

BIOSIMILARS: REGULATORY & DRUG DEVELOPMENT



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US BIOSIMILARS LEGISLATION/REGULATORY PATHWAY

- **BPCI Act**: Biologics Price Competition and Innovation Act of 2009
- BPCI Act signed into law as part of the Affordable Care Act on March 23, 2010
- creates abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological (section 351k; statutory approval pathway)
- FDA Public Hearing → Nov. 2010
- FDA's Biosimilar Guidances → February 2012
- FDA Public Hearing → May 2012

- **BPCI Act**: Biologics Price Competition and Innovation Act of 2009
- BPCI Act signed into law as part of the Affordable Care Act on March 23, 2010
- 12 years market exclusivity for the innovator product
- 1 year of market exclusivity for the first interchangeable biosimilar product; no exclusivity for a biosimilar approval
- confidential exchanges of detailed substantive patent contentions between biosimilar applicant and innovator BLA holder

DEFINITION OF BIOSIMILARITY (BPCI ACT)

- “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”

DEFINITION OF BIOSIMILARITY (BPCI ACT)

(BIOSIMILARS ARE NOT GENERICS!)

- “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components”
 - Differences in impurity profiles are permissible
 - Differences in excipients and formulation of the finished product are permissible
 - Differences in container/closure and delivery system are permissible

DEFINITION OF BIOSIMILARITY (BPCI ACT)

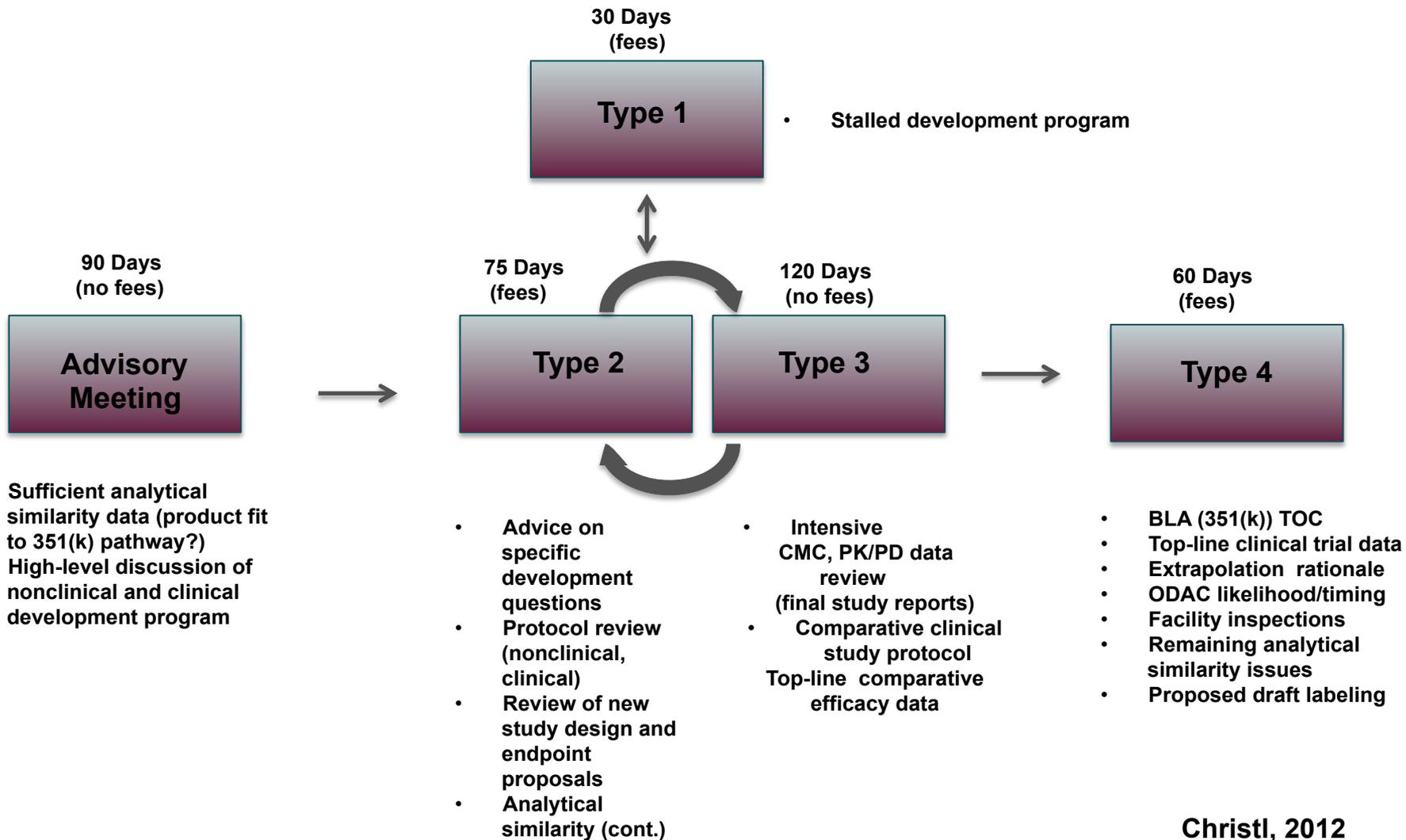
(BIOSIMILARS ARE NOT GENERICS!)

