US FDA Perspectives on Biosimilar Biological Products

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Overview of Presentation

- Statute & Draft Guidances
- Structural & Functional Characterization
- Implementation

Statute

- The Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of healthcare reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.
- The BPCI Act creates an ***abbreviated licensure pathway*** for ***biological products*** shown to be ***biosimilar*** to or ***interchangeable*** with an FDA-licensed ***reference product.***

Overarching Goal: *Efficient, predictable and transparent regulatory pathway*

Draft Guidances

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Sci. Cons.)
2. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Q&A)
3. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Quality)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors… (Mtg.)
5. Clinical Pharmacology Data to Support…Biosimilarity

Always consider entire text and context of guidance excerpts

Statute

- The Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of healthcare reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.
- The BPCI Act creates an
  - ***abbreviated licensure pathway***
  - for ***biological products***
  - shown to be ***biosimilar*** to
  - or ***interchangeable*** with
  - an FDA-licensed ***reference product.***

Definition: Biological Product

- The BPCI Act revises the definition of **"biological product"** in the Public Health Service Act (PHS Act) to include "protein":

  > . . . *a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product,* ***protein (except any chemically synthesized polypeptide),*** *or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings …*

- Historically, some proteins have been approved as drugs under section 505 of the FD&C Act (e.g., human growth hormone), and other proteins have been licensed as biologics under section 351 of the PHS Act (e.g., blood factors, proteins involved in immune response).
- Under the new law, a protein, except any chemically synthesized polypeptide, will be regulated as a biological product.

Revised Definition of a "Biological Product" (Q&A)

- FDA has developed the following interpretation of the statutory terms "Protein" and "Chemically synthesized polypeptide."
  - Protein: Any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size
  - Chemically synthesized polypeptide: Any alpha amino acid polymer that
    1. is made entirely by chemical synthesis; and
    2. is less than 100 amino acids in size.
- An application for a "biological product" must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period

Definition: Reference Product

Reference Product means: the **single biological** product, **licensed under section 351(a),** against which a biological product is evaluated in an application submitted under section 351(k).

Draft Q&A Guidance

- A sponsor may propose use of a non-U.S.-licensed comparator product in certain animal or clinical studies to support a demonstration that the proposed product is biosimilar to a reference product.
- Sponsors must scientifically justify the relevance of the comparative data and establish an acceptable bridge to the U.S.-licensed reference product.

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.

Clinically Meaningful Differences (Scientific Considerations)

- Clinically meaningful differences could include differences in the expected range of safety, purity, and potency of the proposed and reference product.
- By contrast, slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences.

Definition: Interchangeability

Interchangeable or Interchangeability means that:

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product administered more than once, the **safety and reduced efficacy risks of alternating or switching** are not greater than with use of the reference product without alternating or switching.

- **Note:** The interchangeable product **may be substituted** for the reference product without the authorization of the health care prescriber.

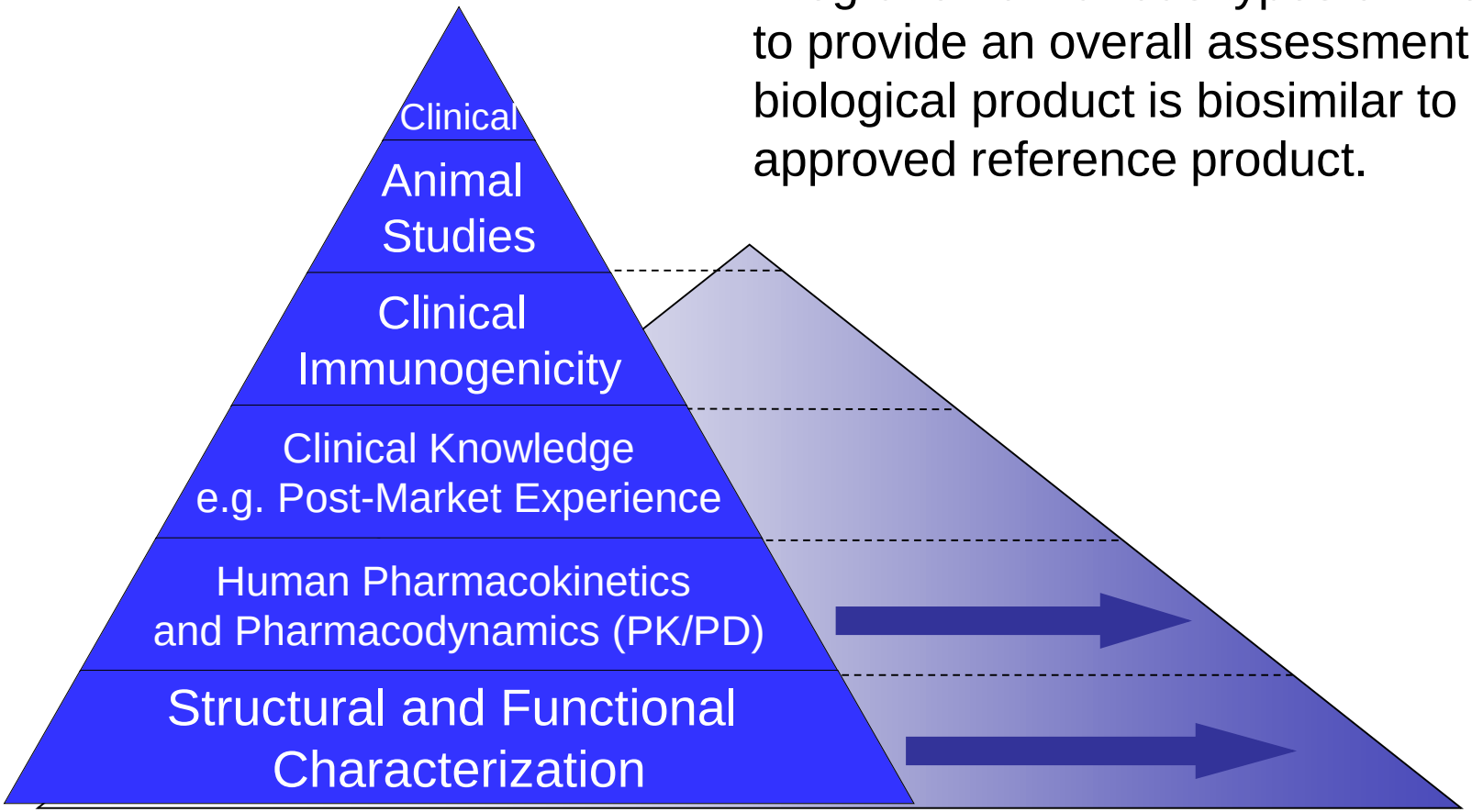
General Requirements: 351(k) Application

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

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed.

