Safe Prescription, Safe Dispensing, Identification and Track&Trace of All Biologicals in the Context of the Re-opened Biosimilars INN Debate

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Why the «Biosimilars INN Debate» has been Re-opened?

- **General frustration regarding divergent naming policies/approaches around the globe**
  - WHO INN Expert Committee discussing various proposals regarding naming of similar biotherapeutic products (SBPs)
- **Safety and track&trace issues with non-comparable biotherapeutics not approved in accordance with WHO SBP guidance (e.g. PRCA cases in Thailand)**
- **Competitive reasons (additional barriers to uptake)**
  - Imminent advent of biosimilar mAbs in the EU
  - Interchangeability(substitution) is part of US statutes

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The Scientific Nomenclature:

Existing WHO INN nomenclature rules are science-based

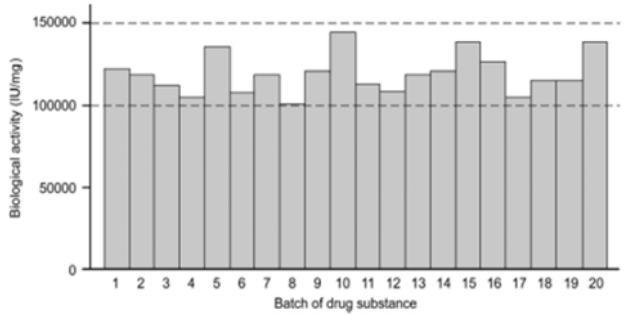
Nomenclature for ALL Biologics should Remain Science-Based

Any naming convention must take into account that biological products always vary

- in the human body
- from batch to batch
- after manufacturing changes
- between manufacturers

"Similar but not identical"

- „Non-identicality" is a normal principle in biotechnology.
- No batch of any biological is „identical" to the others



- The „art" is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability)

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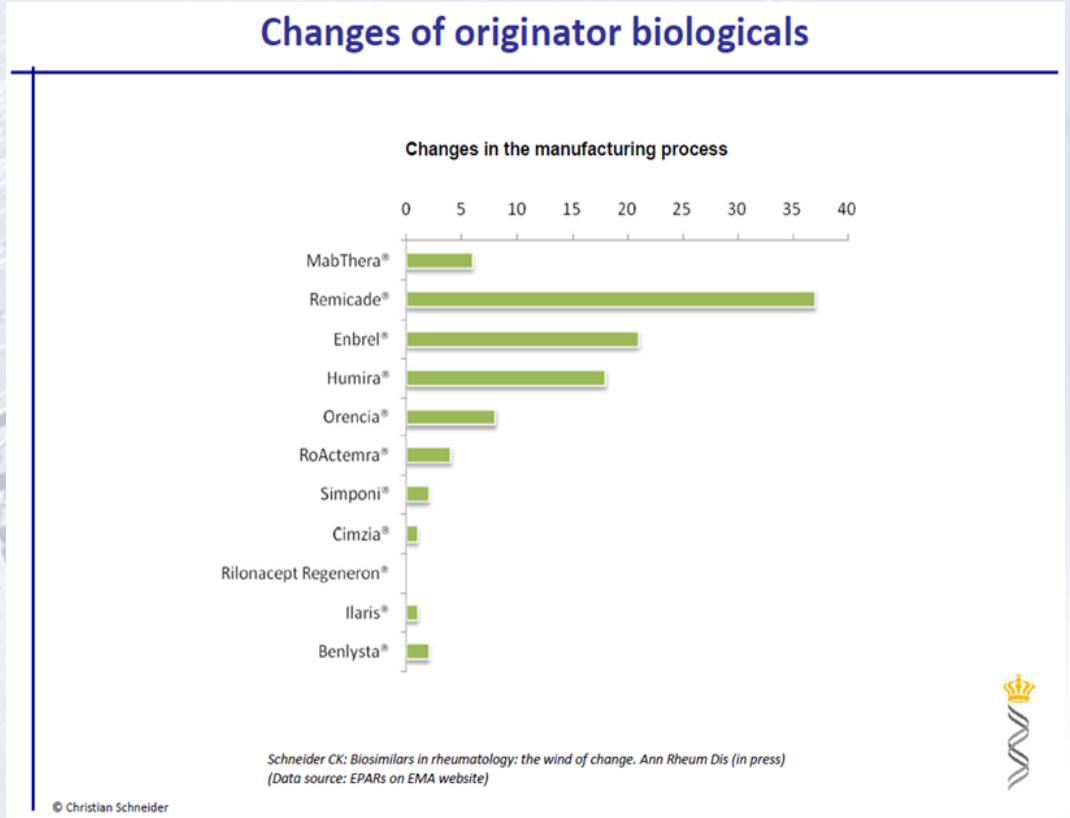
Nomenclature for ALL Biologics must be Consistent

