



SANDOZ

Biopharmaceuticals

Update on Biosimilars

Jim McKay, PhD

Overview

- **Biologics**

- Manufacturing, structure and function, analytics

- **Biosimilars**

- What they are
- Technical development
 - Defining the target, process development
 - Analytical demonstration of similarity

- **Regulatory requirements**

Biologics are much larger than small molecule drugs

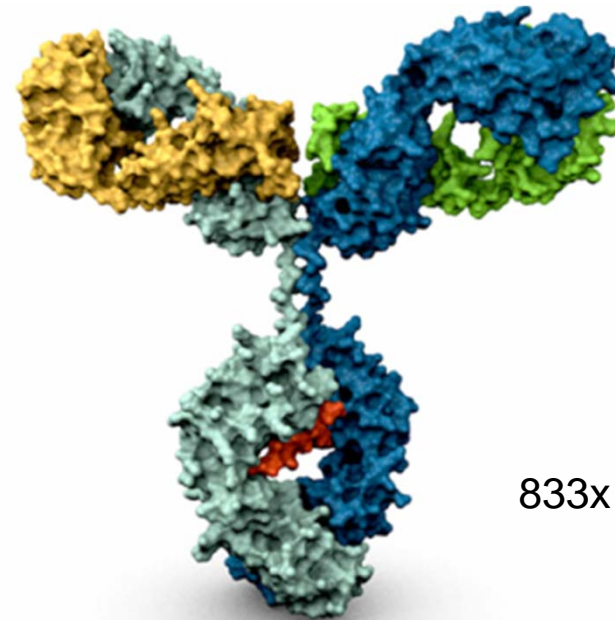
Chemically Synthesized

Made by Living Cells



1x

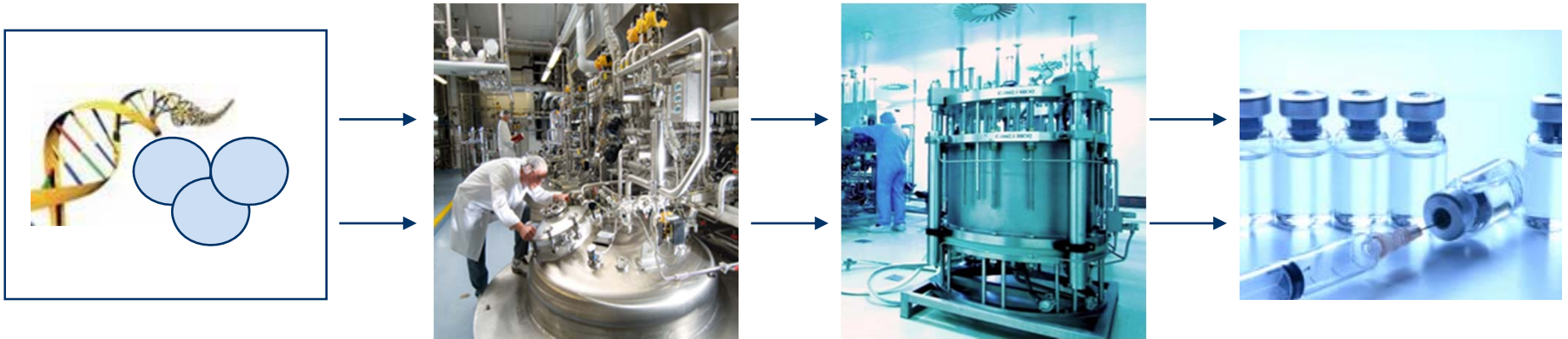
acetylsalicylic acid
0.18 kDa



833x

Monoclonal antibody
~150 kDa

Biologics are produced by living cells



Cell line:
Genetically modify cell
(E. coli, CHO)
to produce
recombinant protein

Upstream process:
Grow cells
in large bioreactors
(fermentation)

Downstream process:
Isolate and purify
using centrifugation,
chromatography, filtration

**Formulate, fill, label,
package**
using centrifugation,
chromatography, filtration

Active substance

Finished product

Adapted from EGA Handbook on biosimilar medicines; available from <http://www.egagenerics.com/index.php/publications/>;
CHO = Chinese Hamster Ovary

