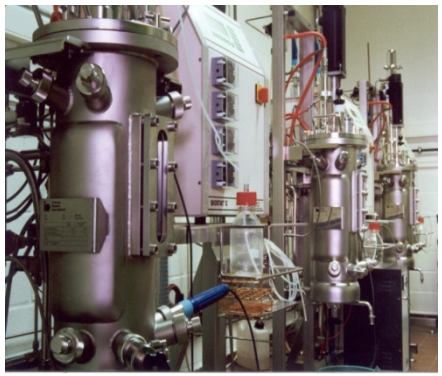


Guidance: ICH Q10 Quality System & Q11 Drug Substance

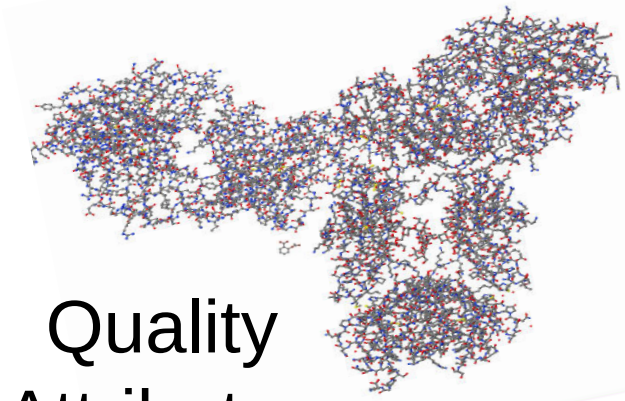
Past Mantra of Biologics: The Product is the Process

Process Changes

Safety
Efficacy



Manufact.
Process



Quality
Attributes

- Comparability
- Biosimilarity

Process Changes-Regulatory Reporting

601.12 An applicant must inform the FDA about each change in the… [conditions] established in the approved license application(s).

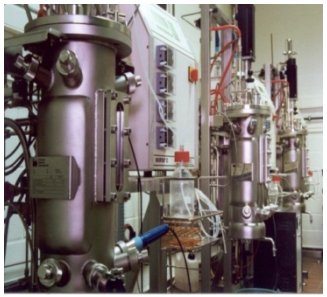
- **PAS**-- substantial potential to have an adverse effect on the… product… safety or effectiveness
- **CBE 30--** moderate potential [of] an adverse effect
  - *In certain circumstances… may be distributed immediately upon receipt…*
- **AR**-- minimal potential to have an adverse effect
- **Protocols** to reduce reporting categories

Established Conditions

for DS/DP, in-process materials can include but not limited to

- Manufacturing and testing facilities
- Source and specifications for biologics starting materials
- Process, including in-process tests and sequence of operations, equipment; and process parameters.
- Specifications, including tests, procedures and criteria
- Container closure system, components, and specs.
- Maintenance strategy for high impact chemometric and/or multivariate models

Generally not considered established conditions: Batch records & analysis, Development, Characterization, & Validation data



