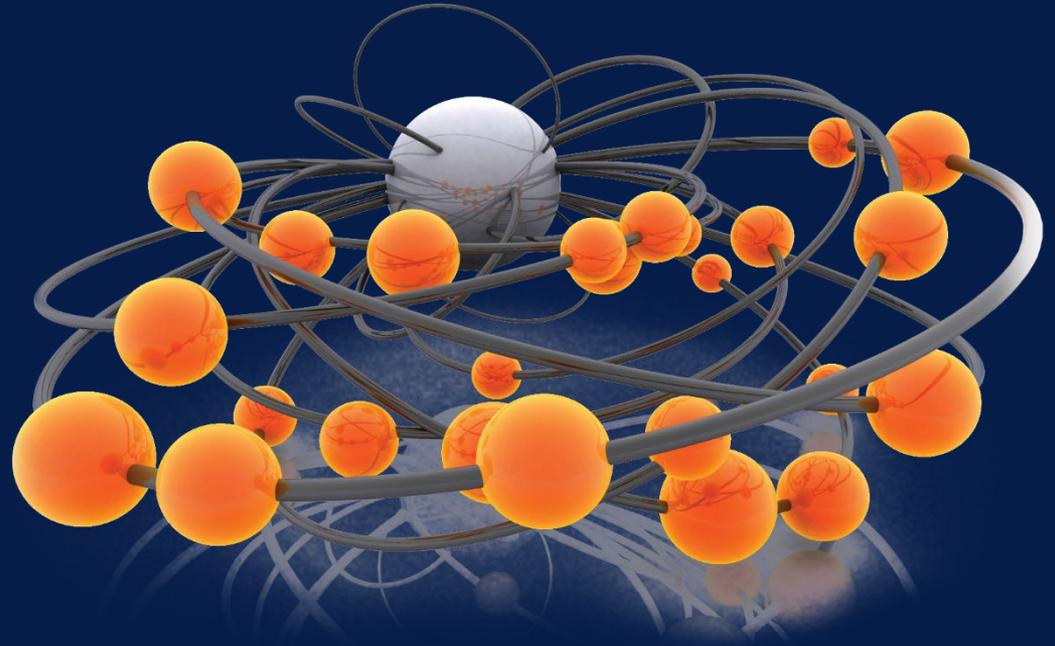


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Biotherapeutics: What's Right for Patients Moving Forward?

Karen Hauda
Sr. Director
May 8, 2013



HCP/Patient Relationship

European Commission Consensus Report

“The relationship between patient and healthcare professional is key to ensuring the best treatment/care decisions and health outcomes for each patient. Patients often do not receive enough information from healthcare professionals that they understand, whereas many health professionals overestimate the amount and quality of information they provide. It is crucial that all available therapeutic options are discussed thoroughly and that healthcare professionals ensure that patients understand the options, relative benefits and risks. Prescription decisions should be based on mutual agreement (*concordance*).”³²

32 Concordance is a term that describes the relationship between patient and prescribing doctor, and the degree to which the prescription is based on a joint agreement. Concordance means that the beliefs and preferences of both the doctor and the patient are taken fully into consideration but the patient’s views take precedence. (Sources: Horne, R: Compliance, adherence and concordance: implications for asthma treatment. *Chest*, 2006;130;65-72; Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, December 2005.)

Agenda

Brief Background: Biotherapeutics and Biosimilars

Regulatory Requirements for Biosimilars

Indication Extrapolation

Interchangeability and Substitution

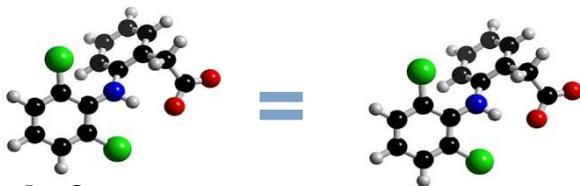
Pharmacovigilance and Naming

Closing Remarks

Chemical Medicines Are Made; Biologics Are Grown

Chemical medicines are chemicals made by chemists out of other chemicals. That's why they are also known as “**small molecules**” or “**chemically-synthesized drugs**”

Following the same “**recipe**” yields **exactly the same product**

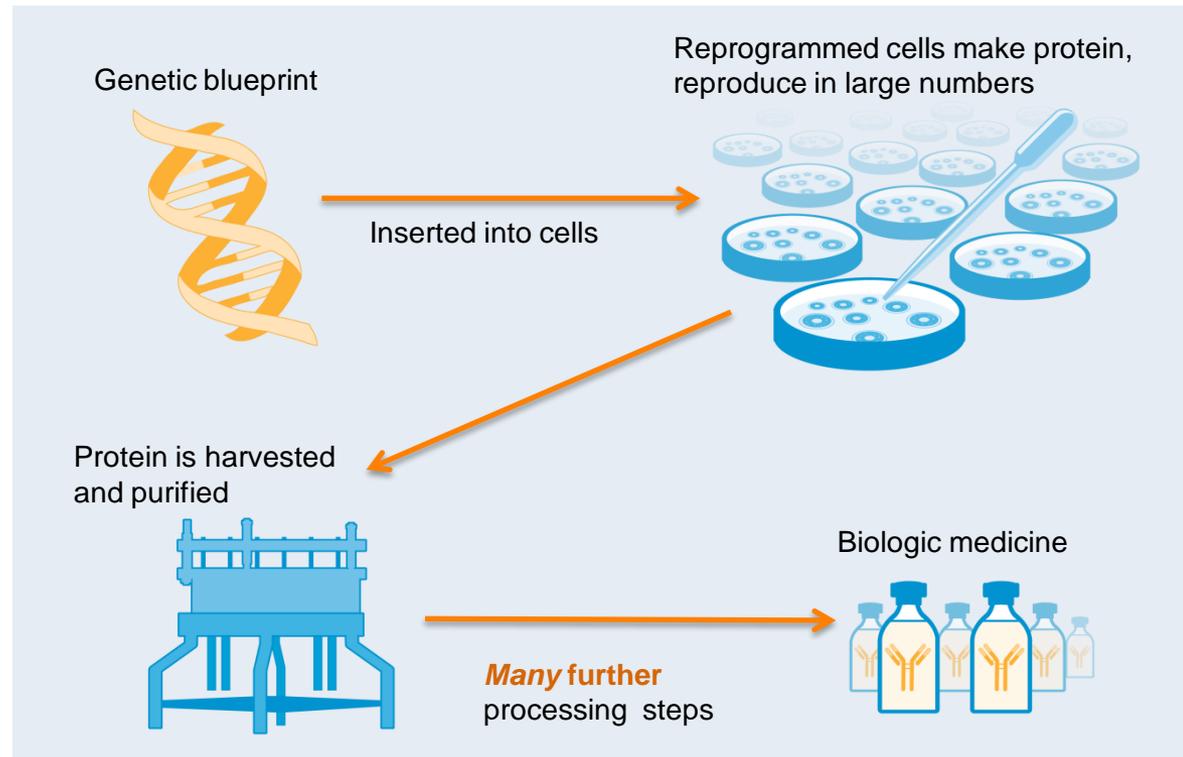


Diclofenac

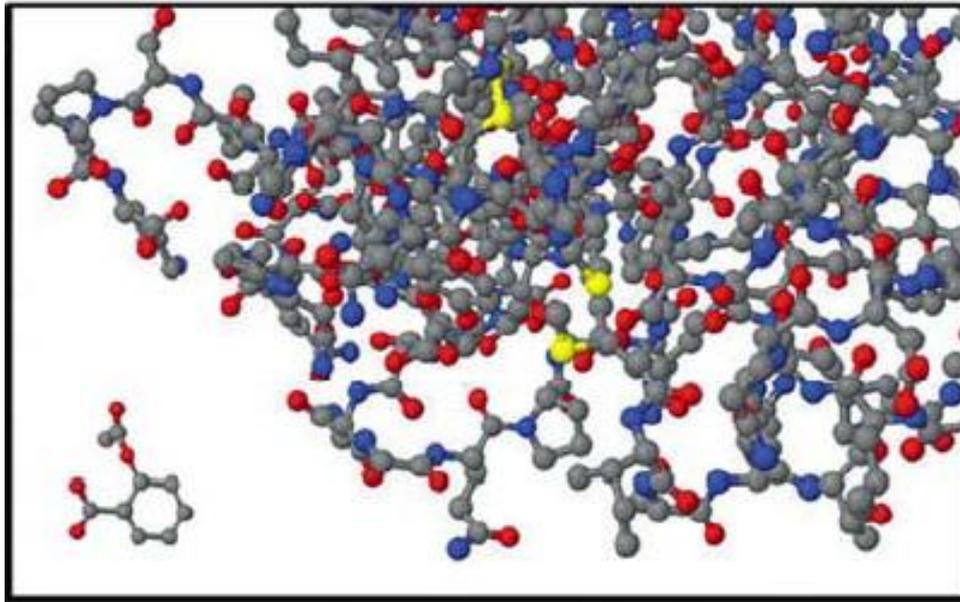
Biologics are *grown* from living things

A biologic must be manufactured under precise conditions, following many exacting steps, to yield a consistent product

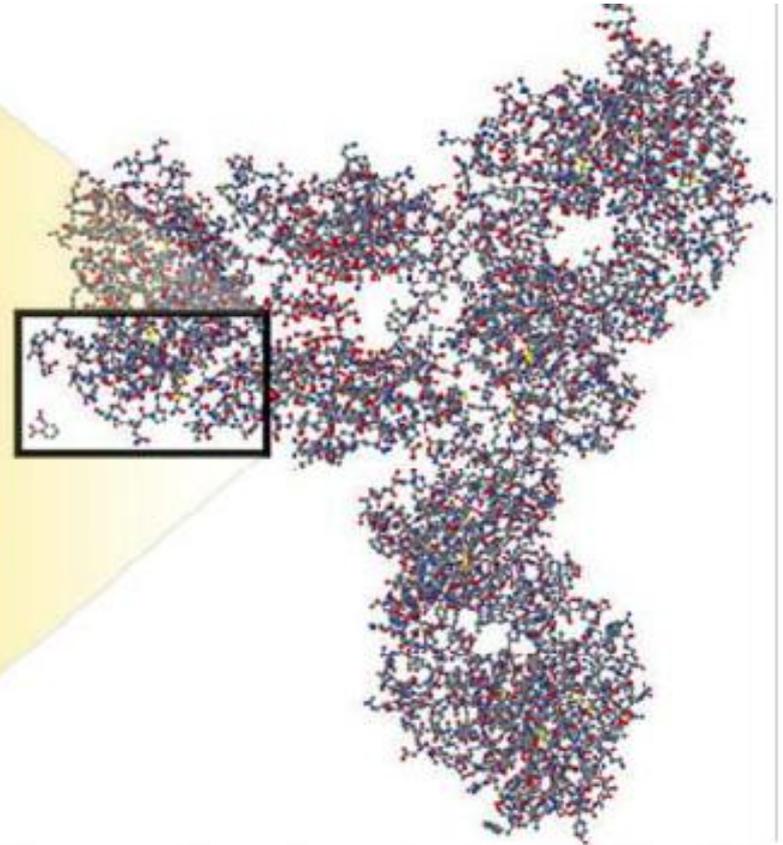
Biologics are highly sensitive to manufacturing conditions



Biologics: Molecular Complexity



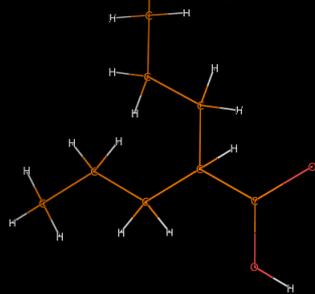
Aspirin



Monoclonal antibody

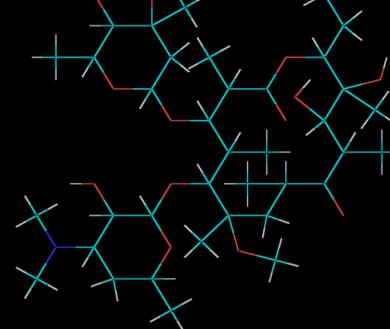
Molecular Complexity of Biologicals

Valproic Acid (Depakote™)



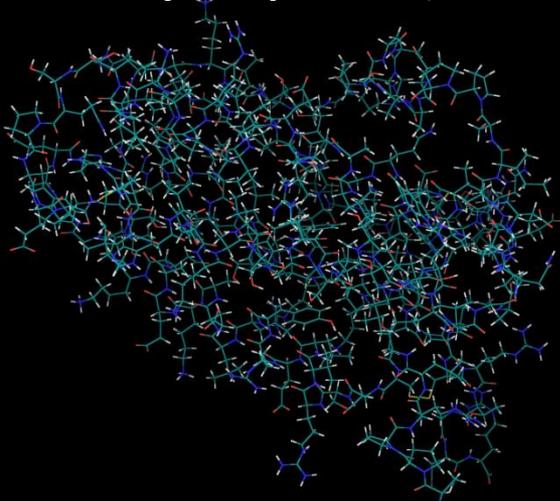
MW: 144.2
Formula: $C_8H_{16}O_2$

Clarithromycin (BIAXIN™)