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Between 2013 and 2018, 7 of the top 10 molecules worldwide will remain biologics¹ with all losing patent protection² in the coming years

Product	Originator	Type	2018 Rev. (USD bn)	2013 Rev. (USD bn)
1. HUMIRA®	AbbVie	Biologic (mAb)	13.4	10.7
2. LANTUS®	Sanofi	Biologic (insulin)	9.5	7.6
3. ENBREL®	Amgen ³	Biologic (mAb)	8.8	8.8
4. REMICADE®	Johnson&Johnson	Biologic (mAb)	8.3	8.4
5. AVASTIN®	Roche	Biologic (mAb)	8.2	6.8
6. RITUXAN®	Roche	Biologic (mAb)	7.3	7.8
7. SOVALDI®	Gilead Sciences	Small molecule	7.4	0,1
8. REVLIMID®	Celgene	Small molecule	7.1	4.3
9. HERCEPTIN®	Roche	Biologic (mAb)	5.8	6.6
10. PREVNAR13®	Pfizer	Vaccine	5.7	4.0

¹ Source: Evaluate Pharma analysis February 2014

² Enbrel patent exclusivity loss in the US in period until 2020 dependent on validity of submarine patents

³ co-marketed by Pfizer and Takeda

Note: All trademarks are the property of their respective owners

Current US Regulatory Approval Pathways



Statute

Application

**U.S. FOOD,
DRUG &
COSMETIC ACT**

(includes a few
biologics, e.g.
GH, insulins)

**U.S. PUBLIC
HEALTH
SERVICE ACT**

(all other
biologics)

NDA

**505(b)2 NDA
Abbreviated pathway**

**ANDA 505(j)
Generic drugs**

**BLA
351(a)**

**BLA
351(k)
Biosimilar Pathway**

What is a biosimilar?

FDA definition¹

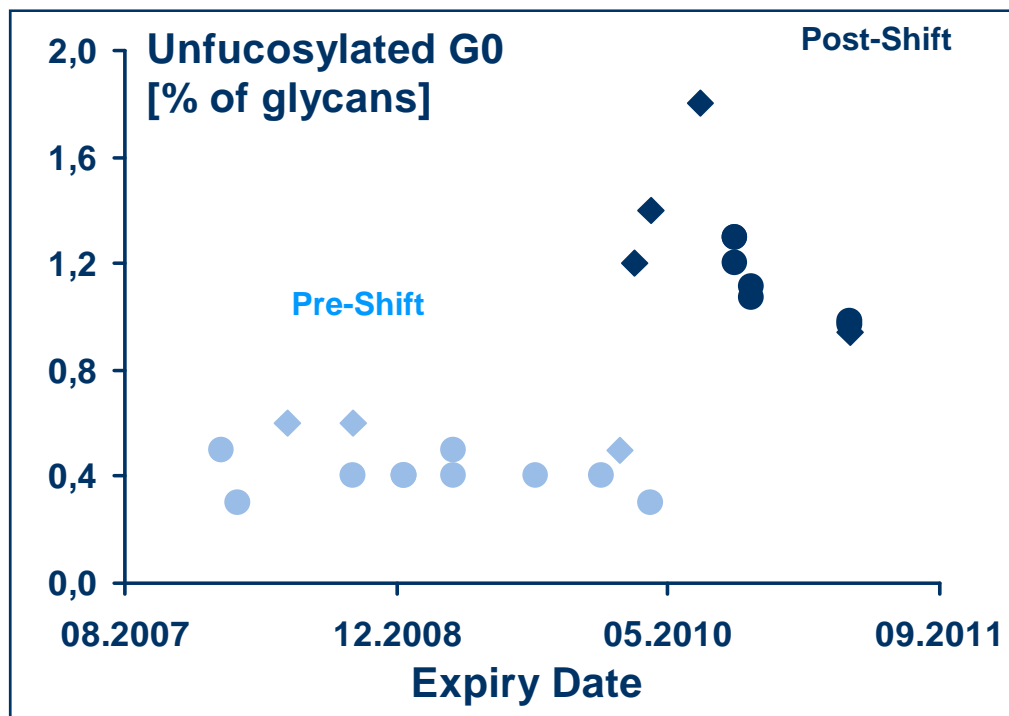
- Biological product that is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components