Control Strategy

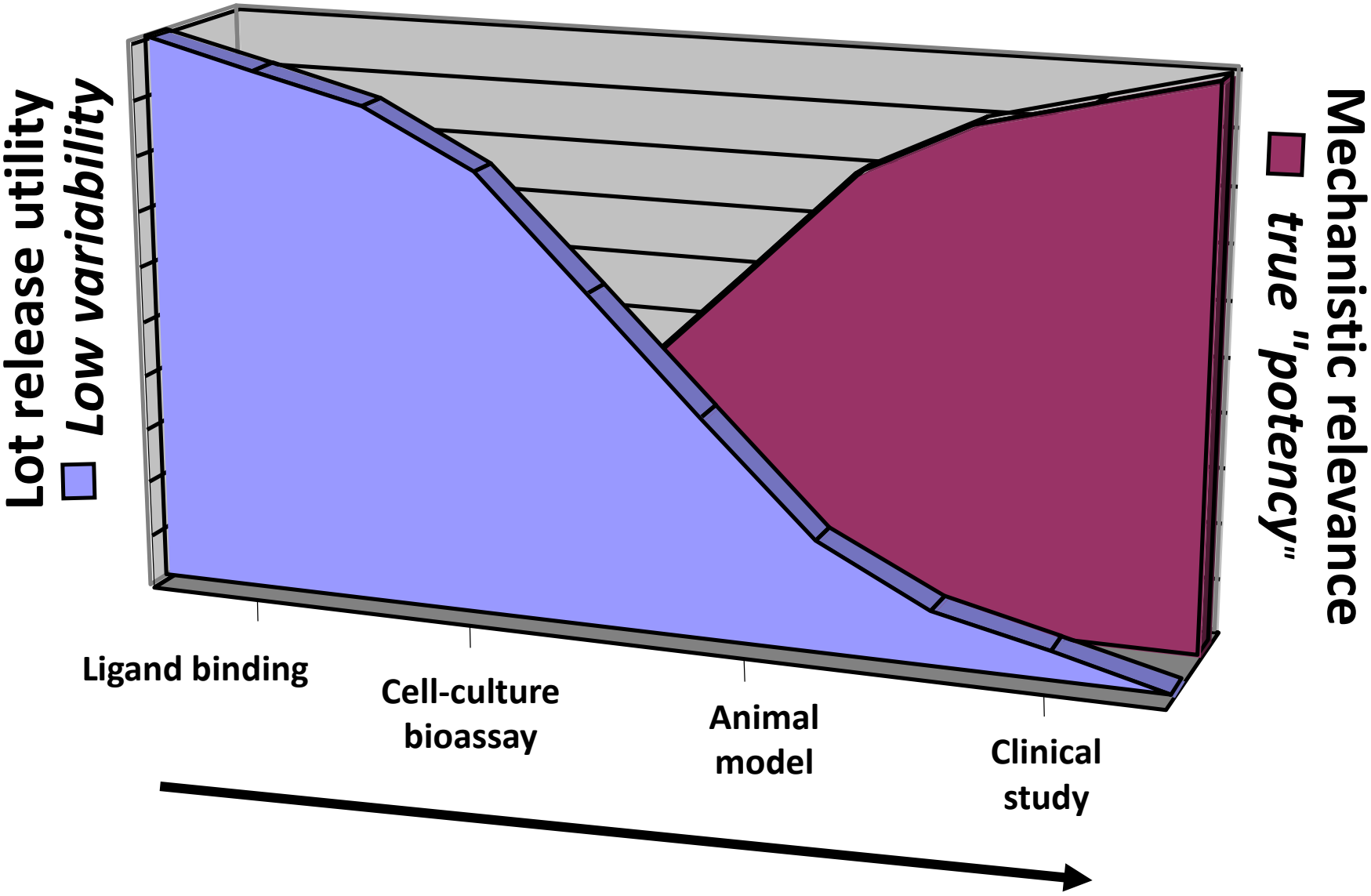
Process Change

Measurement

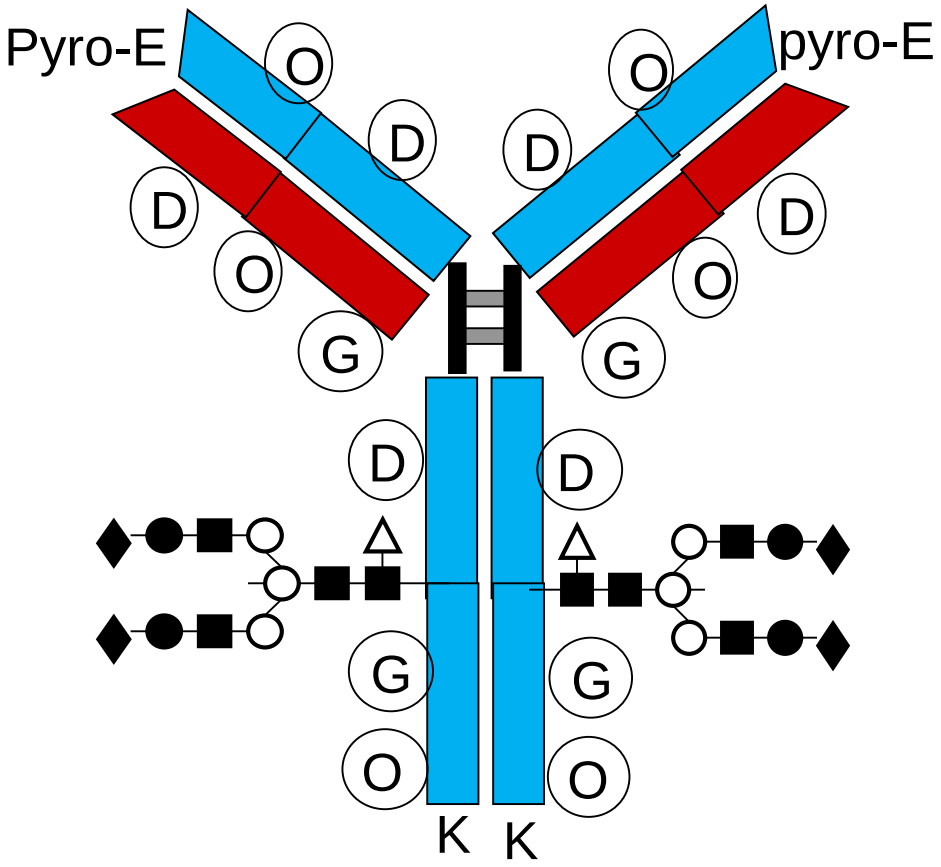
“Measurement is the first step that leads to control and eventually to improvement. If you can’t measure something, you can’t understand it. If you can’t understand it, you can’t control it. If you can’t control it, you can’t improve it.”
— H. James Harrington

“We tend to overvalue the things we can measure and undervalue the things we cannot.”
— John Hayes

