

***61st Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 13-16 October 2015***

Executive Summary

Programme on International Nonproprietary Names (INN)

***Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva***

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EXECUTIVE SUMMARY

INTRODUCTIONS

The Chair, **Prof. Derek Calam**, welcomed participants to the 61st INN Consultation on behalf of Dr Lembit Rägo, Head, Regulation of Medicines and other Health Technologies (RHT) and Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team. Starting in 2014, the three groups coordinated by Dr Wood, the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the Expert Committee on Biological Standardization (ECBS) and the INN Expert Group now meet in parallel and on the preceding day, Prof. Calam gave a short presentation on the Biological Qualifier (BQ) to the ECBS. For this 61st INN Consultation there were a record number of new applications (135) to be addressed.

Dr Raffaella Balocco-Mattavelli, Group Lead, INN Programme, also welcomed participants and gave a short presentation on trends in INN requests. Over the past five years there had been a significant increase in applications due solely to an increase in requests for biological substances. In 2010 biologicals represented 20% of all applications and now they represent 45%. The majority of the biological requests originated from the USA. For this 61st Consultation, this remains the situation although there were a noticeable increased number of requests from China.

NOMENCLATURE of INNs

During the Consultation, a total of 182 INN requests were discussed, including:

- 135 new INN requests, including 72 for biological substances
- 43 outstanding requests
- 4 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 154 new names were selected, which are planned to be published in List 115 of Proposed INNs, while 18 requests were deferred for future discussion. Five requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One request was corresponding to an already published INN. Three amendments are planned to be published in List 114 of p.INN and one objection could not be retained. Three new stems/substems have been selected and 3 suffixes have been promoted to the pre-stem list.

BIOLOGICAL QUALIFIER (BQ)

Two Biological Qualifier (BQ) working documents were tabled: a new concise draft of the BQ proposal and a new and detailed Frequently Asked Questions (FAQs) document. Discussion of the BQ proposal had been ongoing for over two years and the Chair informed the Expert Committee that ultimately their task was to make a recommendation to the WHO regarding adoption of the BQ scheme; it would then be up to WHO to take on-board the recommendation or not.

Dr Patience Holland, vice-chair, INN Expert Group, provided the background to the proposal. In 2012, the INN Committee was asked to develop a global qualifier system for similar biotherapeutic products (biosimilars), but following feedback from stakeholders the proposed scheme was expanded to include all biological substances for which INNs could be assigned. A Working Group was convened to develop the proposed BQ scheme, although it would be the INN Expert Committee and not the Working Group that would have responsibility for it. The objective for the development of a WHO global scheme was to inhibit proliferation of national schemes. Both Japan and Australia had already devised their own schemes although the Australian TGA had suspended its scheme pending the outcome of the BQ system. In addition, the FDA had recently issued draft guidelines for non-proprietary naming of biological products. These developments underlined the need for a single global scheme.

The BQ is to be a standalone qualifier not linked to established non-proprietary names. It would be a tool not dissimilar to CAS numbers, manufacturers' codes or lot numbers; it should help regulators track drug substances and assist in prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescriptions. Its use would be voluntary and would be administered by the INN Secretariat. The proposed scheme comprises a random code consisting of four consonants with an optional two digit checksum. An application for a BQ would be made at the time of submission of a marketing authorisation application to a national drug regulatory authority.

Dr Raffaella Balocco-Mattavelli, Group Lead, INN Programme, outlined the feedback from stakeholders following a third circulation of the proposal. Comments had been received from a broad spectrum of stakeholders including the pharmaceutical industry, government agencies, academics and a variety of healthcare organisations. Overall, approximately two-thirds of commentators were in partial or full agreement with the proposal with one third disagreeing, some strongly. Amongst government agencies, the USA and Canada were in support, Asian and Latin American countries were divided, and individual EU member states were against although the European Medicines Agency itself was not against and was even in partial agreement. Significantly, the US FDA had recently published its own proposal for non-proprietary nomenclature of biologics which was not dissimilar to the BQ, and so discussion is on-going with them to find a harmonised solution.

Dr Kevin Grant, INN BQ Working Group Lead, re-emphasised that the BQ had been designed to be applicable to all biological medicines and would identify a drug substance made by one process under one quality system, regardless of the number of manufacturing sites. The BQ would be assigned to the BQ applicant, who would permit marketing authorisation holders (MAHs) to use it in jurisdictions worldwide for products containing the drug substance. The information provided by a BQ applicant would include their name/address, INN of the drug substance, tradename in all relevant jurisdictions, name/address of MAH's, name/address of manufacturing sites, relevant NRAs and route and date of marketing authorisations. Since some information would be confidential, all data would be stored on a secure WHO database, edited only by certified WHO staff. Limited confidential information would be available to NRAs whilst information available publically would be that which is already in the public domain.

The BQ would be assigned by an online system and so would be available quickly, and would be a relatively un-obstructive and inexpensive way to administer. It would consist of four random consonants plus an optional two digit checksum. The checksum would be issued with the BQ but it would be up to NRAs whether to use it or not; if used, the two digits can be sited in the middle or at the end of the BQ. Regional differences may impact the BQ, for example, one NRA may register a product as a biosimilar with an assigned BQ but a separate NRA may assess a product with the same drug substance as non-comparable to the reference product and thus request a different BQ.

The Committee was informed that the BQ had matured to a point where it could not be improved and that it was now the responsibility of the INN Expert Group to decide whether it had reached the stage for adoption.