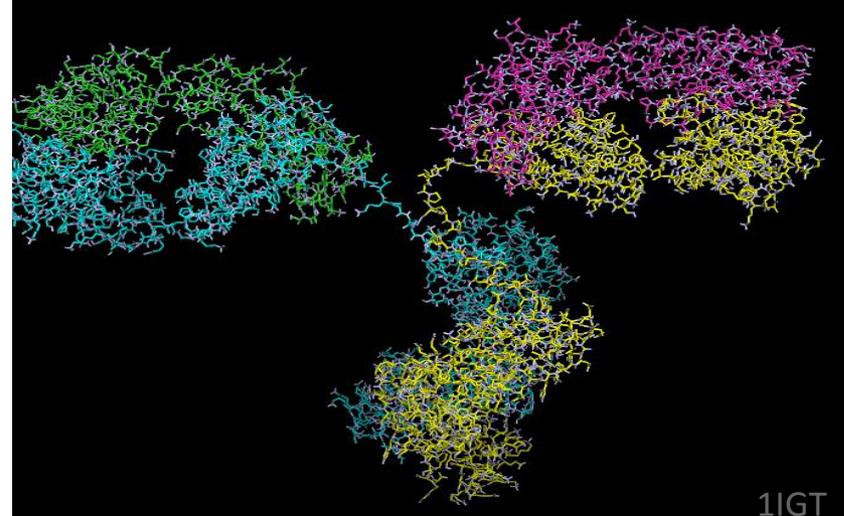
MW: 747.95
Formula: $C_{38}H_{69}NO_{13}$

Human Erythropoietin (EPOGEN™)



MW: 18,464.5
Formula: $C_{821}H_{1331}N_{233}O_{238}S_5$

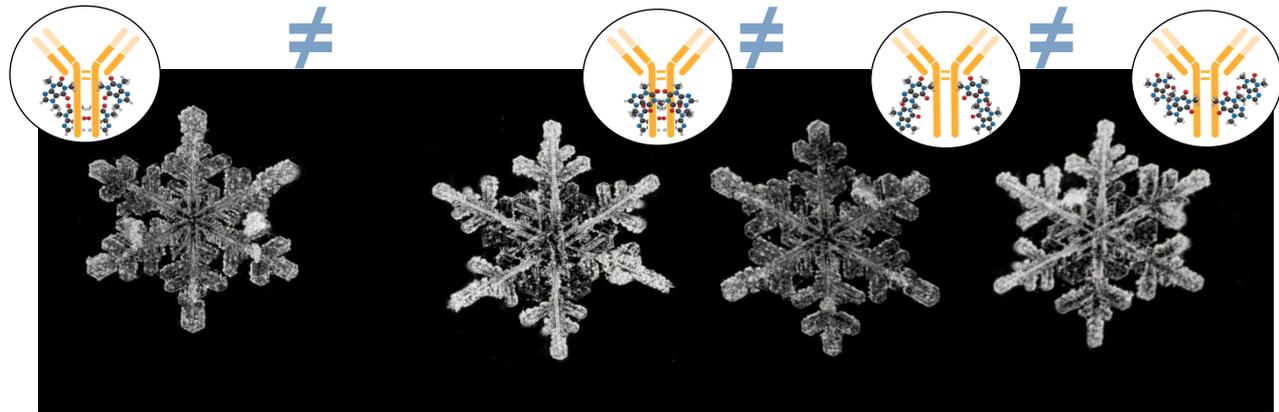
Antibody Structure



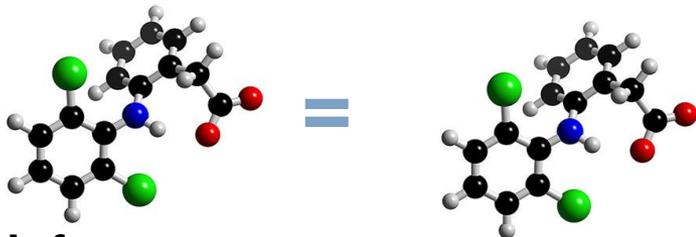
MW: 148,683.5
Formula: $C_{6,440}H_{9,928}N_{1,704}O_{2,011}S_{56}$

Biosimilars Are Only "Similar" to Innovative Reference Products, Not Identical

- Biologics are made in living organisms highly sensitive to external conditions
- Cell lines grown by two different manufacturers will inevitably exhibit structural differences (as illustrated below)
- Biosimilars differ from their innovative reference products and from each other
- They are not "generics" and each must be treated as a unique entity



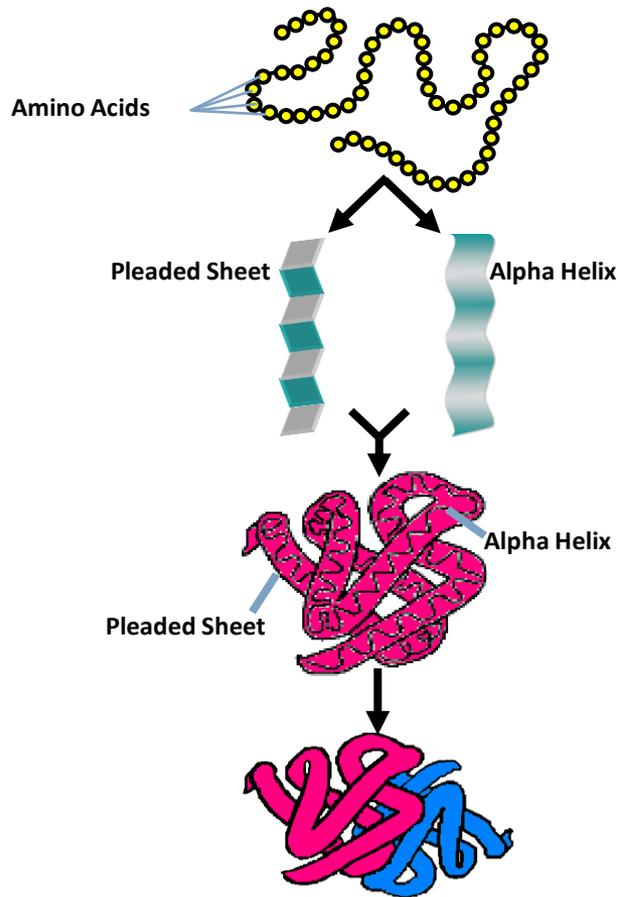
Monoclonal antibodies shown within the circles: the reference product and each biosimilar has different post-translational modifications (in this case, in their glycosylation patterns).



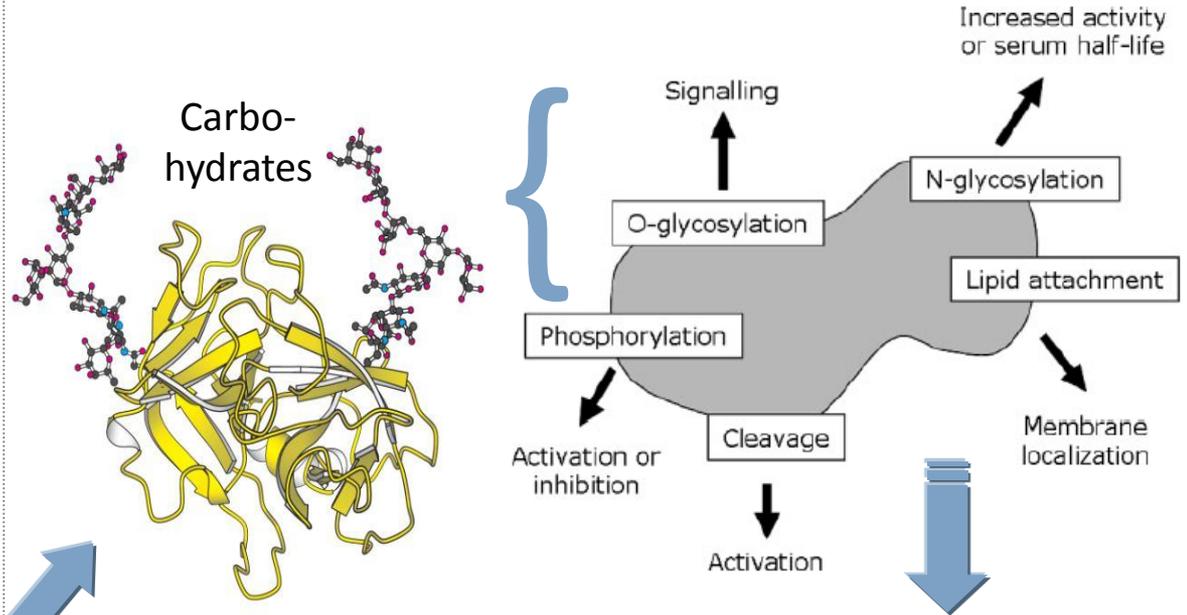
Diclofenac

Protein Function Is Highly Dependent on Final Configuration

Protein's Higher Order Structure - Ideally the Same



Post-Translational Modifications - Will be Different



Mechanism(s) of Action?
PK/PD?
Tissue Distribution?
Efficacy?
Safety?
Immunogenicity?

Modified from Access Excellence of the National Health Museum (<http://www.accessexcellence.org/>)

Protein Science of Biosimilars. *Nephrol Dial Transplant* (2006)[Suppl 5]: v4-v8

Differences Between Small Molecule Medications and Those Based on Biologics

Distinctive Characteristic	Small Molecules	Biologics
Source	Chemical Synthesis	Living organisms (human, animal or microorganism) with DNA/RNA synthesis
Active Ingredients	Unique, well defined	Complex mix of heterogeneous proteins and impurities
Characterization	Well-defined structures, sensitive methods, available standards, discriminators	Limited characterization, difficult to quantify
Immunogenicity ¹	Rare	Potential formation of antibodies , difficult to predict
Manufacturing Process	Highly reproducible, products that do not depend extensively on the manufacturing process	Sensitive to minor changes , products generally very sensitive to the manufacturing process

1. The ability to induce an immune response

What Is a Biosimilar?

Some Definitions

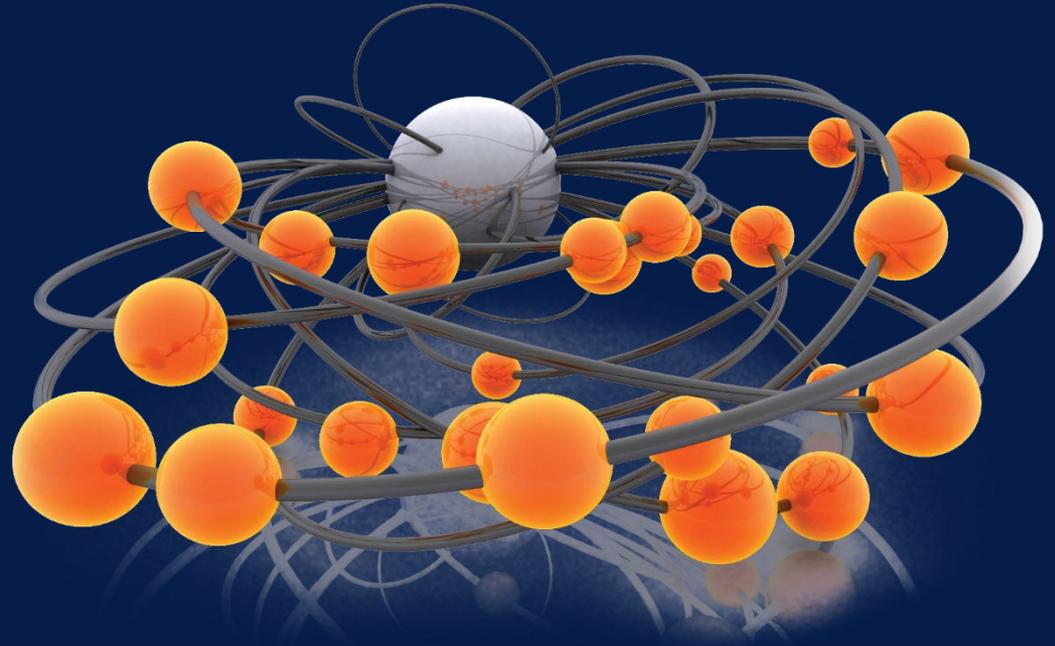
- **EMA guidance:** Biosimilar sponsor is to “**generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorized in the Community.**”
- **US FDA (BPCIA*) definition:** a follow-on biologic means
 - The biological product is **highly similar to the reference product**, notwithstanding minor differences in clinically inactive components; **and**
 - **No clinically meaningful differences exist** between the biological product and the reference product **in terms of the safety, purity, and potency**
- **WHO definition:** “Similar Biotherapeutic Products” is a biotherapeutic product that is **similar** in terms of **quality, safety and efficacy** to an already licensed biotherapeutic product

