NAMING OF BIOLOGICS

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Financial support to participate of meetings and give conferences to Pfizer, Roche, MSD, BMS, Merck Serono and Janssen and Novartis.
SUMMARY
Introduction
Why a Distinguishable Identifier is needed for All Biologics - including Biosimilars
Distinguishable Identifiers and Biosimilars Naming Systems
Concluding Remarks
INTRODUCTION

• Concept of one single non-proprietary name
• World Health Assembly Resolution WHA3.11
• More than 10,000 applications.
• Drug regulation, prescribing, dispensing, pharmacopoeias, labelling, pharmacovigilance and in scientific literature.
HOW TO BUILD AN INN

• Unusual word
• Fantasy prefix (two or more syllables)

Followed by a stem suffix - indicate chemical or pharmacological group or substems to refine.

• **Alvelestat.** Suffix stat - enzyme inhibitor
• ele - subclasse of inhibitors
• alv - fantasy - unique substance
Anib - angiogenesis inhibitors (e.g. pazonib)
Anserin - serotonin receptor antagonists (e.g. ritanserin and mianserin)
Ase - enzymes (e.g. asparaginase)
Azepam - benzodiazepines (e.g. diazepam and oxazepam)
Cain - class I antiarrhythmics (e.g. procainamide)
Mab - monoclonal antibodies
1. 11 general policies for specific classes of biological and biotechnological substances
2. Non-glycosililated products - filgrastim
3. Glycosylated products - epoetin (alpha, beta, zeta, ...)
4. Monoclonal antibodies - fantasy prefix, substem 1 indicate the biological target (tu, li), substem 2(xi, zu, u,) suffix mab
Benefits of Distinguishable Nonproprietary Names for Biotherapeutics

• **Enhances effective adverse events reporting**¹,²
  – Promote effective pharmacovigilance by increasing accuracy of adverse event reporting and potential corrective actions³,⁴

• **Increases accurate prescribing**³,⁴
  – Increase transparency of dispensed product to patients
  – Enhance control of physicians to make prescribing decision
  – Minimize risk of inappropriate, involuntary or automatic substitution

# Biosimilars Are Different from Generics

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<thead>
<tr>
<th><strong>Generic Drugs</strong></th>
<th><strong>Biosimilars</strong></th>
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<tr>
<td>Active ingredient chemically identical to branded counterpart(^1,)(^5)</td>
<td>Active ingredient highly similar to reference biologic medicine(^6)</td>
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<td>Can be copied and manufacturing is less sensitive to process changes(^2)</td>
<td>Impossible to fully copy because of different host cell line and sensitivity to manufacturing process differences(^6)</td>
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<td>Registration requires only analytical/CMC and PK bioequivalence studies(^3)</td>
<td>Abbreviated registration pathway with extensive comparative analytical/CMC data and PK/PD and clinical data to demonstrate similarity(^6)</td>
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<td>Naming processes still largely under discussion with many biosimilars and reference biologics sharing same non-proprietary name(^7)</td>
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<td>Granting of a Market Authorization for a biosimilar does not imply interchangeability or substitutability with its reference(^8,)(^9)</td>
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- CMC, chemistry, manufacturing and controls; PK, pharmacokinetic; PD, pharmacodynamic
Global Positions on Identical vs. Distinguishable Nonproprietary Names for Biopharmaceuticals

**WHO committee draft proposal:** distinguishable Biologic Qualifier appended to INN. Final guidance is pending.

**Canada**
INNs are used, when they exist. Awaiting WHO final decision.

**USA**
FDA has not provided guidance. Recent decisions used pre-fix (tbo-filgrastim, ziv-aflibercept).

**EC/EMA**
Does not support distinguishable INNs. EMA encourages prescribing by brand name, eg, infliximab biosimilar (Remsima) given same INN as innovator.

**Japan**
Mandates Biologic qualifier: Safety Bureau mandates to specify a follow-on biologic, the nonproprietary and brand names should be readily distinguishable.

**Brazil**
Biosimilar guidance does not address naming.

**Australia**
Supports distinguishable nonproprietary names but pending WHO’s official recommendation once issued, “…In the interim biosimilars will use the Australian biologic name without a specific biosimilar identifier suffix, for example a biosimilar to the reference product Neupogen filgrastim would be named ‘TRADE NAME’ filgrastim”.

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WHO, World Health Organization; FDA, Food and Drug Administration; EMA, European Medicines Agency

1. CDER Zaltrap application summary: Accessed August 1, 2013; 2. FDA Week vol. 18, No 36, September 7, 2012;
Latin America Biosimilars Regulatory State of Play: Naming

Mexico – regulations finalized 11/2014; details requirements for biologic and biosimilar registration – developing individual product guidelines

Colombia - issued decree in 10/2014 creating “3rd pathway”; now working on implementing regulations, including immunogenicity guidelines

Argentina – has regulations in place as of 11/2011 and 6/2012

Brazil – regulations in place as of 12/2010; has 3rd/individual development pathway – has not been used to date

Central America & Caribbean - Panama - purportedly interested in adopting Colombia style 3rd pathway; no biosimilars specific regulations

Dominican Republic - Regulations under development

Guatemala - legislation in place as of 11/2011

Costa Rica - regulations in place as of 3/2012

Paraguay - has regulation in place as of January 2015

Uruguay - has regulation in place as of January 2015

Venezuela – draft biotherapeutics regulations published for comment, 2nd draft in preparation

