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GaBI Educational Workshops

First Turkish Interactive Workshop on Regulation and Approval of
SIMILAR BIOTHERAPEUTIC PRODUCTS/BIOSIMILARS

2–3 March 2016, Hacettepe University, Ankara, Turkey

The challenges of nomenclature – INN, biosimilars and biological qualifiers

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

HACETTEPE UNIVERSITY
PPCI Pro Pharma Communications International

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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

INN

The basics

International Non-proprietary Names

- INN -

- 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 Offices

Provides one single name worldwide for active pharmaceutical substances

Structure of the INN

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

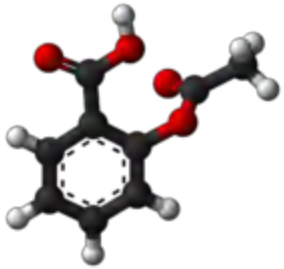
  e.g. *alvelestat*

  alv - ele - stat

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

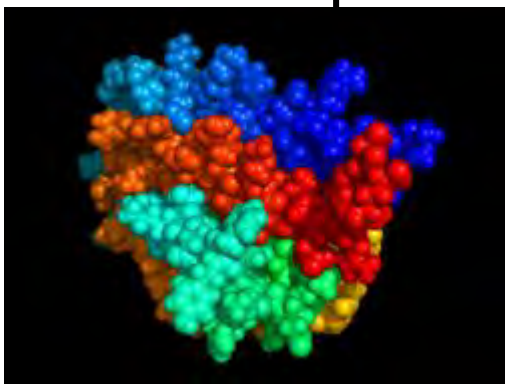
The Biologicals Challenge

- 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

WHO/EMP/RHT/TSN/2014.1

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

INN

for ‘generics’

Off-patent drug copies

Chemical drugs

- exact copies
- termed '**generics**'
- same INN is used

Biological drugs

- not quite exact copies, so 'generic' not suitable
- terminology varies

Biologicals nomenclature

- **SBP, biosimilar, follow-on, subsequent entry, biogeneric, me-too, non-innovator biologic**
- SBP/biosimilar refers to a specific regulatory licensing procedure
- 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”

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 protein 'copies'

- 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

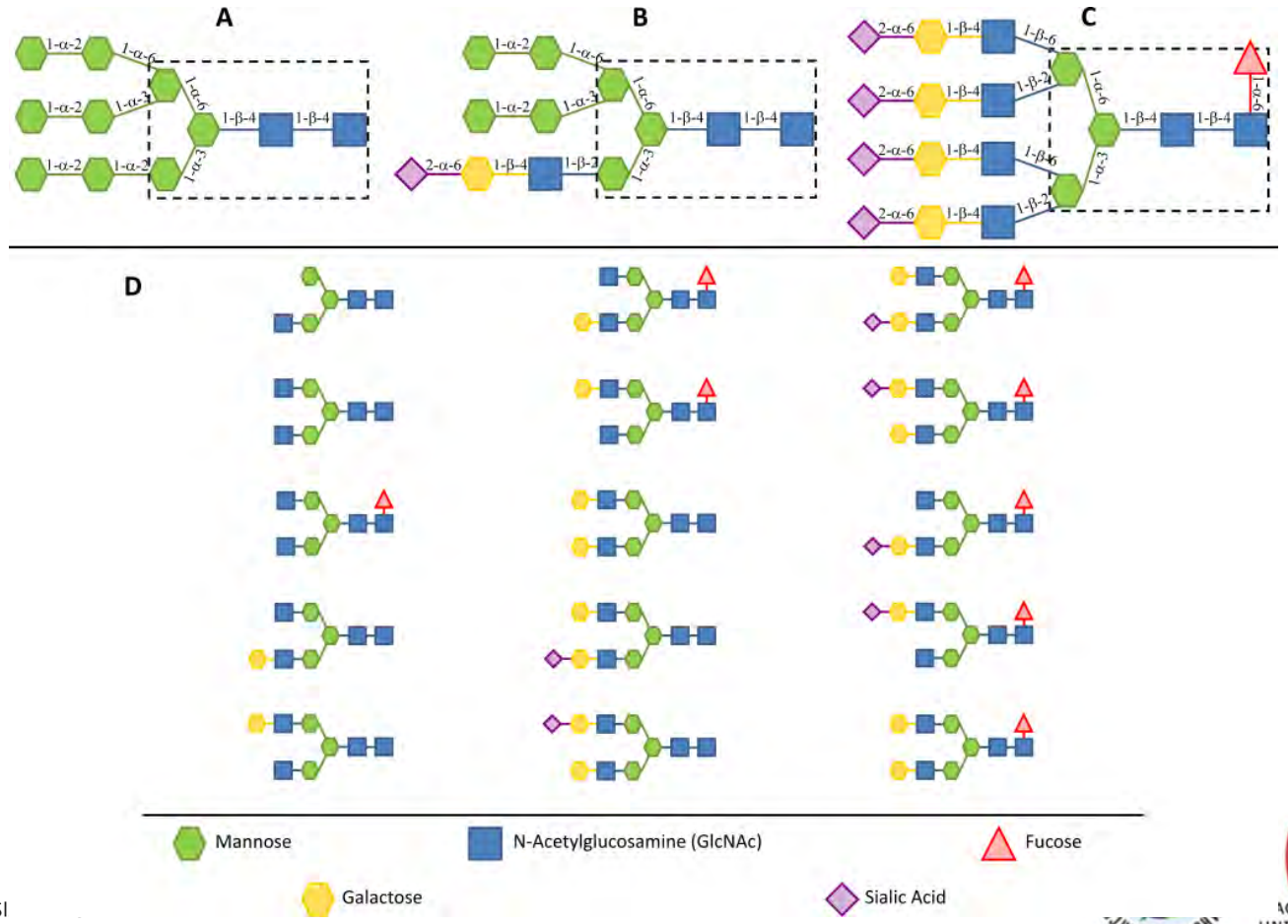
For glycosylated protein 'copies'