AND

- No **clinically meaningful differences** between the biological product and the reference product in terms of the **safety, purity, and potency** of the product
- Two potential approvals
 - **Biosimilar**
 - **Interchangeable biologic**

1. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>, accessed February 19, 2013

Variability is a normal property of biologics



- Monitoring batches of an **approved mAb** revealed a **shift in glycosylation**
- These manufacturing changes are **tightly controlled by regulators**

Schiestl, M. *et al.*, *Nature Biotechnology* **29**, 310-312, 2011)

Changes in manufacturing processes occur multiple times after approval



Changes include e.g.

- Change in the supplier of a cell culture media
- New purification methods
- New manufacturing sites

Source: C Schneider, Ann Rheum Dis March 2013 Vol 72 No 3

Number of changes in the manufacturing process after approval for monoclonal antibodies (mAbs)/cepts authorised in rheumatological indications (A). Products in order of date of approval in Europe (from MabThera, authorised on 2 June 1998 for the initial authorisation in oncology, to Benlysta, licensed on 13 July 2011)

The Structural attributes of biologics can be thoroughly analyzed

Attributes:

- Primary structure
- Mass
- Disulfide bridging
- Free cysteines
- Thioether bridging
- Higher order structure
- N- and C-terminal heterogeneity
- Glycosylation (isoforms, sialic acids, NGNA, fucosylation, alpha gal, site specific)
- Glycation
- Fragmentation
- Oxidation
- Deamidation
- Aggregation

High resolution, orthogonality and redundancy in analytical characterisation provide full understanding

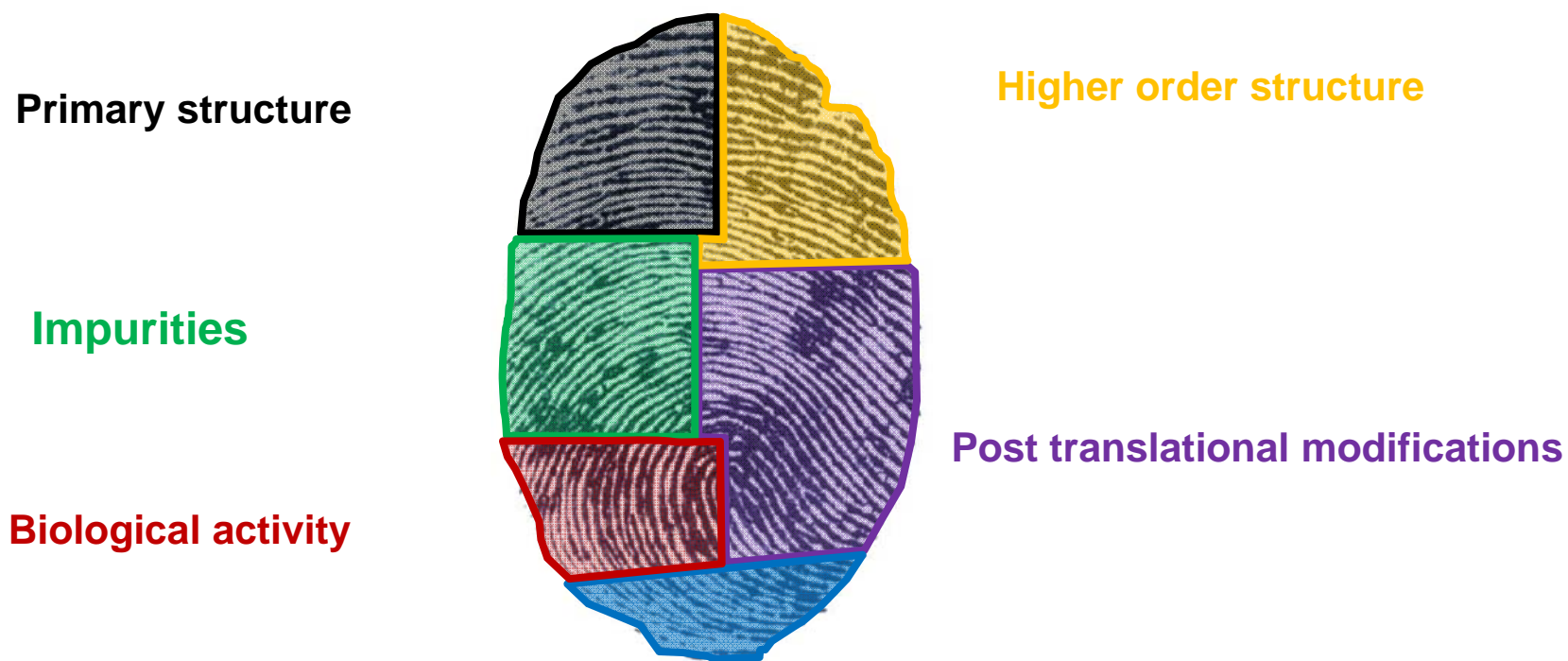
- Primary structure fully accessible to analytical verification
- Set of orthogonal analytical methods available to characterize the identity and amount of related variants with high sensitivity
- Glycosylation profile can be comprehensively determined with regard to identity and content of individual glycans with high sensitivity
- **The combination of ~40 methods yields the complete quality profile with ~100 attributes**