Bioassay Continuum



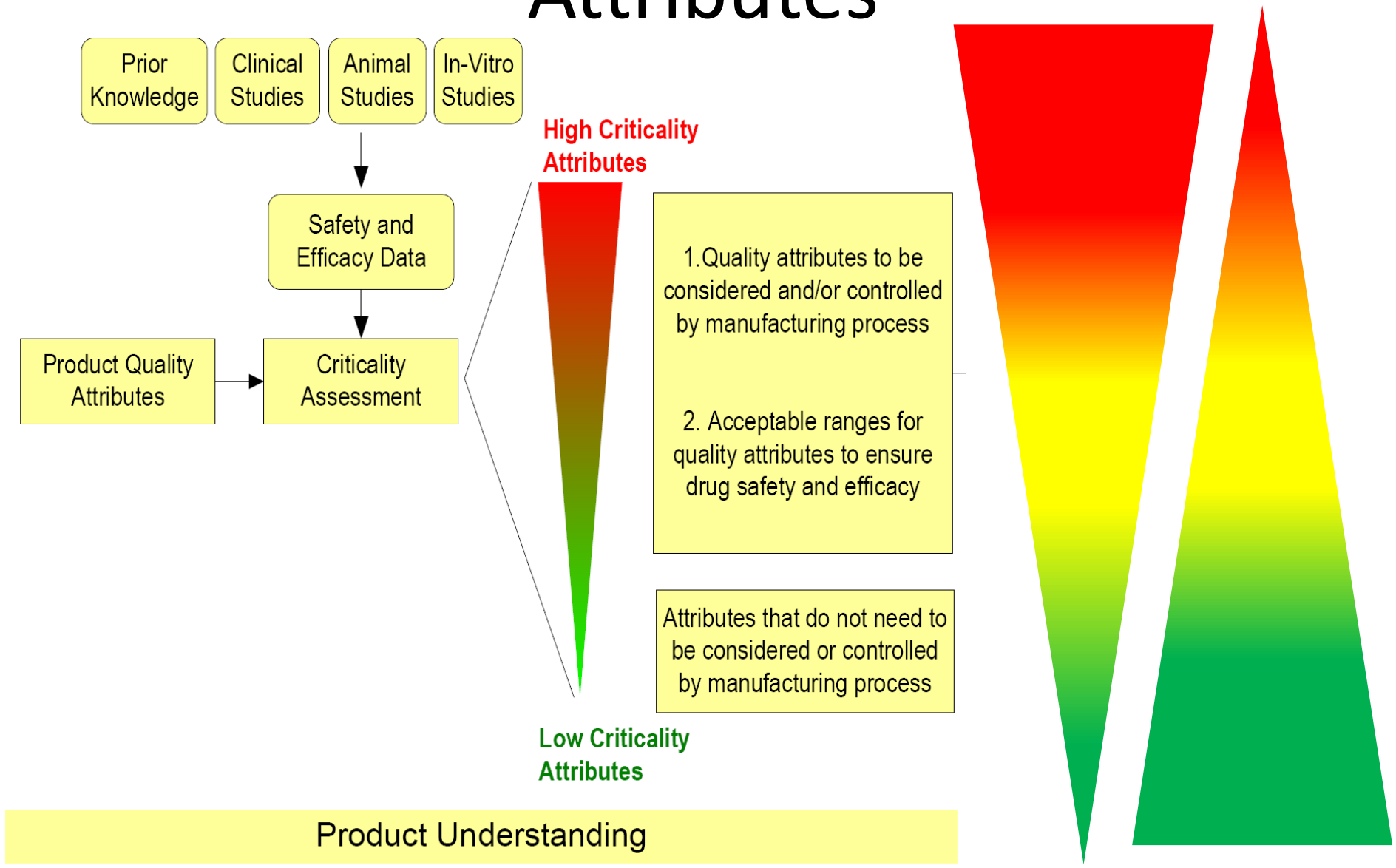
Attributes & Combinatorics



- Pyro-Glu (2)
- Deamidation (3x2x2)
- Methionine oxidation (3x2)
- Glycation (2x2)
- High mannose, Fucosylation G0, G1, G1, G2 (10)
- Sialylation (+5)
- C-term Lys (2)

- $(16{,}920)^2 \approx$ 285 million
- 2 x 12 x 6 x 4 x (10+5) x 2 = 16,920

A-Mab Risk Ranking of Quality Attributes



Conformance to Specification (ICH Q6B)

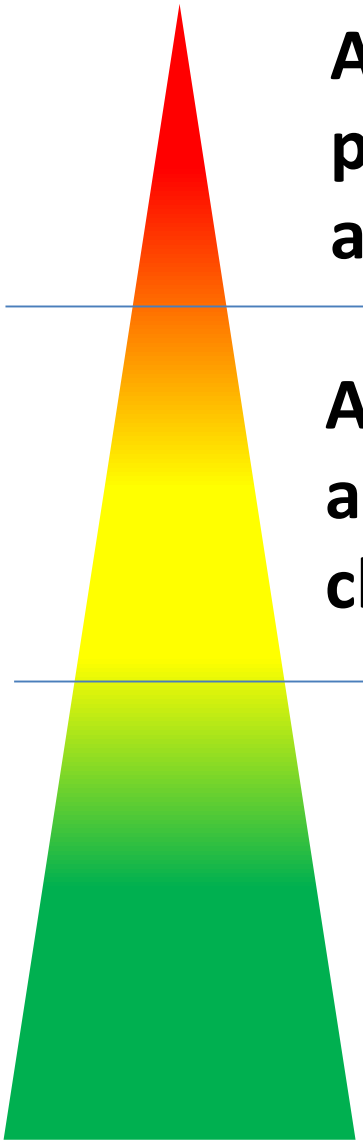
- Specifications are one part of a total control strategy designed to ensure product quality…
- A specification is defined as a list of tests, references to **analytical procedures**, an appropriate **acceptance criteria** which are numerical limits, ranges, or other criteria for the tests described.
- Characterization of a biotechnological or biological product… is necessary to allow relevant specifications to be established.

Process Changes

- When a manufacturing process change has been made that has the potential to have an impact on quality attributes, a complete or limited… characterization… is generally warranted to directly compare the pre-change and post-change product.
- However, additional characterization might be indicated in some cases.

Guidance ICH Q5E

Approach to Biologics & Attributes



Attributes that are kept within pre-defined ranges using testing and other process controls

An extended set of attributes that are evaluated in comparative characterization for process changes

Attributes that are not routinely evaluated as part of either a process control strategy or in comparative characterizations

These may include combinations when they are known to interact

A subset may be evaluated based on the nature of the process change.

Different Regulatory Expectations

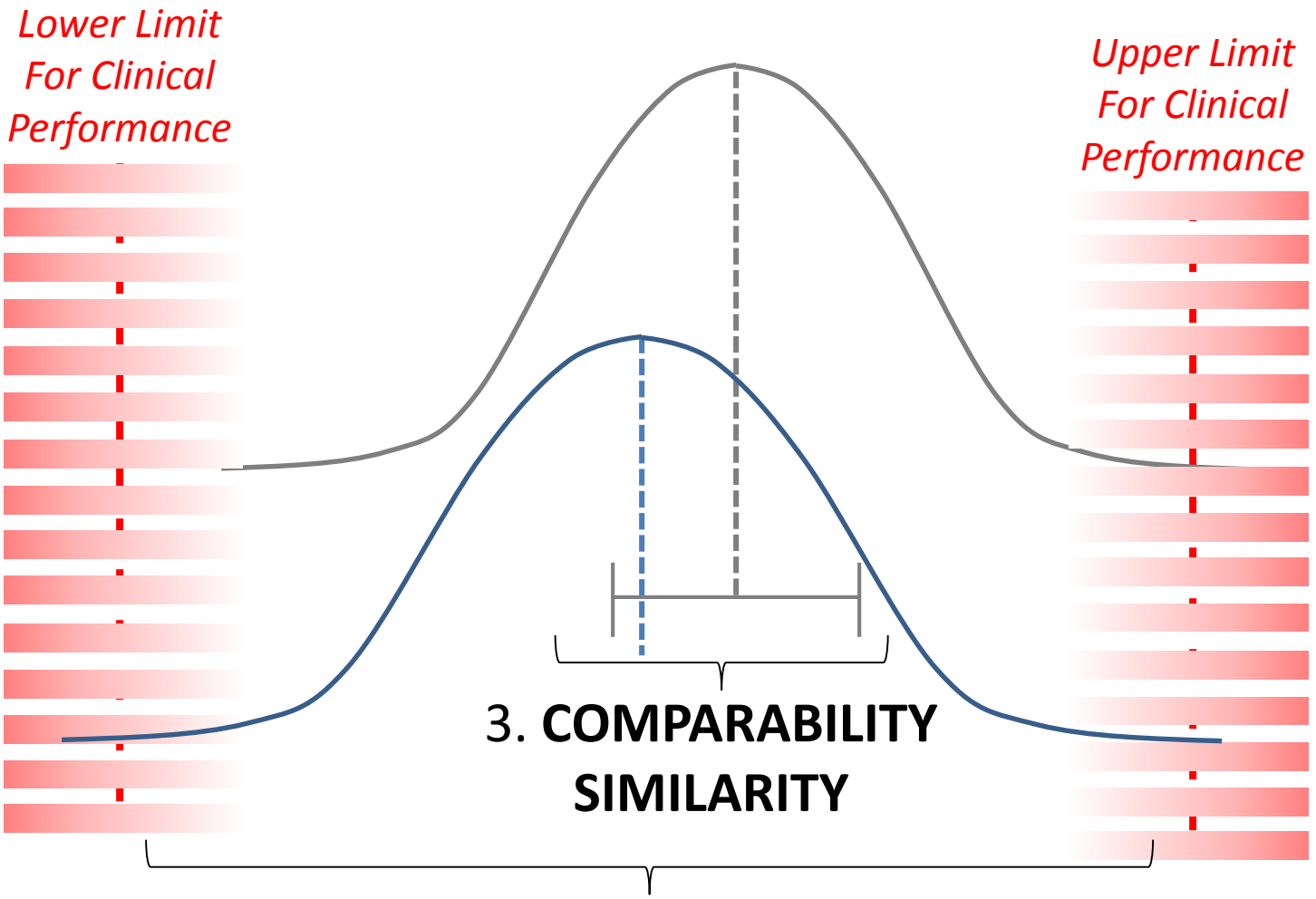
- …characterization studies… [do] not necessarily entail the use of validated assays…
  - but the assays should be scientifically sound and provide results that are reliable.
- Those methods used to measure quality attributes for batch release [specifications] should be validated…