Glycoform profile is dependent on:

- expression system
- fermentation conditions
- downstream processing

➢ Glycosylated proteins from different sources are expected to differ in their glycoform profile and so are given distinct names (a novel Greek letter suffix)

Glycoforms


A
B
C
D
Mannose
N-Acetylglucosamine (GlcNAc)
Fucose
Galactose
Sialic Acid

The Greek letter rule

Where glycosylation is different, or not stated:

- a different Greek letter suffix will be assigned,
- this is regardless of whether they follow a *biosimilar*, *subsequent entry*, *follow-on*, or *stand-alone* registration
- all should follow the 'Greek letter rule'

But, *how different is different?*

Note: 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 *epoein 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

Non-global vs. global nomenclature for SBPs

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 (e.g. *simxxx*)
- **JAN** (Japan) INN followed by [INN of the reference substance, Biosimilar 1]
- **FDA** (USA) has draft guidance for industry on how biological products should be named (more later)

WHO Proposal for Assignment of a Global **Biological Qualifier – the 'BQ'**

- established at the request of regulatory authorities for a global system
- to provide a unique identifier for **ALL** biological drug substances that are assigned INN
- will **NOT** be part of the INN
- can be used for identification, prescribing, dispensing, pharmacovigilance, and to aid transfer of prescriptions globally

What gets a BQ?

- A BQ is provided for a single biological drug substance manufactured by a single process controlled by the same quality system at each manufacturing site globally
- The Applicant is foreseen to be the corporate body that makes or manages the making of the drug substance
- The Applicant allows use of the BQ globally by all marketing authorisation holders (MAH) distributing products that contain the drug substance

The BQ identifier

- 4 letters generated randomly
- avoid vowels, to avoid inappropriate words
- generate circa 160,000 codes
- optional 2 digit checksum
- Example **bcdf** *or* **bcdf12** *or* **bc12df**

Obtaining a BQ

- Use of the BQ scheme by national regulatory authorities is voluntary
- Application is made to the WHO INN Secretariat by the BQ applicant at the time of submission of a marketing authorisation application to a regulatory authority.
- The assigned BQ code is immediately provided by the WHO to the applicant through an automated online system
- A fee is payable so that the scheme is self-funding

Information to be submitted

- Name and address of Applicant
- The INN
- Intended trade name(s) of product(s) in all relevant jurisdictions
- Name(s) and address(es) of Marketing Authorisation Holder(s) (MAH) for which the code is requested and jurisdictions for which they are responsible
- Name and address of relevant manufacturing site(s)
- Regulatory information: relevant regulatory authority, nature of the marketing authorisation (e.g., biosimilar within a named jurisdiction, stand-alone within another named jurisdiction), INN, where and when the substance has been authorised, tradename(s}

Access to the BQ database

- A secure BQ database will be held by the WHO Secretariat
- Access limited to:
  - Security approved WHO staff
  - NRAs, but *read-only* access
  - BQ applicant (own application)
  - information already in public domain freely accessible

FDA (USA) proposal for biologicals

- In August 2015, FDA issued draft guidance for industry on how biological products should be named
- the non-proprietary names should include a core name - the USAN - with a suffix composed of *four lower case letters*, joined to the USAN with a hyphen
- four letter suffix should be devoid of meaning although FDA has invited public comment on alternative formats
- Also, a proposed rule for 6 previously licensed biologics

The BQ scheme

- An entirely new global voluntary nomenclature scheme for biological drug substances
- Adopted by the INN Expert Group at the 61st INN Consultation, Oct 2015
- WHO undertaking an *impact assessment* prior to any implementation
- BQ proposal and FAQ on WHO website

References

- **Biosimilars – why terminology matters**

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

- **Terminology for biosimilars – a confusing minefield**

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

- **The challenges of nomenclature – INN, biosimilars and biological qualifiers**

  Robertson, GaBI Journal 2015;4:1-3

Web links

- **BioReview**: http://www.who.int/medicines/services/inn/BioRev2014.pdf?ua=1
- **BQ proposal**: http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1
- **BQ FAQ**: http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_FAQ_2015.pdf?ua=1