

*Biological Qualifier
An INN Proposal*

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms (TSN)

Regulation of Medicines and other Health Technologies (RHT)

Essential Medicines and Health Products (EMP)

World Health Organization, Geneva

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**Proposal for
Assignment of Biological Qualifiers (BQ)**

Executive summary

Following requests from some drug regulatory authorities, the INN Expert Group recommended that WHO develop a system for assignment of Biological Qualifiers. After discussions among interested parties and approval by the INN Expert Group, to aid in the minimisation of errors in prescription, dispensing, pharmacovigilance and international transfer of prescriptions, a voluntary scheme is proposed by which an application can be made to the INN Secretariat for a Biological Qualifier (BQ). A BQ is a random alphabetic code assigned to a biological active substance on application by a BQ Applicant and used in medicines distributed by a Marketing Authorisation Holder (MAH). The scheme is applicable to all biological active substances (not just biosimilars) to which INNs are assigned and where possible may be applicable retrospectively. The BQ code will be issued by an automated online system. It will not be a constituent part of the INN, but an additional and independent element used in conjunction with the INN. All national and regional authorities are encouraged to use the BQ in conjunction with the product INN, as the availability of a single global scheme would better harmonise international pharmacovigilance efforts and will avoid proliferation of separate and distinct national qualifier systems.

The established procedure for the selection of INNs remains unchanged.

The scheme will be overseen by the WHO INN Expert Group and administered by the WHO INN Secretariat. It will be self-funding through payment of a single fee for each application. Administrative details of the scheme will be explained in due course.

Introduction and Background Information

Biological medicinal products are an increasingly important sector of therapeutic and prophylactic medicines. Biological active substances now comprise more than 40% of applications to the INN Programme and the percentage is increasing. By their nature biotechnological products are not composed of a single, pure substance, but are invariably complex, microheterogeneous mixtures of isoforms of the desired substance.

An INN is specific to a given defined substance regardless of the manufacturer and manufacturing site even though the profile of impurities may not be qualitatively or quantitatively the same. Biological substances are assigned INN by the general principles applicable to all INN and by a specific framework developed especially for them (*see INN for Biological and Biotechnological Substances (a review)-2013- INN Working Document 05.179*)

(<http://www.who.int/medicines/services/inn/BioRev2013.pdf>).

Glycosylated proteins present a more complex situation. The glycan structures are dependent on the nature of the production cell, the conditions of cellular culture and the methods employed in downstream processing. The structures exhibit microheterogeneity and are defined physicochemically by their glycoform profile. To distinguish between glycoform profiles that are known or likely to be distinct, the INN Programme introduced in 1991 a Greek letter second word as part of the INN so that different versions of a glycoprotein would have different INNs. The first part of

the INN is constant where the amino acid sequence is identical whilst the Greek letter is assigned in alphabetical sequence to indicate that the glycoform profile may differ qualitatively and/or quantitatively from other sources of the same glycoprotein. This approach has inadvertently given rise to some confusion because an INN request is generally based on limited structural information available at an early stage of development which is not, nor is it intended to be, as extensive as that found in an application for a marketing authorisation. Since participation in the INN procedure is voluntary, it has been assumed that an INN request for a glycoprotein that has already received an INN implies a known or expected difference in glycoform profile. Furthermore, assignment of a unique Greek letter does not, nor is it intended to, imply that the second or subsequent substance is comparable or not or licensed through a biosimilar regulatory process.

Further complexity in naming was added by the advent of ‘similar biotherapeutic products’ (also called biosimilars, follow-on products, subsequent entry biologics). These are usually licensed on the basis of a comprehensive comparability study between the biosimilar and a previously licensed equivalent, covering quality and limited, targeted safety and efficacy aspects, as outlined, for example, in the *WHO Guidelines on evaluation of similar biotherapeutic products (SPBs)/WHO Technical Report Series 977, Annex 2, WHO (2010)*. Nomenclature has been used to distinguish biosimilar from its reference product and other biosimilars. Some authorities use the INN of the reference substance alone, whereas others consider that a distinctive nonproprietary identifier should be given to each biosimilar. This has been achieved by adding a qualifier that is usually short and separate (for example in Australia and Japan), and in some cases incorporates or alludes to the company name (for example Japan and USA). Thus, at present, the same biological medicine can have different identifiers in different parts of the world.