Biosimilars are those products that are “highly similar” to the reference biologic product based on submission of quality, safety and efficacy data

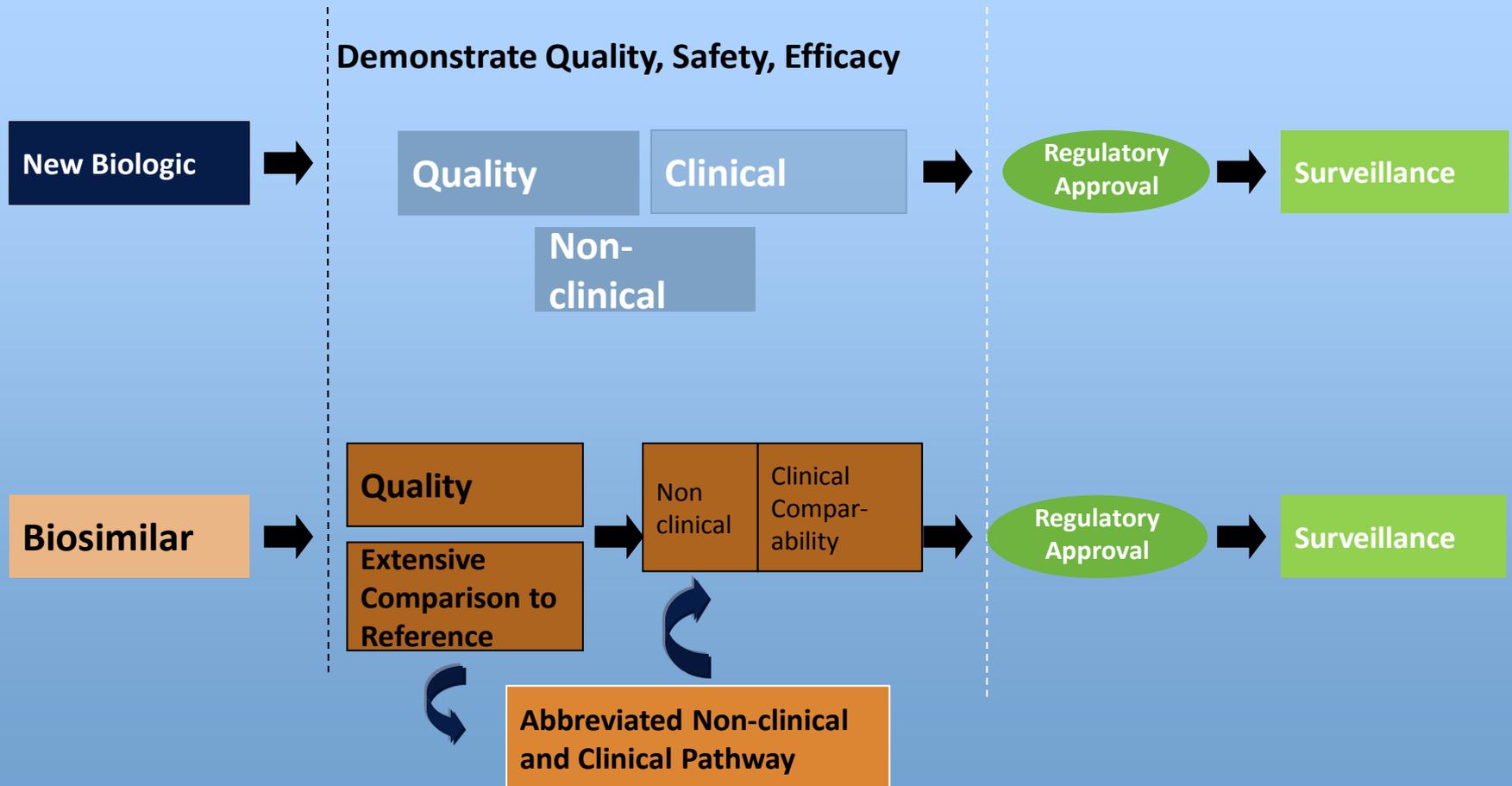
*Biologics Price Competition and Innovation Act of 2009 (BPCIA) – U.S. Law

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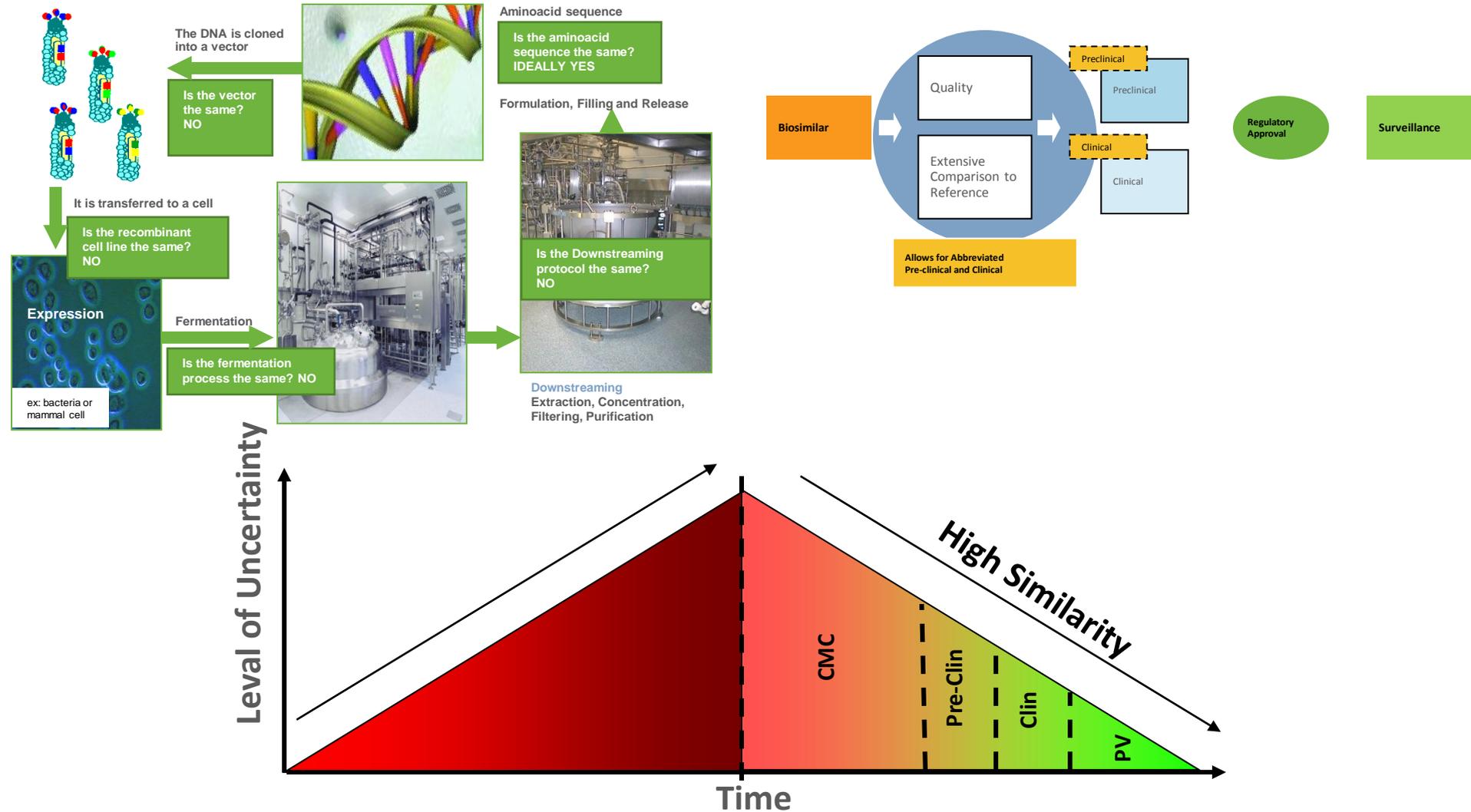
Regulatory Requirements for Biosimilars



Scientific basis for abbreviated biosimilarity pathway



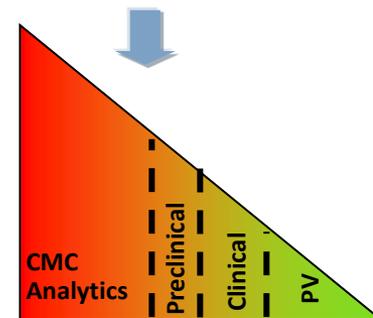
It's All About Minimizing Uncertainty



Chemistry Manufacturing and Control (CMC)

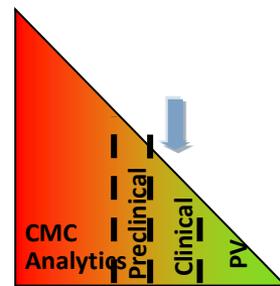
Full CMC data + comparability studies

- A biosimilar is defined by characteristics related to both the molecule (product-related) and its manufacturing process (process-related)
- Both need to be adequately addressed during the CMC portion of the biosimilarity exercise:
 - Full chemistry and manufacturing data
 - Extensive side-by-side (biosimilarity) characterization of biosimilar vs. the Reference Biologic Product (Innovator)
 - Physico-chemical properties
 - Biological activity
 - Purity and impurities
- Results from the CMC comparability exercise determine the extent of data requirements for non-clinical studies in animals



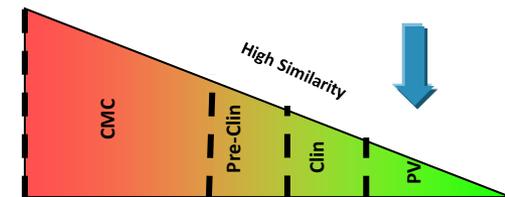
Clinical Data

- **Stepwise procedure:** PK/PD \Rightarrow Clinical Efficacy/Safety trials
- Generation of data with the biosimilar as produced in the final manufacturing process
- The target population (TP) of a particular indication for which the approval is sought and dosage used should represent a clinical test system that is **known to be sensitive enough** to detect potential differences between the biosimilar/biocomparable and the reference biologic¹
 - Studies should be designed as equivalence trials and **sufficiently powered** either to detect any difference in efficacy that are clinically important; in limited cases, a non-inferiority design may be used
 - **Safety data from sufficient number of patients and sufficient duration** to allow for comparison of the nature, severity and frequency of AEs/ADRs
 - The **immunogenicity** of the biosimilar has to be tested using state of the art methods to ascertain the effect of immunogenicity of the product on both its efficacy and its safety (usually a 12-month study is expected).



