

INN for Biosimilars

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# The challenges of nomenclature – INN, biosimilars and biological qualifiers

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A novel global and company specific biological qualifier distinct from the International Nonproprietary Name (INN) is proposed by World Health Organization (WHO) for a biological active substances.

**Keywords:** Biological active substances, biological qualifier, biosimilars, international non-proprietary names

## Introduction to INN

The concept of one single non-proprietary name to be used worldwide for active pharmaceutical substances was established by the World Health Organization (WHO) in 1950, by World Health Assembly Resolution WHA3.11 and became operational in 1953. Since then, there have been more than 10,000 applications for an international non-proprietary name, or INN, as they are commonly called. INNs are intended for use in drug regulation, prescribing, dispensing, pharmacopoeias, labelling, pharmacovigilance and in scientific literature. They are also used by the World Intellectual Property Organization (WIPO), Trademark offices, and Customs and Excise agencies, including the World Customs Organization (WCO).

An INN itself often is an unusual word; this is because the name has information regarding the active substance it represents built into it. Typically, the name begins with a fantasy prefix of one, two or more syllables, followed by a stem suffix. Stems indicate chemical and/or pharmacological relationships and substems that further refine the relationship may be used. Stems do not necessarily exist for every conceivable pharmacological group and when an INN is requested for a new class of drug, a novel suffix is determined which may or may not become established as a stem at a later date. Take the INN *alvelestat* as an example. From the end of the name moving forwards, it is constructed as

follows: the suffix *-stat* is indicative of an enzyme inhibitor, the middle part *-ele-* is a substem indicating a subclass of inhibitors, in this case elastase inhibitors, whilst the prefix *alv-* is the fantasy part that identifies the unique substance represented by the INN. INN and stems have protection within the trademark arena and a list of current stems and substems is issued by WHO [1]. To avoid confusion, which could jeopardize the safety of patients, trademarks should neither be derived from INNs nor contain common stems used in INNs. In contrast to the INN, which is global, non-proprietary, not owned by anyone (including the INN applicant) and applied to the drug substance, medicines usually will also have a company-specific name – the trade name or brand name – that tends to be region-specific, not global, is owned by the company and is applied to the drug product.

## INN for biological medicines

Increasingly, INNs are being requested for complex biological drugs. Biological medicinal products are of increased molecular complexity compared to chemical drugs, including structural microheterogeneity. For biological drugs there has been a need, not only for new stems but for new naming schemes and policies. These new schemes are provided in the WHO publication 'INN for Biological and Biotechnological Substances (A review)' which is updated regularly and available on the WHO website [2].

Currently, there are 11 general policies for specific classes of biological and biotechnological substances. Three particular policies are relevant for this paper – policies for non-glycosylated compounds, for glycosylated compounds and for monoclonal antibodies. For non-glycosylated compounds and specifically non-glycosylated proteins, the naming format is similar to that mentioned above for INN in general, that is identification of the pharmacological group with a stem/substem whilst the specific amino acid sequence, i.e. structure of the protein, is indicated by the fantasy prefix. Thus, the constituent parts of the INN filgrastim are *-stim*, the stem for colony stimulating factors, *-gra-* a substem used specifically for granulocyte colony-stimulating factors, and the prefix *fil-* is a fantasy syllable indicating the specific amino acid sequence of this substance and in this case also the expression system used (bacterial).

For glycosylated proteins, in addition to the naming policy applied to non-glycosylated proteins, differences in the glycosylation (or glycoform) pattern are represented by a Greek letter second word, spelled out in full; for example, there are now nine distinct *epoetin* INN with the second word Greek letters *alfa*, *beta*, *delta*, *gamma*, *epsilon*, *kappa*, *omega*, *theta* and *zeta*, all having the same amino acid sequence for the protein but possibly differing in their glycosylation profile.

INN for monoclonal antibodies (mAbs) are typically composed of a fantasy prefix, substem 1 to indicate the biological target of the mAb, for example, *-t(u)-* for tumour targeting mAbs, and *-li-* for immunomodulating mAbs; substem 2 to indicate

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the type or origin of the mAb, for example, *-u-* to indicate a human derived mAb, and *-xi-* to indicate a mAb of chimeric origin; and finally the suffix/stem *-mab* to indicate that it is a monoclonal antibody. Thus, a monoclonal antibody ending in *-tuximab* would be tumour targeting and of chimeric origin.