BQ updates from National Regulatory Authorities

Food and Drug Administration (FDA), USA

The FDA observer tabled and read out a statement regarding the recently published guidance on naming of biologics that involves implementation of an identifier (see Appendix 1).

In essence, the statement outlined the background to, and the reasons for, the FDA draft guidance. It highlighted the use of a non-meaningful four letter suffix, hyphenated to the USAN, although comments are being sought on alternative formats. The proposed naming convention would apply to originator and biosimilar products as well as to both previously and newly licenced biological products. Alongside the draft guidance, a proposed rule for the designation of non-proprietary names for six previously licenced biologics was published. The tabled statement notes that the FDA's approach has similarities as well as differences to the WHO's proposed BQ. Public comment on the FDA proposal is being sought.

The Chair noted that this was another example of an NRA developing an independent scheme but was appreciative that some elements from the BQ had been incorporated into the FDA rule.

A substantive difference between the FDA and INN proposals is that the INN proposal targets the drug substance whereas the FDA proposal is to apply to the finished product. According to the FDA proposal, their new suffix would be determined by the manufacturer and the manufacturing site but would be used for the product as it is the drug product that gets labelled and not the drug substance.

European Medicines Agency (EMA)

The EMA has been developing regulatory procedures for biosimilars for some time. More recently there had been a major development of pharmacovigilance (PV) with the main thrust being the use of the invented name plus batch number in adverse event reporting. The EU falsified medicines Directive also requires packs to display a barcode with information on the manufacturer. Further, the directive on cross-border prescription focuses on the invented name and is a strong point for traceability through to pharmacovigilance. Whilst reporting can always be improved, there is a driving awareness of using the invented name and batch number within the EU. At the international level, ISO standards are being written and coming on-stream, and contribute to the overall armoury of helping trace drug substances and drug products. Thus the EU, now having a robust PV system in place focused on the invented name, will not be moving forward with the BQ. The EMA is not objecting to the BQ as a proposal, as it recognises the need to avoid a proliferation of local schemes.

Therapeutic Goods Administration (TGA), Australia

The TGA produced guidance for biosimilars in 2013 in which the biosimilar identifier took the form of a '*sim(a).xxx*' suffix. The driving force for this was that the first biosimilar registered in Australia was named according to INN principles for glycoproteins but resulted in the non-INN non-proprietary name *epoetin lambda* because of clear glycosylation differences (with a presumed lack of clinical consequences) with the reference product. In January 2015, this naming policy was put on hold while WHO deliberated on its BQ scheme. It is the stated policy of TGA to align with the international situation as much as possible.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The PMDA welcomed the WHO BQ proposal as this scheme could clarify biological drug substances having the same INN but with potential differences in the efficacy, safety and quality profile. The Japanese Accepted Name (JAN) scheme for biosimilars is already established in which 'biosimilar' and a sequential number are assigned to the name (e.g. Infliximab(Genetical Recombination)[Infliximab Biosimilar 1]) to distinguish it from its originator. Because this scheme is widely accepted by medical practice in Japan, for the time being PMDA is not planning to replace it with the proposed BQ, as long as consistency between the two qualifier systems can be maintained. As the BQ gets used worldwide, the PMDA will discuss further how an INN BQ could be used in the Japanese regulatory process.

Discussion

In discussion, it was queried how the INN Secretariat would handle a request from USAN for an INN where the USAN already had an FDA four letter code attached. However, USAN or INN applications generally occur during early clinical development, well before marketing authorisation is sought, which is when an FDA or BQ code would be requested. But where an FDA code had been provided, it could be introduced into the BQ database; then when a BQ is requested for the same drug substance, the same code could be applied, and vice versa if the BQ came first and the FDA code later.

A potential problem in harmonisation would be if the FDA code was non-random and assigned to a specific manufacturer so that the suffix could be used for all products from one applicant. The BQ Working Group had discarded a company specific code in favour of a random code as the pharmaceutical industry is fast changing, companies get taken over, sold out, products taken from one to another, and so although initial setup would be simple, in 10 years' time it would be confusing and more complex.

The current FAQ text refers only to proteins. It was explained that this was for simplicity, anticipating that the initial applications for a BQ would be for biotherapeutic proteins. Eventually all biological medicines including polysaccharides and nucleotides would be included and the text would be modified to reflect this.

Clarification was sought on the possible replacement of the Greek letter system for glycoproteins by the BQ, which was considered could be beneficial. Greek letter suffixes were introduced in 1991 for all glycoproteins with identified differences in glycosylation, or for glycoproteins from different manufacturers, to provide a distinct INN to indicate that there are differences that might impact on effectiveness or adverse effects. With a distinct BQ applying to individual drug substances, the need for a distinguishing Greek letter could disappear. This would be reviewed alongside the BQ with experience of its use.

Conclusion

The INN Expert Group had been asked to investigate the possibility of developing a BQ scheme. This had been done and a final version had now been presented to the Expert Group. An FAQ document had been prepared and would be made available to stakeholders. The Chair proposed that the INN Expert Group adopt the scheme and that WHO management takes it on-board. There was consensus by the Expert Group to adopt the proposed BQ scheme.

If the recommendation of adoption gets accepted by WHO management, it has to be widely published to ensure stakeholders see what the scheme will be and guide those NRAs that consider adopting the scheme. A number of organisations had requested a pilot study and so the Chair proposed that a way forward could be to publish the scheme and in six months' time initiate an implementation plan involving a three year pilot study with regular (six monthly) reviews by the INN Committee to assess how the scheme had been taken up, how it had been used, how the database was functioning, and how NRAs which had not adopted the scheme made use of access to it. At the end of the pilot study, there would be a final decision on formal adoption by WHO.