Post-Marketing Considerations

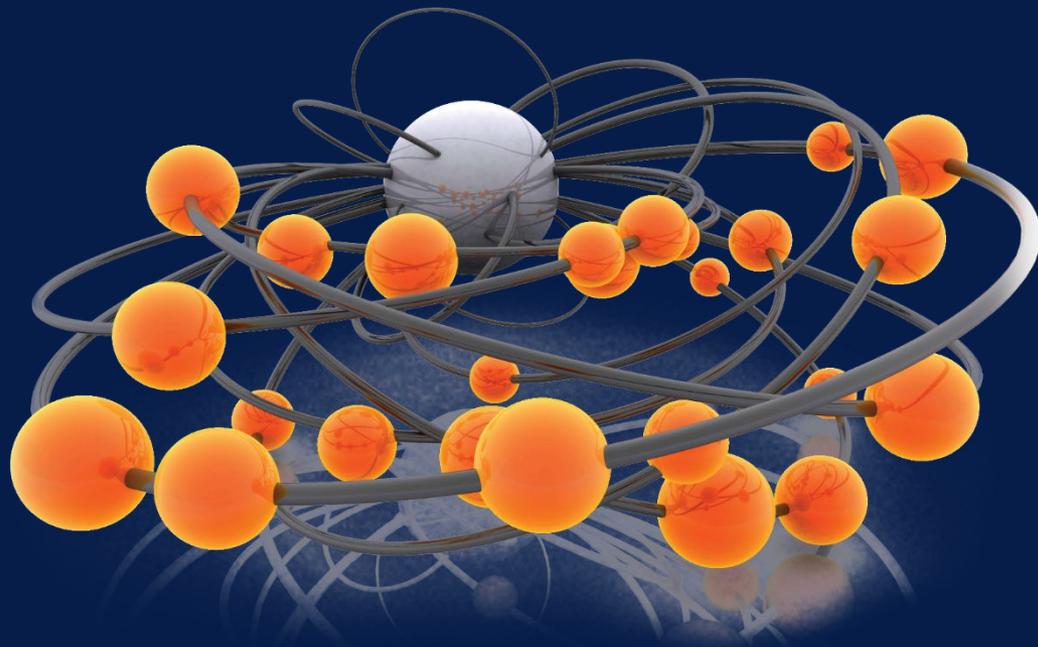
- Post-marketing monitoring is key in ensuring long-term safety and effectiveness of biologics, including biosimilars
- Adequate mechanisms to differentiate between AEs* associated with the reference or the biosimilar product are necessary
- Rare, but potentially serious, safety risks that may not have been detected pre-approval must be addressed
- Use of RMP/REMS*, PASS*, new/existing Registries, etc.
 - Should be strongly considered if not already in place
 - Should be jointly defined by the Sponsor and the RA
 - Should not be less than what is required from the reference**



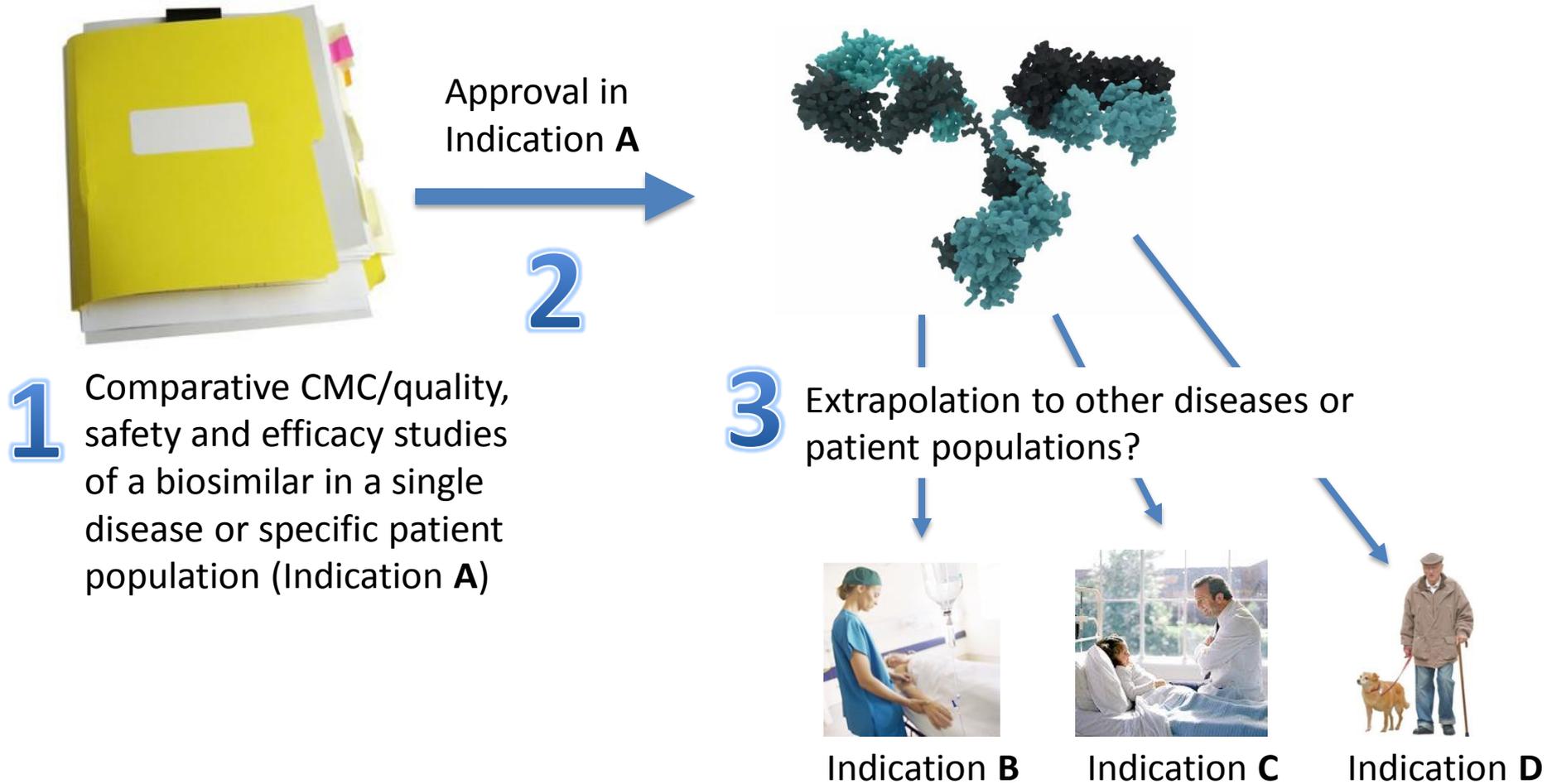
* AEs: Adverse Events; RMP/REMS: Risk Management Plan / Risk Evaluation and Mitigation Strategies; PASS: Post-Approval Safety Study

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Indication
Extrapolation



Indication Extrapolation



Indication Extrapolation

With regard to **extrapolation to other indications**, the **study population and treatment regimen that are the most sensitive** for detecting a difference in immune responses should be selected.

Draft FDA Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Feb 2012

mAbs – Special Considerations

- Highly immunogenic and complex engineered biotherapeutics
- MOAs are in many cases extremely hard to identify or understand
- Animal studies offer little or no value in predicting immunogenicity in humans



- Target complex diseases; "most sensitive" indication is not yet defined

Selecting the “Most Sensitive” Indication and Population

Q1: What is the most sensitive indication
among these indications?

Rheumatoid Arthritis

Crohn's Disease

Psoriasis

Q2: What is the most sensitive patient population within
rheumatoid arthritis?

Methotrexate-Naive

Methotrexate-
Insufficient Responders

Other Biologic-
Insufficient Responders

What If Dosing Regimens Differ?

	Juvenile Idiopathic Arthritis	Crohn's Disease	Psoriasis
Adalimumab Loading Dose (Y/N)	N	Y* Day 1=160mg Day 15=80mg	Y Day 1=80mg Day 8=40mg
Adalimumab Maintenance Dose	Fixed Dose: <ul style="list-style-type: none"> 15Kg to <30Kg= 20mg every other week (eow) ≥30Kg= 40mg eow BMI-based: 24mg/Kg/m ² (max 40mg) eow	40 mg every other week	40 mg every other week
Adalimumab Monotherapy (Y/N)	Y	Y but usually administered with other immune suppressors	Y. Randomized clinical trials have <u>not</u> shown differences in efficacy when used concomitantly with IMS (such as MTX)

Q3: Which of these is the most sensitive indication for the detection of differences?

* This is the loading dose approved in the US by the FDA. In the EU loading Dose is 80mg on Day 1 and then 40mg eow as maintenance dose from Day 15 onward unless a faster onset of action is desirable when the same loading dose as in the US can be used

Which is the “Most Sensitive” Indication / Population?

Anti-Drug Antibody Formation Rate in Various Indications*:



RA=rheumatoid arthritis; PsA=psoratic arthritis; AS= Ankylosing spondylitis; JIA=juvenile ideopathic arthritis; CD=Crohn's Disease; Ps=Psoriasis; MTX=Methotrexate; IMS=Immunomodulator(s); IFX=Infliximab

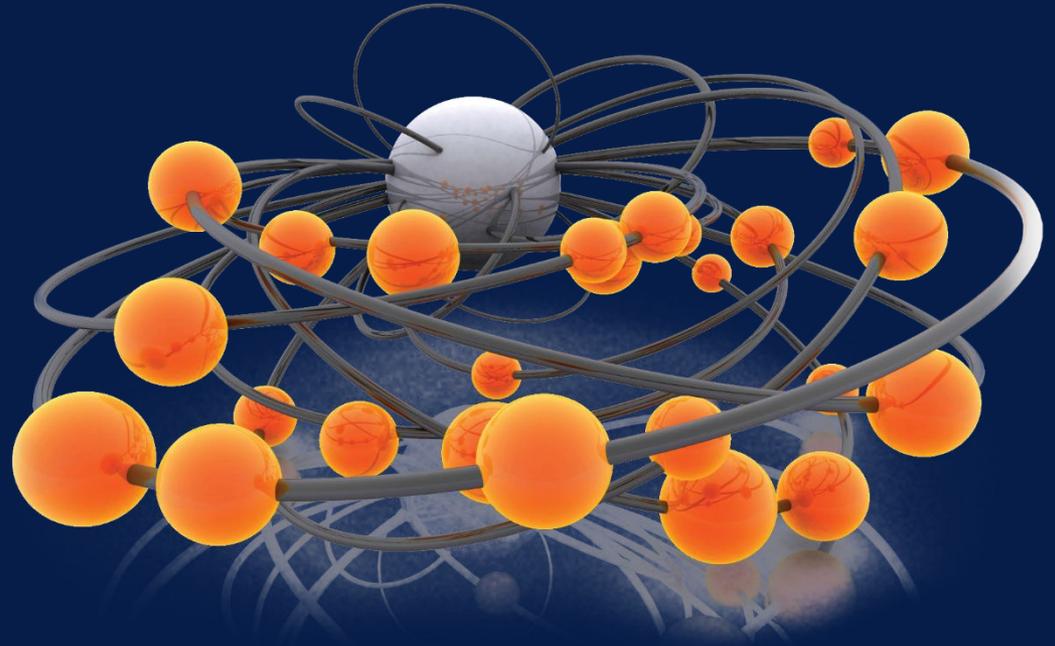
*percentages not shown are not available in HUMIRA's US PI

Indication Extrapolation for Biosimilar mAbs Should Not Be Permitted

- For complex biologics like monoclonal antibodies, science still needs to fully characterize their mechanism of action(s)
- The medical community still needs to determine which indications are the most sensitive for testing
- Clinical immunogenicity cannot be predicted or extrapolated from studies in one indication or population to another
- Until then, indication extrapolation is not justified and clinical immunogenicity of biosimilar mAbs has to be tested in each indication for which approval is sought

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Interchangeability/
Substitution



Interchangeability, Substitution, Switching: What's the Difference?

- **Interchangeable**

- A designation given **by the health regulatory authority** after the biosimilar has proven that it:
 1. produces the **same clinical result as the reference product in any given patient**; and
 2. switching between the biosimilar and the reference product presents **no greater risk in terms of efficacy and safety than the continued use of the reference product**

- **Substitution**

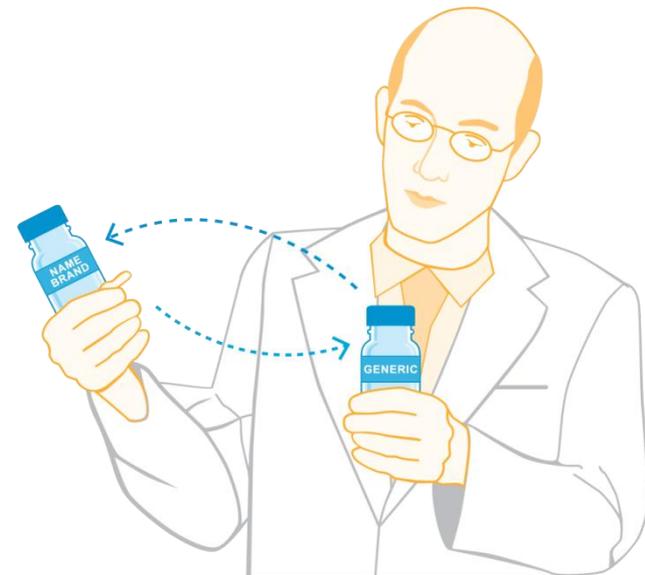
- A process that allows a **pharmacist** to substitute a certain prescribed product by another equivalent product.
- If without the prescribing physician's permission or knowledge (e.g., by the pharmacist), it is considered **"automatic substitution" or "involuntary substitution"**.

- **Switching**

- When a **prescribing physician** determines (in consultation with the patient) that changing a patient's treatment is appropriate whether another biologic product or a biosimilar.