Methods:

- MS (ESI, MALDI-TOF/TOF, MS/MS)
- Peptide mapping
- Ellman's
- CGE
- SDS-PAGE
- CD
- H-D exchange
- FT-IR
- HPLC
- HPAEC
- IEF
- 2AB NP-HPLC
- SE-HPLC
- FFF
- AUC
- DLS
- MALLS

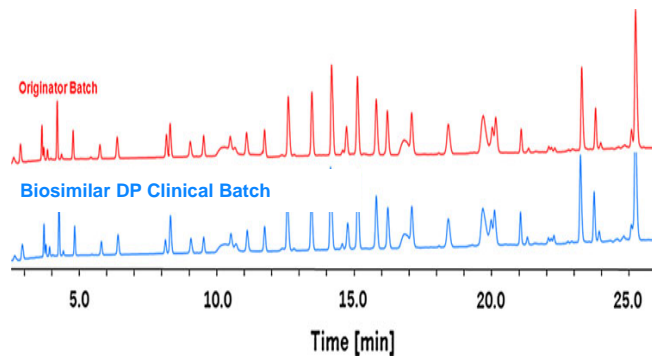
The Biosimilar must be highly similar to the reference product – fingerprint analysis



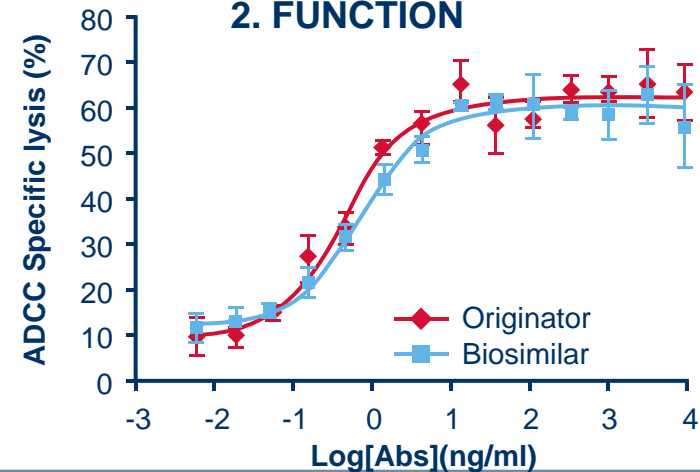
Combination of highly similar attributes supports biosimilarity