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

Totality of Evidence

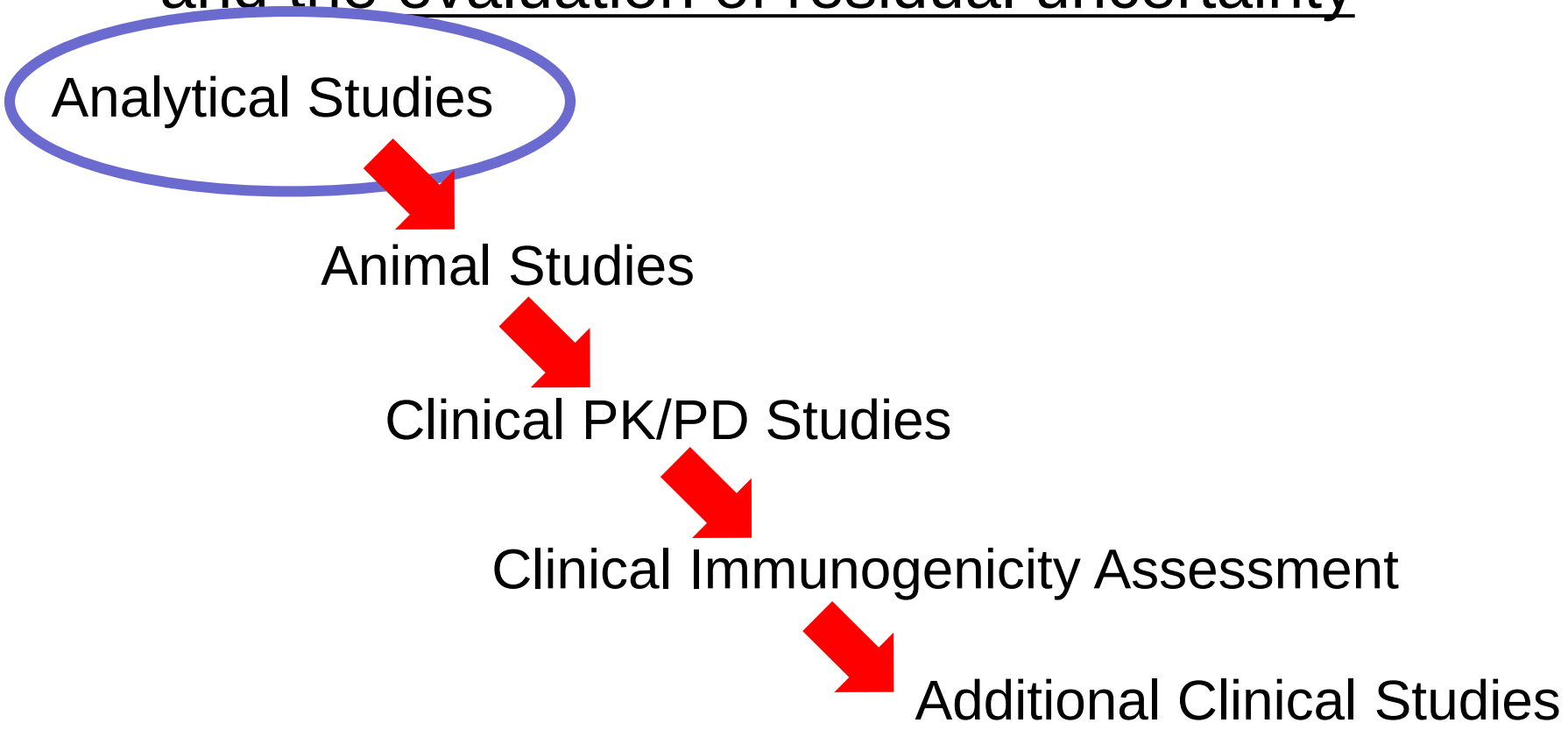


No “one size fits all” assessment :

FDA scientists will evaluate the applicant’s integration of various types of information to provide an overall assessment that a biological product is biosimilar to an approved reference product.

Plan your program

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty*



* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application

Biosimilarity

- *Biosimilar* or *biosimilarity* means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"
- and that "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

How close is close enough?

Quality Considerations Draft Guidance

Sequence

- It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product.
- However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant.

Expression System

- Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered
- The type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities

Impurities & Excipients

- The potential impact of differences in the impurity profile upon safety should be addressed
- Different excipients in the proposed product should be supported
  - Excipient interactions as well as direct toxicities should be considered.

Analytical Tools to Evaluate Proteins

Amino acid sequence and modifications: Mass spectrometry (**MS**), peptide mapping, chromatographic separations

Folding: S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence

Subunit interactions: chromatography, ion mobility MS

Heterogeneity of size, charge, hydrophobicity: Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS

Glycosylation Anion exchange, enzymatic digestion, peptide mapping, CE, MS

PEGylation & isomers: chromatography, peptide mapping

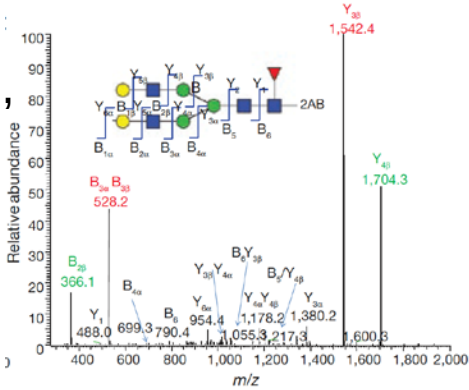
Bioactivity: cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction

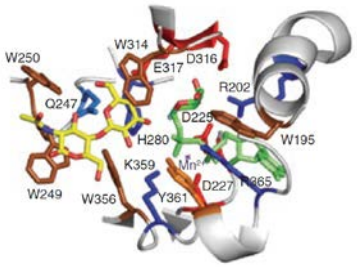
Aggregation: Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy

