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Biological Qualifier
An INN Proposal

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms (TSN)
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Proposal for Assignment of Biological Qualifiers (BQ)

Executive summary

A scheme is proposed in which a unique identification code named a Biological Qualifier (BQ) is assigned to all biological substances having (or eligible to have) INNs. The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescriptions. The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2-digit checksum. The BQ scheme is designed to provide a uniform global means of identification to avoid the proliferation of differing national schemes.

The scheme will be administered by the WHO INN Secretariat who will set up and maintain a secure database of the BQ, INN, the BQ Applicant and relevant manufacturing and regulatory data. The BQs will be immediately assigned to BQ Applicants by an automated online system for use by relevant Marketing Authorisation Holders (MAHs) and National Regulatory Authorities (NRAs). The BQ Applicant will provide the required data to the WHO INN and will update the data when changes occur. An initial fee will be charged to register a BQ which will also cover any updates required so that the scheme is self-funding. Only security-approved WHO Secretariat staff will be able to enter and edit information on the database. All information that is already in the public domain will be available to all on the WHO website. Access to confidential information on the database will be restricted to read-only for NRAs and to their own applications for BQ Applicants.

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 an 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*).

While a single INN has been adequate to identify simple, well-characterised chemical substances, the complex, microheterogeneous nature of biological medicines does lead to differing efficacy and safety profiles of these substances. For this reason differing glycoforms of the same protein were distinguished by adding a Greek letter to the INN. Several national regulatory authorities proposed naming policy or have actually named biological medicines using a prefix, suffix or separate identifier to distinguish conjugates, glycoforms or biosimilars (e.g. Japan, Australia and USA). 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. This was begun in 2012 and has involved several rounds of feedback from stakeholders in general and NRAs in particular, during which it was clearly indicated

by all sectors that the WHO should devise and operate the BQ 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 proposed scheme has evolved from a three letter random code to a four letter random code incorporating a digital checksum.

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
The scheme is intended to provide a unique identification code (Biological Qualifier or BQ), distinct from the INN, for all biological substances that are assigned INNs. The BQ is an additional and independent element used in conjunction with the INN for a biological substance to uniquely identify the active substance in a biological product distributed by a MAH. It is envisaged that the BQ will assist in the identification of biological substances for:

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

The BQ scheme is designed to provide a uniform global means of identification for biological substances and so avoid the proliferation of separate and distinct schemes developed by individual regulatory authorities.

Usage of the BQ
Adoption of the BQ scheme is a voluntary decision of the individual regulatory authority. The scheme is overseen by the WHO INN Expert Group and administered and operated by the WHO INN Secretariat. The scheme is intended to apply to as many biological medicines as possible, so while it will apply prospectively, mechanisms to allow retrospective application are being investigated. 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.

The BQ code
The code will consist of four random consonants and an optional two digits as a checksum. The WHO INN will issue the BQ letters with a checksum, but it is at the discretion of the individual regulatory authority whether the checksum is used as part of the BQ. The form of the BQ may take:

- four letters;
- four letters followed by the checksum; or
- two letters, two digits and two letters, thus mimicking car registration plates to be more memorable.

For instance:

TRADENAME	INN	BQ

GROKINO	anonutropin alfa	bxsh
GROKINO	anonutropin alfa	bxsh08
GROKINO	anonutropin alfa	bx08sh

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 160 000 codes (20^4) (vowels being excluded) and is expected to provide sufficient capacity and flexibility for the foreseeable future.

The checksum is calculated from the four randomly assigned consonants and their position and gives the ability to detect errors in transcription, both the use of an erroneous letter and the transposition of the correct letters.

Who should apply for a Biological Qualifier

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 system globally. This body applies for a BQ for global use and allows its use for substance made in all manufacturing sites demonstrated to be of a similar standard of quality and by all marketing 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 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 BQ Applicant through an automated online system. The BQ Applicant can either:

- supply the BQ directly to regulatory authority/ authorities when the BQ Applicant is also the Marketing Authorisation Holder (MAH); or
- provide the BQ to the MAH making the authorisation application.

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

Application will be made online in an automated system administered by the WHO INN Secretariat. The application and data submitted in it will be held on a secure database at WHO that is operated only by WHO personnel. 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 information to be submitted with the application includes:

- Name and address of BQ 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 the jurisdictions for which they are responsible.
- Name and address of relevant manufacturing site(s) if different to above.
- 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).

It is envisaged that information that is publically available would be made available to all who access the database. Examples of what information might be displayed are given in tables in the FAQ document.

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, for example addition, deletion or changing of manufacturing sites and of trade names.
- Authorisation issued or cancelled by a regulatory authority.
- Changes in regulatory status, for example when approval is obtained from additional regulatory authorities.
- 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, the 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.

Access of the BQ Database to Stakeholders

A secure database will be held by the WHO Secretariat holding details of applications, codes issued, and updated as changes are submitted. The following access to the database would be granted:

- Only security-approved WHO Secretariat staff will be able to enter and edit information on 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 own applications and to see all details pertaining to their own 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.

Lifecycle of the BQ

It is intended that a drug substance would have the same BQ as long as it has the same basic structure (amino acid sequence in the case of proteins) and is marketed with the same INN. A new BQ may be issued by WHO INN if a national regulatory authority determines changes to the substance render it different to the original substance, however the new BQ would be hyperlinked to the original on the BQ database.