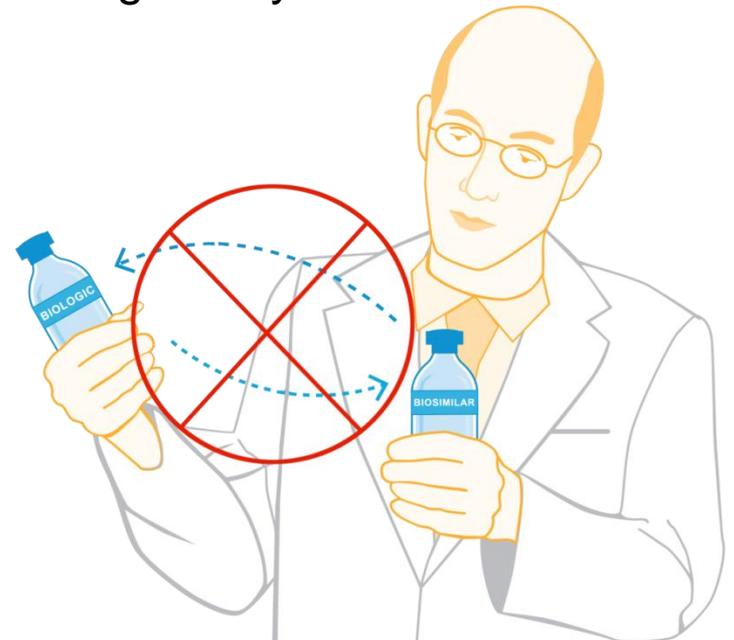
Generic Interchangeability and Substitution

- For generics, **pharmaceutical equivalence = therapeutic equivalence**
- Regulators designate the two as **interchangeable**
 - A physician should be able to switch one for the other and expect comparable benefit and no increased risk in patients
- Depending on local or institutional rules, pharmacists may be authorized or even required to substitute a generic for the original without informing the prescribing physician (**automatic substitution**)



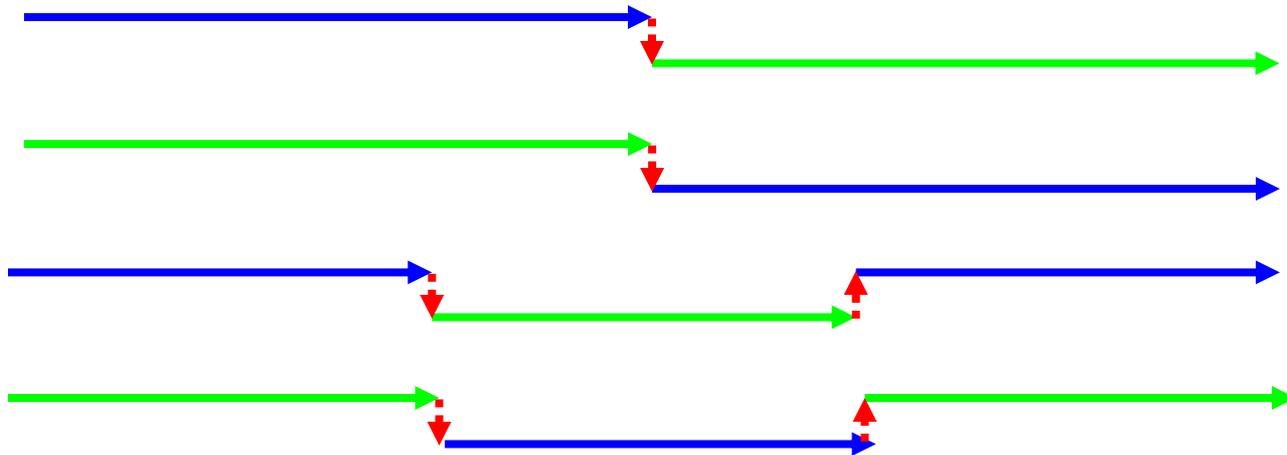
Biosimilars Should Meet High Standards for Interchangeability

- For biologics, including biosimilars **pharmaceutical equivalence \neq therapeutic equivalence**
- Therefore, granting biosimilar status by a regulator **does not imply interchangeability**
 - Depending on the regulatory agency, interchangeability has to be shown by the biosimilar sponsor



Interchangeability

- To be considered Interchangeable by a health authority the biosimilar applicant must demonstrate through **switching studies**:
 - The study design should address **both switching and alternating** (i.e. switching more than once); the recommended design would be a **modified Balaam's crossover trial**:

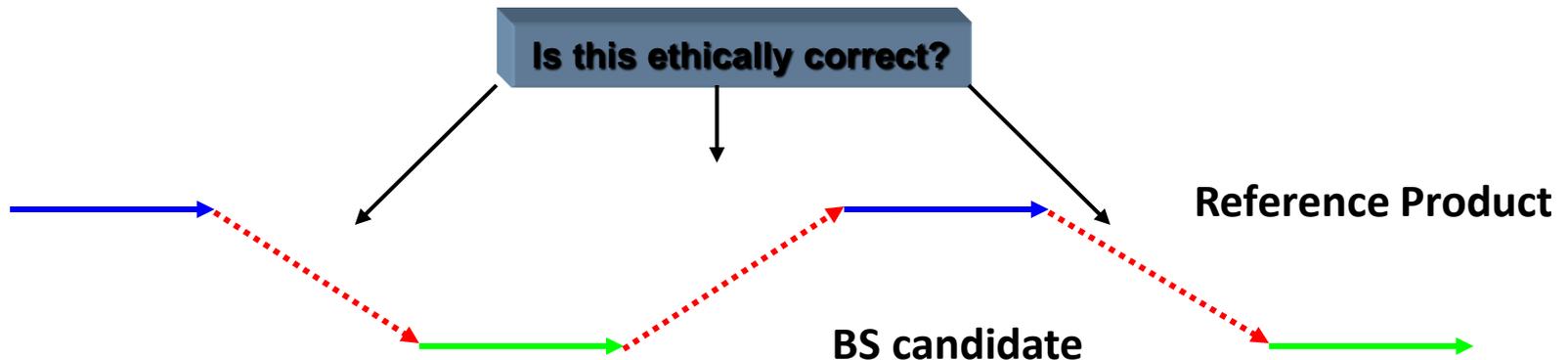


*Biologics Price Competition and Innovation Act of 2009 (BPCIA) – U.S. Law

Interchangeability

- **Issues:**

- long $t_{1/2}$ of majority of biologics → drug effect vs carry-over effect?
- Feasibility of wash-out period(s)?

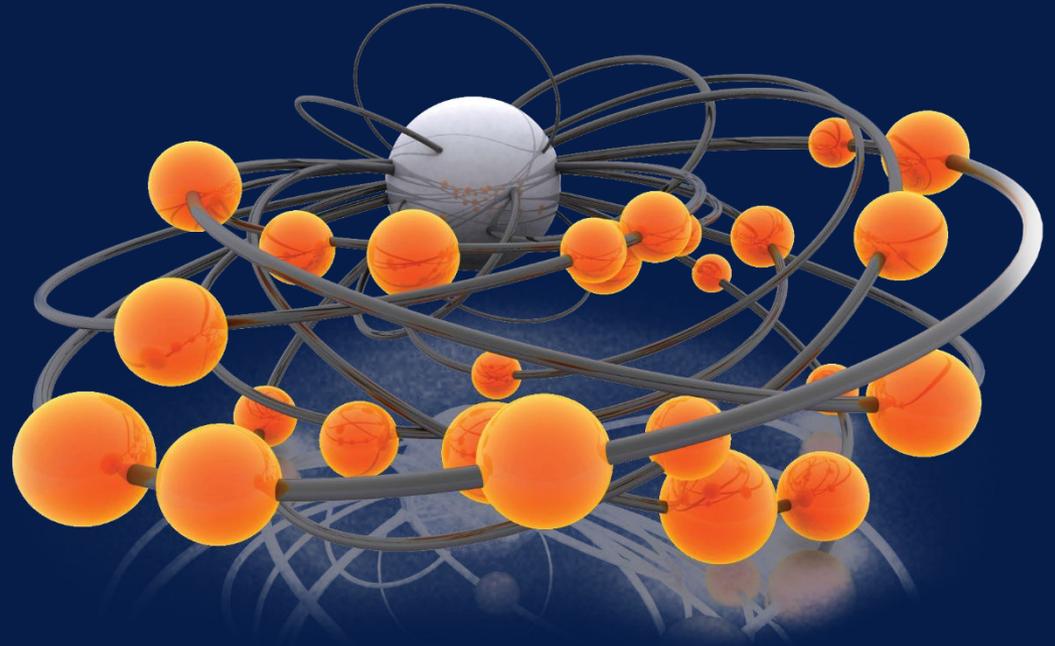


Interchangeability and Substitution Should Not Be Permitted

- Switching and alternating studies **are complex for technical and ethical reasons**; very little data is available on this topic
- No studies with switching as the primary endpoint **have been performed to date** comparing a biosimilar to its reference product
- Until such studies have been performed, interchangeability for any biosimilar, including mAbs, **is not medically/scientifically justified**
- **Only a treating physician who has carefully evaluated the consequences of a patient's response to approved biotherapeutic products should make the decision to alter a treatment regime**

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Pharmacovigilance



Pharmacovigilance Today

Systems developing at different rates, with different requirements

- Many countries still without strong pharmacovigilance systems
- INN system weakening, different approaches to naming at national levels

Focus is on the development of comprehensive pharmacovigilance systems including:

- Need to establish basic pharmacovigilance guidance to ensure patient safety
- Improving identification, naming of products, record keeping
- Increased emphasis on robust adverse event collection/reporting, surveillance, signal detection and evaluation
- Focus on risk in context of benefit
 - Important to take the entire prescription/dispensing/using/ADR reporting chain into consideration for traceability

Risk Management:

The importance of understanding a product's risk

Risk management needs to be appropriately tailored to specific risks including nature, type, seriousness, incidence of adverse drug reactions

A comprehensive pharmacovigilance and risk management plan is fundamental for all biotherapeutic products since even minor differences in the manufacturing process may affect the efficacy and/or safety profile

- Innovator Products
- Biosimilar may have potential for different safety profile than innovator
- Non-comparable biotherapeutics - different safety and efficacy profiles compared to other biotherapeutics of the same product class possibly due to lack of comparability information, i.e. unknown whether and which physicochemical differences exist (Weise, M., et al.)

New EU Pharmacovigilance Legislation*



EU Objectives:

- Strengthen post-authorization regulation of medicines
- Improve efficiency within the industry
- Reduce duplication of Member State efforts

Opportunities:

- Improve patient safety
- Maintain compliance by meeting the new EU PV Legislation
- Adapting to new treatment developments and innovative therapies

**Compliance by all stakeholders is therefore
of utmost importance!**

* New Regulation (EU) No 1235/2010 and Directive 2010/84/EU on Pharmacovigilance became law on 02 July 2012 and 21 July 2012, respectively

Increased emphasis on identification and tracking of biotherapeutics in pharmacovigilance systems

Example: New EU Requirement in EU

Article 102(e) of the Medicinal Products Directive 2011/83/EU, as amended by Directive 2010/84/EU, deals with the identification of medicinal products when reporting adverse events. Article 102(e) provides clarification specifically for biological medicinal products.

The Member States shall:

*(e) Ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to **identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory** which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number [Emphasis added].*

GVP Module VI requires MAH to follow up until batch number, brand name and active substance are known

Common practices of robust pharmacovigilance systems

Clear governance – laws establish national authorities to oversee pharmacovigilance and enforce reporting and monitoring

Central database – like the Uppsala Monitoring Center, safety analysis depends on robust, comprehensive data

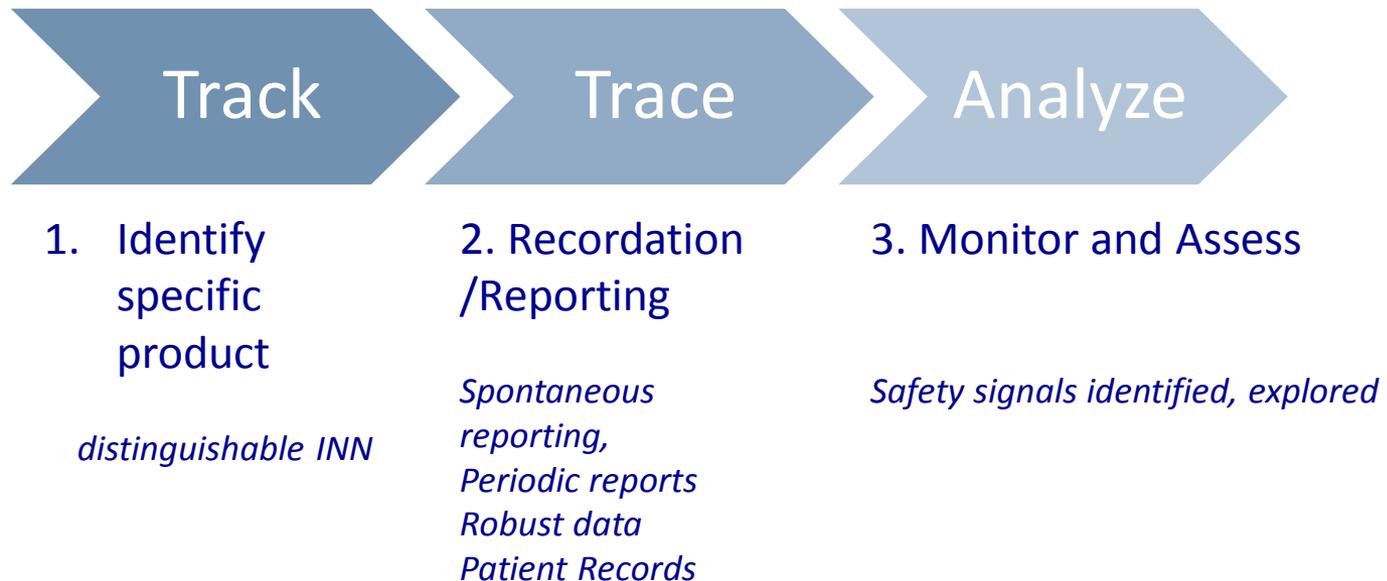
Centralized or closely coordinated analysis – within and across countries, a dedicated unit exists to collect and evaluate adverse events, with appropriate medical information for analysis

Not forgetting the need for clearly identified medicines as the basis of this process...