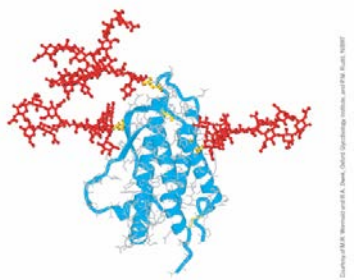
Proteolysis: electrophoresis, chromatography,MS

Impurities: proteomics, immunoassays, metal & solvents analysis

Adventitious Agents: sterility, qPCR, bioassays, clearance



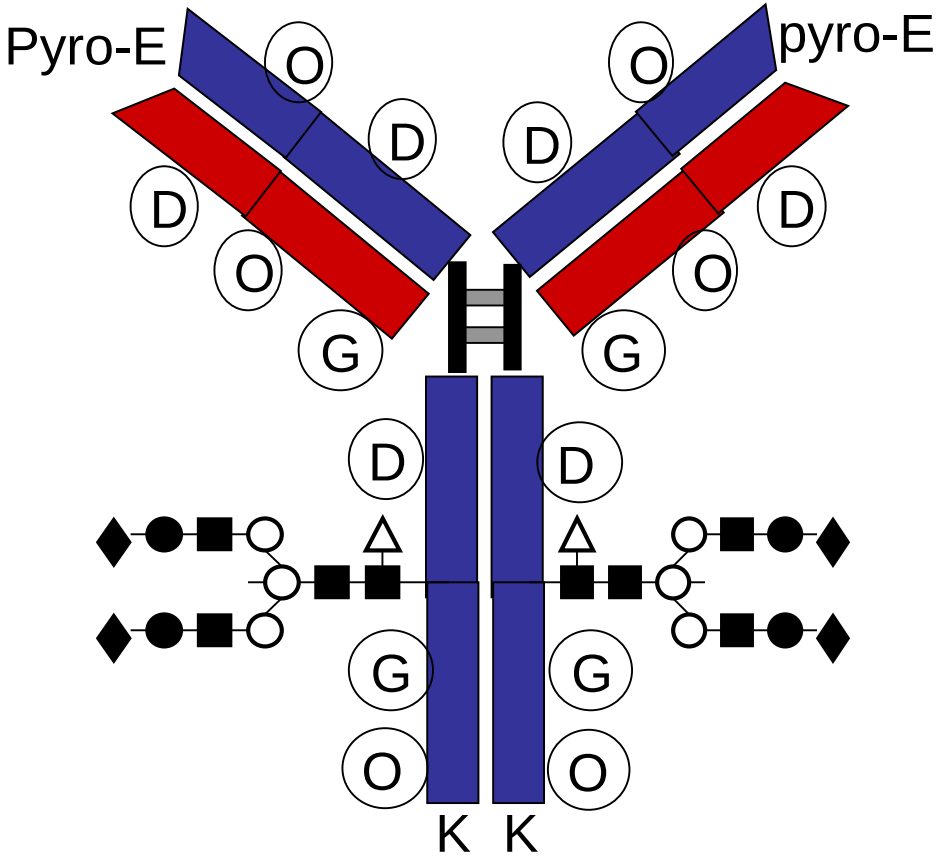




Know your protein!

- Need to understand what is important for the biological activity of the protein
- If multiple MOAs and multiple indications, need to understand MOA for specific indications and critical quality attributes for that MOA
- Need to understand impact of potential post translational modifications
  - Oxidation of methionine and deamidation of asparagine may impact function or immunogenicity of some proteins but not others.
- Use of stress studies to reveal subtle or hidden differences
- Need to understand how combinations of quality attributes interact to impact clinical performance

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)

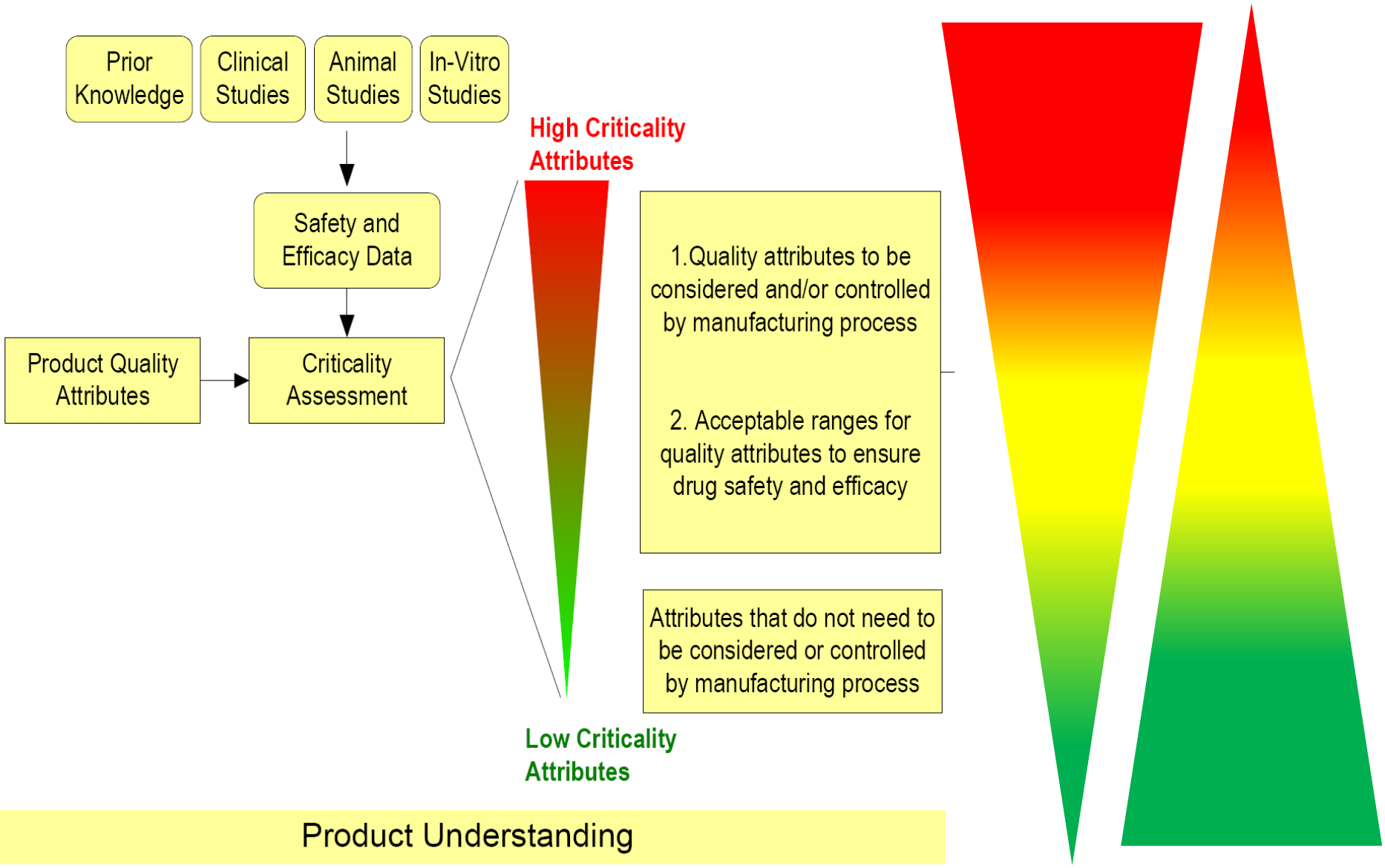
- $(16{,}920)^2 \approx$ 285 million
- 2 x 12 x 6 x 4 x (10+5) x 2 = 16,920

