

*Biological Qualifier
Frequently Asked Questions*

Programme on International Nonproprietary Names (INN)

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Biological Qualifier (BQ) Frequently Asked Questions

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Introduction and Background Information

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, a voluntary scheme was proposed by which an application can be made to the INN Secretariat for a Biological Qualifier (BQ) to aid in the minimisation of errors in prescription, dispensing, pharmacovigilance and international transfer of prescriptions. A BQ is a random alphabetic and digital code assigned to a biological active substance on application by a BQ Applicant and used for medicines distributed by a Marketing Authorisation Holder (MAH). The scheme is applicable to all biological active substances 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.

Several drafts of the Proposal for a Biological Qualifier have been published evoking extensive and detailed response. Attempts were made to incorporate this feedback into the Proposal but this resulted in a large and unwieldy document that aroused even more response. It was therefore decided to produce a proposal that succinctly but clearly outlined the proposed BQ scheme, but draft a document which addressed the issues that had been raised as Frequently Asked Questions (FAQ). This is intended as a living document, regularly updated to reflect current concerns and questions.

What are biological medicinal products?

For the purposes of the BQ Scheme a biological medicinal product is a medicine derived from humans or animals or produced by biotechnology for which an INN has been issued. Because they are derived from living cells or organisms, biological medicines consist of relatively large and highly complex molecular entities, that are often difficult to fully characterise by currently available analytical methods and often display a certain degree of variability or microheterogeneity. Biological medicinal products therefore include all biotherapeutic proteins produced by recombinant technology, purified (not mixtures of) proteins and polysaccharides extracted from animal and human fluids and tissues and non-gene therapy RNA and DNA (e.g. siRNA).

To what biological medicinal products will the BQ apply?

It is proposed that **all** biological medicinal products use a BQ. It is not designed to single out any type of biological medicinal product. Biological Qualifiers will be issued for all drug substances of biological medicinal products including biosimilars, innovator products, non-glycosylated and glycosylated proteins. Only exceptions will be vaccines, impure mixtures and complex biologically-extracted products like menotropin or pancreatin to which INNs are not assigned. At this stage it also does not include oligonucleotides, gene or cell therapies, though when the BQ is established, this may be reviewed.

How has the BQ scheme been developed?

Several national regulatory authorities proposed naming policy or have actually named biological medicines using prefixes, suffixes or separate identifiers to distinguish conjugates, glycoforms or biosimilars (e.g. Japan, Australia and USA). To avoid proliferation of separate and distinct national qualifier systems, the WHO INN Programme

was requested to develop and administer a voluntary and global complementary nomenclature scheme. The nomenclature of biological medicines was therefore reviewed at a number of *ad hoc* meetings convened by the WHO involving stakeholders, regulatory authorities, INN Experts and the INN Secretariat between 2013 and 2015. The majority of stakeholders affirmed that the WHO should devise and operate a scheme, applicable prospectively and, where possible, retrospectively to **all** biological substances assigned INNs. The majority indicated that the most robust and versatile form was a four consonant code with or without a checksum. The BQ scheme would be recognised globally and could be adopted on a voluntary basis by any regulatory authority. The INN Expert Group agreed that this would be a complementary nomenclature scheme that could prevent proliferation of different names and nomenclature policies.

What form will the BQ take?

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 the corresponding 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.

The following fictitious example is worked out in the three possible ways:

TRADENAME	INN	BQ
GROKINO	anonutropin alfa	bxsh
GROKINO	anonutropin alfa	bxsh08
GROKINO	anonutropin alfa	bx08sh

This form has been developed in consultation with national regulatory authorities and stakeholders over several years and, while the form is not the most memorable, it is the most robust and versatile. The use of four consonants means there are 160 000 (20⁴) possible codes, providing sufficient capacity to provide codes for all biological medicines for the foreseeable future.

What is the checksum and what is its purpose?

The checksum is calculated from the BQ's four randomly assigned consonants and their order in the code. The checksum is calculated from the four randomly assigned consonants and their position in the code.

This gives pharmacists dispensing prescriptions or officials checking adverse drug reactions the ability to detect errors in transcription, both the use of an erroneous letter and/or the transposition of the correct letters. It is envisioned that this would be incorporated into dispensing software and invalid BQ's flagged. As this feature is likely to be used mostly in a context of computer use, software developers and relevant national regulatory authorities may apply to the WHO INN Secretariat for the formula and the means to decode the checksum for analysis of entered or electronically transferred BQs.

What other forms of BQ were considered?

The initial proposal was for a three letter code including vowels. When it was decided to make the BQ scheme available for all biological medicines, a four letter code was required and vowels were omitted to exclude most objectionable or promotional meanings. Feedback

suggested linking the code to an abbreviation of the BQ Applicants name to enhance memorability and/or allowing the BQ Applicant to use the same code for all drug substances. This feedback was not utilised because:

- This would effectively make the BQ code a proprietary item
- While this may make a simpler system initially, several years down the line with mergers, acquisitions and purchases, the BQ codes reflecting one BQ Applicant and/or MAH will be used for substances marketed by other BQ Applicants creating confusion and misdirection
- When consulted National Regulatory Authorities preferred a meaningless random code to a meaningful abbreviation.

Is the BQ part of the INN?

The BQ is not part of the INN. It 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 BQ Applicant and/or Marketing Authorisation Holder (MAH).

Does the BQ apply to the drug substance or the drug product?

The BQ is associated with the INN which is applicable to the drug substance or active ingredient not the drug product. However, just as the INN is used in naming ingredients in the labelling of and information associated with the drug product, so the BQ would be used in conjunction with the INN for these purposes for the drug product.

What is the purpose of the BQ?