Many LA countries have developed guidelines for biosimilars, but none have yet addressed the issue of international nonproprietary naming (INN) (as of Dec 2014)

Peru – draft regulations out for public comment as of 11/2014

Bolivia – working on guidance

Chile – regulations in place as of 9/2014

Ecuador – no biosimilar specific regulations in place

Argentina – has regulations in place as of 11/2011 and 6/2012

Disposición 3397/2012 for biologic products; Disposición 7729/2011 for biosimilar drugs; Brazil: (citation needed); Colombia: Decree 1782 of 2014; Mexico: NOM 257 and NOM 177; Chile: NORMA 170 September 6, 2014; Costa Rica: Reglamento Tecnico RTCR 440:2010; Ecuador: Reglamento para la Obtencion del Registro Sanitario, Control y Vigilancia de Medicamentos Biologicos para Uso y Consumo Humano issued on May 17, 2013 (Chapter VII); Formulario de requisitos que se deben adjuntar para el registro sanitario de medicamentos biologicos extranjeros en general y por homologacion (august 8, 2013); Guatemala: Ley 4245; Paraguay : Resolucion S.G. 003 (January 16, 2015); Uruguay: Registro de Medicamentos Biotecnologicos (January 27, 2015)
More than 50 years ago, WHO established the International Nonproprietary Name (INN) Expert Group:
- Mission: To assign a unique nonproprietary name to medicinal substances, so that they could be recognized globally
- 2012-2014: The WHO reported that the current INN system for biologics was ‘not satisfactory’. New naming approaches for biologics are under consideration

Current WHO INN program does not oblige a company to apply for an INN
- In some cases different authorities have assigned different nonproprietary names for the same biologic based on different naming policies
- =>Naming of biosimilars should be addressed globally and soon while the number of registered biosimilars remains relatively small

WHO, World Health Organization

1. 55th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 16-18 October 2012 Executive Summary;
4. WHO Drug Information 19(2) 2005 http://apps.who.int/medicinedocs/pdf/s7917e/s7917e.pdf;
Biotherapeutics Naming & Traceability

Summary

• Due to their unique product characteristics and prescribing practices, all biotherapeutics require comprehensive PV guidance and systems\(^1\)

• Pre-approval strategies to avoid confusing new drug names, whether branded or nonproprietary, are the most effective\(^2\)

• Distinguishable identifiers for innovator biologics and biosimilars will increase transparency and reporting

• Unique INNs for all biotherapeutics, innovator biologics and biosimilars, will promote patient transparency, safety and efficacy\(^3\)

PV, pharmacovigilance; INN, international nonproprietary name

1. Discussion Topics for FDA’s Public Workshop Determination of System Attributes for Tracking and Tracing of Prescription Drugs Feb 15-16, 2011;
WHY A DISTINGUISHABLE IDENTIFIER IS NEEDED FOR ALL BIOLOGICS - INCLUDING BIOSIMILARs

Accurate Prescribing
Effective Reporting
Tracking and Traceability

Substitution may complicate effective pharmacovigilance:

- If physicians are not informed, it may subvert the ability to attribute adverse events to the appropriate agent\(^1\)
- If the onset of the adverse reaction is delayed: Some adverse reactions, including immunogenic reactions such as pure red cell aplasia (PRCA), may develop only after several months of treatment\(^2\)

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A biosimilar may be approved under the same INN as its reference product. Use of the INN alone may cause confusion.

A naming convention may be needed to distinguish biosimilar versions from one another and the originator.
Dr Juan, este paciente utiliza biosimilar o el original?
“Highly Similar” Biosimilarity Considerations for Clinical Practice/Open Debate

A biologic product may not be evaluated against more than ONE reference product\(^1\)

Will transitivity be applied in practice? If A=B and B=C, does A=C follow?

“Comparability studies are performed between a biosimilar and its reference product, but studies between one biosimilar and another are not done; two separate biosimilars may have been compared to the same reference but not between themselves.”\(^2\)

SBP, similar biologic product

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\(^1\) Biologics Price Competition and Innovation Act of 2010
\(^2\) WHO 56th Consultation on International Nonproprietary Names for Pharmaceutical Substances; Executive Summary Geneva, 15-17 April 2013
DISTINGUISHABLE IDENTIFIERS AND BIOSIMILARS NAMING SYSTEMS

Including World Health Organization (WHO) Distinguishable Nonproprietary Names
Biologic Qualifier (BQ) assigned to a biotherapeutic active substance manufactured at a specific site:
- If manufactured at more than one site, same BQ code applied to alternative sites authorized within the same regulatory jurisdiction

A 4-letter code is proposed:
- The code consists of four letters and each code issued will be assigned at random. The choice of letters used will be made to facilitate transliteration into various languages and to avoid meaningful or inappropriate words being used
- Example: Under the proposal, for a biologic such as epoetin alfa, the solution would be to use names such as “epoetin alfa bbbb” and “epoetin alfa cccc”
CONCLUDING REMARKS
Biotherapeutics Naming & Traceability

Summary

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• Pre-approval strategies to avoid confusing new drug names, whether branded or nonproprietary, are the most effective.²

• Distinguishable identifiers for innovator biologics and biosimilars will increase transparency and reporting.

• Unique INNs for all biotherapeutics, innovator biologics and biosimilars, will promote patient transparency, safety, and efficacy.³

▶ PV, pharmacovigilance; INN, international nonproprietary name

Thank you!