The situation is further complicated because, before consensus emerged around the ideas expressed in the current proposal, some products were given “INN-like” names in different parts of the world. For example, an epoetin that is registered in Europe (European Medicines Agency/EMA) using the INN *epoetin alfa* was subsequently registered by Australia (Therapeutic Goods Administration/TGA) with the unofficial but INN-like nonproprietary name *epoetin lambda*. Under the proposal in this paper, the solution would be to use names such as “*epoetin alfa*” for more than one active substance distinguished by a four letter Biological Qualifier “bcdf” or “ghjk” where the name and qualifier could be used as well as the trade or invented name to identify drug products in drug compendia and for prescribing and dispensing records as in: “Eprex epoetin alfa bcdf 4000 I U/0.4 mL injection”.

To avoid proliferation of separate and distinct national qualifier systems, some drug regulatory authorities have requested the INN Programme to develop and administer a voluntary and global complementary nomenclature scheme applicable to biosimilars. The nomenclature of biosimilars was therefore reviewed at *ad hoc* meetings convened by WHO involving regulatory authorities, INN Experts and the INN Secretariat in April 2013, April 2014 and March 2015 and also by the INN Expert Group in October 2013 and April 2015. It was concluded that WHO should devise and operate a scheme, applicable prospectively and, where possible, retrospectively to all biological substances assigned INNs, that could be adopted on a voluntary basis by any regulatory authority and would be recognised globally. The INN Expert Group agreed that this would be a complementary nomenclature scheme that could prevent proliferation of different names and nomenclature policies.

It is acknowledged that the BQ will only be as useful as the breadth with which it is taken up globally, how widely it is recognised and its purpose understood by prescribers, dispensers, patients and those involved in pharmacovigilance. It is therefore necessary that as well as voluntary acceptance of the scheme, regulatory authorities and BQ Applicants should take appropriate steps to bring attention to and explain the existence and purpose of the BQ to these groups of people.

The Biological Qualifier (BQ) scheme

Purpose

This voluntary scheme is intended to provide a unique identification code (Biological Qualifier), distinct from the INN, for all biological substances that are assigned INNs in accordance with information given in the Bioreview (see page 3). While the scheme is intended to apply to as many biological medicines as possible, mechanisms to allow retrospective application are being investigated. Adoption of the BQ scheme is a voluntary decision of the individual regulatory authority. The BQ is used as an additional and independent element used in conjunction with the INN for a biological substance and it uniquely identifies the active substance in a biological product distributed by a MAH. Availability of the BQ scheme will avoid proliferation of separate and distinct schemes developed by individual regulatory authorities. The scheme is overseen by the WHO INN Expert Group and administered and operated by the WHO INN Secretariat. It is envisaged that the BQ will assist in the identification of biological substances for:

- prescription and dispensing of medicines;
- pharmacovigilance (in those jurisdictions requiring it); and
- transfer of prescriptions globally,

as detailed under Use of Biological Qualifiers.

Some regulatory authorities have made the decision that the use of trade name and INN are adequate for prescription and dispensing and that trade name, INN, MAH name and batch number are adequate for pharmacovigilance in conjunction with other tracking systems such as 2D barcoding. The use of the BQ offers a means (a) which uniquely identifies the drug substance even if used alone and/or (b) of crosschecking other information supplied in a prescription/dispensing or pharmacovigilance setting, in the absence of other sophisticated tracking systems.

The code

The code will consist of four random consonants and each code issued will be assigned to applicants at random by an automated online system. The choice of letters used will be made to facilitate transliteration into various languages and to avoid meaningful, trademarked or inappropriate words or acronyms being used. The use of four letters offers more than 160 000 codes (20^4) (vowels being excluded).

