

Report on Biological Qualifier Front Page meeting for International Nonproprietary names (INN) stakeholders.

WHO Headquarters, Geneva, 16 June 2015

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)

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Dr Kevin Grant

INN BQ Working Group Lead (via WebEx)

Dr Patience Holland

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WHO SECRETARIAT

Department of Essential Medicines and Health Products (EMP)

Mr Kees de Joncheere	Director, Essential Medicine and Health Products (EMP)
Dr Lembit Rägo	Head, Regulation of Medicines and other Health Technologies (RHT)
Dr David Wood	Coordinator, Technologies Standards and Norms (TSN)
Dr Raffaella Balocco Mattavelli	Group Lead, International Nonproprietary Names (INN) Programme, TSN and Secretary of the INN Expert Group
Dr Sophie Lasseur	Technical Officer, INN Programme, TSN
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Brand Institute , USA	Jeff Boden, Director of Medical Science and Pharmaceutical Nomenclature
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Canadian Psoriasis Network , Canada	Robert Corbeil, National Executive Director
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INN EXPERT GROUP

INN BIOLOGICAL ADVISORY GROUP

Agenda

Tuesday, 16 June 2015

09h00 – 10h00 *Welcome coffee and registration*

10h00 – 10h45 Welcome and opening remarks

Dr K. de Joncheere, Director,
Department of Essential Medicines
and Health Products

Dr Lembit Rägo, Head
Regulation of Medicines and other
Health Technologies

Dr David Wood, Coordinator,
Technologies Standards and
Norms

Introduction to the INN Biological Qualifier
(BQ) proposal

Dr Raffaella Balocco Mattavelli,
Secretary of the INN Expert Group

Framework to the BQ proposal

Chair: Dr Derek Calam

10h45 – 11h30 Presentation of the BQ proposal survey
results and comments

Dr Kevin Grant, INN BQ Working
Group Lead (via WebEx)

11h30 – 13h00 Questions, Comments and Discussion

13h00 Closure of the meeting

Front page meeting

Welcome

The WHO INN Front Page meeting on the Biological Qualifier (BQ) was opened and participants were welcomed by **Mr Kees de Joncheere**, Director, Department of Essential Medicines and Health Products (EMP). He emphasised the importance of nomenclature for biologicals and biosimilars and with the INN Group having been developing the BQ concept for more than two years, this consultative meeting was important for the Group to hear stakeholders' comments on its progress.

Dr Lembit R go, Head, Regulation of Medicines and other Health Technologies (RHT), echoed the need for WHO to listen to opinions, as this involves a very strategic decision with many responsibilities and foreseen and unforeseen consequences. There has already been extensive consultation and this event is vital to gather even more opinion to take on-board.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team, in welcoming both those present in the meeting room and those connected by WebEx, similarly reinforced that WHO was very much in a listening mode, to hear about stakeholders' concerns and opinions on the BQ.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, International Nonproprietary Names (INN) Programme, welcomed participants with a short presentation on the need to work together and build a consensus on nomenclature, rather than addressing problems independently and pursuing the same political agenda in different directions. Consequently, following a request from regulators and others for advice on nomenclature of biosimilars, WHO and stakeholders have been working together to understand each other's needs and to find a solution. This Front Page meeting would start with two presentations, first on the framework of the BQ proposal and then on an analysis of the comments received and an update of the proposal. Following these, there would be general discussion on the BQ to which all were invited to contribute including those attending via WebEx.

The Chair, **Prof. Derek Calam**, added his own welcome. As noted, the BQ initiative, initially for biosimilars, has been under development for two years and this meeting will help clarify the current position, taking steps to ensure all stakeholders were informed of previous discussions and decisions. Comments and advice provided today will also enable the INN BQ Working Group to present a revised scheme to the INN Expert Group at the October (2015) INN Consultation.