MAb Mechanisms of Action & Structure

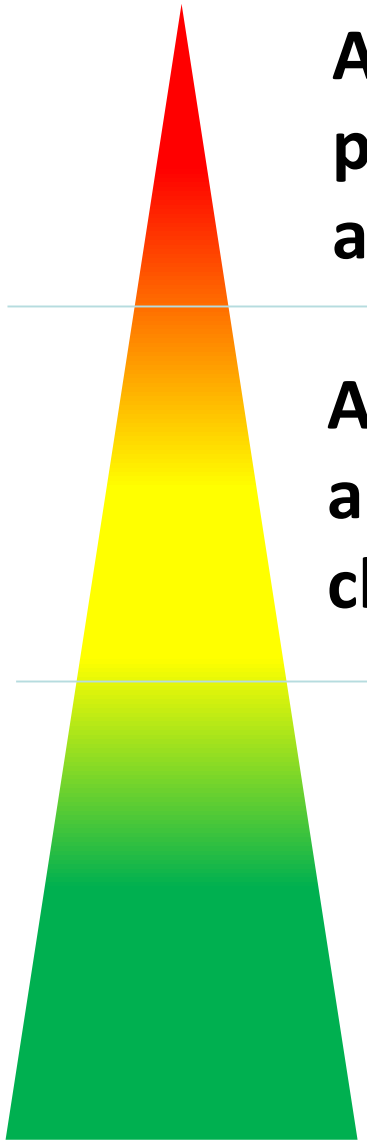
- **Binding to target antigen**
  - Soluble, cell surface or both
  - Density of antigen on cell surface
  - Affinity, binding kinetics
  - Cross reactivity with related antigens
  - Epitope mapping
- **IgG Isotype features**
  - IgG2 disulfide isomers
  - IgG4 half antibody
- **Effector function**
  - High, moderate or low
  - Binding to FcγR, FcRn, C1q
  - Antibody dependent cellular cytotoxicity
  - Complement dependent cytotoxicity
  - Antibody dependent cellular phagocytosis
  - Apoptosis (Fc mediated?)
  - Signal transduction
  - Other

Useful to know location of target cells and type of effector cells present and their FcR expression

A-Mab Risk Ranking of Quality Attributes



Historical 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 in a 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.