A Biosimilar must be highly similar to the reference product at all levels

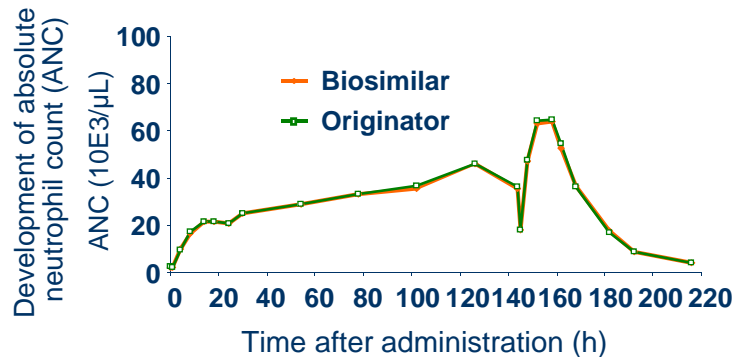
1. STRUCTURE



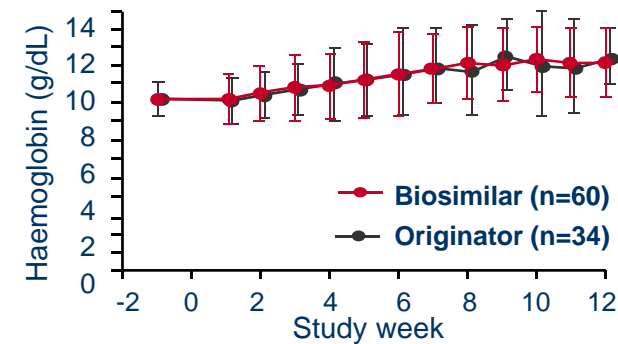
2. FUNCTION



3. PK & PD



4. EFFICACY & SAFETY



ADCC = antibody-dependent cell-mediated cytotoxicity

McCamish et al, ClinPharmacol & Ther 2012

Visser et al, BioDrugs 2013

Gascon P et al. Ann Oncol, Dec 2009;

Weigang-Köhler et al. Onkologie 2009

da Silva et al. Leuk Lymph 2014

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Summary

- Even complex biologics can be fully characterized
- Biosimilars are developed to be highly similar to the reference products
- Similarity is established analytical characterization, and confirmed with clinical studies



Regulatory Requirements for Biosimilars

Biologics Price Competition & Innovation Act

- Science-based pathway based on comparability with FDA discretion as to data required
- Limits biosimilar application to single reference biologic licensed under 351(a)
- The biosimilar application relies on FDA's previous determination that the reference product is safe, pure, and potent
- Two potential approval types
 - Biosimilar
 - Interchangeable biologic

FDA Biosimilars Guidance

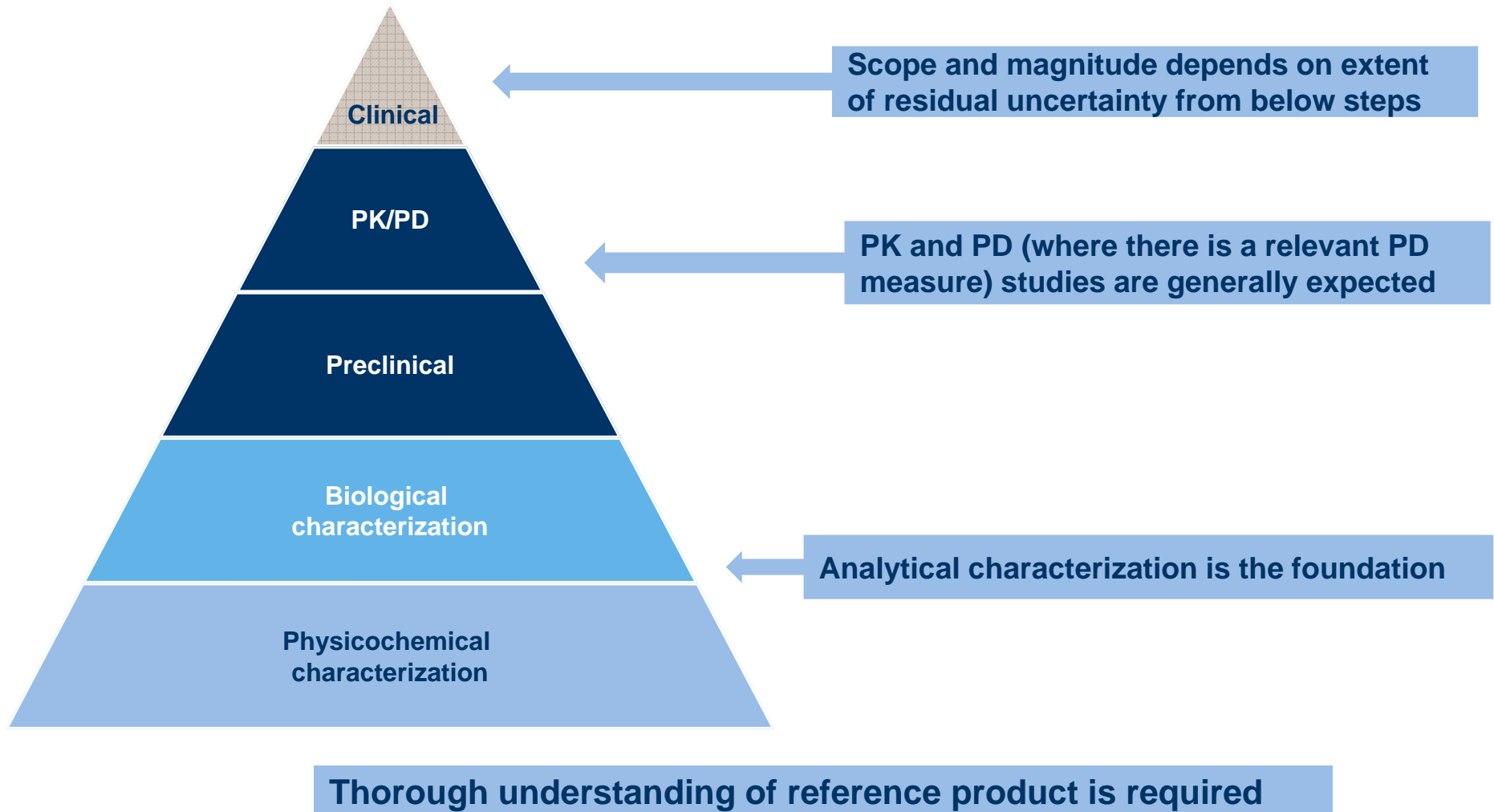
1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – Final, April 2015
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product – Final, April 2015
3. Biosimilars: Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 – Final, April 2015
4. Biosimilars: Additional Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 – Draft, May 2015
5. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants - Draft, March 2013
6. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product - Draft, May 2014