## Biosimilars and INN

Whilst identical copies of a particular chemical drug are known as generics, the name has not been applied to copies of biological drugs because of the high level of complexity and heterogeneity in their structure such that one manufacturer's biological drug will not necessarily be fully identical to the same substance from another manufacturer. Instead of the name 'generic' a variety of terms has been used including similar biological product (SBP), biosimilar, follow-on product, subsequent entry biologic, me-too, and non-innovator biologic, with no global consensus. All terms tend to be used interchangeably, with 'biosimilar' probably being the most common. However, the term biosimilar was originally coined specifically for biological products that have been licensed via a regulatory pathway in which full quality and specific and usually abbreviated non-clinical and clinical studies have demonstrated the product to have a similar quality, safety and efficacy profile to an already licensed reference product, with the reference product itself having been licensed following a full assessment of quality, safety and efficacy, for example, see WHO and European Union (EU) biosimilar guidelines [3, 4]. The frequent but inconsistent and improper use of the term 'biosimilar', and other terms, for products where there has been no comparability regulatory exercise causes confusion, is a potential concern for patient safety and efficacy, and can lead to misconceptions in published reports on apparent problems with 'biosimilars' [5, 6].

In recent years, there has been debate and mounting concern as to what INN should be given to biosimilars. This reveals a further issue and miscomprehension with biosimilar nomenclature because WHO has no policy on how to name a biosimilar. The concept of biosimilarity is a regulatory procedure and INN are not assigned on the basis of how a medicinal product achieves licensure. Indeed, at the time of an INN application, it is usually not known to the INN Expert Group\* what regulatory

pathway will ultimately be followed for licensure of the substance. Furthermore, the INN Expert Group does not receive and is not privy to the vast amount of information submitted in registration dossiers; the amount of data submitted in support of a new INN is quite scant and decisions on INN assignment have to be made before full quality, non-clinical and clinical information on the substance is derived.

INN for non-glycosylated proteins follow the approach for small molecule drugs in that following the first INN assignment for a particular amino acid sequence, no further applications are made. For example, for *somatropin*, a growth hormone derivative, multiple innovator and biosimilar *somatropins* all use the same INN.

The glycoform profile of a glycosylated protein is dependent on the expression system used to manufacture the protein, the fermentation conditions and potentially also on downstream processing. For an INN application for a glycoprotein, where glycosylation is stated to be different, or where no statement is made regarding glycosylation, the INN Expert Group assumes it to be different, and so a new Greek letter second word is assigned. Regardless of whether a glycoprotein is (eventually) subject to a biosimilar, subsequent entry, follow-on or a stand-alone registration process, assignment of the INN follows the above rule for glycoproteins. It is important to emphasize that the INN for a glycosylated protein reflects the structure and nature of the substance and is not influenced by the status or the pathway followed for its registration with a regulatory authority. Unfortunately, one issue remains and that is how to determine how different is 'different'. Interestingly, glycoform differences can occur as a result of manufacturing changes to an already licensed glycoprotein but this has not resulted in a change to a previously assigned Greek letter INN.

The Greek letter system has not been without its complications. Janssen-Cilag's erythropoietin (EPO) Eprex® had been assigned the INN *epoetin alfa*; this was subsequently licensed within the EU by an innovator stand-alone registration pathway. Despite a distinct glycosylation profile, the EPO biosimilar HX575 (from Sandoz) adopted the same INN of its reference product, *epoetin alfa*. In Australia, the Therapeutic Goods Administration (TGA) reacted to the distinct glycosylation profile of HX575

and assigned it the ABN non-proprietary name epoetin lambda. Thus, a single bi-therapeutic product has a regional non-proprietary INN-like name distinct from the INN used within the EU. Notwithstanding this particular situation, the Greek letter system in general works well.

## Pharmacovigilance and INN

A strong and reliable pharmacovigilance and post-authorization risk management system cannot rely solely on the INN. Reporting of adverse events should rely on other characteristics of a drug, such as the brand name of the product, the manufacturer and the batch or lot number as well as the INN. However, a survey of adverse event reporting by physicians in the EU, conducted by the Alliance for Safe Biologic Medicines in 2013, found that 17%, or one in six physicians, still reported only the INN and only slightly over half reported both the INN and the brand name [7]. Also, slightly over 25% of physicians never reported the batch number whilst only 40% always included the batch number in adverse event reports.

