First Latin American Educational Workshop on
Similar Biotherapeutic Products

20 January 2015, Sheraton Maria Isabel Hotel & Towers, Mexico City, Mexico

James S Robertson, PhD, UK

- Member and Rapporteur of the WHO INN Expert Committee
- Previously of NIBSC, UK (now retired)

GaBI Educational Workshops

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The challenges of nomenclature – INN, biosimilars and biological qualifiers

James S Robertson, PhD

20 January 2015

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

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Disclaimer

Any opinions or views expressed in this presentation are those of Dr Robertson and are not to be construed as representing the policies of the WHO or the

WHO INN Programme

International Non-proprietary Names
- INN -

Provides one single name worldwide for active pharmaceutical substances

- Established in 1950 by WHO by resolution WHA3.11, operational since 1953
- Intended for use in: drug regulation, prescribing, pharmacopoeias, labeling, pharmacovigilance, scientific literature
- WIPO/Trademark Offices
- Customs & Excise

Structure of the INN

- Fantasy prefix + stem/appropriate suffix
- Stems indicate chemical and/or pharmacological group relationship; substems may also be used

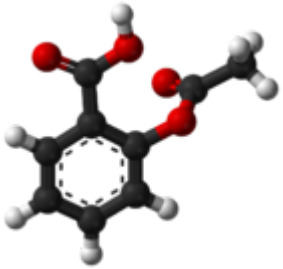
  e.g. *alvelestat*

  alv – ele - stat

  fantasy prefix – elastase inhibitors - enzyme inhibitors
- INNs and stems have protection within trade mark arena
- 'Stems' book

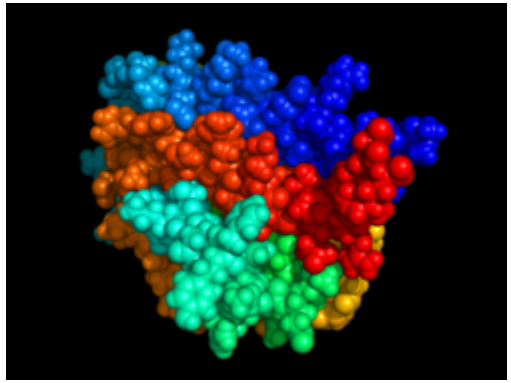
The Biologicals Challenge

- Increased complexity of biological substances versus chemical drugs
- Micro-heterogeneity
- The need for new naming schemes or policies



Aspirin

MW 180 D



Erythropoietin

MW 34,000 D

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DRAFT

World Health Organization

INN Working Document 05.179.
Distr. :RESTRICTED
ENGLISH ONLY
10/11/2005

INN FOR BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES

(A REVIEW)

Programme on International Nonproprietary Names (INN)
Quality Assurance and Safety: Medicines (QSM)
Medicines Policy and Standards (PSM) Department

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General policies

- **Non-glycosylated proteins**

Identification of the group with a stem(substem) and the specific amino acid sequence by a random prefix,

e.g. *fil - gra - stim* = *filgrastim*

- **Glycosylated proteins**

Differences in the glycosylation pattern represented by a Greek letter second word spelled out in full,

e.g. *epoetin alfa, beta, etc.*

- **Monoclonal antibodies**

INN for monoclonal antibodies are composed of a prefix, substem 1, substem 2 and suffix/stem,

e.g. ri – tu – xi – mab = rituximab

SBP Nomenclature

- **SBP, biosimilar, follow-on, subsequent entry, biogeneric, me-too, non-innovator biologic**
- All terms used interchangeably with 'biosimilar' even where no comparability exercise (as per EU/WHO biosimilar guidelines)
  - causes confusion
  - is a potential concern for patient safety and efficacy
  - can lead to misconceptions in published reports on apparent problems with "biosimilars"
- Are all 'biosimilars' really biosimilar?