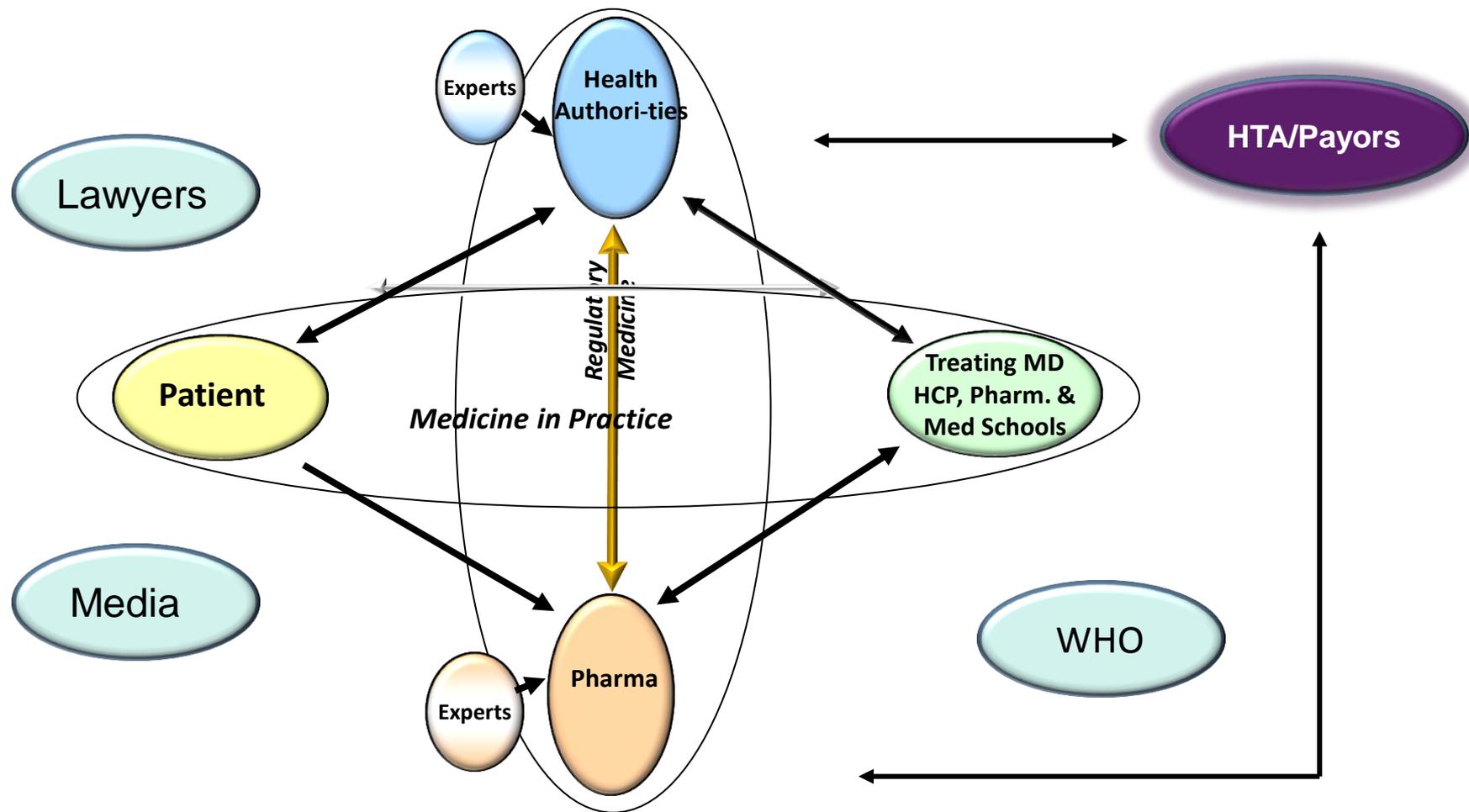
In Summary

Due to their unique product characteristics and practices in prescribing and use, all biotherapeutics – innovator, SBPs and non-comparable biotherapeutics – **require comprehensive pharmacovigilance guidance and systems.**

Effective, global pharmacovigilance for patient safety requires that we:



Effective pharmacovigilance: Needs not only effective systems, but active participation

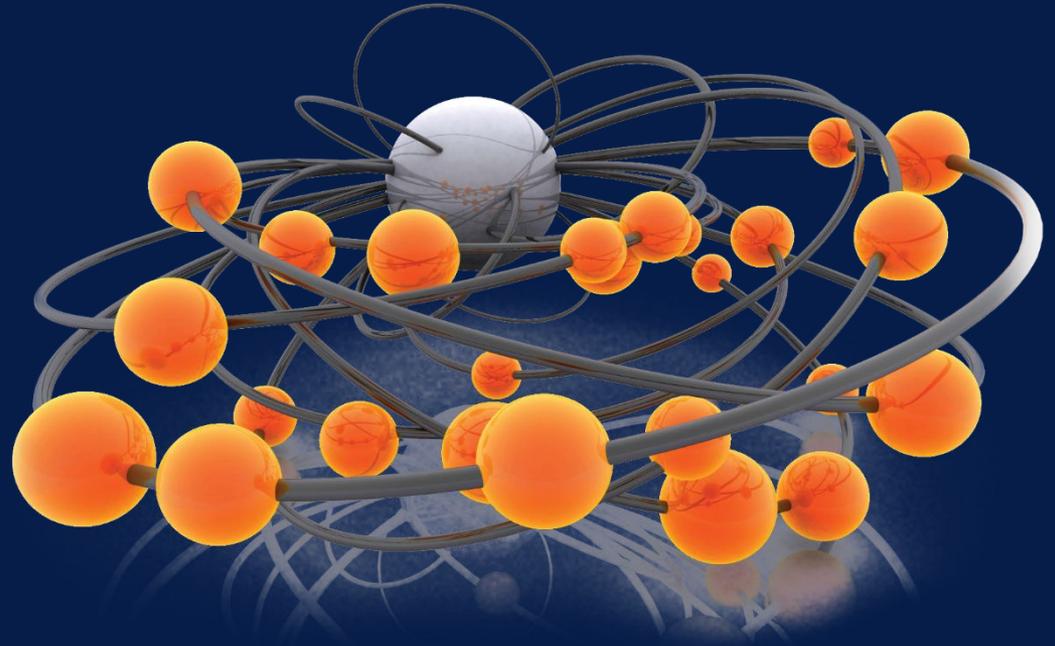


How engaged are all stakeholders in pharmacovigilance?

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Track and Trace begins with naming and prescribing

Overview of global practices



Biotherapeutics – a more complex mix

Innovator Biotherapeutic

- Novel product, derived from living material, generally with patent protection
- Marketing authorisation through full regulatory dossier
- Clinical trials are performed in every indication receiving regulatory approval

Biosimilar

- Product highly similar to an innovator biotherapeutic that has already been authorized (reference medicinal product)
- Subject to a tailored regulatory data package establishing biosimilarity through comprehensive comparability exercise

Non-comparable Biotherapeutic

- Product that is not approved in accordance with the WHO SBP guidelines, e.g.
 - Product developed on its own and not directly compared and analyzed against a licensed reference product
 - May or may not have been compared clinically
 - Can be subject to regulatory approval, but in some settings of a more abbreviated nature
 - Products with unclear approval standards

Tracking and tracing biotherapeutics – Challenges for the INN system

INN plays a central role in:

- National pharmacovigilance and traceability systems
- National systems for substituting medicines

Limited control over use of existing INNs

- Applicant decides if new INN wanted/required
- If existing INN is chosen, National Regulators need to ensure implementation of WHO naming system

Under current WHO criteria, possible for multiple biologics to have the same INN with different clinical characteristics

As a result: **no clear INN differentiation between similar products**

INN Naming Policy For Biosimilars

Current policy: *INN biosimilar name = INN reference product name*
(if the amino acid sequences are the same)

Identical amino acid sequences?	Significant post-translational modifications?	Impact on INN Names	Examples
Yes	No	Same INN Names	somatropin (Humatrope [®] and Valtropin [®])
Yes	Yes	INN names different but related (Add Greek letters α, β)	epoetin alfa (Eprex [®]) epoetin zeta (Silapo [®])
No (one or more amino acid is different but codes for same protein)	No	INN names different but related (Begin with different prefixes)	darbepoetin alpha (Aranesp [®])

Vodicka MA. Global Dis-Harmonization of Biosimilar Naming and Labeling. Hogan Lovells Biosimilars Law Blog. Last accessed 26 June 2012 at <http://www.biosimilarslawblog.com/2012/01/18/global-dis-harmonization-of-biosimilar-naming-and-labeling/>

Current situation for biosimilar naming – different approaches globally

Japan	Australia	US	Canada	Brazil	EU
Adopted Distinct non-proprietary naming using INN as base	Generally follows EU system of approval for naming	USAN Council works closely with WHO to harmonize names for substances	No specific policy on naming for SBPs	No specific policy on naming for SBPs	Uses INN system, but recommends Trade Name be used in addition to distinguish among biotherapeutic products
Example: INN – follow on 1 INN – follow on 2	Made exception for epoetin SBP – gave distinct name Naming policy currently under discussion	Naming policy currently under discussion	Naming policy currently under discussion	Naming policy currently under discussion	Indicates WHO INN system will remain established system in EU

WHO INN Report:

Issues with naming systems for biotherapeutics

INN modifications for simpler recombinant biologics:

- Used numbers and Greek letters, with mixed success¹
- Multiple interferons now “interferon beta-1 α ”

Brand Name	INN Name	Route / Dosing Schedule ²
Avonex [®]	Interferon beta-1a	i.m. 30 mcg injected once each week
Rebif [®]	Interferon beta-1a	s.c. 22 or 44 mcg, injected three times a week
Betaseron [®]	Interferon beta-1b	i.m. 0.25 mg injected every other day