Same scientific criteria apply for assessing & approving **comparability/similarity,** hence the **same scientific criteria for naming** must be used if

- a product is found to be comparable after a manufacturing change, and if
- a biosimilar is found to be comparable/similar to its reference product

If comparability/similarity is not met, a different INN should be allocated



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Reminder: INN is a Nomenclature System for Active Substances

Intent of INN is …	is Not …
Identification of active substance, not the finished product	Sole means of identification of a medicinal product or its impurities
Nomenclature: means of classifying and cataloguing pharmacological classes	Statement of therapeutic equivalence of a medicinal product
	Means for tracking and tracing the use of medicine

INN is a nomenclature system for active substances
The INN has never been the primary means for clinical decisions by physicians, nor more than a single valuable component of robust track and trace systems for products dispensed by pharmacists

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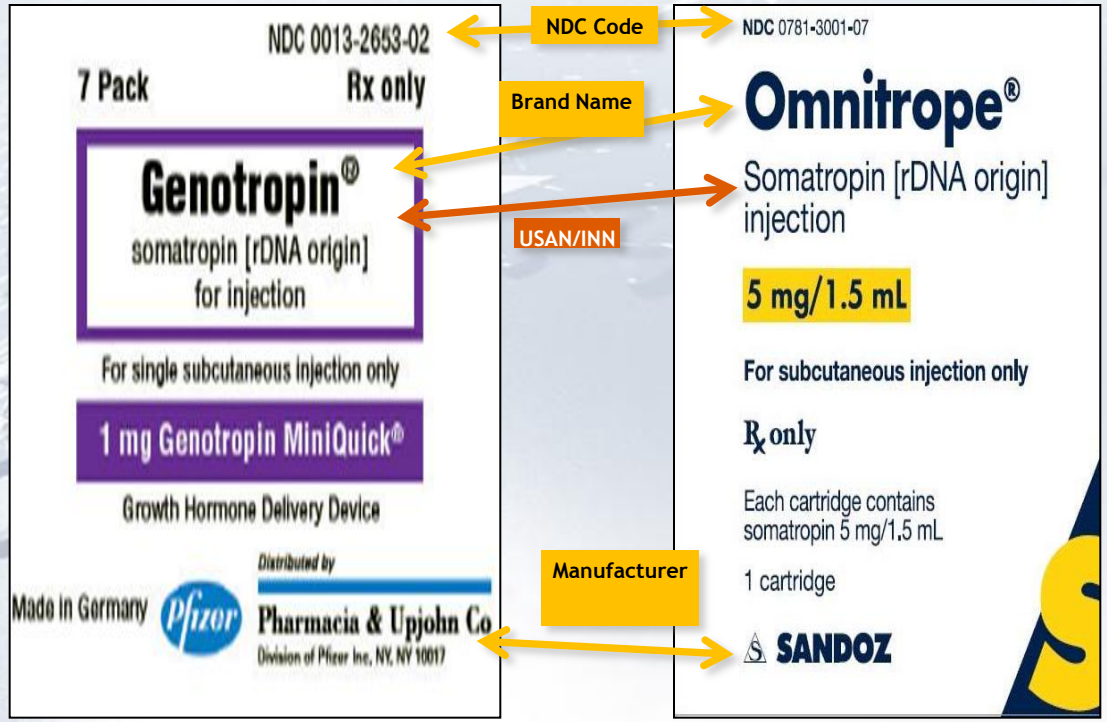
Clear Identification of All Biologics incl. Biosimilars:

Brand names are consistently used for clear identification of biologics

The Current System Includes Redundant Means of Identification

- Brand names
- Manufacturer
- Batch number
- INN (USAN for US)
- NDC (for US)



Many barcoding approaches are in place

A Brand Name is a Unique Identifier

- **As required by EU law, every medicine will either have**
  - an invented name, or
  - the name of the active substance together with the company name/trademark
    - both naming options constitute distinguishable brand names

- **A brand name has to be approved by regulators to ensure that the brand name cannot be confused with other brand names**

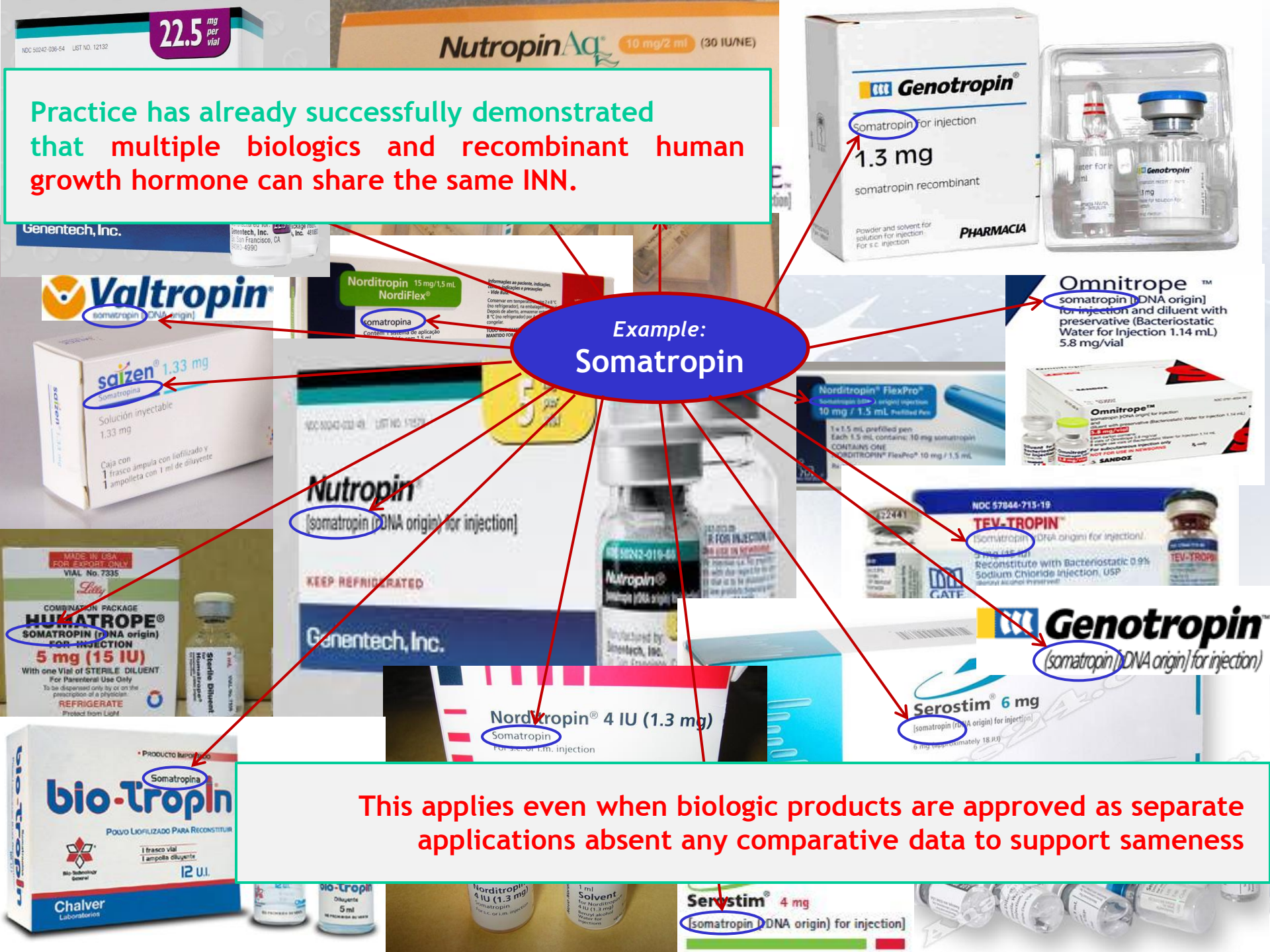
- **A brand name, which is a unique identifier, is key information to clearly identify a given biologic product, including biosimilars**