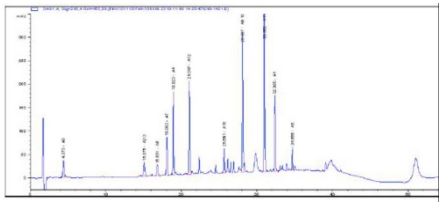
Through the Looking Glass

Based on an comment from Nadine Ritter

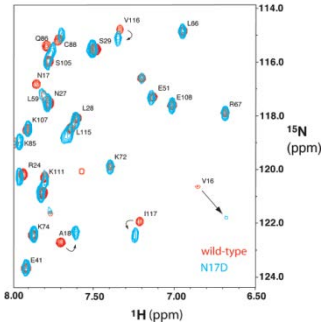
Fingerprinting

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

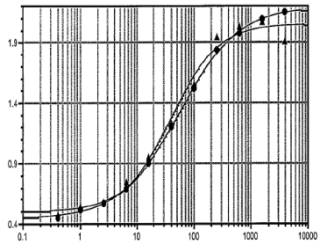
Sequence & Modifications



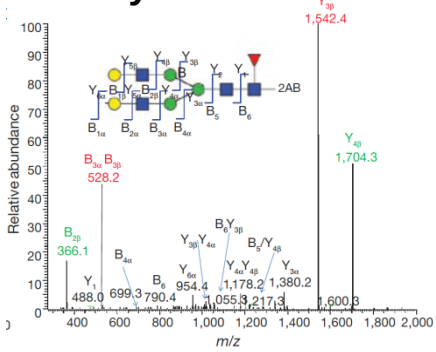
Higher Order Structure



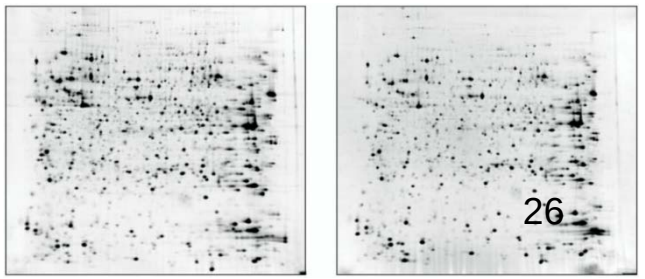
Bioactivity



Glycoforms

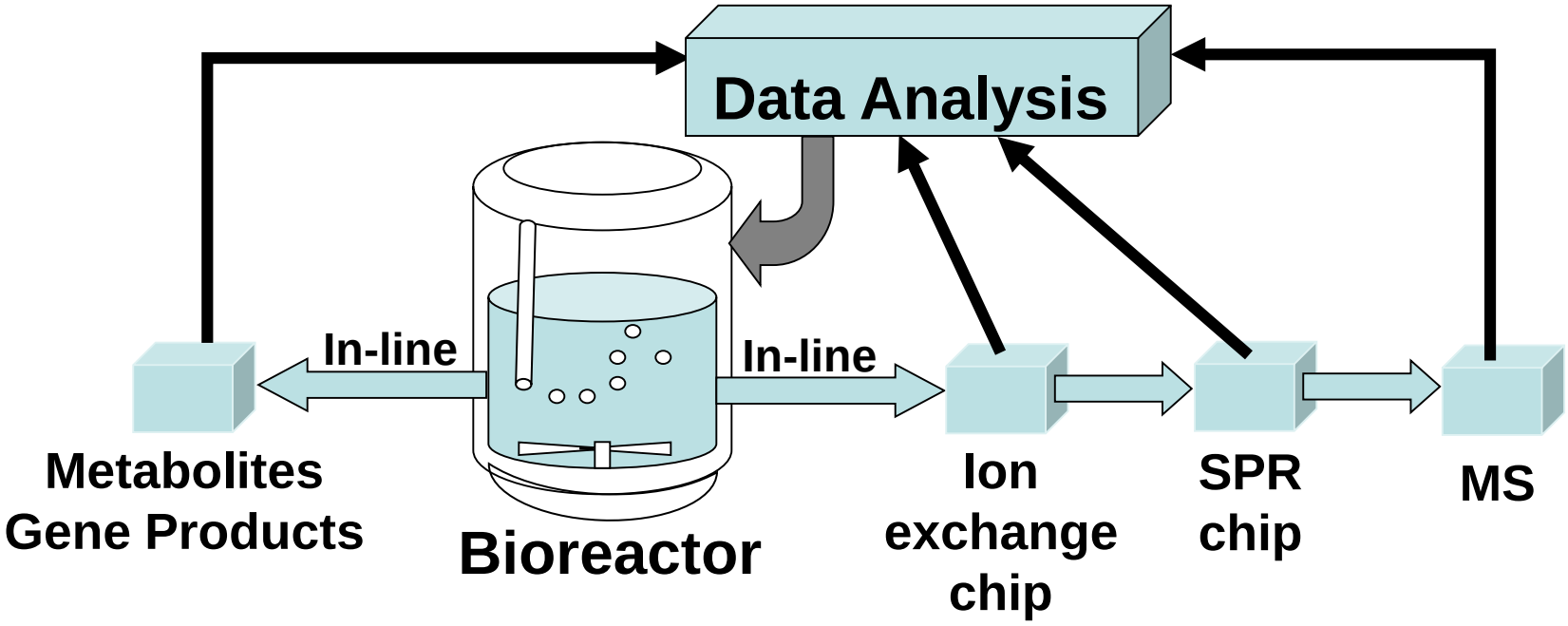


Impurity Profile



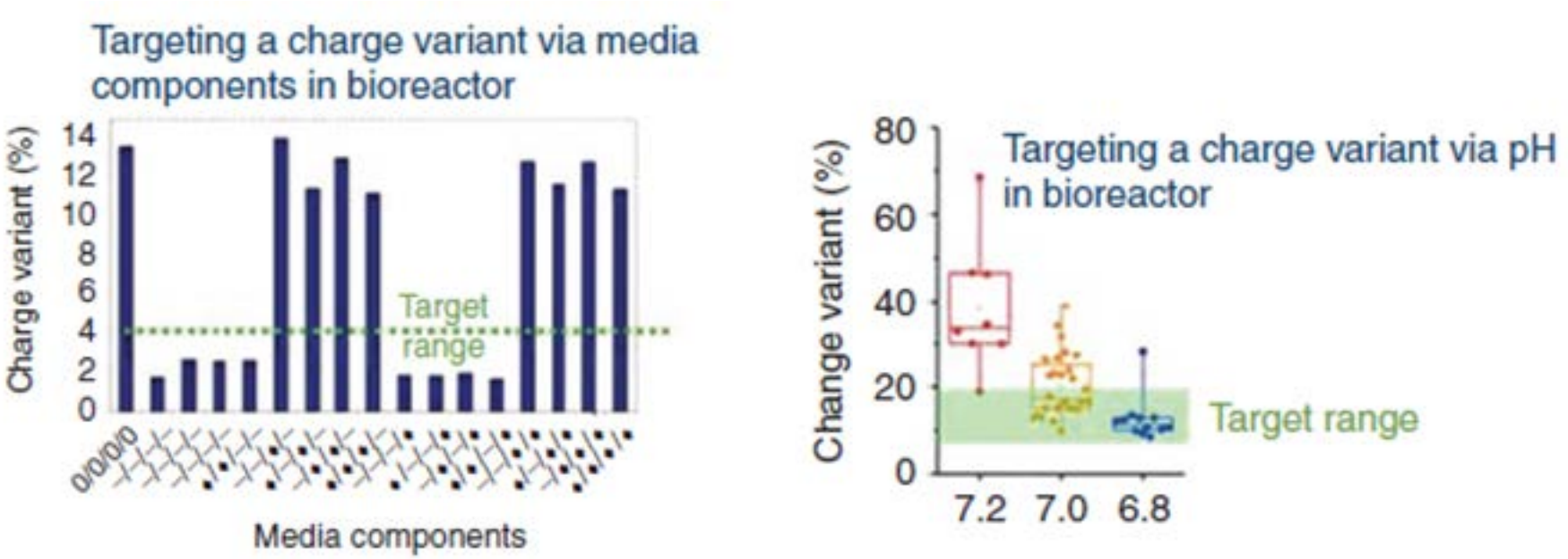
Advanced Manufacturing Development & Processes