Introduction to the BQ Proposal (Prof. Calam)

The WHO INN programme was initiated in 1953 and has been adopted by almost all 200 WHO member states. Its purpose is to assign unique INN for new active substances. To date, more than 10,000 applications have been received with biologicals now accounting for 40% of current requests. For small molecule drugs, the INN established by the innovator is used by generic manufacturers, who do not involve the INN Programme. In contrast, the issue of biosimilars is complex. The term biosimilar began to be used with *somatropin* (74)(36), when generic versions came on the market, and then especially for glycoproteins. Biosimilar regulatory routes may or may not exist and some products may be viewed as biosimilar in some jurisdictions but not in others. At the start of the BQ initiative, certain jurisdictions wanted to qualify biosimilars via the INN and different national schemes began to be developed. A more sensible solution was for WHO to develop a global identification system. The task of developing a scheme was accepted by the INN Expert Group in 2013 and a first draft of a Biological Qualifier was prepared. Prof. Calam emphasised that the BQ scheme was not an initiative of WHO or the INN Programme but arose from a request from regulatory authorities for a global system. In preparing the first draft, the INN Group agreed that the INN itself gets left unchanged, that any scheme is separate from INN, and with some further input from Drug Regulatory Authorities (DRAs), that any scheme should be applied to all biologicals and not just biosimilars (with the exception of vaccines, blood products and complex mixtures which do not receive INN). It was also agreed that the development would be overseen by the INN Expert Group and administered by the INN Secretariat, which would set up a BQ database, with advice from the Expert Group on how data would be disseminated.

The first draft was published for comment in August 2014 and as comments arrived it was decided to establish a separate INN working group to review and redraft the proposal in light of these comments. By December (2014), 300 pages of comment had been received, following which a new draft was prepared. This was presented at a closed Regulatory Forum held in March 2015 and then further refined for discussion at this Front Page meeting (version 2.2, June 2015¹).

The first draft proposed that the BQ scheme should be voluntary, would be separate from the INN, would apply to the drug substance, be a 4-letter code assigned to a specific manufacturing site, would apply to all biologicals, that WHO would hold data in a secure database, and that entries would be updated as necessary. After consultation and comments received on the first draft, all reference to biosimilars has largely been removed to avoid any suggestion that they are being singled out, as this might impact their use. The proposal was also modified to assign the BQ to the applicant and not the manufacturer or manufacturing site. Further clarification on the role of a BQ and on the confidentiality of the database was added. Following the closed Regulatory Forum there was additional fine tuning.

The framework of the BQ scheme with its application to all biologicals is now reasonably clear although various details require clarification. It has been suggested that the preferred 4-letter code should include a checksum as such a code would not be memorable and there is a need to ensure its accuracy in transcribing. A 5th 'check' digit could ensure that the code had been entered correctly (electronically) and flag errors if not. With regard the database, the exact licensing information to be stored needs clarification. A key feature would be that data would not be deleted and that the database would provide a complete history of the substance including the timeline of first registration, subsequent registrations, and tradenames.

A majority of respondents appeared to support the BQ scheme, some more strongly than others; a minority said that it is not needed or not wanted. However, it would be voluntary and where sophisticated identification and tracking schemes are already in place, it may not be needed. WHO advises 200 member states many of which do not have sophisticated facilities in place for accurate pharmacovigilance.

In summary, the issues that remain to be refined include defining precisely the BQ applicant, how data is updated, how those DRAs that implement the scheme could encourage its use, the form of the code, the need for a checksum and retrospective application.

INN BQ Working Group Feedback (Dr Kevin Grant)

An analysis of the one hundred plus comments received on the first draft showed that a good majority of respondents were at least in partial agreement with the proposal. Respondents comprised a wide variety of stakeholders, from industry and manufacturers' associations, through organisations representing clinicians, patients, pharmacists and funding bodies, to academics, government agencies and personal respondents. Strong support was received from clinical and patient organisations and industry, whilst poor support was received from pharmacist organisations and personal respondents; government bodies, manufacturers and funding organisations were more evenly divided. Amongst government respondents, Canada was supportive, Latin American and Asian governments were divided, and European governments were not supportive although curiously, the European Medicines Agency (EMA), the European Union central medicines agency had a neutral position. The March (2015) Regulatory Forum held largely reinforced the nature of government support observed in the comments.