Prescribers Use Consistently Brand Names for Biologics

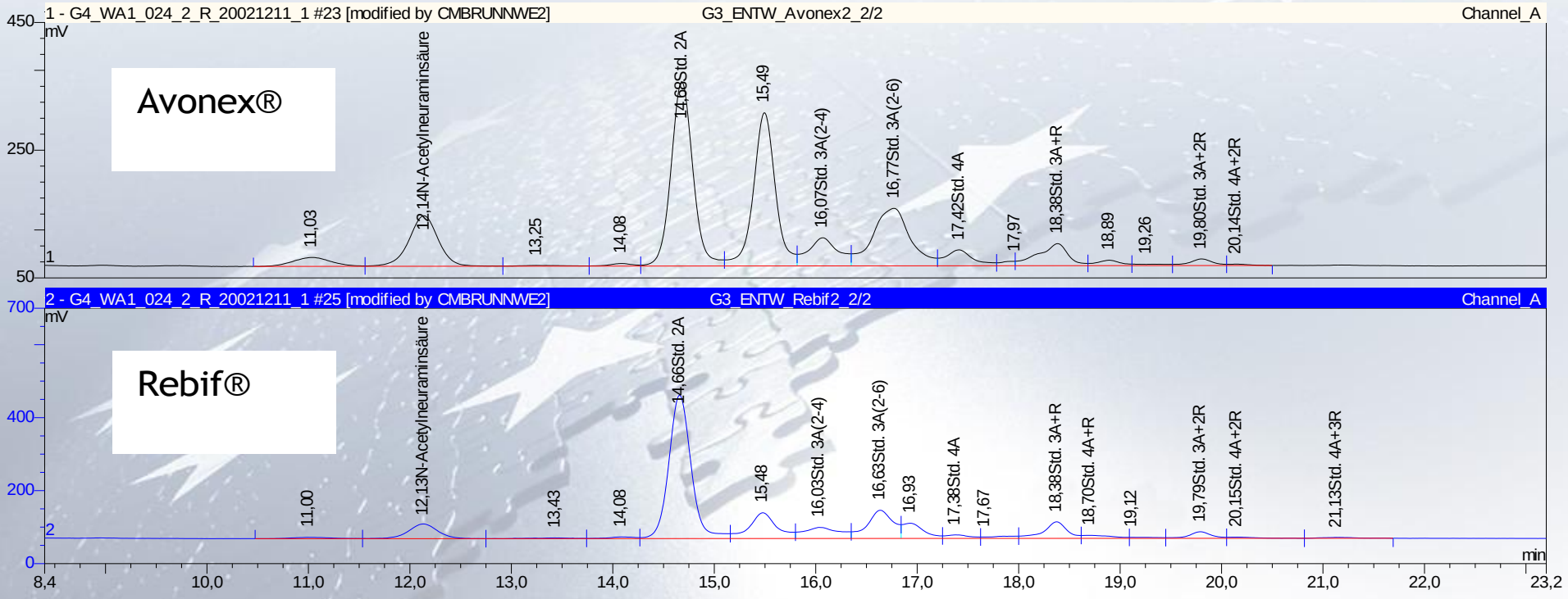
- **Biological products are prescribed by the brand name**
  - INN prescribing is increasingly used only for small molecule generics
  - INN alone is not the basis of the prescription for biologics