Guidance ICH Q5E

Guidance: Analytical Procedures and Methods Validation…

- Pre-specified validation protocol with justified acceptance criteria under cGMP
- Typical validation characteristics are
  - Specificity , Accuracy
  - Precision (repeatability, intermediate precision, and reproducibility)
  - Linearity, Range, Quantitation limit, Detection limit
- Evaluation of robustness

Different Expectations of Analytical Tests



2. PART OF <u>ONGOING</u> MANUFACTURING **CONTROL STRATEGY**

1. **CHARACTERIZATION**

Lifecycle Management of Analytics

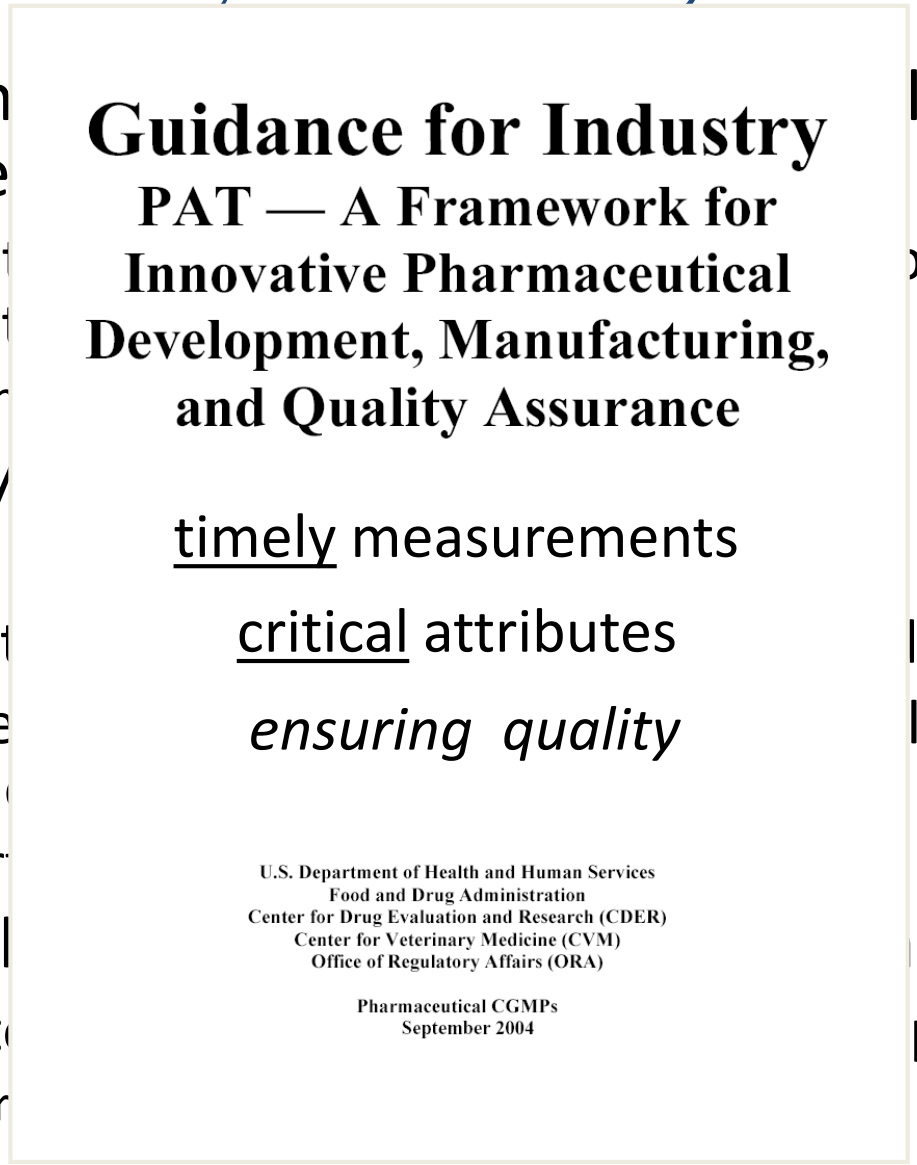
- New technologies may allow for greater understanding and/or confidence when ensuring product quality.
- In anticipation of life cycle changes in analytics, an appropriate number of samples should be archived… for comparative studies.
  - for complex products that are sensitive to manufacturing changes….
  - should include samples that represent pivotal clinical trial material and marketed product.