- “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”
 - Differences in the active substance can be permissible, e.g. differences in terminal sequence, glycosylation, other posttranslational modifications
 - Expression system need not be the same; however, use of alternative expression systems is discouraged in the guidance

FDA'S BIOSIMILARS ORGANIZATION

- CDER/CBER Biosimilar Implementation Committee (Co-Chairs: Janet Woodcock, M.D., Karen Midthun, M.D.)
- CDER, CBER Biosimilar Review Committees (BRC)
- CDER BRC: Chair: John Jenkins, M.D.; Lead: Leah Christl, Ph.D. (Associate Director for Therapeutic Biologics/ Biosimilars)
- BRC participate in meetings with Sponsors and contribute to FDA's formal positions/official meeting minutes
- will review all BLAs submitted under section 351(k) of the PHS Act (i.e. all Biosimilar applications)

FDA'S BIOSIMILARS MEETINGS



FDA DRAFT BIOSIMILAR GUIDANCES (2012-2014)

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb. 2012)
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Feb. 2012)
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb. 2012)
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (**March 2013**)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (May 2014)

UPCOMING BIOSIMILAR GUIDANCES (2015)

- Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
- Considerations in Demonstrating Interchangeability to a Reference Product
- Labeling for Biosimilar Biological Products
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity

Originator vs. Biosimilar Development

New Drug Application based on Federal FD&C Act (505b1, 505b2) and BLA based on PHS Act (351a)	Abbreviated licensure pathway in section 351(k) of the PHS Act for 351(a) products
Innovative Medicine: finding the right drug for the right patient for the right disease	Similar (not exact copy) version of an approved biologic, known patient and disease
Full development: CMC, Non-Clinical and Clinical	Specific and Targeted development: CMC, minimal Non-Clinical and abbreviated Clinical – leveraging prior knowledge
Phase 1, 2 (POC, Dose-Ranging) and 3 (confirmatory)	Limited Phase 1 and 3 comparative trials
Comprehensive pre-approval safety	Immunogenicity as the key safety element

Originator vs. Biosimilar Development

Generally two placebo-controlled superiority trials

Each indication and patient population has its own clinical trial(s)

Both Step-wise and Learn and Confirm Paradigm

Patients and physicians both highly motivated to participate due to unmet medical need and improving healthcare through innovation

Active-controlled equivalence or non-inferiority trials

Extrapolation possible from one indication/population to other based on MOA and PK/PD

Step-wise, totality of evidence approach

Often less enthusiasm for participation from patient and physicians in the western world; better participation in less developed world due to the opportunity of accessing cutting-edge medicines at a lower cost

UNDERLYING REGULATORY FRAMEWORK / EXPECTATIONS

- A biological product that is demonstrated to be “*highly similar*” to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly available information regarding FDA’s previous determination that the reference product is safe, pure and potent.
- Data requirements for a Biosimilar application will be less than a full complement of product-specific preclinical and clinical data required for an original BLA application
- FDA may waive any of these data requirements if it finds the data are “unnecessary”
- FDA has a “longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources...and avoiding ethical concerns associated with unnecessary duplication of human or animal testing.”

SELECTION OF REFERENCE PRODUCT

(CRITICAL TO STREAMLINING CLINICAL PROGRAM)

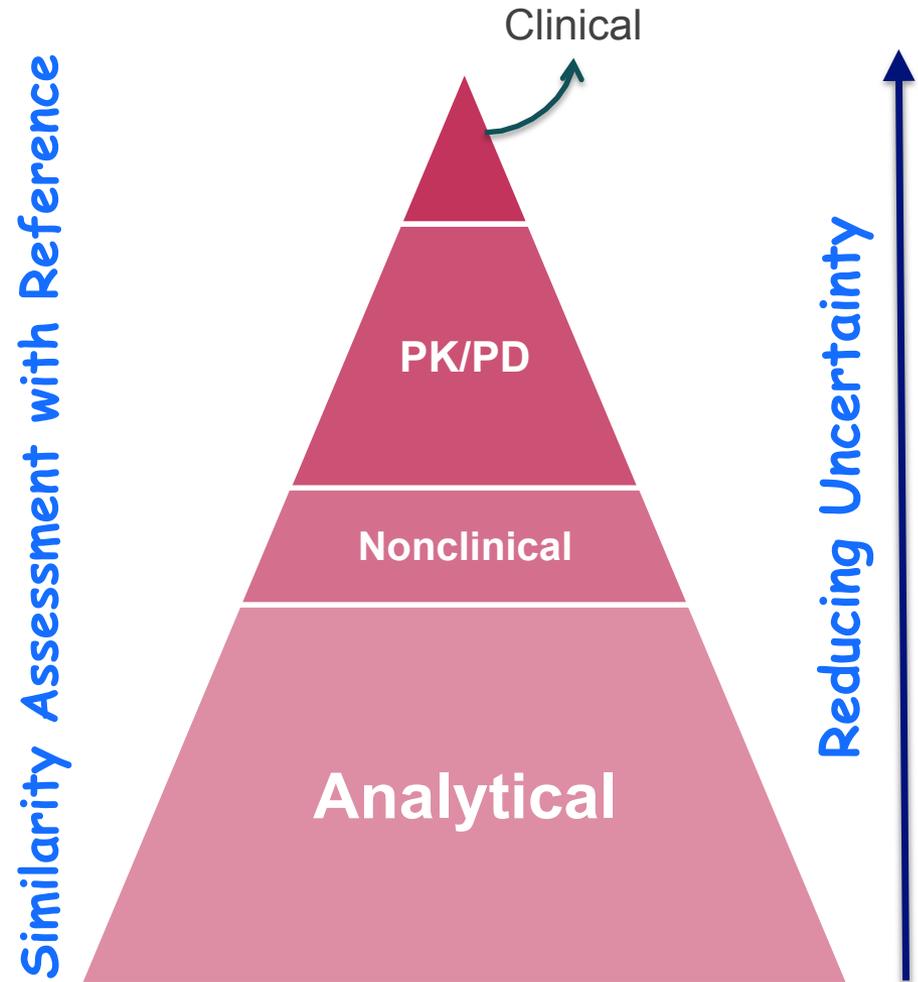
- **BPCI Act:** to obtain licensure a Sponsor must demonstrate that the proposed product is biosimilar to a single reference biological product that previously has been licensed under section 351(a) of the PHS Act
- To avoid unethical/redundant animal/human studies, FDA allows use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product
- The ex-US reference product must be extensively bridged to the US-approved product via an integrated panel of analytical (in vitro), nonclinical, and clinical studies
- FDA states that in order to establish an acceptable bridge to the US licensed reference product “likely would include a clinical PK and/or PD study conducted with the US licensed reference product”; Agency seems to prefer 3-arm study
- EMA recently changed to allow use of ex-EU reference product in clinical studies
- FDA highly unlikely to accept use of non-US licensed reference product in pivotal studies supporting interchangeability