- **In countries, where INN prescribing exists for small molecule products, prescribers are advised or mandated by regulators to prescribe all biologics by their brand name**

- **Different INNs between biosimilar and its reference product will induce confusion, hide class adverse effects, and lead to potential medication errors**


Practice has already successfully demonstrated that multiple biologics and recombinant human growth hormone can share the same INN.
Example:
Somatropin
This applies even when biologic products are approved as separate applications absent any comparative data to support sameness
22.5 mg per vial
Nutropin Aq 10 mg/2 ml (30 IU/NE)
Genentech, Inc.
Genotropin
Somatropin for injection
1.3 mg
somatropin recombinant
PHARMACIA
Valtropin
somatropin (rDNA origin)
Norditropin 15 mg/1,5 mL NordiFlex®
somatropina
Omnitrope ™
somatropin [rDNA origin] for injection and diluent with preservative (Bacteriostatic Water for Injection 1.14 mL) 5.8 mg/vial
saizen® 1.33 mg
Somatropina
Solución inyectable
1.33 mg
Norditropin® FlexPro®
10 mg / 1.5 mL
Nutropin
[somatropin (rDNA origin) for injection]
KEEP REFRIGERATED
Genentech, Inc.
NDC 57844-713-19
TEV-TROPIN
Reconstitute with Bacteriostatic 0.9% Sodium Chloride Injection, USP
HUMATROPE®
SOMATROPIN (rDNA origin) FOR INJECTION
5 mg (15 IU)
With one Vial of STERILE DILUENT
For Parenteral Use Only
REFRIGERATE
Genotropin
(somatropin [rDNA origin] for injection)
Norditropin® 4 IU (1.3 mg)
Somatropin
Serostim® 6 mg
[somatropin (rDNA origin) for injection]
bio-tropin
Somatropina
Pó Liofilizado Para Reconstituir
12 U.I.
Chalver
Laboratórios
Serostim® 4 mg
[somatropin (rDNA origin) for injection]

Same INN for Avonex/Rebif 'Interferon beta 1a'



Glycosylation profile of Avonex® (top)and Rebif® (bottom) using HPAEC-PAD (high pH anion exchange chromatography with pulsed amperometric detection; Method: Enzymatic deglycosylation and desialylation of Interferon beta 1a and subsequent separation of the released glycans unsing a Dionex LC system with CarboPac PA100 column according to the application notes of Dionex; 2A: biantennary glycans; 3A: triantennary glycans; 4A: tetranatennary glycans; source of the data: Sandoz GmbH

FDA Approved Medicines Sharing the Same INNs and Never Triggering INN Debate (idem in EU)

Avonex®	**Interferon Beta-1A**	Biogen	May 17, 1996	BLA 103628
Rebif®		Serono Inc	March 7, 2002	BLA 103780
Betaseron®	**Interferon Beta-1B**	Bayer Healthcare Pharms	July 23, 1993	BLA 103471
Extavia®		Novartis	August 14, 2009	BLA 125290
Asellacrin® 10, Asellarcrin® 2	**Somatropin**	EMD Serono	July 30, 1976	NDA 017726
Crescormon®		Genentech	April 6, 1979	NDA 017992
Accretropin®	**Somatropin Recombinant**	Cangene	January 23, 2008	NDA 021538
Bio-Tropin®		Ferring	May 25, 1995	NDA 019774
Genotropin® and Genotropin® Preservative Free		Pharmacia and Upjohn	August 24, 1995	NDA 020280
Humatrope®		Eli Lilly	March 8, 1987	NDA 019640
Norditropin® Flexpro and Norditropin® Nordiflex		Novo Nordisk	June 20, 2000	NDA 021148
Nutropin® and Nutropin® AQ		Genentech	Nov. 17, 1993 and Dec. 29, 1995	NDA 020168 and NDA 020522
Omnitrope®		Sandoz	May 30, 2006	NDA 021426
Saizen®		EMD Serono	October 8, 1996	NDA 019764
Serostim®		EMD Serono	August 23, 1996	NDA 020604
Tev-Tropin®		Ferring	May 25, 1995	NDA 019774
Valtropin®		LG Life	April 19, 2007	NDA 021905
Zorbtive®		EMD Serono	December 1, 2003	NDA 021597