However, the Committee was informed by WHO that prior to any implementation, WHO would wish to undertake an impact assessment because the scheme not only had a bearing on NRAs but over wider aspects of public health. The World Health Assembly had made a statement regarding greater access to biotherapeutic medicinal products and since the BQ scheme had a potential to impact on such access, it was unacceptable for WHO not to consider this prior to implementation. In the meantime, WHO could accept making the BQ proposal adopted by the INN Expert Group publicly available together with the FAQ.

The Chair felt that the INN Expert Group had gone as far as it could but it was clear that there were other factors that impacted on the Group's decision. He clarified that establishing a three year pilot study to generate data would be a preliminary implementation; full implementation would occur after the three year study, if deemed appropriate. However, it stands that the INN Expert Group recommends adoption of the scheme and that it was up to WHO what needs to be done in that context.

In conclusion, WHO emphasised its recognition of the work done on the proposal and thanked the INN Experts for this. The message was that the work was very important and now that there was a scheme agreed by the INN Expert Group, and what it looked like, the WHO can now proceed with an impact assessment.

INN PUBLICATION

Dr Sophie Lasseur, INN Programme Secretariat, gave a presentation on the publication and validation of proposed INN. The increase in more complex requests, especially for biologicals such as monoclonal antibodies and gene therapy products, was highlighted. Alongside the INN, information on the substance such as its chemical name, a description or definition of it, its structure, information on the intended action and use, the CAS RN and the molecular formula (where appropriate) are published. The information published gets validated by INN Experts by cross-checking information supplied by applicants with other sources such as CAS, scientific literature and patents. Chemical substances follow IUPAC nomenclature whilst the amino acid or nucleotide

sequence is published for proteins and nucleic acids/gene therapy products, respectively. INN application forms list the information required for the request although additional information may be sought following approval of the INN. However, it may be useful to provide applicants with a separate document detailing the type of information required for the wide variety of substances for which INN are sought. Both the INN Secretariat and the Chair were very grateful for the Experts who contribute much of their time to publication issues.

CELL THERAPY NOMENCLATURE SCHEME

Naming cell therapy products had been discussed by the INN Experts for several years with proposed schemes getting more and more complicated. At the previous INN meeting four options were discussed: (i) no INN scheme; (ii) directly adopt the USAN scheme; (iii) adopt the most recent INN proposal and negotiate with USAN to harmonise schemes; (iv) adopt a much simpler scheme and negotiate with USAN to harmonise. All had agreed that one single simplified scheme would be best.

Professor Armando Genazzani, Cell Therapy Nomenclature Working Group Lead presented a proposed simplified scheme to the INN Expert Group. In order to keep cell therapy INN simple, the proposal is to discard many of the previously proposed infixes and have such information in the definition component of the INN. The suffix *-cel* would be retained. This would be always preceded by an infix identifying the cell type, for example, *-fi(b)-* for fibroblasts and *-tu-* for tumour cells. An infix for manipulated cells such as *-gen-* for genetically modified cells or *-fus-* for fused cells was proposed; this infix would precede the infix for cell type. As usual, the word would be prefixed with a fantasy syllable. The draft scheme will be available on the INN website. The approach would greatly reduce the number of syllables within a cell therapy INN. Discussions with CBER and USAN had been good and both were supportive of more simple names and were prepared to implement this simplified approach if adopted by the INN Experts. The INN Group would accept as much as possible the infixes used by USAN but would not use the *-T*, *-L*, *-X* suffix that USAN uses to denote autologous, allogeneic and xenogeneic cells respectively whilst USAN would retain this feature. The INN would include such information in the Definition.

The Working Group's proposal for a simplified cell therapy naming scheme was adopted.

Other cell therapy issues

CBER and EMA consider genetic modification of autologous cells to be gene therapy whereas USAN considers this to be cell therapy. Eventually a solution needs to be found and in the meantime it was felt that the INN should treat applications on a case-by-case basis. Whilst it would be worthwhile not to be contradictory with regulatory definitions, there could be differences of opinion between different regulatory agencies. Certainly, when the infix *-gen-* is used, most certainly for genetically modified allogeneic cells, the details would be expanded in the Definition. In addition, for genetically modified cell therapy, it was felt best not to give a separate name for the gene vector, at least for the moment.

ANTIBODY DRUG CONJUGATES

A small working group has looked into the issue of 'look-alike sound-alike' names which, according to the Institute for Safe Medication Practices (ISMP) National Medication Error Program, is responsible for up to a quarter of error reports. The group reported that in 2013, Medsafe, the US FDA and Health Canada alerted regulators to the potential for medication errors between *trastuzumab* (78)(40) and *trastuzumab emtansine* (103)(65). During clinical development in the USA, four patients received the antibody-drug conjugate instead of the antibody by itself. The patients suffered from grade 2 thrombocytopenia and increased liver transaminases; one patient died but there was no proof that the incorrect medication was responsible. The FDA responded to this by modifying the conjugate INN with the prefix *ado-*; however the effectiveness of this is unknown. The Roche/Genentech global safety database reported three cases in the US post-marketing, suggestive of product confusion, but there was a lack of detail in the data provided to draw any firm conclusion. EMA data from the EU indicated four cases of confusion during clinical investigation and post market research from Roche/Genentech reported twelve medication errors, but again with no details. Three cases were reported by Health Canada.