Guidance: Analytical Procedures and Methods Validation

Assay Modernization

– A Good Idea, But Not as Easy as It Sounds

- Implemen l methods for sterility te
  - Three alt one comparable in sensitivit
    - Rajesh
- Use of NM in a polyvalent vaccine
  - NMR dat l was inaccurate
  - Thus the lysaccharide compon
    - Rober
- NMR metl nt
  - Also det parin
    - Edwar



Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

timely measurements

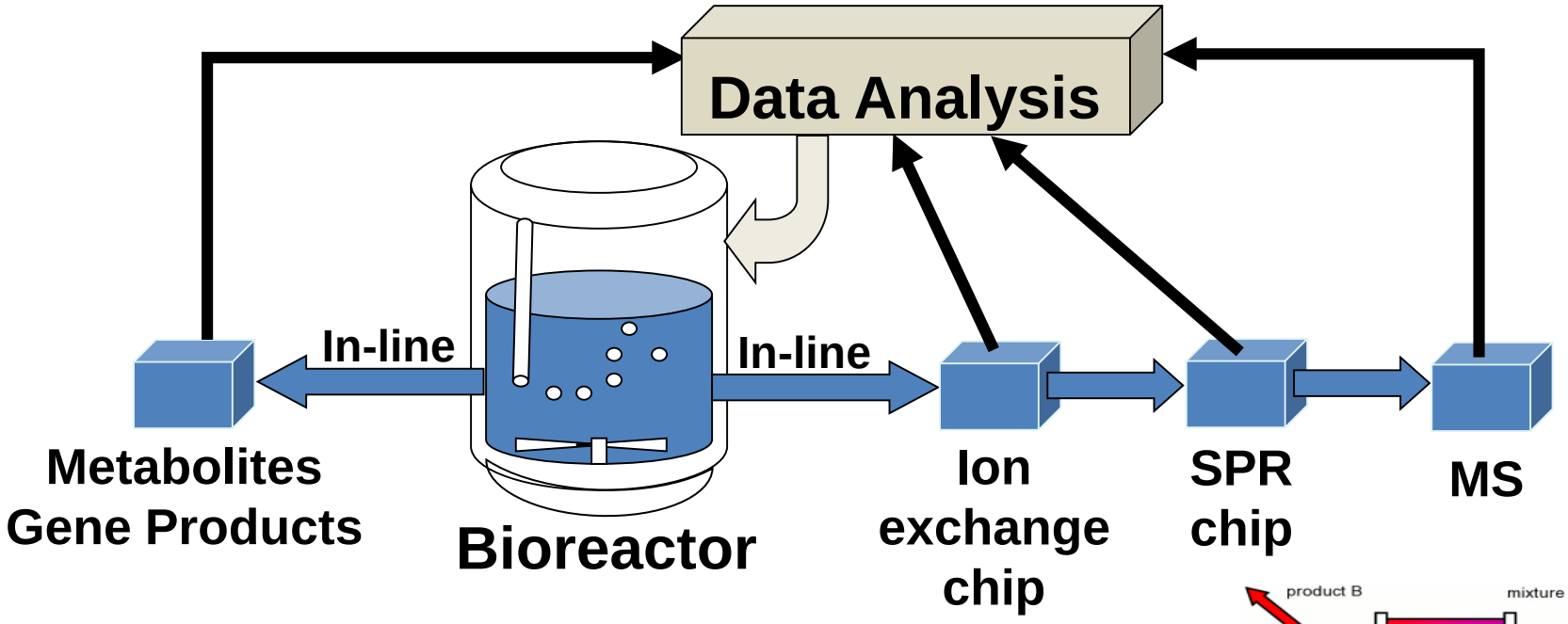
critical attributes

ensuring quality

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

Integrating Analytics into Manufacturing



Maintenance strategy for high impact chemometric and/or multivariate models

21 CFR 210.3

Regulatory Definition of "Lot"

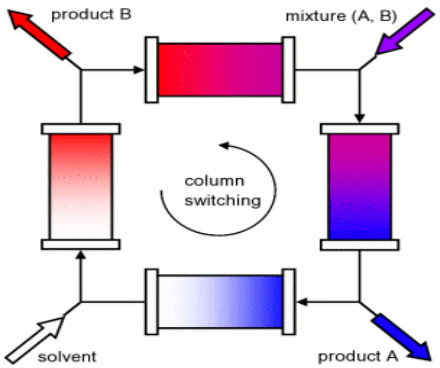


Image from
www.worldofchemicals.com

Biosimilarity

- ....typically will be more complex and will likely require more extensive and comprehensive data than assessing the comparability of a product before and after a manufacturing process change made by the product's sponsor.
  - [the sponsor has] extensive knowledge and information about the product and the existing process…
  - the manufacturer of a proposed [biosimilar] product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, acceptance criteria)

Quality Considerations Guidance

Definition: Biosimilarity

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

General Requirements: 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from**:

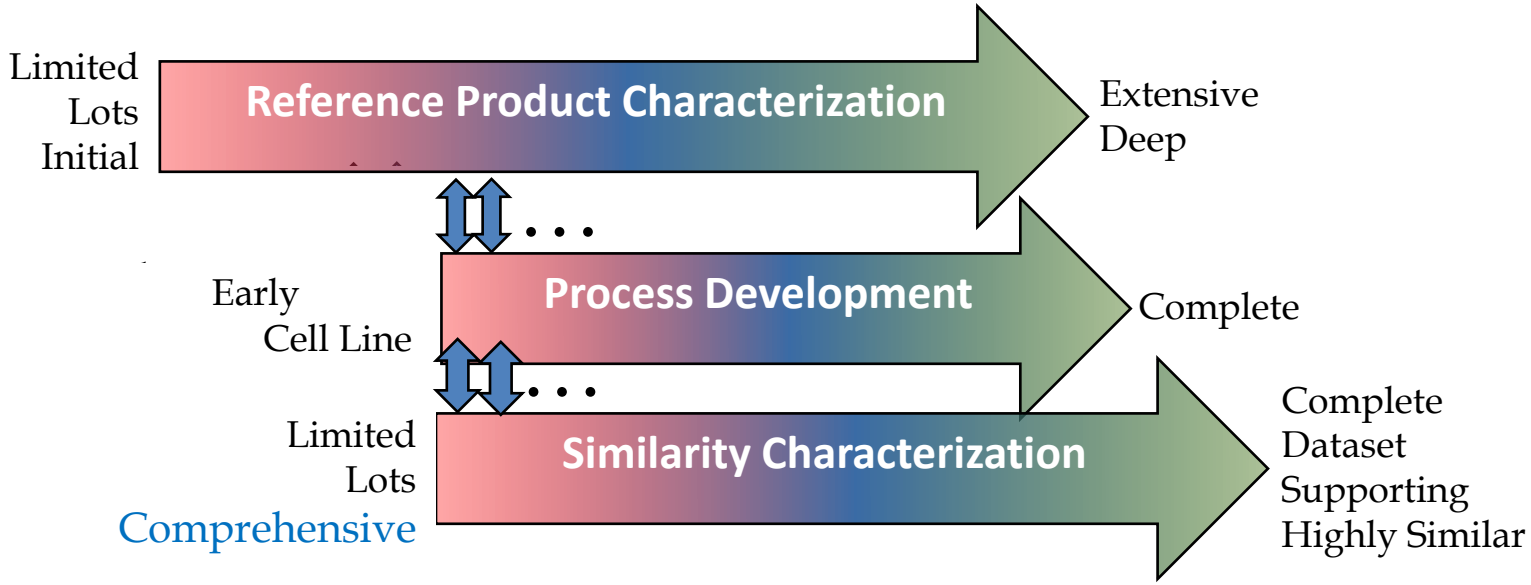
- **Analytical studies** [illegible] biological product [illegible] notwithstanding [illegible] inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study** [illegible] ment of imm[illegible] phar[illegible] monstrate safet[illegible] cond[illegible] the reference product is licensed.