Starting with Clone Selection……



Manufacturing Development

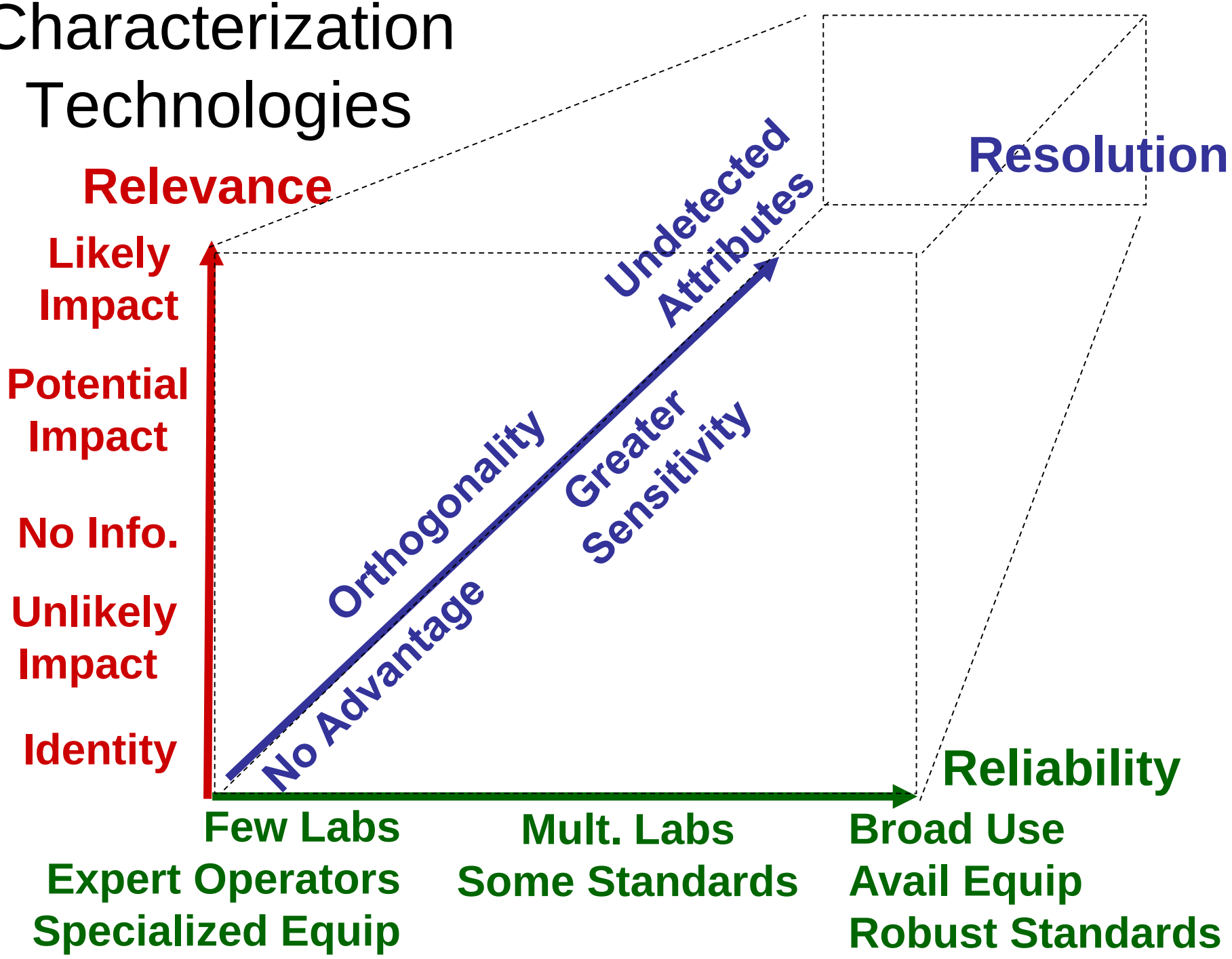
Mark McCamish and Gillian Woollett The State of the Art in the Development of Biosimilars *Clinical Pharmacology & Therapeutics* (2012); 91 3, 405–417. doi:10.1038/clpt.2011.343
Figure 2b



Characterization

- Setting an unachievable bar?
  - Nat Biotechnol, 2005. **23**(9): p. 1054-8
- No!
- Advances in characterization are opportunities
  - Important to understand what attributes are present and how they can vary
- Methods to use
- How to deal with greater information
  - Need a balance between flexibility & uncertainty
  - Links to clinical performance

Characterization Technologies



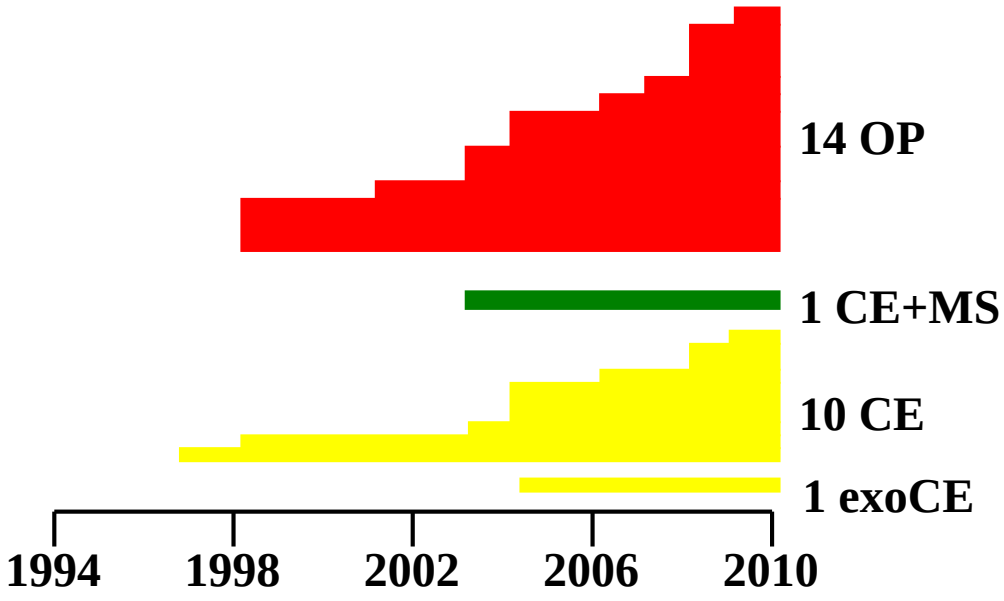
CE Applications for Biologics (from Wassim Nashabeh, GNE)