Brand Name®	The blue background means the product has been withdrawn but not for safety or efficacy reasons, and so the product is still available as a reference product

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Tracking and Tracing of All Biologics incl. Biosimilars:

Actual PV data reveals that current tracking and adverse event reporting works well for biosimilars

Brand Name + Batch Number

- New EU PV legislation: "*Member States shall ensure,….., 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 medicinal product* and the batch number.*"
  - *Name of the medicinal product as approved, which is never INN alone

Directive 2001/83/EC, as amended; Article102, 1st paragraph, point (e)

Patients Rely on Brand Names for Biologics

- Brand names are used by patients and also facilitate suspected ADR reporting

- Patients usually do not report adverse drug reactions by INN
- Proposing different INNs/INNs with unique identifiers for biosimilars will confuse patients especially when prescribers decide to switch from the originator to a biosimilar product or vice versa

Current INN, Naming and PV System are Working Well in Europe

- Invented name or sometimes INN + trademark/name of MAH are used to brand biosimilars

- EU study on the traceability of biologics in spontaneous reporting systems during the period 2004 - 2010* (even before new PV legislation) showed that product identification of biosimilars was well ensured in Europe
  - 96.2% product identification across 3 product classes
  - 98.9% for epoetins

* The "Vermeer study" on traceability of biopharmaceuticals in spontaneous reporting systems in the US and the EU (presented in July 2012 at an EMA stakeholder meeting by Sabine Strauss/MEB, Member of the EMA Pharmacovigilance Risk Assessment Committee

http://www.ema.europa.eu/docs/en_GB/document_libary/Presentation/2012/05/WC500127934.pdf

Actual Sandoz PV data demonstrates current system works without unique INNs/biosimilar identifier

Sandoz Argus Adverse Event Report - worldwide (Omnitrope includes US data)

Binocrit/ Abseamed/ Epoetin Alfa Hexal	Omnitrope	Zarzio
Total Spontaneous (HCP, Non-HCP) ADRs through 28 Feb 2013: 166	Total Spontaneous (HCP, Non-HCP) ADRs through 25 Feb 2013: 1067	Total Spontaneous (HCP, Non-HCP) ADRs through 28 Feb 2013: 126
Reported as product name •Binocrit: 91 •Epoetin Alfa Hexal: 10 •Abseamed: 62 •erythropoetin alfa: 3	Reported as product name •Omnitrope/ Scitropin: 1059 •somatropin: 8 (multiple received from HA, hence no follow-up)	Reported as product name •Zarzio: 108 •Filgrastim Hexal: 8 •GCSF: 1 (via HA) •filgrastim: 9 (multiple were spontaneous reports derived from clinical trials)
~Patient exposure (days) = 66,898,161 (8/2007-2/2013)	~Patient exposure (days) = 33,235,331 (10/2005 - 8/2012	~Patient exposure (days) = 3,456,506 (2/2009-1/2013)

Suffixes Add Nothing to Better Pharmacovigilance but Create Confusion and Possible Barriers to Access

Epoetin alfa = epoetin zeta = same reference product

- In 2003 no INN guidance or experience existed for « biosimilar applicants »
  - Bioceuticals (Stada) submitted an INN application to WHO
  - Once unique INN allocated by WHO: EU legal obligation to use it
- Hospira post-marketing experience reinforces:
  - Per EU PV legislation, traceability is by brand name and batch number, as most cases identified as “Retacrit”
  - Use of suffix does not enhance value to PV reporting as even with receipt of an “epo zeta” case, cannot differentiate between “Silapo” or “Retacrit”
  - Different suffix “alfa” vs “zeta”can cause confusion among patients/prescribers; creates potential barriers to trade/access if tender specifications allocate different categories and volumes to different suffixes (e.g. Spain)