TOTALITY OF THE EVIDENCE

STEPWISE---
STARTING WITH ANALYTICS

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

From Product to Process Understanding!

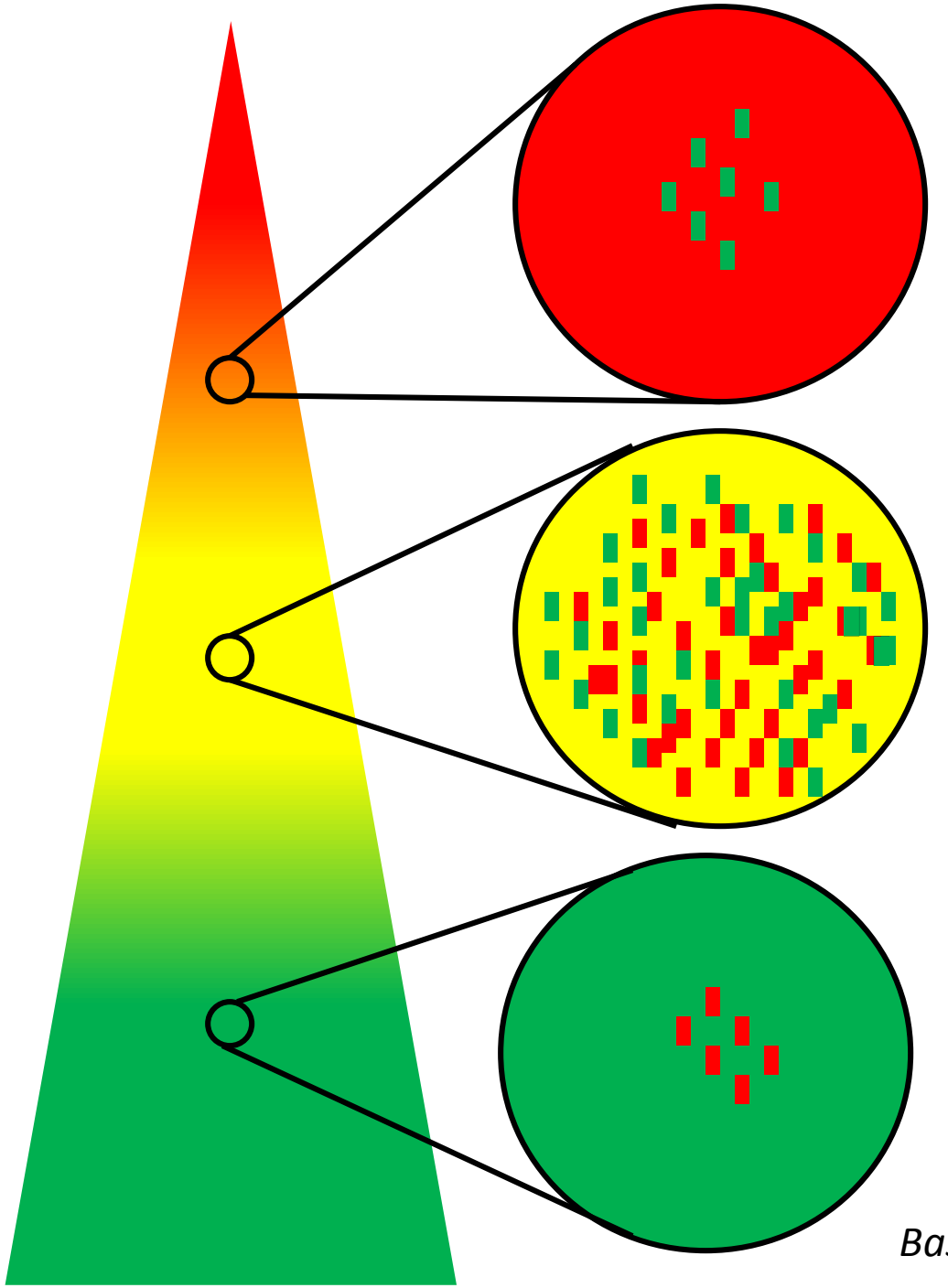


Developmental Research	IND Enabling	Initial Clinical Studies	Additional Clinical Studies

Where are we?

A journey of a….. begins with a few…..

- Sandoz announces FDA accepts its application for biosimilar version of filgrastim (July 24, 2014)
  - *Approved 3/6/2015*
- Now multiple public announcements of submissions or filings of biosimilar applications including but not limited to the following reference products, infliximab, pegfilgrastim & epoetin alfa
- Greater than 80 meeting requests for more than 15 reference products



Through the Looking Glass

Based on an comment from Nadine Ritter

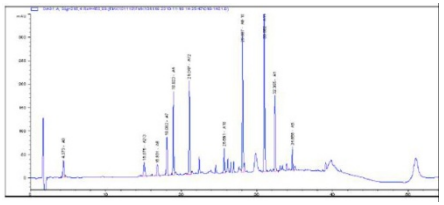
Fingerprint-like

- It may be useful to compare differences in the quality attributes… using a meaningful fingerprint-like analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods.
  - may lead to… a more selective and targeted approach to subsequent animal and/or clinical studies.