## Regional nomenclature schemes

Individual regulatory regions are starting to create their own non-proprietary nomenclature schemes for biosimilars. The TGA in Australia plan to add a second word comprising the prefix *sim-* followed by a fantasy single syllable to each biosimilar. The Japanese Accepted Name (JAN) for biosimilars uses the INN followed (in parentheses) by the name of the reference substance + BS1, BS2, etc. In the US, FDA has given short prefixes to three stand-alone registered biologics – *tbo-filgrastim*, *ziv-aflibercept* and *ado-trastuzumab emtansine*. For at least the latter product, this was done for safety reasons to distinguish it from the non-conjugated mAb *trastuzumab*, which itself is a registered drug with a differing dosage profile.

## Biological qualifiers

In the face of regional development of nomenclature schemes for biosimilars, and at the request of some regulatory authorities, WHO has proposed the development of a global biological qualifier (BQ) for biological medicines. This would provide a unique identifier for all biological active substances that are assigned an INN; but whereas the INN is a common and public non-proprietary name for a given active substance, the BQ would be applied to a particular manufacturer's

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active substance. The BQ would not be part of the INN and it is envisaged that it would enhance identification, prescribing, dispensing and pharmacovigilance of biological medicines.

A draft scheme for such a BQ was published on the WHO website in July 2014 with comments requested from stakeholders by 19 September 2015 [8]. It emphasized that the BQ would not be part of the INN, would be a voluntary scheme, would be applicable to all biological substances, would uniquely identify the manufacturer or the manufacturing site, would be overseen by the WHO INN Expert Group and would be administered by the WHO INN Secretariat. It was proposed that the qualifier itself would consist of a four-letter code generated randomly and would avoid vowels to avoid inappropriate words; this would have the capacity to generate 160,000 unique codes. The draft scheme highlighted that the BQ would be valuable for physicians and nursing staff, pharmacists, regulatory authorities, health authorities and patients.

The Executive Summary of the 59th INN Consultation held 14–16 October 2014 provides feedback from stakeholders on the draft BQ scheme [9]. Over 100 comments were received from a mix of stakeholders, with opinions being expressed both for and against the proposal. Overall it appeared that two-thirds of commentators including those in industry, academics and patient groups expressed some level of agreement. Pharmacist associations were noted as generally not being in favour. The Summary further noted that negative comments appeared to arise from misunderstandings, with a particular area of confusion being the role of the BQ.

A revised draft of the BQ proposal was posted on the WHO/INN website in June 2015 [10]. The new draft emphasises that the BQ is to be applied to all biological active substances that can be assigned INN and not just to biosimilars. A major change in the revised scheme is that the original proposal to apply the BQ to a specific manufacturing site has been withdrawn and instead the BQ applicant *'is foreseen to be a corporate body that makes or manages the making of a single substance by a single process controlled by the same quality substance globally'*. Thus, an active substance manufactured at more than one site *(by a single process controlled by the same quality substance*

*globally)* will have the same BQ as long as the substance from the different sites is deemed comparable by the regulatory authority(ies) involved. In the event that they are not deemed comparable, a separate BQ would be applied, but the two BQs would be hyperlinked in the WHO BQ database. The nature of the code – a random four-letter code – remains the same, whilst useful tables illustrating how a hypothetical BQ would apply are provided in the updated proposal.

In summary, this proposal would be an entirely new global nomenclature scheme for biological active substances. Will it be used, and by whom? Does it have advantages over existing nomenclature and traceability systems including the INN, the brand name/trade name, the company name, lot or batch numbers, and in the US the national drug code? Whilst there has been good support for the BQ, not all organizations are in favour of it [11]. WHO held a Biological Qualifier Regulatory Forum on 30 March 2015 and a Front Page Meeting with INN Stakeholders on 16 June 2015. Clearly, there is continuing debate over the need for and the format of a novel global BQ.

**\*Author's note**

The INN process is organized and administered at WHO by the INN Secretariat; the INN Expert Group comprises an international group of experts in drugs and drug nomenclature and is responsible for the assignment of INN and the development of INN policy.

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**Disclaimer**

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