Newly Established ISO Standard for Identification

- Standards Development Organisations (ICH, ISO, CEN, HL7, IHTSDO, IHE, CDISC, GS1)-work started in 2006
- **Worldwide system for internationally harmonised data definitions to establish UNIQUE IDENTIFIERS for medicinal products to be used during their entire life-cycle**
- **Rationale**
  - driven by regulatory and pharmacovigilance requirements originally developed by ICH
  - aiming at a lasting framework of internationally accepted and relevant standards
  - allows exchange of medicinal product information in a robust and reliable manner
  - **Under implementation in the EU**: Commission Implementing Regulation(EU) N° 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities

Identification of the Medicinal Product (IDMP)

- **IDMP standard: unique identification of the medicinal product**
  - EN ISO 11615:2012 - Data elements and structures for the unique identification and exchange of regulated medicinal products
  - EN ISO 11616:2012 - Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information
  - EN ISO 11238:2012 - Data elements and structures for the unique identification and exchange of regulated information on substances
  - EN ISO 11239:2012 - Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
  - EN ISO 11240:2012 - Data elements and structures for the unique identification and exchange of units of measurement

More «Unique Identifier» Requirements Adopted in EU

- Falsified Medicines Directive 2001/62/EU established legal framework for unique identifier (identification of individual packs)
- Cross Border Care Directive 2012/52/EU laying down measures to facilitate the recognition of medical prescriptions in another Member State
  - *"In contrast, the brand name of a medicinal product should only be used to ensure clear identification of biological medicinal products…. "*

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Conclusions and Recommendations

Summary of EGA Conclusions

1. **Current INN system is working well for all biologics**
2. **Actual pharmacovigilance data reveals that current tracking and adverse event reporting works well for biosimilars**
3. **There is no scientific and public health rationale to introduce a specific INN naming policy for biosimilars**
4. **Unique INNs/unique identifier for biosimilars**
   - would be discriminatory and redundant given that several robust unique identifier frameworks for all biologicals are established
   - will be another source of divergent global implementation
   - will not correct worldwide deficiencies in adverse event reporting and traceability
   - does not address safety and track & trace issues of non-comparable biotherapeutics not approved in accordance with WHO SBP guidance

Unique INNs/INNs with Unique Identifier for Biosimilars should be avoided

- **It undermines the scientific concept**
  - of biosimilarity and reflects a misunderstanding of this concept
  - of comparability on which changes in originator products are based today
- **It inhibits patient access and therefore undermines public health benefits**
- **Furthermore it will lead to:**
  - confusion among health care professionals, patients and regulators
  - obscured class effects and difficulty tracking worldwide PV
  - potential medication errors
  - a pseudo-proprietary naming system, undermining the value of the entire INN naming system globally
  - a situation in which non-comparable products in less regulated countries will carry the same INN and highly similar products in highly regulated countries will carry a different INN

EGA's Recommendation: Maintain Current INN System

- The development of a biosimilar product is targeted to match the reference medicinal product through the application of state-of-the-art science and technology in head-to-head studies
- Regulatory authorities have the expertise and the data to make the judgment of whether comparability/similarity has been demonstrated between a biosimilar and its reference product
  - If comparability is achieved, the product is a biosimilar and will be designated with the same INN
  - If not, the product is not a biosimilar, and application for a different INN will need to be submitted to WHO
- Same INN for biosimilars **helps to improve the understanding of the biosimilar concept:** demonstrated high similarity allows biosimilar to refer to safety and efficacy of the originator reference product

Ways Forward to Ensure Patients' Safety Worldwide

- Expand the common practice of systematic recording of brand names of all biologics prescribed, dispensed or sold
- Develop further methods to facilitate reporting and retrieval of batch numbers worldwide
- Further educate patients and healthcare professionals on biologics in general
- Support WHO in rolling out worldwide the scientific principles outlined in the WHO guidance for evaluation of similar biotherapeutic products (SBP) and establishment or improvement of national PV systems worldwide
- **Shared ambition: access for patients to high quality biopharmaceuticals worldwide**