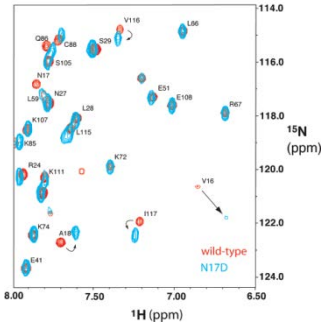
Fingerprinting

- *Above & beyond risk-based comparative characterization*
- *Meaningful subsets & patterns*
- *Not a dot counting exercise*

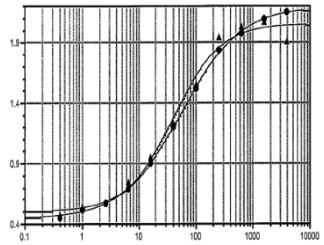
Sequence & Modifications



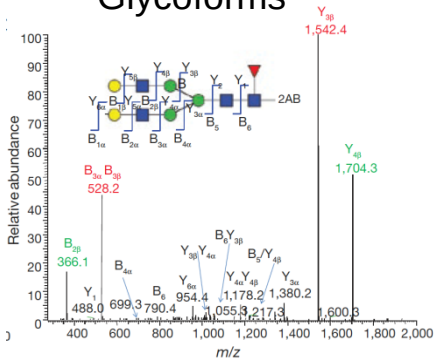
Higher Order Structure



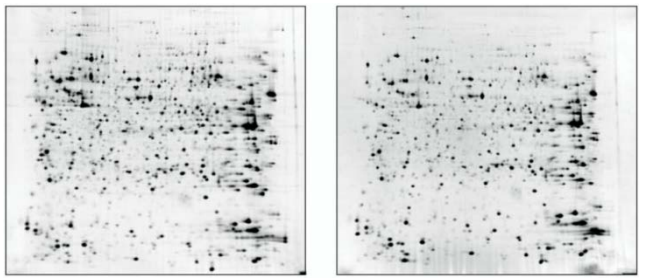
Bioactivity



Glycoforms

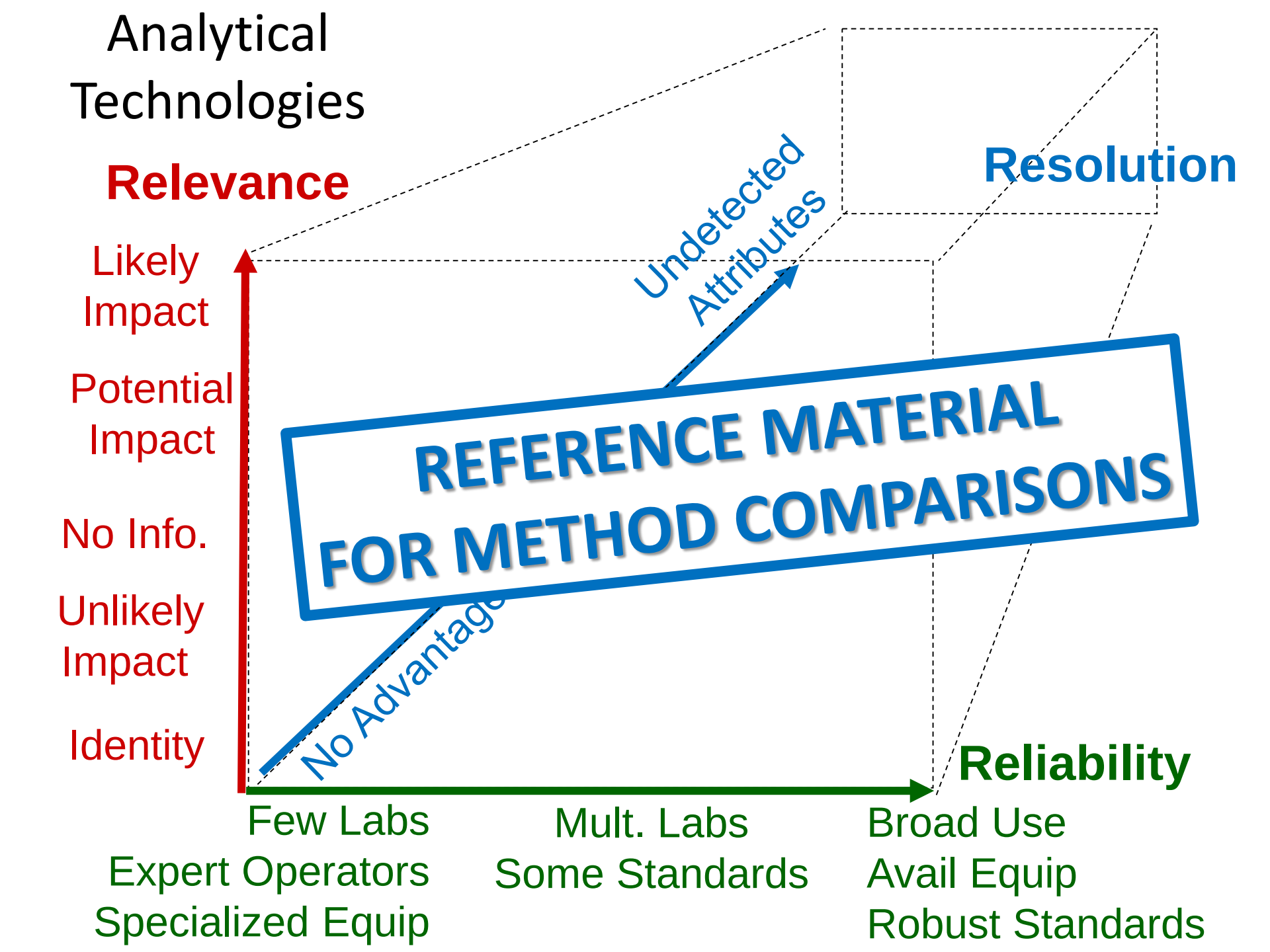


Impurity Profile



CE Applications for Biologics (from Wassim Nashabeh, GNE)

1981-1983	Initial Publication of “Zone Electrophoresis in Open Tubular Glass Capillaries” in Analytical Chemistry (81), followed by a paper in “Science” (83)—both widely credited with the launch of modern CE
1983-1988	Increased use in academic labs and few characterization or feasibility studies in industry (often in collaboration with academic labs)
1989	First international symposium HPCE (high performance capillary electrophoresis) held in Boston with the introduction of first commercial CE instruments, indicating growing use within academic centers—First conference was chaired by Prof Barry Karger
1997	Submission and approval by the FDA of two CE methods to be used as part of the control system QC release for a MAB—cIEF (identity) and Glycan analysis
1999	Launch of “CE in the Biotech and Pharmaceutical Industry” Symposium, reflecting acceptance and growing use in Pharma—Symposium is currently in its 12th year with international attendance and regulators on Organizing Committee; Also first mention of “CE” in ICH Q6B in appendix 6.1.2 (c)
2001-2005	Advances in instrumentation continued with significant expansion in applications (including CE-MS for Characterization), imaged cIEF and the introduction of platform methods
2006-present	Method becomes routine, with general chapters being developed in pharmacopeias
2010	ICH Q4B—Global Harmonization of the General Chapter on CE in USP, EP, JP


Analytical Technologies
Relevance
Likely Impact
Potential Impact
No Info.
Unlikely Impact
Identity
Resolution
Undetected Attributes
REFERENCE MATERIAL FOR METHOD COMPARISONS
No Advantage
Reliability
Few Labs
Expert Operators
Specialized Equip
Mult. Labs
Some Standards
Broad Use
Avail Equip
Robust Standards

Funding

- Enhancing Regulatory Science for the Risk Based Assessment of Emerging Manufacturing Technologies (U01)
- PAR-15-187
- to support the advancement of regulatory science that can facilitate the implementation and the assessment of emerging manufacturing technology in the pharmaceutical sector.
- http://grants.nih.gov/grants/guide/pa-files/PAR-15-187.html
- http://grants.nih.gov/searchguide/search_guide.cfm

BioFAST

BioMANufacturing Program

and more...