Two major changes to the proposal were made based upon the comments: removal of virtually all reference to biosimilars and assignment of the BQ to the BQ applicant and not to a manufacturer or manufacturing site regardless of the number of sites or number of Marketing Authorisation Holders (MAHs) for that substance. Any single substance made under the same quality controlled process would be assigned one BQ regardless of the number of manufacturing sites. Text has been added stating that the BQ should not be seen as a standalone identifier but as a check on the tradename and

¹ http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf?ua=1

INN in prescribing and in pharmacovigilance. The confidentiality of the database has been addressed further and what is now proposed is that data on display would be data already publically available. In version 2.2, a table illustrates how a BQ given to an active substance in one jurisdiction may (or may not) be used by subsequent jurisdictions. Where a regulator deems a specific active substance to be not comparable, a new BQ would be warranted but would be hyperlinked to the BQ previously assigned to that substance. It was emphasised that comparability would be assessed by a regulatory authority and would not and cannot be assessed by WHO/INN.

Where the amino acid sequence of a protein active substance remains unchanged during its lifecycle, the assigned BQ would remain unchanged. However, a change in glycoform profile which is considered by the regulator to make the substance non-comparable to the earlier product would trigger a new BQ (and a new Greek letter for the INN). Upon adoption of the BQ scheme, the Greek letter INN feature would remain in place and only once a BQ system is established might dropping the Greek letter policy be reviewed.

The original proposal for the form of the BQ was for a 4-letter (minus vowels) code. Further suggestions included letters indicating the type of medicine and the country, a 4-6 digit sequential code, a 2-3 letter code for the MAH plus a 2-3 digit code, and a sequence of words, numbers and letters indicating differences in amino acid sequence, glycosylation and copy versions. The 2-3 letter MAH/2-3 digit code was discussed extensively at the Regulators Forum with the opinion of regulators being against this and in favour of the original 4-letter code. As mentioned above, a 5th letter checksum could be added, which would verify the accuracy of a 4-letter code, or indeed a checksum could be applied to all forms of a BQ, and this needs to be discussed further.

Dr Grant ended by noting that the removal of references to biosimilars and assigning a BQ to the applicant and not the manufacturing site should increase support for the BQ, and INN will continue to develop and implement the BQ concept.

DISCUSSION

General remarks

ALIFAR (Asociación Latinoamericana de Industrias Farmacéuticas) voiced its opposition to the BQ proposal, highlighting that the creation of distinctive INN for biosimilars (INN plus 4 letters) would give rise to confusion for both doctors and patients, and adversely impact the biosimilars market. The Association considered that the first option to distinguish the different products with the same active pharmaceutical ingredient (API) is the product trademark plus the INN. The second option could be to use the INN plus the company name, in order to distinguish each product. The introduction of a data matrix code or RFID, already in use in some countries in Latin America, would enhance traceability. Track and trace should be included in the regulatory requirements for biological products market authorization. It is the strongest tool for the identification of different products, and it would be an essential part of INN group recommendations.

In addition, the Association did not think that the survey data clearly showed a majority in favour of the scheme, with for example 55% of DRAs being against the proposal.