QUALITY CONSIDERATIONS

- FDA recommends to quantify differences in quality attributes between the biosimilar and reference product(s) using a “fingerprint-like analysis algorithm” incorporating a large number of product attributes and their combinations assessed with highly sensitive, state of the art orthogonal analytical methods
- cell-based functional assays although sometimes highly variable are critical for comparison of all functional domains of the biosimilar and reference product; functional assays are also essential for detection of neutralizing antibodies
- if rigorous structural/functional comparison shows minimal or no difference bet. the proposed biosimilar product and multiple lots of the reference product, the stronger the scientific justification for a “selective and targeted approach to animal and/or clinical testing to support demonstration of biosimilarity”
- FDA is fully aware that some reference products have had multiple versions on the market without apparent differences in safety and efficacy

HIGHLY SIMILAR ANALYTICAL AND PK / PD DATA = LOWER RISK OF CLINICALLY MEANINGFUL DIFFERENCES

- Risk-Based, Stepwise, Totality of Evidence
- Analytical Characterization is the foundation
- PK/PD is a key component of initial clinical assessment
- Comparative Immunogenicity assessment expected
- Additional Clinical studies, if needed

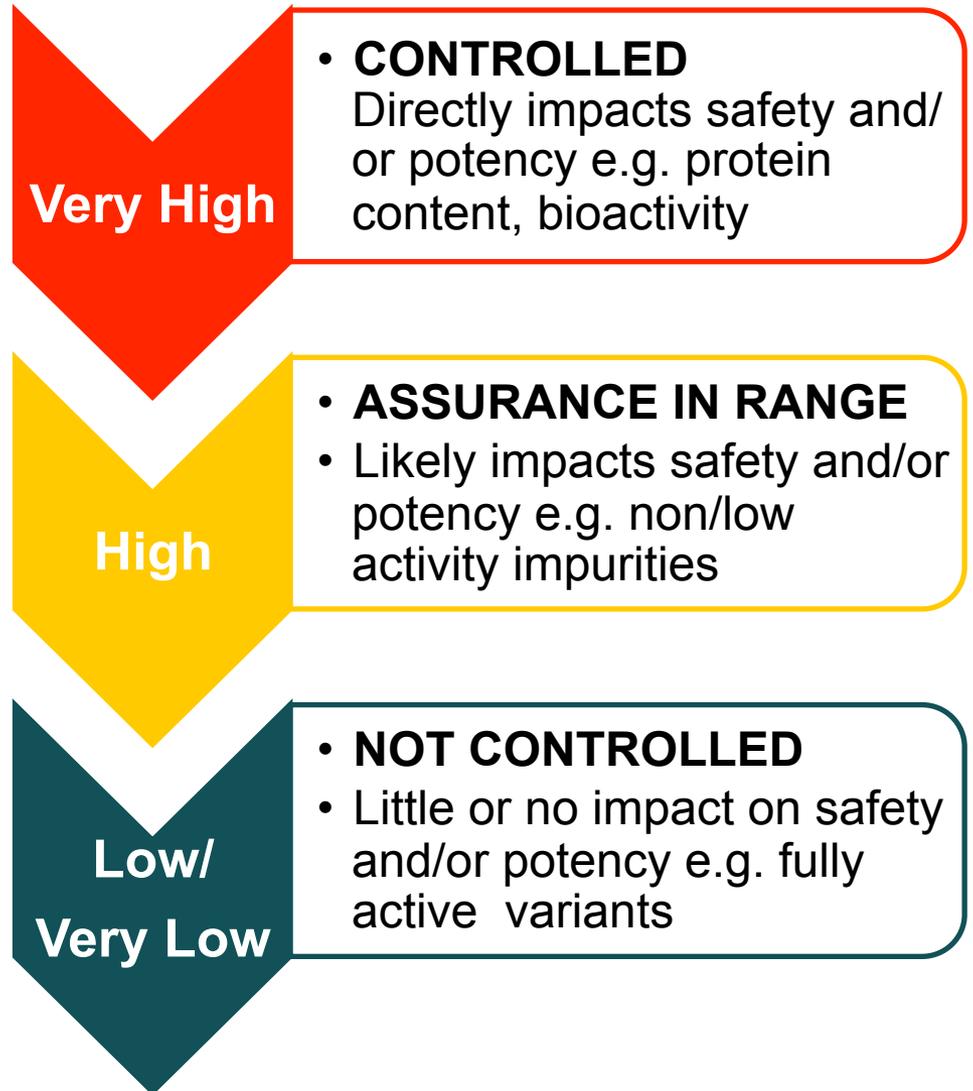


CRITICALITY ASSESSMENT OF CRITICAL QUALITY ATTRIBUTES (CQA)