The BQ scheme is intended to provide a unique identification code, 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 BQ Applicant and/or Marketing Authorisation Holder (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:

- all biological medicines having the same biological substance to be globally identifiable, which would promote rational prescription, dispensing and use;
- clear identification to enable global traceability of biological medicines, aiding pharmacovigilance (in those jurisdictions requiring it) and contributing to patient safety; and
- transferring prescriptions between countries.

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 an alternate and acceptable 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.

Will the BQ affect access to similar biotherapeutic products?

Because the initial requests made to establish the BQ were by NRA's intending to use it for

similar biotherapeutic products (or biosimilars), the perception was built up that the BQ would distinguish biosimilars from other biological medicines. This is not the case. From the first published version of the BQ Proposal in Jul 2014, the BQ Scheme has always been intended to apply to all biological medicines with no distinction, where possible retrospectively. The impact of the BQ on access to biosimilars (and price savings through their use) is therefore likely to be minimal.

In addition, the perception that having a difference in the non-proprietary name obstructs the uptake of a biosimilar medicine is based on the two instances in which a different Greek letter was assigned and impacted countries whose legislation mandates identical names for reimbursement. The BQ is not part of the drug substance INN and should have no effect in those countries. One of the initial objectives of the BQ Scheme was so that biosimilars could have the same name as the reference medicine. In addition, a recent publication (Grabowski, Guha & Salgado Biosimilar competition: lessons from Europe *Nature Reviews Drug Discovery* 2014;13:99–100) indicates that price incentives and quota systems have the greatest effect.

Is a BQ mandatory?

The BQ scheme is voluntary. Adoption of the BQ scheme is at the discretion of the individual regulatory authority. 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.

Who should apply for a BQ?

The applicant for a BQ (termed the BQ Applicant in the BQ Proposal) is foreseen to be a corporate body that manufactures (or manages the manufacture) of a single substance by a single process controlled by the same quality system globally. This body applies to the WHO INN for a BQ for global use and allows its use for drug substance made in all manufacturing sites demonstrated to be of a similar standard of quality and by all manufacturing authorisation holders (MAH) authorised to distribute 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.

How should a BQ Applicant apply for a BQ?

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 Authorization Holder (MAH) or provide the BQ to the MAH making the authorisation application.

When 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 and provision of the BQ to the NRA by the BQ Applicant and/or MAH.

How is the BQ scheme funded?

A fee will be levied for each application so that the BQ scheme is self-funding. No further fee will be imposed for processing updates to the information submitted for the BQ code, so

the initial fee will be set taking this into consideration.

When should a BQ Applicant apply for a BQ?

It is envisaged that the BQ Applicant will apply for a BQ just before the time of submission of a marketing authorisation application to a regulatory authority or when requested to do so by a regulatory authority. As the BQ code is immediately provided by the WHO to the BQ Applicant through an automated online system, there should be no hindrance to the application or processing of the submission by the NRA.

How should a BQ be used?

The scheme will provide a BQ for all biological substances that are assigned INNs to be used as an additional and independent element 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;
- pharmacovigilance (in those jurisdictions requiring it); and
- transfer of prescriptions globally.

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.

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.

Pharmacists

- In hospitals and in the community to identify the specific product dispensed for a patient in addition to INN and tradename.

- As a valuable cross-check to minimise misprescription.

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 in or visiting foreign countries.

What will the BQ database contain?

All information submitted by the BQ Applicant will be stored in the secure WHO INN database. This information includes:

- Name and address of BQ Applicant
- INN
- BQ
- 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 authorised, tradename(s).

How will the BQ database work and who can access it?

When an application is made by a BQ Applicant, the data will be stored in a secure database 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 personnel will be able to enter or edit the 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.

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.

What will the BQ database look like?

All information that is already in the public domain will be made available on the WHO INN website, namely the BQ and associated INN, the BQ Applicant and for each jurisdiction, the tradename, MAH, type of application and date of registration. The data displayed would be those summarised in the fictitious examples in the tables below.

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

BQ = bxsh Checksum=08	INN = anonotropin alfa		BQ Applicant = Pharma Innovation			
Country/NRA	Non-prop. name	BQ	Trade name(s)	MAH	Type of application	Date changed
Europe/EMA	anonotropin alfa	NU*	Grokino	Pharma Innovation	Stand alone	2015
USA/FDA	anonotropin alfa	bxsh	Grokino, Macrogon	Michaelson & son	Stand alone	2015
Canada/Health Canada	anonotropin alfa	bx08sh	Macrogon	Cando Therapeutics	Stand alone	2015
Australia/TGA	anonotropin alfa	bxsh08	Grokino	AusGro Inc	Stand alone	2015

* NU – Not used

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

BQ = rtyp Checksum=54	INN = anonotropin alfa		BQ Applicant = Excel Biosimilars			
Country/NRA	Non-prop. name	BQ	Trade name(s)	MAH	Type of application	Date changed
Europe/EMA	anonotropin alfa	NU*	SimaGro	Excel	Biosimilar	2015
USA/FDA	anonotropin alfa	rtyp	SimaGro	Excel	Biosimilar	2018
Canada/Health Canada	anonotropin alfa	v135rs**	Bigon	Excel	Stand alone	2017
Australia/TGA	anonotropin alfa	simrtyp54	SimaGro	Biotech Agency Inc	Biosimilar	2015

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

Will the BQ change over the lifetime of the drug substance?

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. If a change is made in which the glycosylation for instance is found to be different, then a new Greek letter and BQ would be assigned. This lack of comparability would need to be determined by the regulatory authority. 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. Means of making the link between such differentiated BQs when NRA's exchange pharmacovigilance data or collate data over longer periods of time will need to be investigated, but the link will be clear on the BQ database.

Will the BQ replace the Greek letter for differing glycoforms?

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. 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.