In response, the Chair pointed out that the position taken by ALIFAR was based and influenced by the first draft of the proposal in which there was over emphasis on biosimilars and that the scheme was not adequately explained first time round. The current draft has removed virtually all reference to biosimilars making it clear that the BQ is for all biological medicines whether developed as a biosimilar or not. The Chair also emphasised that INN would not be modified, that the BQ scheme is separate and that it would operate in parallel. With regard to analysis of the comments received on the first proposal, the opinion of all government respondents, health ministries as well as DRAs, is more or less split. The initial analysis was perhaps overly optimistic but at the Regulators Forum, the position of some government responders appeared to be shifting to a more positive tone. Finally, the

introduction by some countries of a data matrix code demonstrated the need for an additional identification system and this is precisely what the BQ is intended for, but at a global level, to avoid a proliferation of different systems in different jurisdictions.

The **Permanent Mission of Brazil** to the UN shared some of ALIFAR's concerns and remained unconvinced that it would help minimise prescription errors. The proposal needed further improvement and should not be rolled out until everyone is certain about its value. A new draft should be prepared and sent to DRAs for further comment and discussion. The Chair reassured the Permanent Mission of Brazil that their tabled comments would be considered by the BQ Working Group as it is comments like these that would lead to strengthening of the scheme.

A **participating pharmacist** was surprised that pharmacists commenting on the first draft were not supportive; he himself supported a BQ for tracking, pharmacovigilance and assuring the proper supply of medicines and felt that they should look further into it. The Chair thanked the participant for these comments and thought that it probably derived from prescribing being more sophisticated in some countries and less so in others. Some pharmacists seemed to think that they had sufficient information without a BQ and apparently also because they did not want to change their computer systems.

National nomenclature schemes

The WHO efforts to avoid proliferation of separate national policies were welcomed but it was queried as to whether countries that had initiated their own scheme would withdraw them and apply the BQ. Dr Balocco-Mattavelli informed the meeting that several jurisdictions appeared to be willing, in principle, to go in this direction, including Japan, Canada and Australia.

BQ applicant

The latest draft removed the application of a BQ to the manufacturing site. Rather it would be given to the BQ 'applicant', which was foreseen to be a corporate body that makes or manages the manufacture of a single substance by a single process controlled by the same quality assurance programme globally. Clarification was requested whether the corporate body would be a regional MAH or a global parent company; however this was not yet fully clear. Essentially, when an applicant first requests a BQ, it would likely be the entity that first requested the INN for that active substance. When that entity expands manufacture to other sites and if the substance made at any additional site is deemed to be comparable by a regulatory authority, the same BQ would apply. Any other company making the same active substance is likely to be doing so under a different manufacturing process and so would have a distinct BQ, i.e. if a different quality process applies, then a different BQ would be required. Some of this was illustrated in the tables provided in the current version (2.2) of the BQ proposal. It was emphasised however that WHO does not have the resources or the mandate to assess quality and this must be undertaken by a regulatory authority.

Retrospective application

The initially proposal called for retrospective application of the BQ. It transpired however that legally this may not be possible in some jurisdictions. But where a substance was already marketed, information could gradually be fed into the database; for example, when there was a manufacturing change that required DRA authorisation, a DRA or even the MAH could conceivably request a BQ at that stage.

BQ code

Alternatives to the originally proposed 4-letter code were suggested by respondents to the first draft, including a combination of letters to indicate the type of medicine and the country, a simple sequence of 4-5 digits, and a 2-3 letter code for the MAH plus 2-3 digits. At the Regulatory Forum, despite the weakness of the 4-letter code, DRAs felt that on balance, it was the best choice. If a more geographically precise origin of material was desired, the ISO 2-letter country code could be included but generally DRAs felt that 4 letters would suffice.

A criticism of the 4-letter code was that it is not memorable and it was mooted that doctors and patients would prefer memorability. The form of code involving 2-3 letter MAH/2-3 digits would be more memorable. Also, it was noted that the first USA biosimilar has a 4-letter code, apparently designating the MAH, appended to the INN although the Chair commented that this approach would be unlikely to work in the long term. Whilst the alternate 2-3 letter MAH/2-3 digit code would clearly add a proprietary element to the INN, this would not be a reason to reject it; indeed the BQ code in whatever form will be proprietary, and there is value in that for patients, whether they have to look up the code on the web versus the MAH appearing directly as part of the code.