CQAs → reflect composition of DP & structural and bio properties of DS

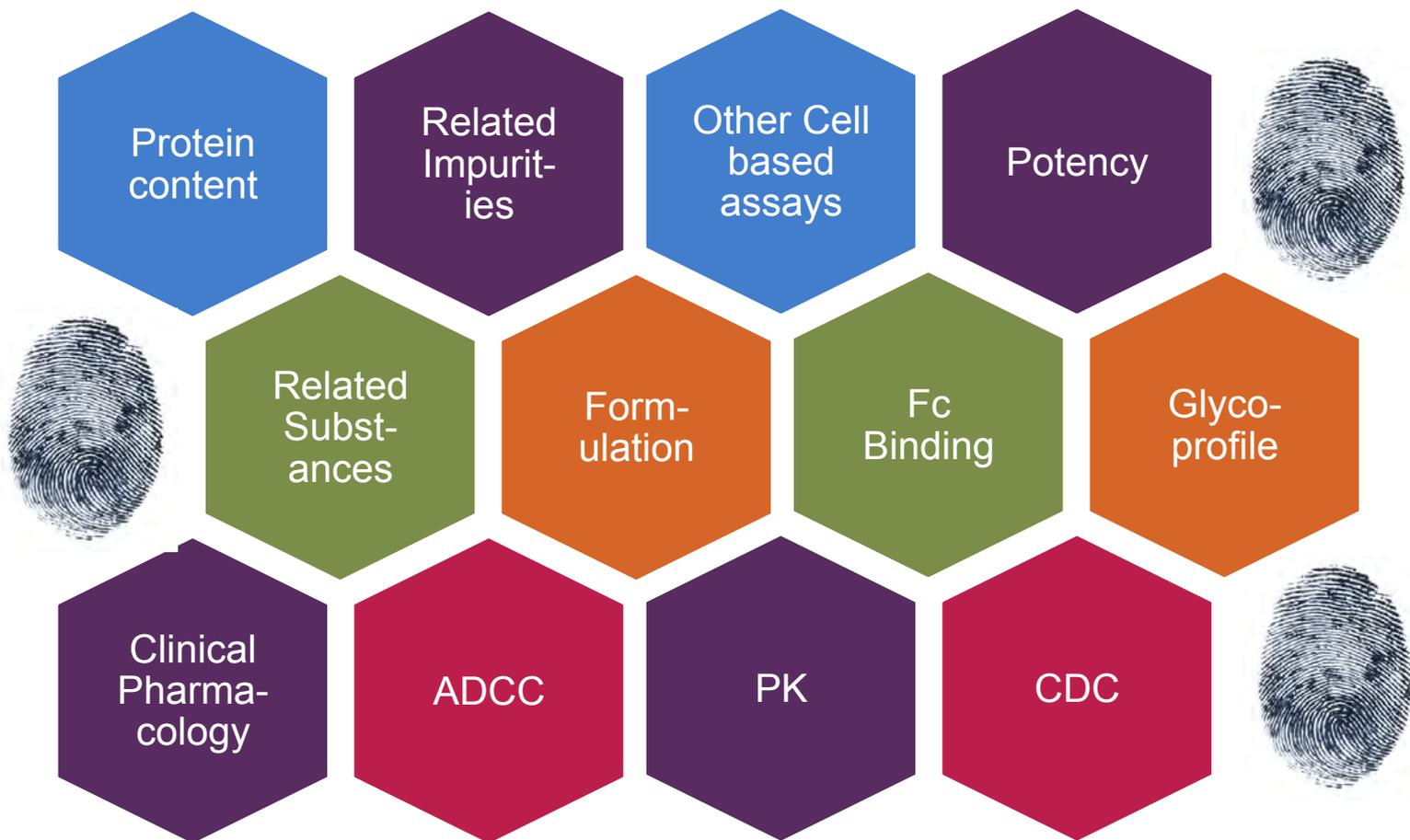
Criticality assessment is based on:

- **Prior knowledge**
- **Requires comprehensive literature search**
- **Comparative biological, non-clinical or clinical data on test vs. RMP**



FINGERPRINT MATCH

- Above & beyond risk-based comparative characterization
- All attributes/properties match regardless of relevance

