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The challenges of nomenclature – INN, biosimilars and biological qualifiers

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Disclaimer

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

GaBI Educational Workshops

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

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
Biologics 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)

Galactose

Sialic Acid

Fucose
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 2\textsuperscript{nd} 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 61\textsuperscript{st} INN Consultation, Oct 2015
• WHO undertaking an \textit{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