IBBR INSTITUTE FOR BIOSCIENCE & BIOTECHNOLOGY RESEARCH

NIPTE The National Institute for Pharmaceutical Technology and Education

Dusquesne University
Illinois Institute of Technology
Purdue University
University of Connecticut

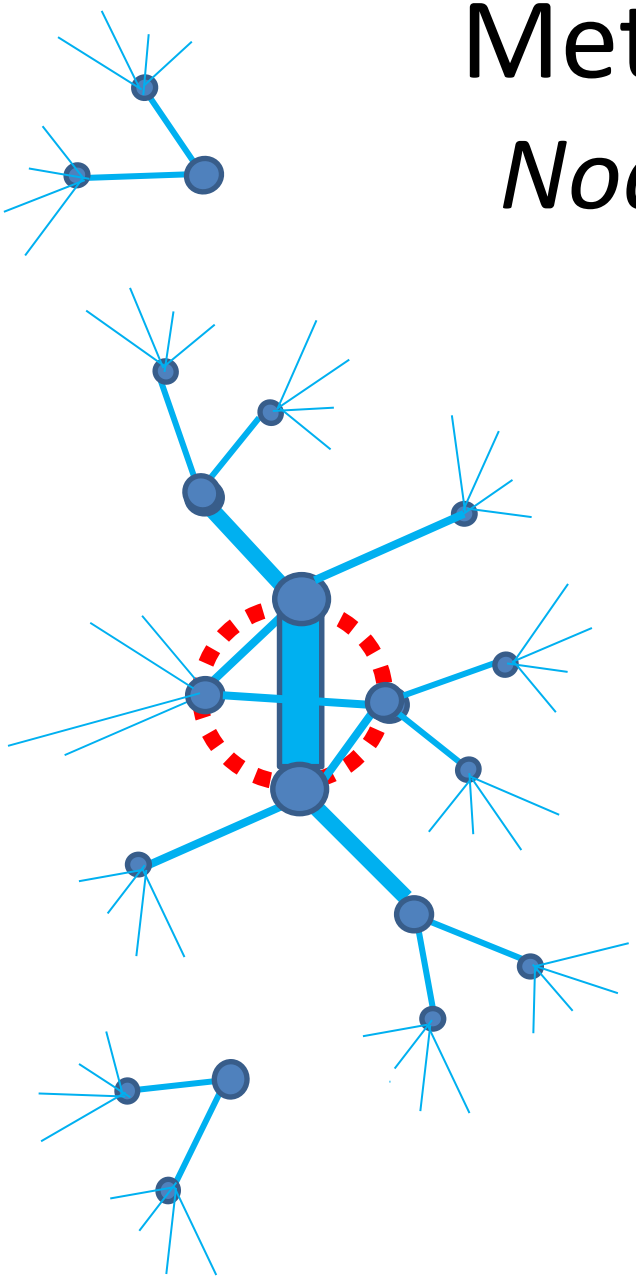
University of Michigan
University of Puerto Rico
University of Rochester
University of Wisconsin

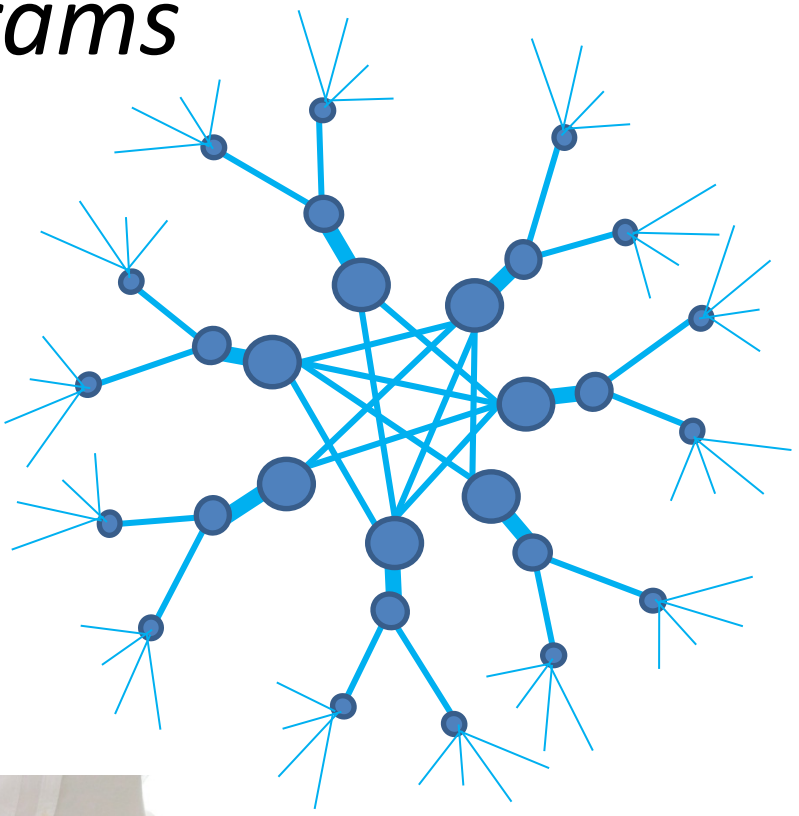
University of Iowa
University of Kansas
University of Kentucky
University of Maryland Baltimore

Northeastern University
The Barnett Institute of Chemical and Biological Analysis

Meta-Consortia

Node Diagrams





Summary

- Roles of Analytics in Biological product quality
- Examples of regulatory expectations for analytics
- Potential for advances in analytics
- Role of analytics in Biosimilars
- Opportunities for research coordination