It is proposed that the BQ is issued for all drug substances of biological medicines including biosimilars, innovator products, non-glycosylated and glycosylated proteins. Only exceptions will be vaccines, impure mixtures and complex biologically-extracted products like heparin or pancreatin to which INNs are not assigned. The four letter code is expected to provide sufficient capacity and flexibility for the foreseeable future.

Who should apply for a BQ

The applicant for a BQ (termed 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. This body applies for a BQ for global use and allows its use for substance made in all manufacturing sites demonstrated to be comparable and by all manufacturing authorisation holders (MAH) distributing products which contain the substance. Should a regulatory authority find that a manufacturing site does **not** produce a comparable product, they may require application for a different BQ for that manufacturing site, but the two BQ's would be hyperlinked in the INN BQ database.

Application for a Biological Qualifier code

The application for a Biological Qualifier code is made to the WHO INN Secretariat at the time of submission of a marketing authorisation application to a regulatory authority, by the BQ Applicant. The assigned BQ code is immediately provided by the WHO to the BQ Applicant through an automated online system, who then provide it to the pertinent Marketing Authorization Holder (MAH) where the BQ applicant is not itself the MAH, or directly to regulatory authority/ authorities who have requested it where the BQ Applicant and MAH are one and the same. A fee for each application is payable so that the scheme is self-funding. No further fee is levied for processing updates to the information submitted for the BQ code. Consequently, the initial fee will be set taking this into consideration.

For situations wherein a previously licensed biological drug substance is to be assigned a BQ at the requirement of a regulatory authority, the same application procedure occurs with the immediate provision of a BQ through the automated online application system. The initial fee would also apply in this situation.

Information to be submitted in an application

All information submitted will be treated as confidential and not disclosed outside the WHO Secretariat except under the conditions described under 'The database of Biological Qualifiers and Access to Stakeholders', below. The application and data submitted in it will be held on a secure database at WHO that is operated only by WHO personnel.

The information to be submitted with the application includes:

- Name and address of BQ Applicant
- 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 the jurisdictions for which they are responsible
- Name and address of relevant manufacturing site(s) if different to above.
If an active substance is manufactured at more than one site, the active substance deriving from such alternative sites and associated with the same BQ Applicant responsible for the set of marketing authorisations for medicinal products will be given a single BQ code. The different sites are listed under this BQ in the WHO/BQ database, but are accessible by only WHO staff and regulatory authorities.
- 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 approved by other authorities, tradename(s).

It is envisaged that information that is publically available would be that summarised in the tables below.

Table 1 – Information included in hypothetical naming for BQ database A

BQ = jmgd	INN = anonutropin alfa		BQ Applicant = Pharma Innovation			
Country/NRA	Non-prop. name	BQ	Trade name	MAH	Type of application	Date changed
Europe/EMA	anonutropin alfa	NU or	Grokino	Pharma Innovation	Stand alone	2015
USA/FDA	anonutropin alfa	jmgd	Grokino, Macrogon	Michaelson & son	Stand alone	2015
Canada/Health Canada	anonutropin alfa	jmgd	Macrogon	Cando Therapeutics	Stand alone	2015
Australia/TGA	anonutropin alfa	jmgd	Grokino	AusBiotechInc	Stand alone	2015

* NU – Not used;

Table 2 – Information included in hypothetical naming for BQ database B

BQ = rtyp	INN = anonutropin alfa		BQ Applicant = Excel Biosimilars			
Country/NRA	Non-prop. name	BQ	Trade name	MAH	Type of application	Date changed
Europe/EMA	anonutropin alfa	NU*	SimaGro	Excel	Biosimilar	2015
USA/FDA	anonutropin alfa	rtyp	SimaGro	Excel	Biosimilar	2018
Canada/Health Canada	anonutropin alfa	vlrs**	Bigon	Excel	Stand alone	2017
Australia/TGA	anonutropin alfa	simrtyp	SimaGro	Biotech Reg. Agency	Biosimilar	2015