References

- Terminology for biosimilars – a confusing minefield

  Thorpe and Wadhwa, GaBI Journal 2012;1:132-4

- Biosimilars – why terminology matters

  Weise et al., Nature Biotechnology 2011;29:690-3

  - Biosimilar
  - Me-too biologic, Innovator Biologic
  - Second/Next Generation Biologic, Biobetter

Biosimilars and INN

- There is no INN policy for biosimilars
- Biosimilar licensure is a regulatory procedure
- INN Group may not be aware of licensure pathway
- INN Group does not receive information submitted in registration dossiers
- Decisions on INN have to be made before full information on substance is available

For non-glycosylated proteins

- non-glycosylated proteins can follow approach for small molecular generics
- following the first INN assignment, no further applications are made
- *somatropin*
  - multiple innovator products all use the same INN
  - biosimilars / follow-ons use the same INN
- *filgrastim*
  - all biosimilars use the same INN as the original product

For glycosylated proteins

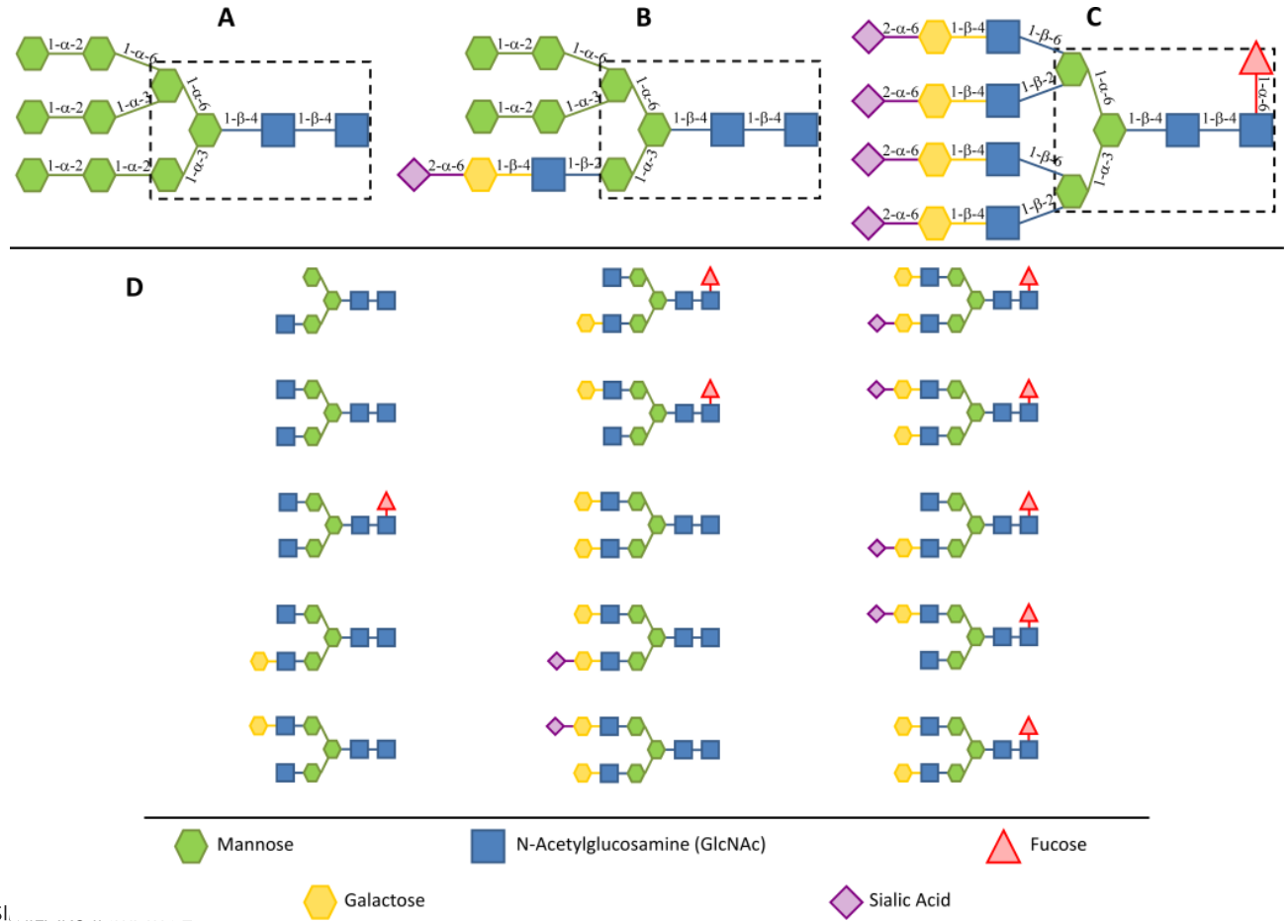
- Glycosylated proteins from different sources are expected to differ in their glycoform profile and so are given distinct names (new Greek letter)
- Whether