Dr Gilles Mignot presented the review carried out by the *ad hoc* working group. The group concluded that the rate of occurrence of medication errors between *trastuzumab* and *trastuzumab emtansine* cannot be effectively determined but that reported cases highlight the potential for serious harm. The group also concluded that risk mitigation strategies were needed such as the use of the brand name plus the INN, or clearer distinguishing packaging and labelling, but with promotion of the INN as the standard for drug nomenclature. Finally it concluded that the addition of a prefix such as *ado-* or a suffix such as the BQ, requires further evaluation, but that simply changing the order of two word names or adding a suffix/prefix was unlikely to be the answer. It was mooted that the solution could lie in shared responsibility between healthcare workers, IT, regulators, the INN Programme and health authorities.

The Chair felt that there was not much the INN could do towards risk mitigation for such conjugates at this time. When considering applications for drug conjugates, the INN Experts need to be more aware; in the past when *trastuzumab emtansine* was adopted there was no appreciation of the issues that would arise. Reflection on current policy remained valuable but there was little evidence that a short prefix such as *ado-* would suffice. In the meantime the Chair felt that the Expert Group should continue with the use of two word names but at the same time strive to reduce the risk of medication errors.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

The British Pharmacopoeia (BP) is part of the MHRA (UK medicines regulator). BP is responsible for two publications, the BP and the British Approved Names (BAN). The latest edition of the BP is the BP 2015 which was published in August 2015. BP 2016 contained 37 new monographs, 142 revised monographs and is available in three formats, hard copy, online, and as a download. The BP 2016 will be legally effective from the 1st of January 2016. Following stakeholder engagement, BP works with other internationally recognised pharmacopoeias to produce harmonised standards which can be accepted across regions.

The BAN is published every five years with a supplement published annually. The latest BAN is the BAN 2012 Supplement 4 which was published in August 2015 and will be legally effective from the 1st of January 2016. BAN supplement 4 contains 30 new BANs; these are mainly INNs for products that have recently been granted licences from either MHRA or EMA. BAN 2017 will be the next publication to be published and is currently being worked on; it is anticipated that it will include approximately 25-35 new BANs as well as the consolidated BANs from BAN 2012 Supplements 1 to 4.

The BP has recently launched a new website, which has been well received by users and will be developed further over the next few years. The new website has consolidated two previous websites and will contain useful information on current and future projects and programmes of work.

European Directorate for the Quality of Medicines & HealthCare (EDQM)

Some years ago the name of the EDQM was changed to the European Directorate for the Quality of Medicines & HealthCare. This reflected the fact that a number of additional tasks had been taken on by the EDQM, in particular relating to the quality and safety of organ transplants and blood transfusions. Several publications are available on these issues, including the Blood Transfusion Guide (18th Edition), Organ Transplantation Guide (5th Edition), Tissue and Cells for Human Application (2nd Edition), and Volume 20 of the Newsletter Transplant, containing international figures on donation and transplantation in 2014, across the globe.

The principal publication of the EDQM is the European Pharmacopoeia (Ph. Eur.), and Supplement 8.7 was recently published (early October 2015); the final instalment for the 8th Edition, Supplement 8.8, is undergoing final preparations before publication in January 2016. Every 3 years a new edition of the Ph. Eur. is published, and the 9th Edition will appear in July 2016. Due to the increasing number of pages, the 9th Edition will be published in three volumes instead of two. One of the major

changes is a rationalisation and harmonisation of the way that the degree of hydration is presented in the monograph titles.

A new version of the EDQM website has recently been launched, adopting responsive web design to facilitate its use on tablets and mobile devices. It is part of an effort to harmonise the way that the EDQM websites are presented and provide a more user-friendly interface. Last November also saw the launch of the new Standard Terms database, which provides controlled vocabularies in 33 languages (including some non-European languages) for pharmaceutical dose forms, routes of administration and packaging items, and is used throughout Europe for Marketing Authorisation Applications, product labelling and electronic communications.

This year marks the 60th anniversary of the European flag, which was originally adopted by the Council of Europe in 1955, and approximately 30 years later was also adopted by the European Union. A booklet is available describing the origin of the flag, and also showing how the Council of Europe and European Union work together, while also indicating the differences; for example the European Union has 28 member states while the Council of Europe has 47, with many observers including the EU itself and the WHO.

International Union of Biochemistry and Molecular Biology (IUBMB)

IUBMB is mainly concerned with enzyme nomenclature and since the previous INN meeting, 95 new enzymes have been published, with one new sub-sub-class, 27 entries modified, 13 transferred to a new number and four deleted, making a net new entries of 82 enzymes.

If INN wants to use IUBMB EC numbers for enzymes it should bear in mind that IUBMB records characterised enzyme catalysed reactions and not proteins. Hence to be unique the species from which it was originally obtained should be stated.

The EC number for an INN may be found by searching the website¹. This is a string search and so the whole name may not be needed. Each entry has links to other databases, for example BRENDA, ExPASy, Kegg, Metacyc and if relevant Merops, PDB, UM-BBD, and may have the CAS registry number. All identified alternative names are listed. Hence a search of the website may locate the relevant entry although the name used in the INN application is not the accepted name. The other names include gene names as many authors refer to enzymes in this way. Ambiguous and incorrect names are flagged. Many entries have links to diagrams of metabolic pathways involving that enzyme.

IUBMB welcomes information on enzyme reactions not listed and that are well characterized. However it should be noted that a reaction is interpreted as the same if the peripheral parts of the substrate do not significantly affect the reaction. Some enzymes give more than one product from the same starting substrate. These may be listed as separate enzymes where each is rated as a separate different reaction.