* NU – Not used ** deemed not comparable – new BQ issued, hyperlinked to rtyp

Updating information

To be of value the data held should be kept up to date. The WHO INN should be informed and the database updated following:

- Changes to information published in the database at the time that a code is issued or when the original marketing authorisation is granted, for example addition or deletion of manufacturing sites and of trade names
- Changes in regulatory status, for example when approval is obtained from additional regulatory authorities
- Authorisation issued or cancelled by a regulatory authority

- Withdrawal of active substance and/or product or tradename

The database will carry the date of the most recent change.

Updates are the joint responsibility of the BQ Applicant and relevant marketing authorisation holder and the relevant regulatory authority and are sent to the WHO INN Secretariat as soon as a change has been approved.

Lifecycle of the BQ

It is intended that a drug substance would have the same BQ as long as it has the same amino acid sequence and is marketed with the same INN. If a change is made in which glycosylation is found to be not comparable, then a new Greek letter and BQ would be assigned. This lack of comparability would need to be determined by the regulatory authority and the WHO INN should then be informed and a new BQ requested by the BQ Applicant at the behest of the marketing authority holder and/or regulatory authority. This may mean that the same drug substance may have different BQs in different jurisdictions if different assessments of the comparability are made by the regulatory authorities, but this is likely to be rare and hyperlinks between the two database entries would be introduced.

The database of Biological Qualifiers and Access to Stakeholders

A secure database will be held by the WHO Secretariat holding details of applications, codes issued, and updated as changes are submitted. Only the WHO Secretariat staff will be able to make changes to the database.

All regulatory authorities will have full read-only access to the database.

BQ Applicants will be able to make applications for a code or update online, will be able to track the progress of the processing of their applications and to see all details pertaining to their previous applications.

All information that is already in the public domain will be made available on the WHO INN website except for details about manufacturing site(s) and any other commercially sensitive information.

Use of Biological Qualifiers

The codes already adopted for existing national systems and as proposed for the WHO scheme are intended to be unique identifiers of the active substance from a given source. This information can be used in various ways and for various purposes. Potential users and uses of BQs include:

- **Regulatory authorities**
 - As a database of sites of manufacture of biological active substances
 - As an information source of approved biological substances
 - As a means of identifying selected products and their authorisation globally
 - As part of systems to uniquely identify substances and products in recording licencing/registration, prescription advice and pharmacovigilance in accordance with the legislation and policy of each jurisdiction..
 - To assist the decision-making process when issues of substitution and interchangeability are considered.

Where required, as a tool in pharmacovigilance systems in addition to INN, tradename and, for many biologicals, batch number. While the BQ may seem redundant, its use will provide a valuable cross-check of the veracity of the other information provided.

For establishing nomenclature for labelling and product literature

- **Health authorities**

As an additional means of identifying substances and products in prescription and reimbursement systems

For prescription purposes to minimise misprescription particularly when the INN alone is used for prescribing

To facilitate decision-making processes for the purposes of funding, substitution and interchangeability

- **Pharmacists**

In hospitals and in the community to identify the specific product dispensed for a patient in addition to INN and tradename. Again the use of the BQ will provide a valuable cross-check to minimise misprescription. .

- **Healthcare professionals**

For prescription

As an aid to identifying issues associated with patients' responses to different products containing substances with the same INN

When advising a patient what medicines to use in foreign countries.

- **Patients**

Patients, particularly those on long-term therapy, who receive different products containing the same active substance could use it as a monitoring tool to detect differences in their individual response to these treatments.

The BQ will indicate what biological medicines to use when residing or visiting foreign countries.

It is envisaged that the BQ scheme will be used in conjunction with the Greek letter scheme until such time as the BQ is widely and comprehensively used and the concurrent use of the two schemes is reviewed.