  biosimilar, *subsequent entry*, *follow-on*, or

  stand-alone registration,

  all should follow the Greek letter rule
- An INN will only be provided if applied for

Glycoforms and Greek letters



Assignment of Greek letters

- Glycoform profile is dependent on:
  - expression system
  - fermentation conditions
  - downstream processing
- Where glycosylation is different, or not stated,
  - a different Greek letter will be assigned
- But, *how different is different?*
- Glycoform differences may occur as a result of manufacturing changes
  - but no change in previously assigned Greek letter

Greek letter complications

- Janssen-Cilag's EPO (Eprex®) got the INN *epoetin alfa*
  this was an innovator stand-alone registration (in EU)
- EPO biosimilar HX575 (Sandoz) adopted the INN *epoetin alfa* of its reference product Eprex®, despite a distinct glycoform profile
- In Australia, the TGA reacted to the distinct glycosylation of HX575 and gave it the ABN non-proprietary name *epoetin lambda*!
  - ➢ Single product, different (INN/ABN) non-proprietary names
- Other EPOs, correctly, have further Greek letters
  epoetin zeta, biosimilar to *epoetin alfa*
  epoetin theta, stand-alone EPO (*epoetin beta* as comparator)
- Interferons alfa, beta, gamma, are an exception

INN and pharmacovigilance

- A strong and reliable pharmacovigilance and post-authorization risk management system cannot rely solely on the INN
- Reporting of adverse events should (also) involve
  - product/brand name
  - manufacturer
  - batch or lot number

Alliance for Safe Biologic Medicines 2013 EU physicians survey

Reporting AE's

- 17% report only INN
- 29% report only brand name
- 54% report both

Recording batch number

- 27% never
- 33% sometimes
- 40% always

Dolinar RO, Reilly MS. Generics and Biosimilars Initiative Journal (GaBI Journal). 20143;3(2):58-62.
doi: 10.5639/gabij.2014.0302.018

Non-global SBP Nomenclature

Individual countries creating their own non-proprietary schemes

- TGA (Australia) plan to add a 2nd word *sim-* plus an extra single syllable unique to each SBP
- JAN (Japan) INN followed by the [name of the reference substance + BS 1]
- FDA (USA) has given short prefixes to three standalone biologics – *tbo-filgrastim*, *ziv-aflibercept* and *ado-trastuzumab emtansine*

Proposal for Assignment of Biological Qualifiers (BQ)

Draft – July 2014

- Being established at the request of regulatory authorities for a global system
- To provide a unique identifier for all biological substances that are assigned INN
- Will not be part of the INN
- Can be used for identification, prescribing, dispensing and pharmacovigilance

The Draft BQ Scheme

- **NOT** part of the INN
- Voluntary
- Applicable to ALL biological substances
- Uniquely identifies manufacturer / manufacturing site
- Overseen by WHO INN Expert Group
- Administered by WHO INN Secretariat

The BQ code

- 4 letters generated randomly
- avoid vowels, to avoid inappropriate words
- generate circa 160,000 codes

Value of the BQ

- Physicians and nursing staff
- Pharmacists
- Regulatory authorities
- Health authorities
- Patients

The BQ

- An entirely new global nomenclature scheme for biologics
- Who will use it ?
- What advantages has it over existing nomenclature and traceability systems ?

  i.e. INN, brand name/trade-name, company name, national drug code (US)