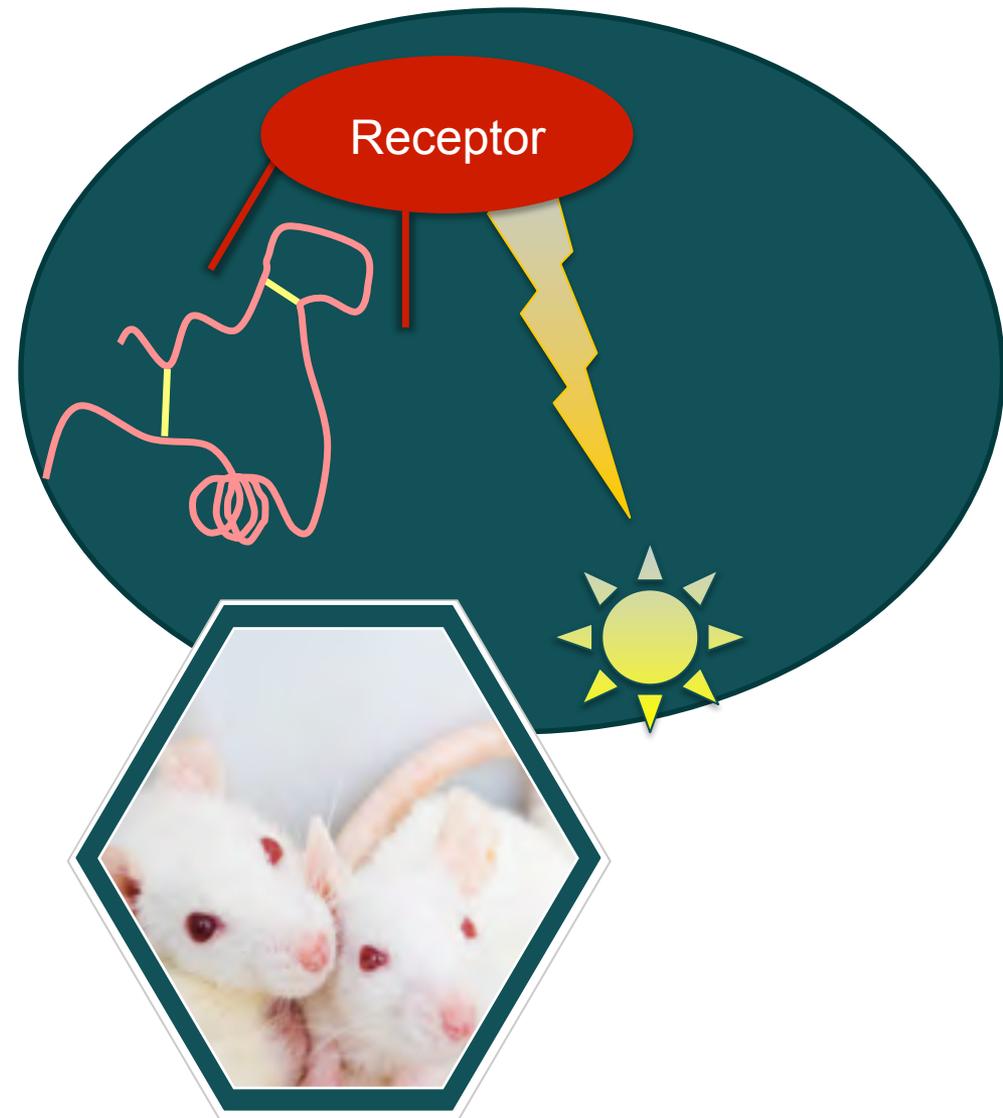


BIOLOGICAL ACTIVITY

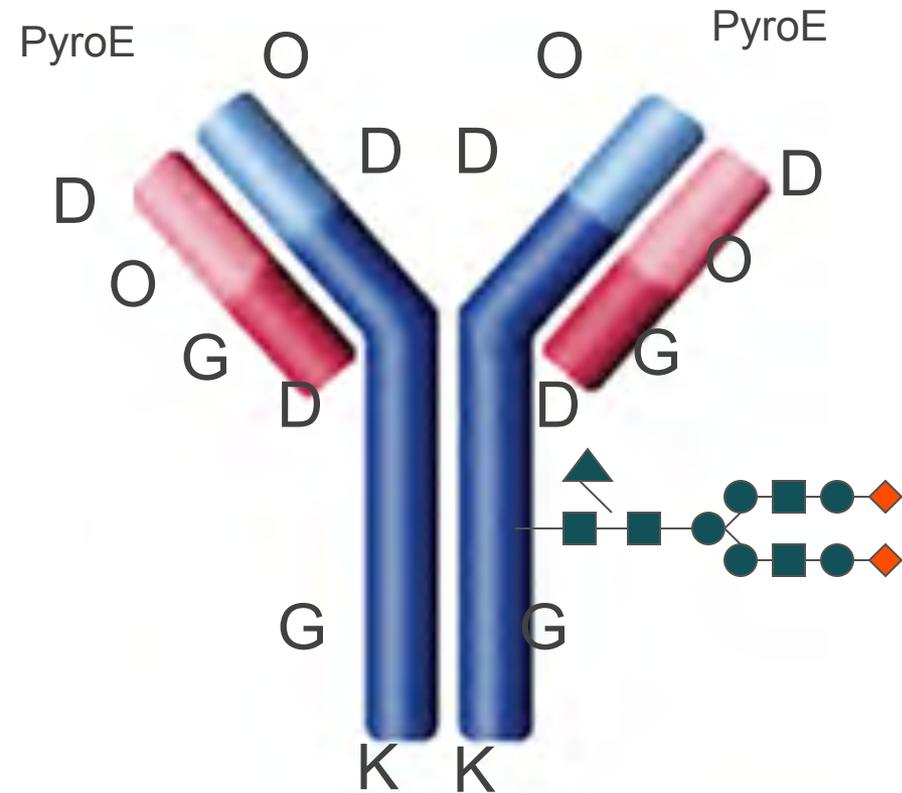
Orthogonal Approach

Set up various assays to measure broad panel of biological effects:

- Receptor binding
- Downstream signalling e.g. protein activated by phosphorylation
- Effect on cell e.g. growth, death, secretion
- In vivo effects
- Relevant biological effects always have **very high criticality**



MONOCLONALS HAVE MANY BIOLOGICAL EFFECTS BUT NOT ALL ARE RELEVANT TO THERAPEUTIC EFFECT



• Target Binding

- ELISA
- SPR
- Target bearing cells

- Apoptosis
- Down stream signalling
- Cytokine release
- Neutralisation

• Fcγ Binding Ia IIa IIIa (V/F), IIIb, Rn

- ELISA
- SPR
- Ex vivo
- C1q

- ADCC (Target/ Effector)
- Regulatory Φ induction
- Disease models

ANIMAL STUDIES *(SCIENTIFIC CONSIDERATIONS GUIDANCE)*

- Animal studies are considered relatively insensitive to detect differences between biosimilars and reference products due to small sample size, intra-species variations, lack of pharmacologically relevant species, etc.
- Scientific justification for limiting the scope of animal toxicity studies can be discussed at the Biosimilar Initial Advisory Meeting (for example)
- Most biosimilar developers conduct head-to-head, repeat-dose, toxicity and toxicokinetic studies in a single species (ex. rat)
- Animal immunogenicity studies are not predictive of human responses but have value in terms of detecting differences in molecular structure or impurities/excipients not picked up by analytical/biological in vitro tests
- Nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies not required for biosimilars

PHARMACOKINETIC STUDIES (“PK/PD SIMILARITY”)

- **Pivotal part of biosimilarity program**
 - Also required for small molecule generics
 - 3-way testing may be needed to bridge to studies employing reference product sourced from outside the region (relates to US and EU)
- **Key Considerations** (study design)
 - As for small molecules primary endpoints are AUC_{0-t} , AUC_{0-inf} , C_{max}
 - BUT
 - Equivalence margin needs to be justified not de facto 80 -125%
 - Elimination endpoints are important secondary endpoints
 - Healthy subjects preferred over patients (if ethical)
 - Single-dose or steady state
 - May be required to bridge indications

Clinical Requirements - US

- **Program (Phase 1 then Phase 3)**
- PK (or PK/PD) similarity assessment (equivalent systemic exposure)
- once PK/PD BE to reference product is established typically at least one phase 3 efficacy study will be required for approval to demonstrate therapeutic equivalence
- a two-sided, therapeutic equivalence design with margins ideally based on pivotal trials supporting approval of the reference product is required
- in certain cases, FDA would entertain the use of different primary efficacy endpoints than were used for the reference product
- proposed endpoints need to be scientifically justified as being able to detect clinically meaningful differences in safety and efficacy between the biosimilar and reference product
- Phase 3 study population needs to closely mimic pt. pop. used to support reference product licensure; in addition, the study population should be sensitive to differences between the biosimilar and reference products

HOW MUCH CLINICAL DATA?

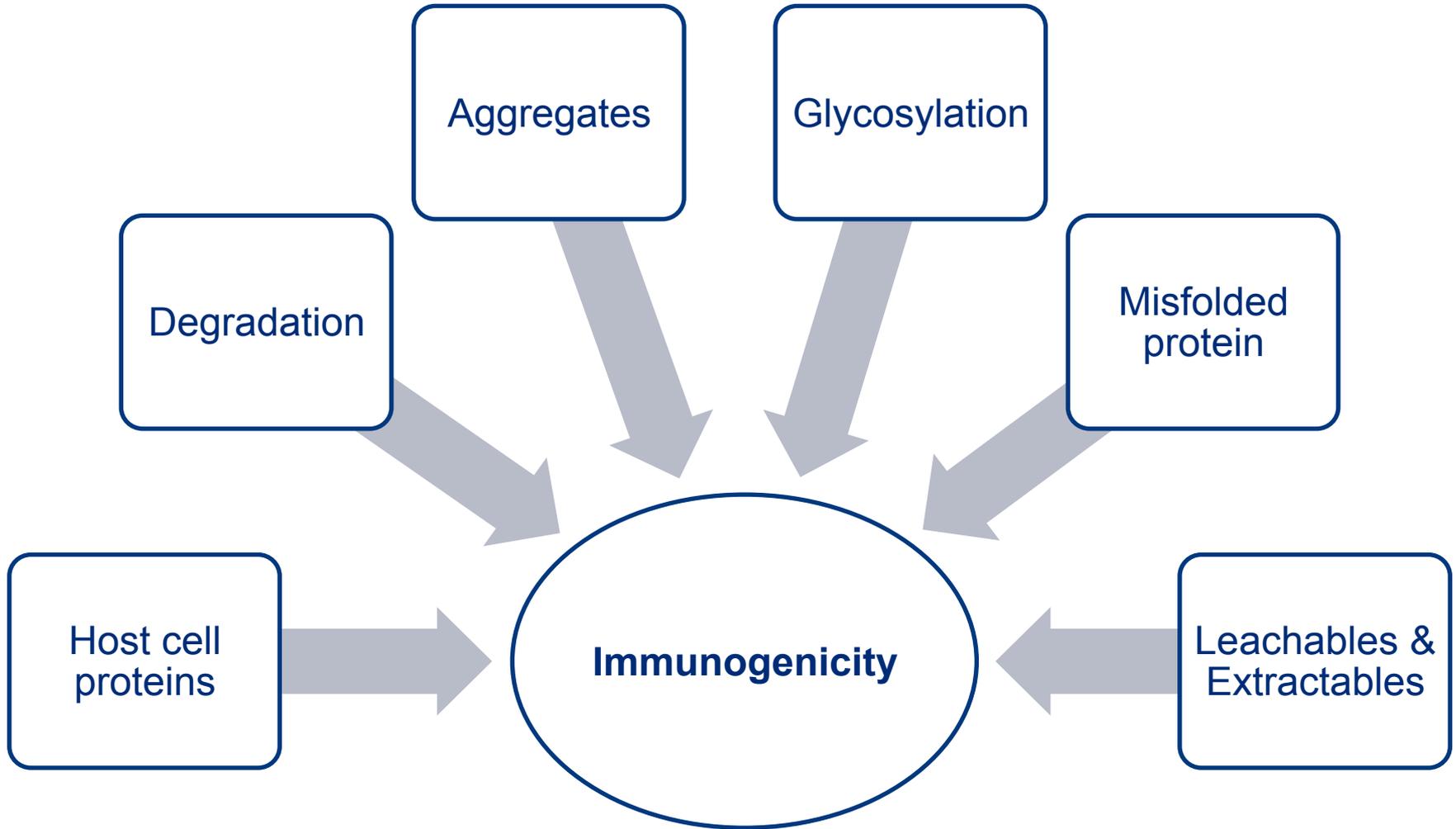
- Comparative clinical trials required if residual uncertainty efficacy following PD studies or no suitable marker exists
- CHMP/FDA will require study to be conducted in most sensitive patient population including non-licensed indications
- Safety data must be sufficient and monitored post approval
- Clinical therapeutic equivalence margins should be prespecified and justified, primarily on clinical grounds (non inferiority trials not generally accepted)
- Assay sensitivity has to be ensured i.e. trial design should maximize detection of difference (sensitive population, steep part of dose response curve, etc.)
- FDA may require "switching" for products in chronic use