International Union of Pure and Applied Chemistry (IUPAC)

A new IUPAC publication of relevance to this meeting is ‘The brief guide to the Nomenclature of Inorganic Chemistry’ of which a free PDF is available². Dutch, German, and Spanish translations are in preparation; others are planned. The document was designed to be printed on four sides of a folded A3 page. It will parallel similar brief guides to polymer nomenclature³, physical constants and a planned one on organic nomenclature. The new guide will be published as a pull out supplement in *Chemistry International*. Another publication to note is Nomenclature and graphic representations for chemically modified polymers (IUPAC Recommendations 2014)⁴ which also is available free from the web.

¹ www.enzyme-database.org/

² *Pure Appl. Chem.*, 2015, **87**, 1039-1049. doi.org/10.1515/pac-2015-0505

³ *Pure Appl. Chem.* 2012, **84**, 2167-2169.

⁴ *Pure Appl. Chem.* 2015 **87**, 307-319, erratum page 441

Work continues on identifying inconsistencies and errors in the new *Nomenclature of Organic Chemistry, IUPAC Recommendations and Preferred Names 2013*, RSC 2013⁵.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The mission of the Division of Pharmacopoeia and Standards for Drugs of the PMDA is to prepare Japanese Accepted Names (JAN) as the JAN Secretariat and to prepare the Japanese Pharmacopoeia (JP) as the JP Secretariat. The JAN Expert Committee has 17 members and meets four or five times per year, assessing 50-60 submissions each year. For the period April 2016 through October 2016, 36 names were added to the JAN. The JP will publish its 17th edition in January 2016, containing 1,962 Monographs, 78 General Tests and 50 General Information. In September 2016, the English version of JP17 will be published and also the International Meeting of World Pharmacopoeias will take place in Tokyo.

United States Food and Drug Administration (FDA)

The update from the US FDA representative was essentially the document that was tabled during the BQ discussion (see Biological Qualifier/update from NRAs/US FDA).

United States Pharmacopoeia (USP)

The USP is making efforts to reach out and be a significant healthcare agency worldwide. It has worked with the United States Agency for International Development (USAID) to help developing countries address issues of poor quality medicines by creating the program 'Promoting the Quality of Medicines' (PQM). PQM serves as a primary mechanism to help USAID-supported countries strengthen their quality assurance (QA) and quality control (QC) systems by building training centres with analytical laboratories. In 2013, USAID extended the PQM program for five years and expanded its geographical reach.

The USP convention was held in June and was the first convention for its new leadership. The 'Nomenclature, Safety and Labelling' committee became 'Nomenclature and Labelling' committee, with the safety aspects being addressed in the newly formed 'Healthcare Quality' committee. Throughout its near 200 year history, USP has worked to ensure patients receive high-quality, safe and effective medicines. USP achieves this through its legally recognized role in setting public standards for purity, quality, strength, packaging, and labelling of drugs and biologics. As part of this role, USP is involved in a well-established drug naming system, which includes naming of biologics. USP is different than other pharmacopoeias in that it is an independent standard setting organization not part of the federal government. In addition, its role is written in the legislation such that the USP monograph title is recognized for the purpose of labelling for both biologics and chemical drugs. The recently published FDA rule on naming six biological products, three of them based on *filgrastim*, make monograph development very difficult as the USP cannot have two different monograph titles for products with the same identity and it cannot refer to more than one compendial name in the same monograph. USP is working on comments to be submitted for both recent FDA publications on biologics nomenclature.

IDMIS

Dr Antonio Romeo, IDMIS Manager, INN Programme, reminded Experts on how to access the IDMIS system for entering comments post-meeting, since there are differences in doing this compared to entering pre-meeting comments. He also reminded Experts on accessing the electronic Share System where meeting documents other than INN applications can be posted and accessed.

He reiterated the use and value of WebEx for small working group meetings, noting that with such a system one has visual as well as audio contact with other meeting participants although use of a phone for connecting to a meeting usually gives superior sound quality.

CLOSE of MEETING

⁵ See www.chem.qmul.ac.uk/iupac/bibliog/BBerrors.html for a list of the main corrections.

In closing the 61st INN Consultation, the Chair thanked the Experts for their work, both at and prior to the meeting, on the record number of applications, the most there had ever been. He thanked especially the INN Secretariat for the massive amount of work they perform in the background. This was the Chair's 25th Consultation and on standing down from the chair he gave his best wishes to all, and especially to Dr Patience Holland who would succeed him as Chair.

In return, Prof. Calam was thanked not only for his excellent chairing of the 61st Consultation but also for his great leadership through these past 25 Consultations and in doing so the immense contribution he has made to the INN Programme.

NEXT MEETING

The 62nd INN Consultation will take place at WHO Headquarters, Geneva, 12-15 April, 2016.

OPEN SESSION for INN Stakeholders

61st INN Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 13 October 2015

The Open Session for INN Stakeholders meeting adjoining the 61st INN Consultation was opened and participants welcomed by **Dr Patience Holland**, vice-chair, INN Expert Group.

Dr Lembit Rago, Head, Regulation of Medicines and other Health Technologies (RHT), joined in welcoming participants to the Open Session which he noted had been running for several years. It provides an open platform upon which stakeholders can raise concerns, forward opinions, or provide experts with extra information. It is also vital for increasing transparency. Dr Rago wished all a productive meeting.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team, also extended a warm welcome to experts and stakeholders alike, for this two hour session where views and concerns can be expressed. He highlighted a new WHO policy of increased transparency of experts and expert groups, whereby the biographies of experts are posted on the WHO website for public scrutiny in advance of meetings.