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf> ;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>

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Overview of FDA Approach to Biosimilarity - Totality of Evidence and Stepwise Approach



Structural and functional characterization - identifying and justifying differences

“The **foundation** for an assessment of biosimilarity ... involves the robust characterization of the proposed biosimilar product, including comparative physicochemical and functional studies.”

Clearly describe and discuss differences and to the extent possible justify differences as not being clinically relevant

- Functional and animal testing can be used to investigate observed structural differences
- Product- and process- related impurities should be identified, characterized
- Finished dosage form of multiple lots should be analyzed

Clinical Pharmacology - critical to demonstrating biosimilarity

- **Supports a demonstration that there are no clinically meaningful differences**
 - PK - degree of similarity in drug exposure
 - PD - assess whether or not there are clinically meaningful differences
- Supports justification for extrapolation of indications
- Contributes to safety & immunogenicity evaluation

Clinical Studies - scope and magnitude of program

No need to independently establish the safety and efficacy of biosimilar product

- Scope depends on the extent of residual uncertainty from structural and functional characterization
- Need to consider safety risks and efficacy concerns for reference product
- PK and PD data and immunogenicity data generally expected - can justify no clinical safety and effectiveness studies (phase 3 studies)

Interchangeability requirements not addressed in FDA guidance

Definition: Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider

According to statute:

- Demonstrate biosimilarity
- Can be expected to produce the same clinical result in any given patient
 - “expectation” meaning a population approach to be used
 - high level of analytical similarity is a more sensitive consideration as to whether the molecule will behave the same in any patient
- If administered more than once, the risk in terms of safety or diminished efficacy when switching between the biosimilar and the reference product is not greater than the risk of using the reference without switching

Extrapolation of Indications Scientific Justification Needed

Scientific justification for the tested and extrapolated indications need to consider:

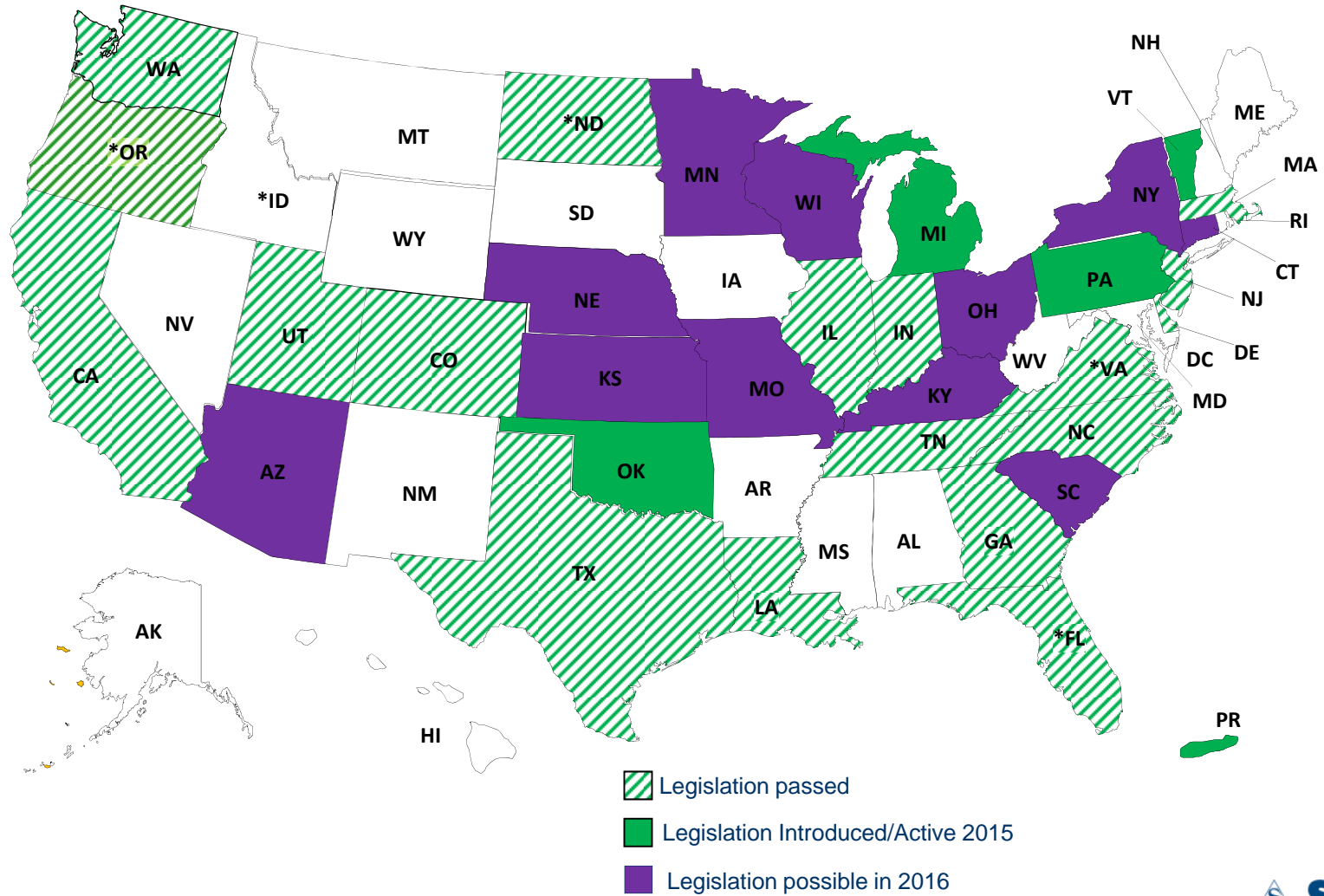
- Mechanism of action
- PK and bio-distribution in different patient populations
- Safety differences in each indication and patient population
- Based on similarity of the molecule and totality of the evidence

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259809.htm>

Thank You

Questions??

State substitution legislation



Substitution bills passed to date

- Summary of Bills passed prior to 2015

- Indiana
- Delaware
- Massachusetts
- Florida
- North Dakota
- Oregon (2013, notification requirement expires 01/01/16, substitution still permitted)
- Virginia (2013, notification requirement expired 07/01/15, substitution still permitted)

- States passed in 2015

Utah

New Jersey (signed into law yesterday)

Colorado

Louisiana

Tennessee

Texas

Georgia

California

Washington

North Carolina

Illinois