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

CE for Evaluating Glycosylation

Database: Glyco-assays over last 16 years
Read, Park & Brorson, Biotechnol Appl Biochem. 2011

- **Other glyco-analytic method**
  - **OP= oligosaccharide profiling**



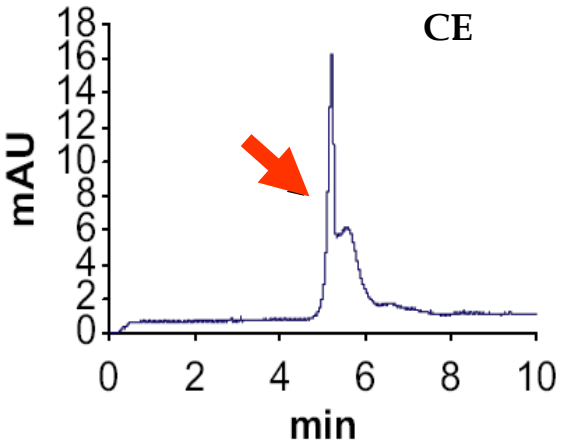
- 23 BLAs
- Most BLA applications contain glyco-analytic data
  - More for product characterization vs. lot release
- CE= Capillary electrophoresis

- **Many other modalities not covered here**
  - **MS, combinations**

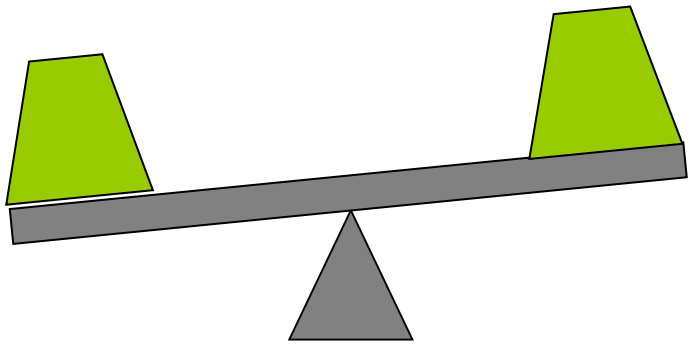
Heparin Adverse Events

- Oversulfated chondroitin sulfate is a contaminant in heparin (Nat Biotechnol. 2008 Jun;26(6):669-75)
- **CE is a routine assay for current complex product**
  - **would have picked up contaminant in crude, API or finished product**

Biomaterials. 2008 (36):4808-14.



Update Analytical Methods



Assay Modernization

– A Good Idea, But Not as Easy as It Sounds – WCBP 2011

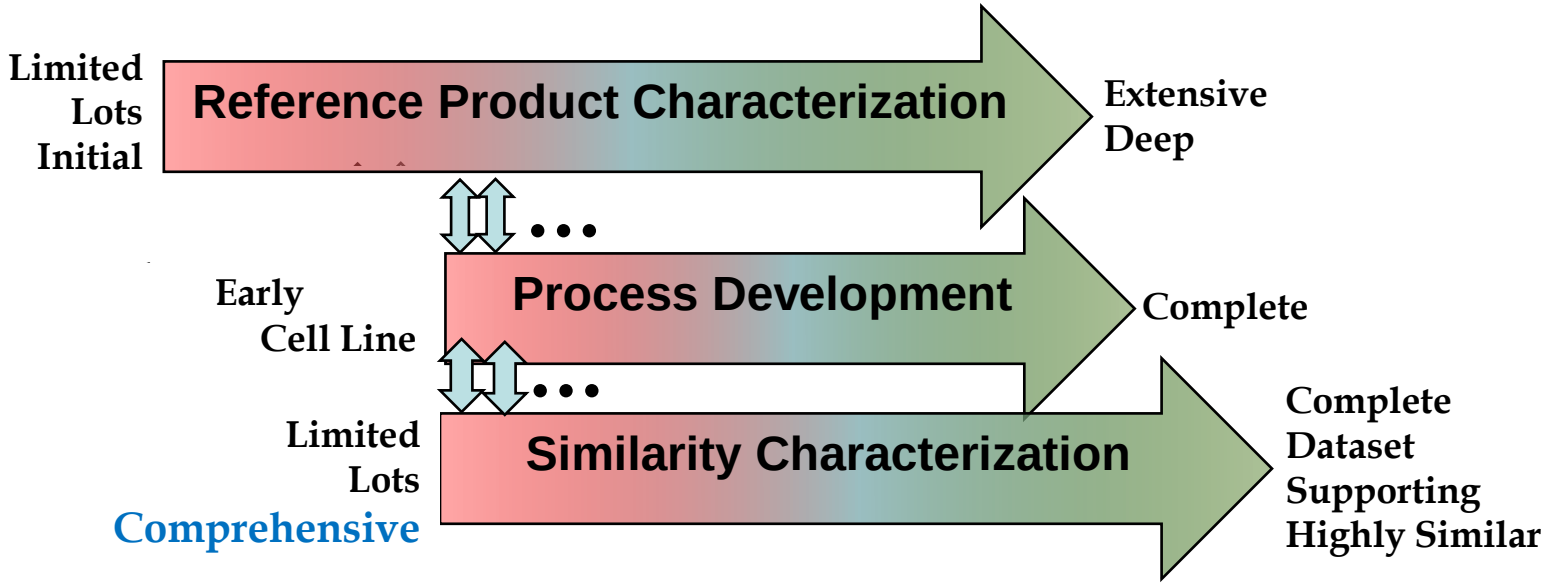
- Implementation of rapid microbiological methods for sterility testing
  - Three alternative methods evaluated only one comparable in sensitivity
    - Rajesh Gupta, *OCBQ, CBER, FDA*
- Use of NMR to identify polysaccharides in a polyvalent vaccine
  - NMR data on solvents showed LOD method was inaccurate
  - Thus the weight-based concentration of polysaccharide components was inaccurate
    - Robert Sitrin, *Merck & Co, Inc.*
- NMR method to assess OSCS contaminant
  - Also detected other variants- acetylated heparin
    - Edward Chess, *Baxter Healthcare Corporation*

Approach to Reverse Engineering for Developing a Biosimilar Product

Based on reference product quality attributes

- **Develop expression construct and cell line**
  - **Preliminary attribute characterization**
  - **Design to match host cell proteins**
- **Reverse engineer upstream manufacturing**
  - **Media composition and fermentation parameters**
  - **Growth characteristics**
  - **Match product attributes**
- **Reverse engineer downstream purification**
  - **Match product variants and process impurities**
- **Formulation**
  - **Match stability profile**

From Product to Process Understanding!