Dr Raffaella Balocco-Mattavelli, Group Lead, INN Programme, was pleased to greet colleagues and friends, both old and new.

The Chair, **Prof. Derek Calam**, added his welcome to both old and new colleagues. Whilst the meeting was termed an Open Session, in reality all items discussed should be kept confidential. The agenda was divided into two parts, the first would have four presentations covering policy issues and the second part would focus on specific INN applications. The original purpose of the Open Session was to allow INN applicants to provide more details regarding their applications; representation on policy matters was relatively new and had been very valuable.

PRESENTATIONS on the BQ PROPOSAL

Alliance for Safe Biologic Medicines (ASBM)

The ASBM was grateful for the opportunity to speak and praised WHO on its leadership on this issue. The Alliance has conducted several surveys on healthcare attitudes to drug identification. It had noted a developing consensus amongst prescribers and patients for support for distinguishable names, clear product identification and accountability, whilst there was significant potential for confusion if a distinguishing name was lacking. At this meeting data were presented from two new surveys, one involving Latin American physicians and one on US pharmacists. In the Latin American survey, the importance of distinguishable names was highlighted although a majority of those surveyed used only the INN in identifying a medicine in a patient's records whilst 28% use the INN only when reporting AEs. There was overwhelming support (94%) amongst Latin American physicians (N=399) for the BQ scheme, as there was amongst European, American and Canadian physicians. The Alliance is encouraging its members to comment on the FDA draft guidance for biologics nomenclature noting however that the proposed suffixes for six products would be hard to remember and more meaningful names would be better.

With the increase of biosimilars in the US, pharmacists have been warming to the idea of distinguishable naming and the use of suffixes, and so support what has been done to establish the BQ. A recent survey of US pharmacists demonstrated a need for improved understanding of INN for biosimilars and the ASBM has been providing continuing education courses for pharmacists in this area. The survey also highlighted that a good majority of those polled would like the FDA to require distinguishable names whilst a strong majority felt that a distinguishing suffix should be meaningful and not random, with a preference for a manufacturer suffix.

The Alliance highlighted the value of clear communication and collaboration between healthcare providers but emphasised that the BQ should be meaningful, memorable, and communicative to healthcare providers, rather than meaningless and random.

European Generic medicines Association (EGA)/European Biosimilars Group

The vision of the EGA is to provide sustainable access to quality medicines. The Association appreciated the effort WHO was making to avoid a proliferation of divergent schemes for biologics around the world; although despite this, proliferation continues. Biosimilars have been systematically developed to be highly similar to their reference products. In highly regulated markets, regulatory authorities determine if sufficient comparability/similarity has been demonstrated; where it is demonstrated, no new INN should be required, and drug substances from different manufacturers should therefore be entitled to get the same INN. It was also highlighted that the intent of INN is the identification of the drug substance and not of drug products.

To identify specific drug products, a variety of identifiers are available such as the tradename, 2-D data matrix code (being established within the EU under the Falsified Medicines Directive), ISO standards, national drug codes and unique batch numbers. EGA highlighted in particular the ISO standards for identification of medicinal products (IDMP) which are currently being implemented in Europe. These international standards have been developed to establish a lasting framework which allows exchange of medicinal product information in a robust and reliable manner. These ISO standards, developed first within ICH and then in collaboration with various global stakeholders, cover also unique identification of each substance, defined based on what they are and not on how they are made or used. Thus does a new identifier add real value or would it simply increase complexity and confusion? Consequently, the EGA does not support the BQ in its current form – a random identifier can cause confusion, is hard to remember and is likely to be miss-spelled or even not recorded. Furthermore, any new identifier system must be tested systematically to ensure it does not do more harm than good. EGA believed that the WHO proposal should not be implemented before a majority of regulatory authorities agree to its use and with the recent publication of FDA guidance, called for increased international dialogue. EGA remained supportive of the use of trade names or the INN plus company name, but whilst it appreciated the efforts of WHO to maintain a globally unified naming system for biological medicines, it did not support the BQ proposal in its current form and called for a moratorium.

In discussion, the value of ISO standards was acknowledged but that they needed to be adopted internationally, citing the various formats for presenting dates, which remain non-aligned at the international level. However there was probably merit in WHO continuing to look into these and to what extent the BQ may fit into ISO standards.

It was also noted that several points raised by the EGA were valid, but only in Europe which has an enforceable tracking system. Whilst the EU had stated that it would not use the BQ, there are many other countries that may use it as a way of tracking and in prescribing. Further, whilst the EGA representative had also commented that more needs to be done to assess the impact of the BQ, the window of opportunity in which regulatory authorities could adopt the BQ system was closing as national entities such as the FDA created their own identifier system. Thus, to delay would exacerbate the situation of inconsistent national naming.

Generic Pharmaceutical Association (GPhA)

The WHO proposal of a 4-letter non-meaningful qualifier was a concern to the GPhA. It felt that the BQ would increase complexity and the non-meaningful aspect would be confusing. In addition, it was not clear that it would provide the enhanced pharmacovigilance it sought. The GPhA affirmed that if the BQ was to be fully considered it must be independently tested before moving forward. It also requested that the BQ scheme not be finalised until a consensus was reached by regulatory authorities.

Globalisation of names is an important component of identification and so naming must be simple and intuitive. Currently drugs have two names, the brand name for the product and the WHO INN for the drug substance, a global non-proprietary name based upon rules that are science-based and adequate.

INNs have never been the name of the final product; other names or unique identifiers are for product recognition including the company name, lot number or the US national drug code number. In addition, distinct packaging design with multiple distinguishing identifiers supports the adequacy of current identification systems, including for biosimilars. Consequently, the GPhA cast doubts on the value of an additional BQ identifier.