An interesting analogy was presented – that of airline flight numbers: they have an active substance, in this case a specific aircraft, and each flight has its own distinguishing flight number which provides information on who owns it, who operates it, the route and departure time. The flight number provides those in the air industry immediate information on which flight is being addressed; a similar type of approach with medicines might be useful.

Checksum

Comments were sought from participants on the use of a checksum – a 5th letter on the 4-letter code which would validate the correctness of the code. It was commented that when a prescriber wrote a prescription for a controlled substance, a specific number was added to the prescription and the pharmacist could determine from this if the prescription was genuine. In a similar fashion a checksum for the BQ made sense; it would be an additional safety check that a BQ had been transcribed correctly. One downside of the checksum approach was that as the calculation required would unlikely be done manually, it required users to have appropriate software to interrogate the checksum, and not all pharmacists globally would have this. It was also commented that given that simplicity was key for the successful adoption of a system, a 5th letter checksum would make the code even less memorable. Ultimately, would it provide the desired added value?

Use

The last section of the proposal provides information on how a BQ could be used. It was not the role of the Working Group to say how it should be used; it will be up to stakeholders to adopt the scheme and use it as they may and the Group appreciates that it may not understand what is important to individual stakeholders.

The proposal states that for Health Authorities, the BQ could be used for funding, substitution and interchangeability (among other things), and the rationale for this statement was queried. WHO informed the meeting that this had come out of the Regulatory Forum, that especially for interchangeability, regulators requested that this was added to the document as a possible use, with no further comment, simply that it could be used in this way.

Pilot scheme/Training/Impact

Testing the BQ scheme prior to implementation was proposed to avoid the BQ doing more harm than good. The Chair noted that a pilot scheme could be considered and could involve the WHO in identifying a DRA enthusiastic to test the scheme. Alternatively a mock-up system could also be considered. The idea of training was also suggested and the Chair agreed that this could be important in applying the scheme although the INN Group itself was not in a position to undertake a training session. This would be better undertaken within a jurisdiction that makes use of the scheme.

Also, once implemented, there would be interest in knowing its impact on pharmacovigilance or other aspects, and a system to assess impact would be useful. The WHO felt that if there was sufficient interest for this that it could be arranged with industry and regulators.

Confidentiality

Concern was expressed about the confidentiality of the BQ database as it was felt that it being held by WHO staff was not considered a guarantee of confidentiality. In reply, WHO noted that INN applications include a considerable amount of confidential information, more than would be requested

for the BQ, and all information is securely encrypted and protected. WHO staff and INN Experts are required to sign legally binding confidentiality agreements, with Experts' access protected by encrypted certification. WHO affirmed that extensive efforts had been taken to ensure confidentiality of information in INN applications and this would apply to the BQ database also. The only data that would be accessible to others would be what is already publically available.

Fees

Fees have been discussed but no amount decided. There would be one fee only with no subsequent fee for any updates to the database. The BQ needs to be self-funded, but the fee should be less than the fee for an INN application, which is \$12,000.

Next steps

Following this Front Page meeting a revised draft will be tabled at the October (2015) INN Consultation, and following the Experts' approval, the revised draft will be published on the WHO website for comments.

Close of meeting

The Chair gave his thanks and appreciation to all for contributing to the meeting, noting that some issues had been clarified but that others had been raised. The BQ Working Group would consider all comments and present the next draft at the October 2015 61st INN Consultation, but there was currently no rigid timescale.

Mr Kees de Joncheere, thanked the INN Chair, the INN BQ Working Group, the INN Group Lead and the other WHO staff for their contributions to this complex issue. For these nomenclature issues, there were consequences for patients, prescribers, and others; some issues were clear and some were not and that WHO would continue with this consultative process. Thanks were proffered to all participants for their continued input with the hope that the end result will be for the benefit of patient safety.