Developmental Research	IND Enabling	Initial Clinical Studies	Additional Clinical Studies

Best Practices

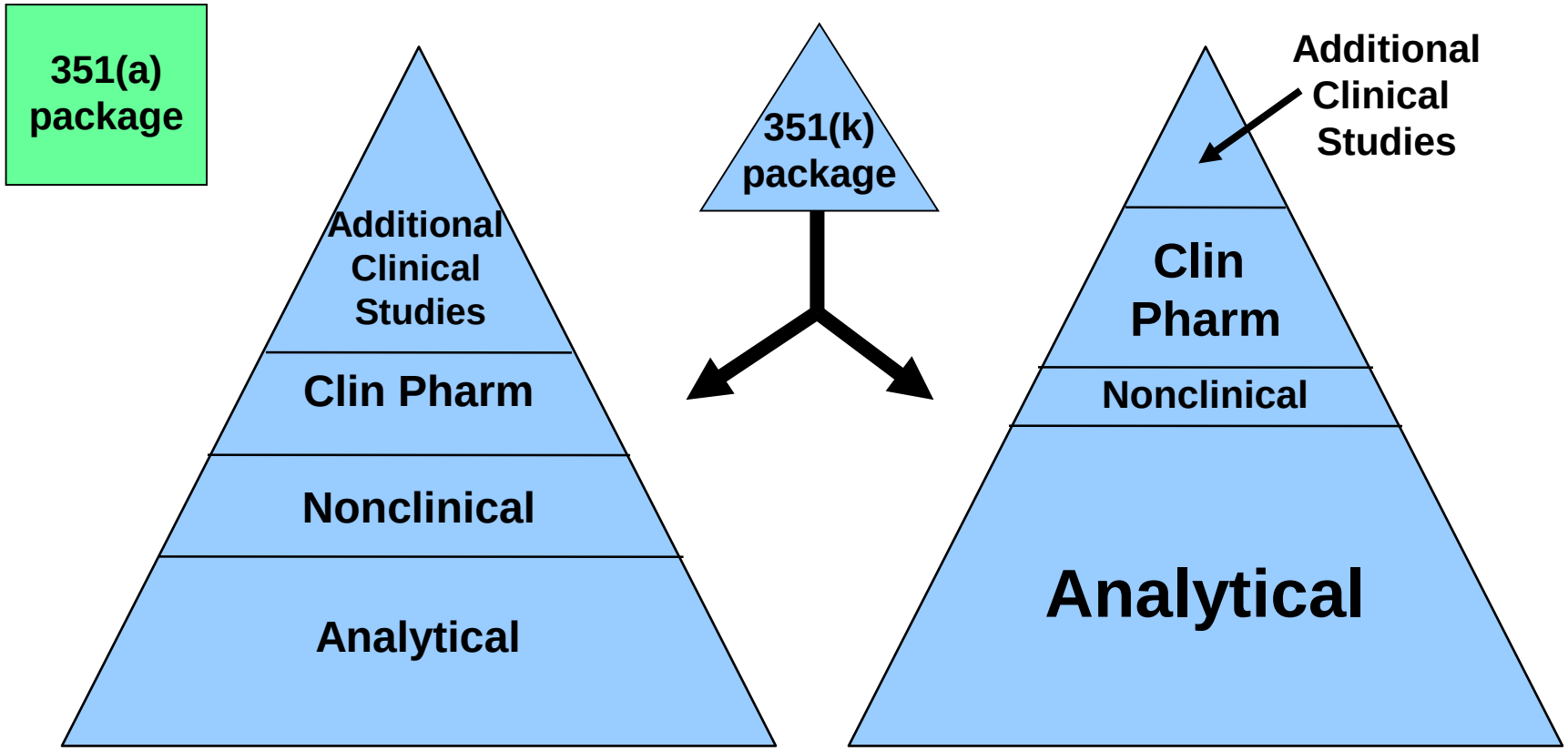
- Have a plan for development, not a speculative plan
- Early characterization data are key
  - Comparative and non-comparative
  - Proposed biosimilar and reference product
- Requesting meetings
  - Plan ahead based on when data expected
  - Remember CDER's internal review process
  - One Pre-IND/IND for biosimilar development program
- Be thorough and transparent; Provide rationale and justifications and as much data as possible
- Iterative Process; Issues still under discussion at FDA

Development Framework:

Comparative Analytical Characterization Continuum

- Cannot be biosimilar
- Similar
  - Needs additional information to determine if highly similar (e.g., additional analytical data, or other studies to determine if minor differences are “clinically inactive components”)
- Highly similar
  - Permits a selective and targeted approach to determine if biosimilar
- Highly similar with fingerprint-like similarity
  - Permits a more selective and targeted approach to determine if biosimilar

Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences



Multiple approaches to demonstrate biosimilarity

Quality as the Foundation

The Bottom Line

- The goal is to **demonstrate biosimilarity** between the proposed product and a reference product.

- The goal is not to independently establish safety and effectiveness of the proposed product.

Workload: 351(k) Proposals

- 13 (11;18%) reference products
- 62 (50; 24%) mtg. requests for proposed biosimilars
- 53 (37; 43%) initial sponsor meetings held to date
- 22 (13; 69%) INDs for proposed biosimilars
- Multiple internal meetings for each sponsor meeting
- Development programs include:
  - Prospective development programs
    - "Global" programs
  - "Retrospective" development programs
    - Programs seeking licensure in US for similar biological products licensed outside the US

Future Directions

- Guidance Documents
  - Finalize the five draft guidances, and
  - determine plans for future policies on biosimilars, including guidance on clinical pharmacology data
- Education & Outreach
  - Education WG, Webinars and presentations at professional society and clinical specialty meetings
- Issues: Transition to biological products, Interchangeability, etc.
- Continue to meet with sponsors & interact with other regulatory agencies

Acknowledgements

- Leah Christl
- Marjie Shapiro
- & many others…

Thank you for your attention

Questions?