

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 to similar biotherapeutic products (SBPs). After discussions among interested parties and approval by the INN Expert Group, a voluntary scheme is proposed by which an application can be made to the INN Secretariat for a Biological Qualifier (BQ). A BQ is an alphabetic code assigned at random to a biological active substance manufactured at a specified site. The scheme is applicable to all biological active substances to which INNs are assigned and is applicable retrospectively. The BQ code will not be part of the INN, whose selection by the usual procedure will remain unchanged. Where use of a BQ is considered by an authority to be desirable, availability of a single global scheme will avoid proliferation of separate and distinct national qualifier systems. 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. The pharmaceutical industry and patients are accustomed to the development of generic versions of chemically synthesised small molecule medicines. These can be shown to be bioequivalent and may often be substituted for one another at the point of dispensing. Because of their structural complexity, the complexity of their manufacturing processes using living organisms, the greater difficulties in achieving consistency of manufactured batches and the often complex long-term effects of their administration to a patient, bioequivalence cannot be easily established for a product containing a biological substance. For those reasons, many regulatory systems take a different approach between similar biotherapeutics and generic chemical medicines. These 'similar biotherapeutic products', also called biosimilars, follow-on products, subsequent entry biologics, are hereafter referred to as 'biosimilars'. They are usually licensed on the basis of a comprehensive comparability study between the new source of active substance and a previously licensed equivalent, covering quality and limited 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).

An INN is specific to a given defined substance regardless of the manufacturer. For a small molecule, the substance in the generic product has the same structure as in the originator and the same INN is used for it, although the profile of impurities in the generic substance 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>). For a biological substance that is a non-glycosylated protein, the structure of the biosimilar is the same as that of the originator and the same INN has been used; consequently the INN Programme has received no applications for a new INN for a non-glycosylated biosimilar.

In contrast, 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 micro-heterogeneity and are defined physico-chemically 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 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 or will be licensed through a biosimilar regulatory process.

Increasing numbers of biosimilars have been developed and approved for marketing in a range of countries. For nomenclature, some authorities use the INN 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 the company name. In one instance, modification of the INN itself has been proposed (US). This variety of nomenclature approaches means that, 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 non-official but INN-like non-proprietary name *epoetin lambda*. Under the proposal in this paper, the solution would be to use names such as “*epoetin alfa bbbb*” and “*epoetin alfa cccc*”.

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 and April 2014 and also by the INN Expert Group in October 2013 and April 2014. It was concluded that WHO should devise and operate a scheme, applicable prospectively and 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.

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). It is intended to apply prospectively and retrospectively. Adoption of the BQ scheme is a voluntary decision of the individual regulatory authority. The BQ is used to complement the INN for a biological substance and it uniquely identifies directly or indirectly the manufacturer and manufacturing site of the active substance in a biological product. 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.

The code

The code will consist of four letters and each code issued will be assigned at random. The choice of letters used will be made to facilitate transliteration into various languages and to avoid meaningful or inappropriate words being used. The use of four letters offers more than 160 000 codes (20^4) (vowels being excluded). This is expected to provide sufficient flexibility for the foreseeable future.

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 prospective marketing authorisation holder. The assigned BQ code is provided by WHO to the applicant and to the pertinent regulatory authority. 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.

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 its availability', below. The application and data submitted in it will be held on a secure database at WHO that is operated by WHO personnel.

The information to be submitted with the application includes:

- Name and address of applicant
- INN
- Trade name(s) of product(s)

- Name and address of manufacturer of the active substance for which the code is requested
- Name and address of relevant manufacturing site(s) if different to above.
Note: The manufacture of the active substance may involve more than one distinct geographic location. Where this is the case, the individual sites together with the nature of the process(es) occurring at each site are provided.
If an active substance is manufactured at more than one site, the active substance deriving from such alternative sites and authorised within the same regulatory jurisdiction will be given a single BQ code. The different sites are listed under this BQ in the WHO/BQ database
- Regulatory information: relevant regulatory authority, nature of the marketing authorisation (e.g., biosimilar, stand-alone), INN, where and when the substance has been approved by other authorities, tradename(s).

Updating information

To be of value the data held should be kept up to date. The minimum updates are

- Changes to information published in the database at the time that a code is issued, 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 marketing authorisation holder and the relevant regulatory authority and are sent to the WHO INN Secretariat as soon as a change has been approved.

The database of Biological Qualifiers and its availability

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 will be able to make changes to the database.

All regulatory authorities have access to the full database.

Information in the database is made available on the WHO INN website except for details about manufacturing site(s) and any other commercially sensitive information.

An application for a code is submitted online and the applicant has access to the status of the application.

Use of Biological Qualifiers

The impetus for setting up the scheme for assigning Biological Qualifiers came originally from regulatory authorities who perceived the need for a system of identifying biosimilars and possibly other biologicals. 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
As part of systems to uniquely identify substances and products
To facilitate decision making process on substitution and interchangeability
As a tool in pharmacovigilance systems
For labelling and product literature
- Health authorities
As an additional means of identifying substances and products in reimbursement systems
For prescription purposes
To facilitate decision making process on substitution and interchangeability
 - Pharmacists
In hospitals and in the community to identify the specific product dispensed for a patient in addition to INN, tradename and, for many biologicals, batch number.
 - Physicians and nursing staff
For prescription
As an aid to identifying issues associated with patients' responses to different products containing substances with the same INN
 - Patients
Patients, particularly those on long-term therapy, who receive different products containing the same active substance and detect differences in their individual response to these treatments.