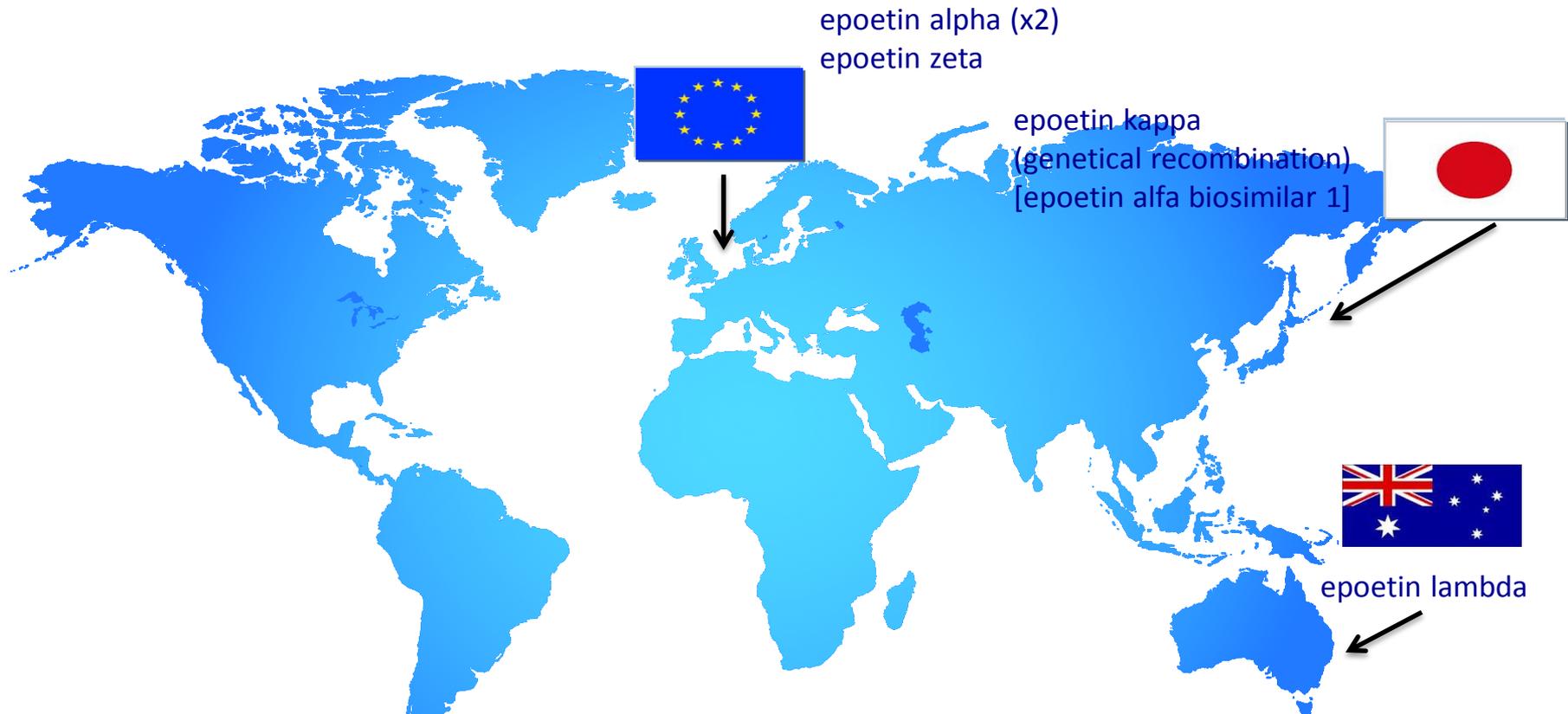

Same INN name, different administration and different safety/efficacy profiles

1. Meeting report of the 47th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 18-20 November 2008, Page 3. Last accessed 18 June 2012 at <http://www.who.int/medicines/services/inn/47thFINALINNreport.pdf> AND Rader RA. *BioProcess Int.* 2011;9:26-33

2. EBE - EFPIA Position Paper Naming of Biosimilar Medicinal Products: Option for Addressing distinguishable Safety Concerns. Page 4. 7 July 2006 Last Accessed 20 December 2011 at http://www.ebe-biopharma.org/documents/biosimilars/biosims_ebeefpiaiposition_naming+_7july2006.pdf.

Around the World:

Selected nonproprietary names for Epoetin Alpha biosimilars



WHO INN System is voluntary, but coordination with WHO seems to be weakening for biotherapeutic products

US FDA approval of tbo-filgrastim

Nonproprietary name: tbo-filgrastim

Proprietary name: *pending*

Approved under the full Biologics License Application process and filed before the BPCIA* became law

What are the ingredients in tbo-filgrastim?

Active ingredient: tbo-filgrastim

Inactive ingredient: glacial acetic acid, sorbitol, polysorbate 80, sodium hydroxide, and Water for Injection.

FDA Week (vol. 18, No 36, September 7, 2012)

“FDA determined that a unique nonproprietary name (tbo-filgrastim) is required to distinguish this product from Neupogen (filgrastim), a previously licensed biological product that contains a related drug substance” the agency said.”

“The nonproprietary name tbo-filgrastim is intended to differentiate this product from Neupogen to minimize medication errors and facilitate post-market safety monitoring”

“The agency also said it intends to evaluate the need for distinct nonproprietary names on a product-specific basis”

* BPCIA = Biologics Price Competition and Innovation Act of 2009

INN prescribing practices for biotherapeutics (including biosimilars, non-comparables) (1)

Some jurisdictions *require* prescribing by INN

- China prohibits prescribing biotherapeutics by proprietary name (with an exception for a patented biotherapeutic with a new active ingredient)
- Colombia prohibits prescribing reimbursed biotherapeutic by proprietary name
- Latvia prohibits prescribing reimbursed biotherapeutics by proprietary name at the initiation of therapy (physicians may prescribe by proprietary name to continue a patient's treatment on a particular medicine)

Requirements for prescribing by INN are still being proposed

- In Russia, a draft Ministry of Health decree would mandate INN prescribing

INN prescribing practices for biotherapeutics (including biosimilars, non-comparables) (2)

- Even where prescribing by proprietary name is allowed, it is **sometimes discouraged**
 - E.g., Indian regulatory authorities recommend prescribing by INN and have directed physicians in hospitals to prescribe by INN
 - E.g., A healthcare professional association in the Netherlands has recommended prescribing by INN
- EU *requires* brand name plus INN for biotherapeutics in prescriptions under the Cross-Border Healthcare Directive
- UK has provided guidance:
 - On prescribing: ***“when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed”***.⁽¹⁾
 - On recording: ***“in addition to the substance please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch-number, on the report”***.⁽²⁾

(1) British National Formulary, <http://www.bnf.org/bnf/go?bnf/current/PHP60-general-guidance.htm>, accessed 2 April 2013

(2) MHRA Drug Safety Update Volume 6, Issue 4, **November 2012**

Biosimilars in the EU: Naming system ambiguity

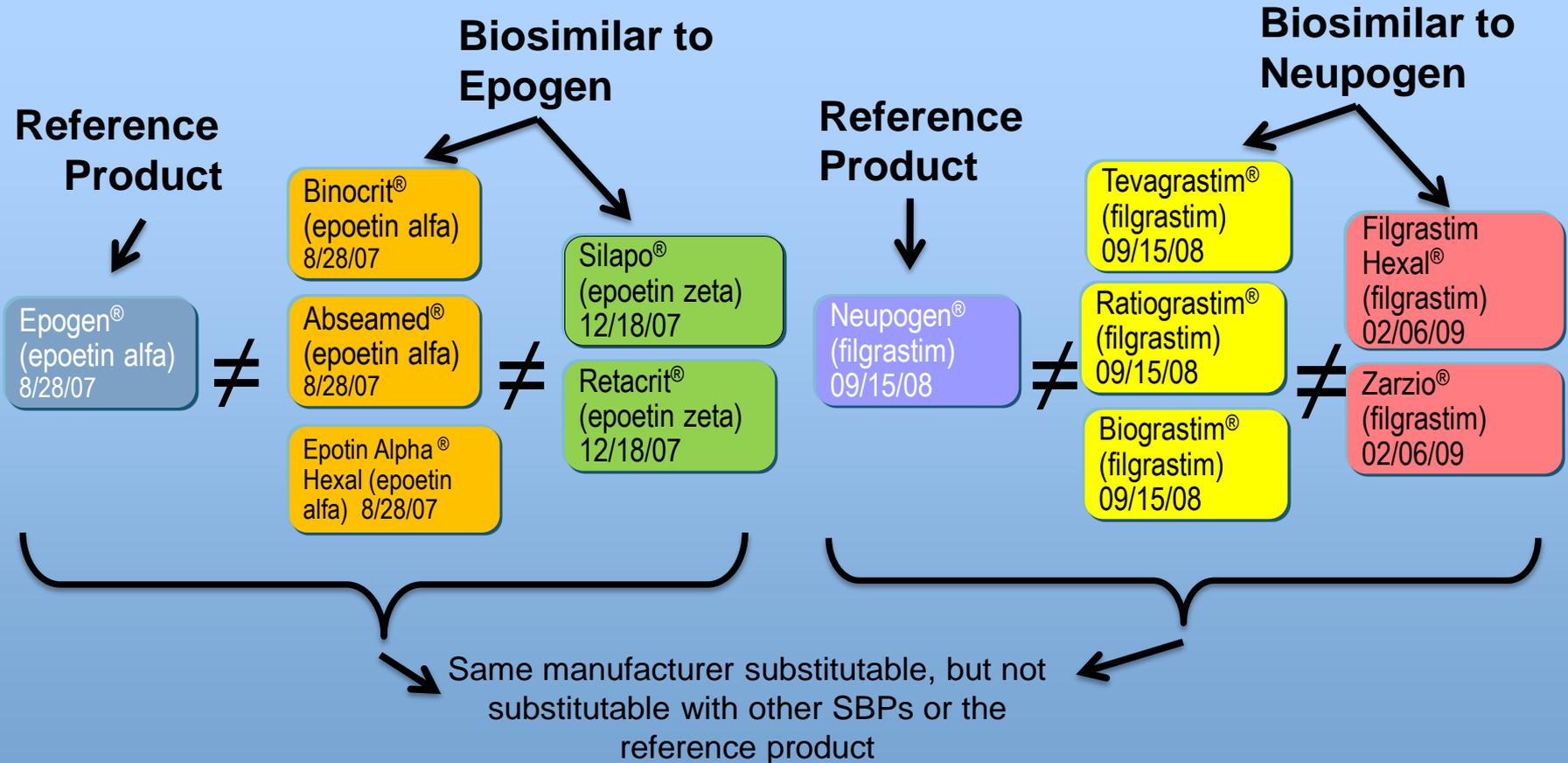
Biosimilars and Brands in the EU (as of July 2012)

<u>Brand name of reference product</u>	<u>Brand names of biosimilars</u>	<u>INN Name</u>
Genotropin®	Omnitrope®	Somatropin
Humatrope®	Valtropin®*	Somatropin
Eprex®	Abseamed®, Binocrit® and Epoetin alfa Hexal®	Epoetin alfa
	Retacrit® and Silapo®	Epoetin zeta
Neupogen®	Biograstim®, Ratiograstim® and Tevagrastim®	Filgrastim
	Filgrastim Hexal® and Zarzio®	Filgrastim
	Nivestim®	Filgrastim

* EMA website accessed 25 April 2013; Valtropin – authorized and then withdrawn

Germany – Biosimilar substitution policy

Why brand name is not enough



Note: Binocrit, Abseamed and Epoetin Alfa Hexal all rely on the same dossier and are thus identical. Retacrit and Silapo rely on the same dossier and therefore are identical to each other. Filgrastim Hexal and Zarzio rely on the same dossier. Tevagrastim, Ratiograstim, and Biograstim rely on the same dossier, being identical.

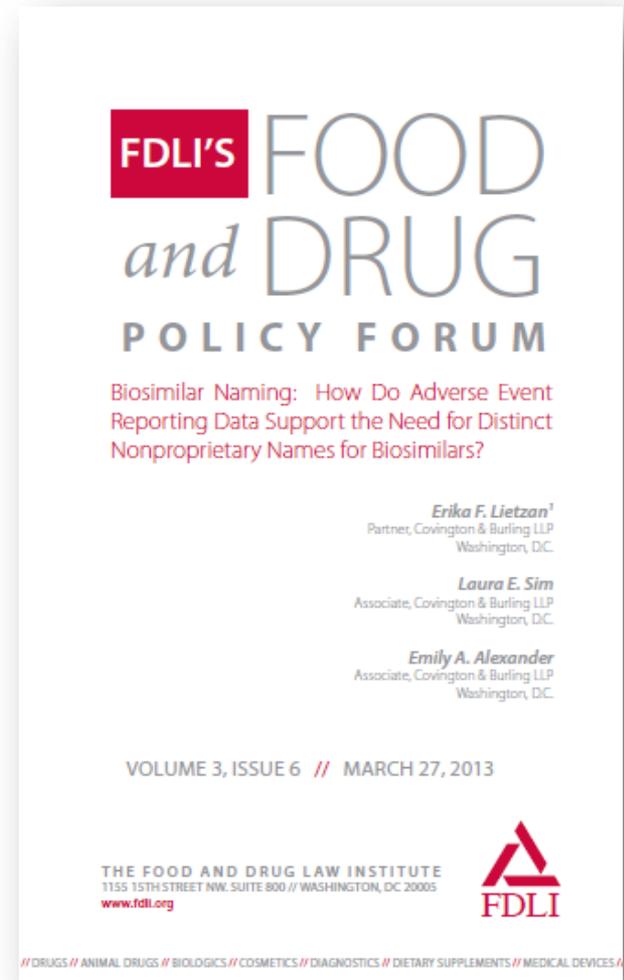
Recent research highlights challenges, Even for small molecule medicines

Data from FDA's Adverse Event Reporting System (FAERS) was utilized for an assessment of **eight small molecule drugs** to see how adverse event reporting practices might affect the need for distinct names for biosimilars

Analysis of adverse event (AE) reporting for non-biological drugs revealed **increases in the rate of AE reports to prescriptions after generic introduction attributed to the originator which ranged from approximately 5 times the rate of pre-generic introduction to over 411 times the rate of pre-generic introduction despite dramatic decrease in innovator sales** for 6 of the 8 drugs

Finds that AE reporting in practice suffers – for various reasons - from widespread product misattribution and gaps in information that hinder traceability of small-molecule medicines