ASSESSMENT OF CLINICAL IMMUNOGENICITY

(SCIENTIFIC CONSIDERATIONS GUIDANCE)

- must establish no clinically meaningful differences in immune response between biosimilar and reference product
- structural, functional, and animal data generally not adequate to predict immunogenicity in humans
- at least one clinical study in sensitive patient population assessing immunogenicity of biosimilar versus US reference product
- “sensitive” meaning that development of anti-drug antibodies has a measurable effect on safety/efficacy; pt. population in which adverse outcomes most likely
- FDA open to one-sided, NI design to assess comparative immunogenicity (i.e. biosimilar can have decreased immunogenicity relative to reference product!)
- minimal follow-up period for chronically administered biologics should be one year; 6-12 months of data required in primary marketing application

KEY QUALITY ATTRIBUTES THAT IMPACT IMMUNOGENICITY

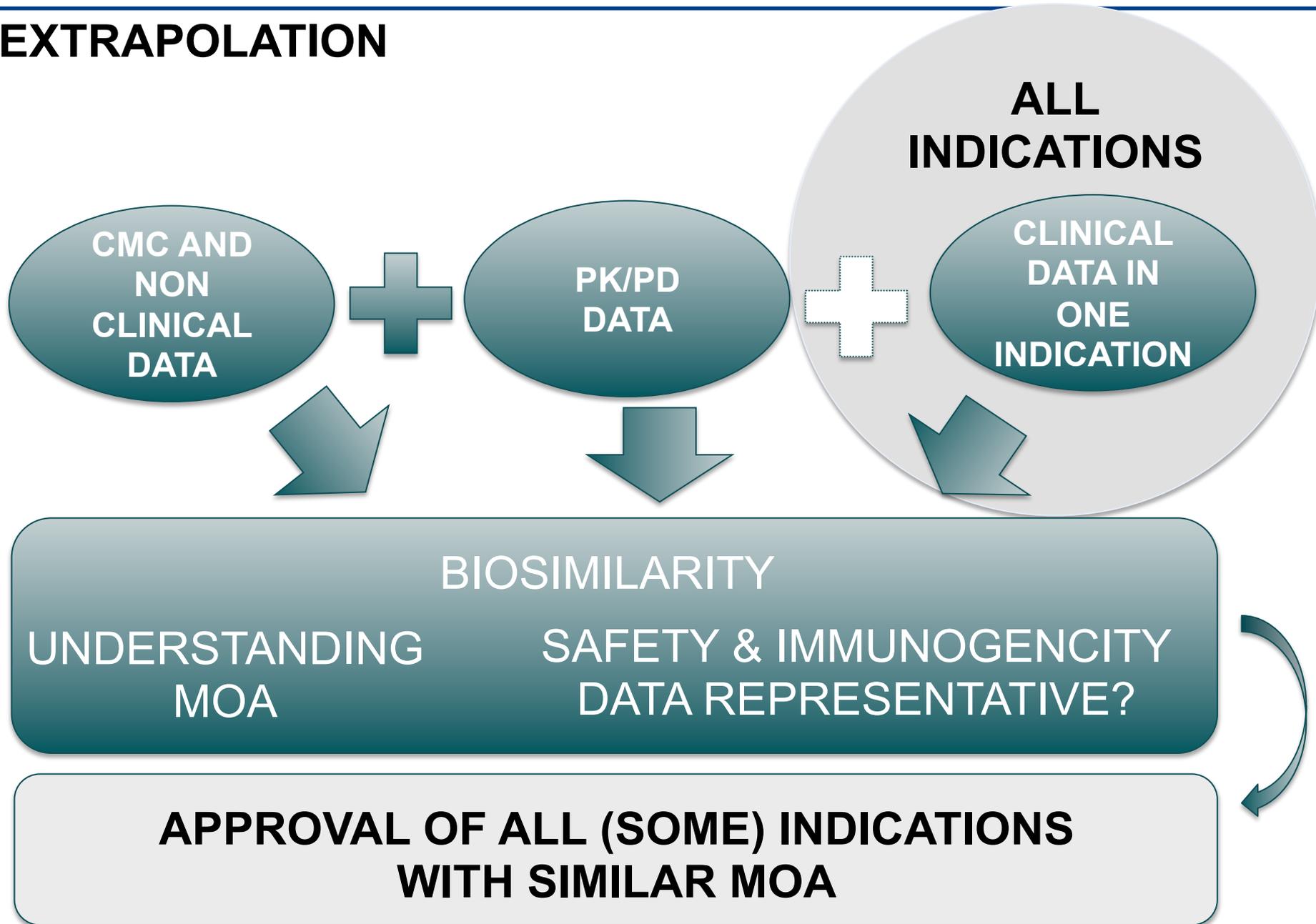


EXTRAPOLATION ACROSS INDICATIONS

(BIOSIMILARS: QUESTIONS AND ANSWERS GUIDANCE)

- **Q.I.11:** “Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?” – “Yes”
- Scientific justification for extrapolation is based primarily on a detailed comparison across indications of the following parameters:
 - a) mechanism of action (target/receptor distribution, binding affinity, molecular signaling),
 - b) PK/PD profile, and
 - c) expected toxicities (pharmacological/off-target)
- Non-comparative safety/PK/immunogenicity data in other patient populations might also be required for extrapolation

EXTRAPOLATION



DEFINITION/STATUS OF INTERCHANGEABILITY

- **BPCI Act**: an interchangeable biological product is “biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient and for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch”
- **FDA (Feb. 2012)** → “At this time it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product”

DEFINITION/STATUS OF INTERCHANGEABILITY

- clear that FDA first needs to figure out optimal designs for phase 3 equivalence trials establishing biosimilarity before applying this experience towards addressing interchangeability
- whether randomized clinical trials and/or comparative post-marketing safety/efficacy data will be required to achieve interchangeability status is not clear
- “single-switch” assessment: “as a practical matter, it may be important to see safety and immunogenicity data in patients transitioning from the originator to the biosimilar product to support a demonstration of biosimilarity”
- unlikely FDA will accept comparisons with a non-US licensed reference product to support interchangeability status

COMMON BIOSIMILARS

- Filgrastim
- Epoetin
- Trastuzumab
- Infliximab
- Adalimumab
- Rituximab
- Bevacizumab
- Etanercept