The GPhA's message was that safety is enhanced with globalisation of non-proprietary names. INNs help healthcare professionals identify the active ingredient and biological medicines are typically dispensed in a controlled setting, usually in hospitals, clinics or specialist pharmacies, with detailed dispensing records for individual patients. The random identifier currently proposed by the US FDA was also a concern to the GPhA and along with other associations it advocated the use of the same INN where products contain the same active ingredient. A unique INN was not necessary to distinguish biosimilar products and was opposed by pharmacy and medicine stakeholders.

Application of the BQ needed to be voluntary and should not be implemented in highly regulated jurisdictions such as the EU where legal measures are in place to unambiguously identify biological products. If used it should be applied retroactively and prospectively. It should not be required for prescribing and should not include a manufacturing site designation. While the intent of the WHO INN Committee was to provide guidance on how to use the BQ, if not improved upon, there would be unintended consequences that could lead to unequal adoption, impact patient access and, potentially, safety.

The FDA representative added that the proposed FDA rule and guidance, whilst very similar to the WHO BQ, was arrived at independently from BQ development. The proposed rule for six products was considering meaningful suffixes with the company name and one option would be to use the same company code for each active ingredient. However, the FDA and WHO have been working together to resolve differences between the two proposals.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

IFMA strongly supported the concept of a BQ and supported the WHO's efforts to develop a BQ scheme. It viewed the BQ as an important adjunct to pharmacovigilance systems and would enhance patient safety by acting as a global link, especially as pharmacovigilance procedures were not harmonised and varied between countries. The IFPMA recommended application of a BQ to all biologicals and not just biosimilars. The 4-letter code was supported although a memorable code was preferred to a random one. Indeed, it would be useful to link it to the parent company responsible for global licensing and to use the same BQ for each of a parent company's biological drug substances. That would enhance memorability, avoid a proliferation of BQ and assign clear responsibilities regarding product tracking and pharmacovigilance. Alignment of the WHO BQ with national practices such as the recent FDA proposal was supported. Whilst it would be better to have active use of a BQ by DRAs, the IFPMA understood that there may be passive use of BQ by DRAs and where this occurred DRAs should accommodate its use so that marketing authorization holders did not have to undertake separate product labelling and other information for that jurisdiction. Finally, the added value that the BQ offers in support of traceability and PV necessitated its introduction as soon as possible.

In summary, the IFPMA strongly supported the adoption of a BQ linked to the parent company responsible for global licensing. It supported a 4-letter code, with memorability preferred, and proposed that the same BQ gets assigned to each parent company drug substance. The IFPMA further recommended the WHO to work with other DRAs to harmonise a single global qualifier and DRAs should implement the BQ as soon as possible.

In discussion, it was noted that all four speakers had raised the issue of memorability. This had been an issue for the BQ Working Group also. The use of codes linked to an applicant's name had been canvassed at an earlier meeting with regulatory authorities and whilst opinion was divided, the majority preferred a random code so that codes do not get changed when a company gets bought, sold or taken over. Using the same BQ for all products by the same company was also considered by the

Working Group but feedback from DRAs indicated that they did not wish a code linked to a particular sponsor.

In trying to convey the problems that had been faced by the BQ working group, the Chair added that the INN Expert Group has been trying to develop a robust scheme that will survive intact for 20 or more years. Whilst memorability would be good, the increasing number of biologicals manufacturers, companies being bought, dissolving, and products getting sold between companies, the value of a company specific BQ would be greatly diminished and so the Group had discarded this form of BQ.

PRESENTATIONS on INN APPLICATIONS

Aquinox Pharmaceuticals, Inc.

A request for an INN with a novel stem for the Aquinox compound AQX-1125 in 2014 had been deferred for more information on the mechanism of action and the company was present at this Open Session to justify its request. AQX-1125 is an activator of lipid phosphatase SHIP1 with anti-inflammatory and anti-chemotactic activity. SHIP1 is expressed predominantly in hematopoietic cells and is a negative regulator of the PI3K-Akt pathway. There are currently no unique stem classes for compounds that modulate phosphatases that are not immune-suppressants. With nonclinical and clinical data suggesting an absence of steroid activity, the company therefore proposed a new INN stem, *-sipavor* or *-sipactor*, to encompass this novel mode of action of phosphatase activation.

Further, AQX-1125 is not an androgen, having an open B-ring and not an intact 4-ring steroidal structure. It is not immunosuppressive and has none of the toxicities known for androgens. The company maintained that its inclusion in the androgen class of anabolic steroids could cause confusion in identification of potential use indications and appropriate patient populations.

With other SHIP1 modulating compounds in the pipeline and with no pre-existing stem that AQX-1125 fits into, the company respectfully requested the assignment of a novel stem with *-sipavor* or *-sipactor* being proposed.

Ignyta Inc.

A lead Ignyta compound RXDX-101 had been assigned the INN *entrectinib* but this had been the subject of a formal objection on the basis that *entrectinib* is a homophone of the family of genes that encode for TrkA, TrkB and TrkC proteins (NTRK genes). The company made representation at the Open Session to justify retention of *entrectinib*.

RXDX-101 is a first-in-class inhibitor of TrkA, TrkB and TrkC proteins. Hence, Ignyta had proposed the infix *-trec-* to connote this unique protein target. Importantly, RXDX-101 targets Trk protein receptors and not the genes that encode them, emphasising that it has no effect at the genetic level. Thus, any concern regarding *entrectinib* as a homophone of the NTRK genes is irrelevant and should be discarded.