With these lessons applied to the anticipated introduction of biosimilars in the USA, the authors conclude that distinct nonproprietary names for biosimilars would promote their traceability

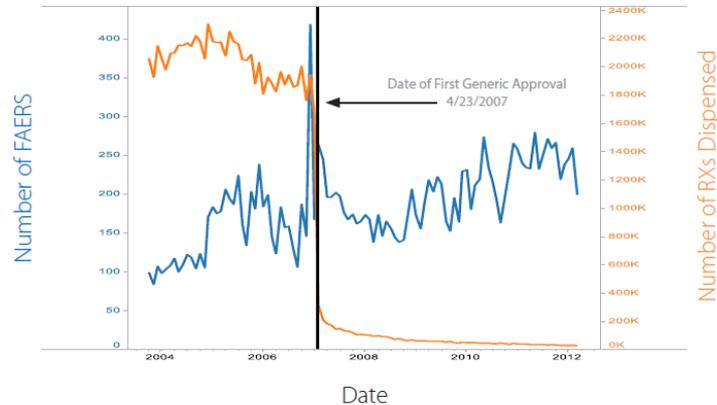


* Abbvie sponsored study and publication

Recent Research Highlights Challenges, Even for Small Molecule Medicines

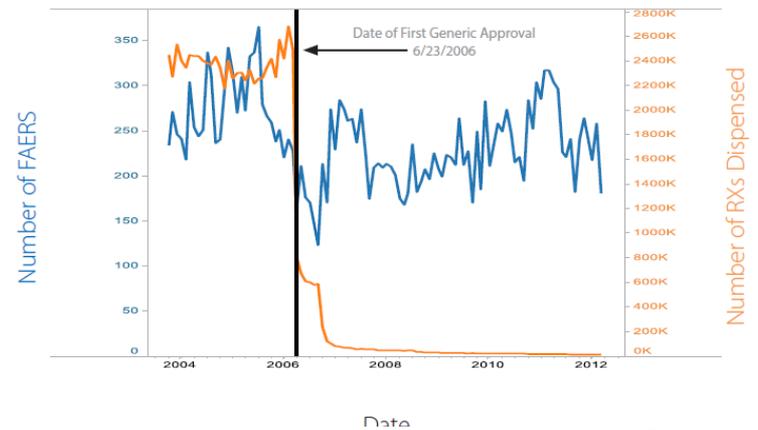
Ambien (zolpidem tartrate) (oral tablet)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



Zocor (simvastatin) (oral tablet)

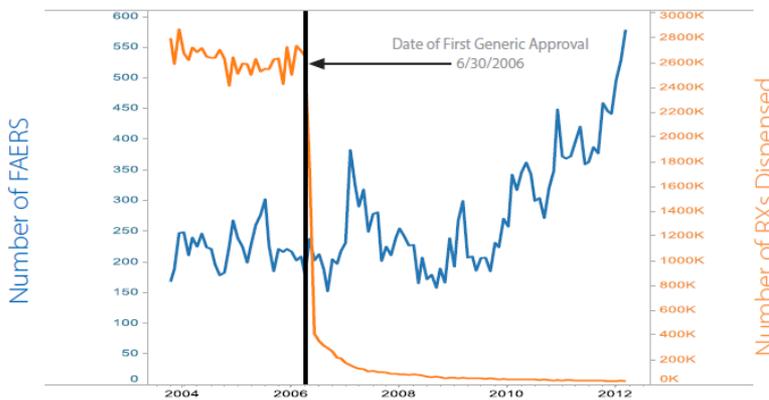
Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



Legen

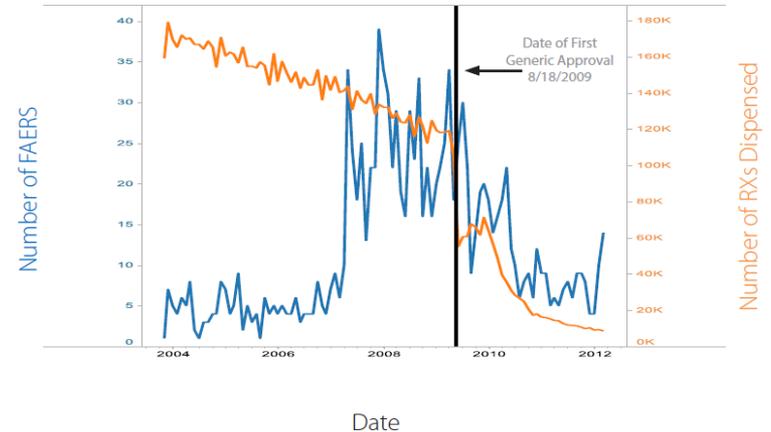
Zoloft (sertraline hydrochloride) (oral tablet & oral concentrate)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



Catapres TTS (clonidine) (extended release transdermal film)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed

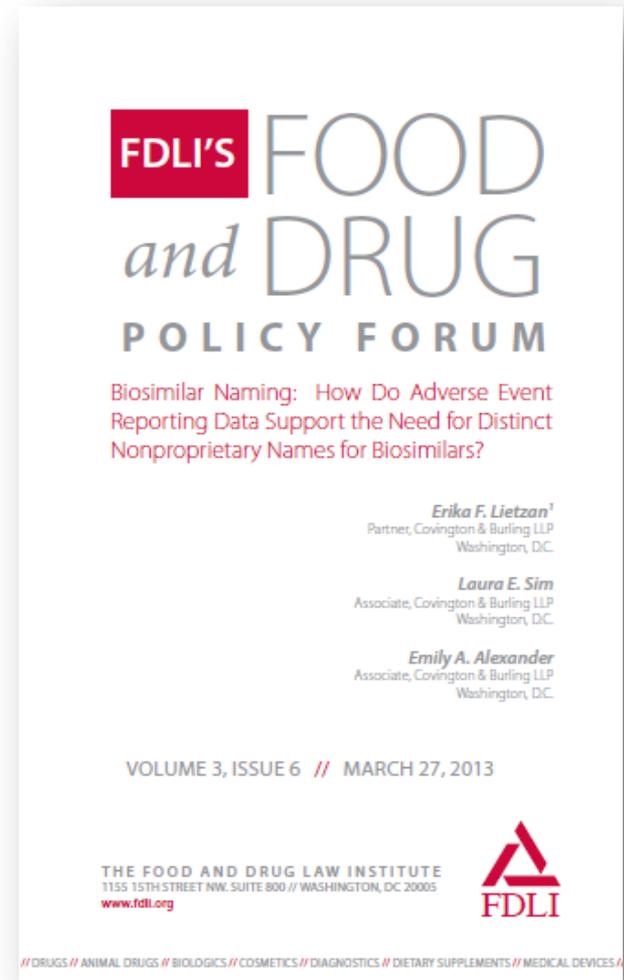


Source: EF Lietzan et al., FDLI Food and Drug Policy Forum, Volume 3, Issue 6, March 27, 2013; <http://www.fdl.org/~resources/resources-order-box-detail-view/biosimilar-naming-how-do-adverse-event-reporting-data-support-the-need-for-distinct-non-proprietary-names-for-biosimilars>

Recent research highlights challenges, Even for small molecule medicines

Concludes that to facilitate robust and accurate pharmacovigilance for biologics,

- Require that each biosimilar label bear a nonproprietary name that distinguishes the product from the reference product and from other biosimilars that cite the same reference product
- Issue guidance on the process through which FDA will work with biosimilar sponsors to assign “distinct” nonproprietary names
- The reporting of AEs only by product name (brand or nonproprietary) is not sufficient for proper identification
- Work with the World Health Organization and national regulatory agencies around the world to help develop consistent naming policies for biosimilars



* Abbvie sponsored study and publication

Practical Aspects

- INN is still the most consistently and widely reported piece of information on adverse event (AE) reports, but safe prescription and dispensing for biotherapeutics requires more

Biotherapeutics are not Synthetic Molecules & Biosimilars are not Generics:

- Correct recordation of AE is key to accurate and effective signal detection
 - Lot numbers not routinely recorded
 - Brand name not always available or present
- Interchangeability/Substitution
 - Not all products will be approved for all indications
 - Automatic substitution of biological products is not compatible with high levels of patient safety
 - Right of the prescriber (physician) and patient to choose appropriate product based on proper and transparent information

Benefits of Unique Non-proprietary Names for Biotherapeutics

Unique INNs:

- **Minimize risk of unintentional prescribing**
- **Minimize risk of inappropriate, involuntary or automatic substitution**
- **Promote effective track and trace pharmacovigilance**
- **Increase accuracy of reporting and eventual corrective action**
- **Increase transparency of dispensed product to patients**
- **Enhance control of physicians to make prescribing recommendation**

Key lessons

- Due to their unique product characteristics and practices in prescribing and use, **all biotherapeutics require comprehensive PV guidance and systems**
 - Effective, global pharmacovigilance for patient safety through the establishment of a reliable risk-benefit profile requires that Regulatory Agencies effectively Track and Trace AEs
- Countries and Provinces/States are attempting to determine the best practice to promote safety and encourage competition
- Practices may not only vary between countries, but also within Provinces or States of a specific country
- Some countries are moving to unique non-proprietary naming or unique identifiers to distinguish products
 - Trade name as unique identifier is not enough

Biotherapeutics: What's Right for Patients

- 1) Data submission requirements that provide for a stepwise approach to **demonstrate high similarity**: full CMC/quality and manufacturing data with side by side comparability, comparative pre-clinical studies designed to detect differences, Phase 1 studies to comparable pharmacokinetics (and if relevant pharmacodynamics), and Phase 3 to show equivalent efficacy and safety
- 2) Indication Extrapolation – **only when scientifically supported**, which is not currently the case for mAbs.
- 3) No automatic substitution – **physician decision and patient knowledge is paramount**. Switching studies should be conducted before determination of interchangeability and methodology is currently scientifically and ethically complex.
- 4) Robust Pharmacovigilance and post-marketing surveillance that provides for **individual product identification throughout prescribing , dispensing and treatment – distinguishable INN**

Thank you!

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Comparison of EU, US & Japanese Guidelines (1)

	EU	US (Draft)	Japan
Name	Similar Biological Medicinal Product	Biosimilar	Follow-on Biologic
Scope	<p>Substance of biological origin with a combination of physico-chemical-biological testing and control of the production process for characterisation and determination of quality.</p> <p>- Eg. Low molecular weight heparins (LMWH)</p>	<p>Includes biologics but very specific definition of a protein which must have <u>sequence more than 40 AA</u>.</p> <p>- Chemically synthesized polypeptide is made fully by chemical synthesis and is less than 100 AA. - A chemically synthesized polypeptide is not defined as a biologic product</p> <p>- A copy of LMWH approved as a generic</p>	<p>- Highly purified recombinant proteins, polypeptides and their derivative which can be analyzed by analytical methods.</p> <p>- Highly purified non-recombinant proteins can be also included.</p> <p>- Consult PMDA if in doubt</p> <p>- Polyglycans, Nucleic Acid are out of scope</p>
General Features	Very thorough and elaborated guidance. Overarching guidance (issued Oct 2005) and several category-specific guidance	Three-documents general draft guidance issued Feb 2012	General guidance and QA document issued March 2009

Comparison of EU, US & Japanese Guidelines (2)

	EU	US (Draft)	Japan
Scientific approach	Stepwise approach with emphasis on Robust and full quality package that will determine the extent of clinical data needed	Stepwise' and 'Totality of the Evidence' approach. Extensive quality data and less comprehensive non-clinical/clinical package if supported by quality/CMC	Generally in line with EU approach Consultation with PMDA is highly recommended
Non-proprietary naming	Follows WHO	Under Discussion	RP and Biosimilar have different non-proprietary names
Reference Product (RP)	Use RP approved in EU, may supplement US or Jap RP as supporting data	-Legislation: Use US-licensed RP -Draft guidance: Use US-licensed RP. Non-US RP can also be used but subject to stringent requirements	Use RP approved in Jap
Inter-changeability (IC)	Not regulated at the EMA level. Not allowed in MS	IC concept is Included in the Law but not covered in the guidance	Not allowed
Extrapolation of indications	<u>Possible</u> , but justification needed on whether MoA same or not, clinical experience in the most sensitive population, available literature, Possible safety issues	<u>Possible</u> , but sufficient scientific justification is needed based on several possible criteria, including MoA and ; most sensitive patient population	<u>Possible</u> , but rationale is needed that similar effects can be expected pharmacologically in other indications if same MoA as RP

Comparison of EU, US & Japanese Guidelines (3)

	EU	US (Draft)	Japan
Pharmacovigilance	Clinical safety of BS needs to be monitored post-approval, including continued risk-benefit assessment	PV is required but additional details are not very clear in the draft guidelines	Post-Marketing Study, Discussion with PMDA necessary re. RMP