SANDOZ ODAC MEETING LESSONS (FILGRASTIM; 1/7/2015)

- FDA very motivated to approve first biosimilar and start with simplest case
- Sandoz followed Amgen product over several years (~50 lots)
- Sandoz ~5 years of clinical safety/efficacy data from EU experience
- Sandoz/FDA agreed on four-tier CQA classification system in terms of potential clinical impact of Filgrastim structural/functional properties
- Need for comparative efficacy data in patients → simple molecular structure, clinically relevant PD marker, multiple dose level PK/PD assessment in HV, low immunogenicity concerns, narrow approved indication spectrum → **MINIMAL RESIDUAL UNCERTAINTY ACHIEVABLE**
- Most other biosimilar development programs will be much more challenging

KEY DIFFERENCES BETWEEN EU/US BIOSIMILAR PATHWAYS

- there are no product-specific guidances in the US while many exist in the EU (ex. EPO, GCSF, hGH, insulin, IFN)
- Interchangeability status clearly defined by US regulation versus not at EU legislation (Decision at national level; General view biosimilars not interchangeable)
- In EU, patents are outside the regulatory framework versus requirement for BLA to be reviewed by originator to determine possible patent infringements in US (complex process covered by BPCI Act)
- newly approved biologics have 10-year data exclusivity in EU and 12-years in US; in US newly approved biosimilar has 0-years; interchangeable biosimilar (first one only) has 1-year
- insulin, hGH, other products previously approved via NDA are not eligible for biosimilar pathway in the US
- **key unresolved issues**: statistical methods, product naming (nomenclature), interchangeability (also substitution), patent litigation, product labelling, product drift (post approval), non-inferiority vs equivalence trial design, etc.

BIOSIMILAR NOMENCLATURE

INN

- WHO propose 4 letter suffix to differentiate products with same INN but from different manufacturers

EU Invented name

- Submit to EMA Name Review up to 18 months and preferably 4-6 months prior to submission.

FDA

- may require unique USAN for non-interchangeable biosimilars
- Invented name

KEY CONCLUSIONS

- **Analytical data forms the foundation of biosimilarity exercise**
- **Need to assess criticality of all CQAs**
 - those that have very high impact on clinical effect need to comply with strict equivalence criteria
 - requires complete understanding of protein structure-function relationships
- **Highly similar analytical and human PK/PD similarity data lowers the risk of clinically meaningful differences**
 - very limited clinical program could be acceptable
- **If a comparative clinical study is necessary**
 - selection of appropriate pt. population/endpoints is critical
 - extrapolation depends upon solid scientific rationale