RXDX-101 is performing well in on-going phase II studies. An example was provided of a 46 yr old male with metastatic NSCLC who had not responded well to several prior therapies, who required supplemental O₂, and was in a hospice. One month treatment with *entrectinib* resulted in near complete resolution of disease in the lung whilst the drug also seemed to pass the blood brain barrier with metastases in the brain also resolved or reduced.

The company proposed that the given pINN exemplifies the principles of the INN. There was a strong precedence established by previous INN nomenclature for targeted kinase inhibitors such as the *-brutinib* infix connoting Bruton tyrosine kinase inhibitors. The name *entrectinib*, with a *-trec-* infix had been adopted as a pINN and a USAN, and with it having no effect on NTRK gene expression, the company respectfully requested retention of *entrectinib*.

UCB pharma SA

UCB0942 is a novel chemical entity in development specifically for the treatment of highly drug-resistant focal seizures. UCB0942 had been specifically designed to combine an imidazothiadiazole heterocycle and a pyrrolidone moiety within a specific chemical scaffold to provide a unique dual-

mechanism of action and enhanced anti-epileptic activity. The drug demonstrated greater efficacy in animal models when compared with available anti-epileptic drugs and was currently in phase II development. The company sought an INN that reflected the unique structure, function and efficacy of this specifically designed new chemical entity.

The imidazothiadiazole motif is unprecedented in the field of anti-epilepsy drugs and was the only heterocycle offering the right balance of properties for both SV2 and GABA-A receptors. The pyrrolidone moiety is essential for SV2 affinity and is not sufficient on its own to afford differentiated *in vivo* efficacy. Thus, it is a dual acting compound whose unprecedented anti-epileptic efficacy did not result from a simple juxtaposition of pharmacophoric elements; all substituents and groups are essential within a specific scaffold for the dual pharmacology profile.

It had broad spectrum activity and remarkable efficacy in ten preclinical models of seizures and epilepsy and had superior efficacy against drug-resistant seizures. It had even greater efficacy in a mouse model compared to a combination of levetiracetam and diazepam that attained the same binding levels to SV2A and GABA-A.

The company requested an INN that reflected the unique structure and efficacy of UCB0942 and proposed a *-nil* stem to denote the GABA-A agonism and a *-sevo-* or *-race-* infix. Several names with these infixes/stem were proposed.

CLOSE OF MEETING

The Chair remarked that all presentations had been very helpful. Discussion on the BQ continues and the presentations from the three INN applicants would be very useful to the Group by providing additional detailed material regarding their applications. Stakeholders are allotted very little time but the presentations were very valuable to the INN Committee. Expressing his thanks to all, the Chair closed the session.

APPENDIX 1

Tabled statement from the Food and Drug Administration (FDA), USA

- FDA has carefully considered the appropriate naming convention for biological products in the U.S. market to help ensure the safety of patients, improve pharmacovigilance, and avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway.
- On August 27, 2015, FDA issued draft guidance for industry on how biological products should be named. The FDA believes that the nonproprietary names of all biological products should include a core name that is the name adopted by the USAN Council, when available, followed by a hyphen and a designated suffix composed of four lower case letters.
- In the United States, the vast majority of our healthcare uses electronic systems to prescribe and record the administration of drugs, and the name is a common identifier of the products throughout these systems. The use of the hyphen to connect the core name to the suffix will help ensure that the name appears in these systems as one unit and will help minimize the risk that the suffix will be dropped or lost.
- This approach will enhance FDA's ability to track adverse events to a specific manufacturer and biologics license application, which includes manufacturing site information, so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address any problems. It will also enable surveillance systems to detect safety signals throughout the lifecycle of a product.
- With respect to format, FDA's current thinking is that the designated four letter suffix should be devoid of meaning.
- However, FDA has invited public comment on alternative formats for the designated suffixes, including:
 - Whether the suffix should be meaningful, such as a sequence of four letters derived from the name of the manufacturer, known in the U.S. as the license holder.
 - Whether the suffix should be unique to each product or shared by each biological product manufactured by the same license holder.
- We propose to apply the convention to originator products as well as biosimilars. And, we plan to apply this naming convention to both previously licensed and newly licensed biological products.
- Consistent with this intention, FDA issued a proposed rule at the time we issued the draft guidance. The proposed rule would require the designation of nonproprietary names that contain a distinguishing suffix for six previously licensed biological products.
- We also are continuing to consider whether an interchangeable product should be assigned a unique suffix or should share the same suffix as its reference product. Under the U.S. law, there are two types of biological products that may be approved under an abbreviated licensure pathway - biosimilar products and interchangeable products, which must be biosimilar and meet additional standards.
- FDA's approach has some similarity - as well as differences - with the World Health Organization (WHO) proposal, "Biological Qualifier—An INN Proposal" that was presented in June 2015. Overall, we believe the approach we have outlined may be compatible with the BQ and achieve similar goals.
- FDA recognizes that the WHO INN Committee is still evaluating the comments received on its proposal, and we too are still considering comments on our draft guidance. We have invited public comment on our draft guidance along with some targeted questions of interest to FDA, including how biological qualifiers generated by WHO should be considered in the determination of an FDA-designated suffix for a U.S.-licensed biological product, were the INN Biological Qualifier proposal adopted.
- The FDA welcomes comments to the public docket on the draft guidance until October 28th and on the proposed rule until November 12th. Instructions for submitting comments to the public docket can be found on the FDA webpage www.fda.gov/biosimilars.