

***64th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 4-7 April 2017***

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***

© World Health Organization 2017

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

64th Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 4-7 April 2017

EXECUTIVE SUMMARY

INTRODUCTIONS

The 64th INN Consultation was opened by Mrs Emer Cooke, new Head, Regulation of Medicines and other Health Technologies (RHT), which oversees the work of Technical Standards and Norms (TSN), of which the INN Programme is a part.

Mrs Cooke highlighted that the overall goal of the diverse activities of RHT is the access of safe high quality medicines to patients. To enable that the department has to consider not only what goes into a Marketing Authorisation or a Prequalification but also that systems are in place to ensure authorised medicines get to patients, to follow-up with pharmacovigilance, to identify falsified medicines, and to provide appropriate feedback following problems in order to protect patients. Overall, all processes need to be integrated and contribute to this final aim of access to safe, quality, and efficacious medicines, and the work of the INN ensuring that medicines are appropriately named is an important contribution to those goals. Mrs Cooke looked forward to contributing to the important work of the INN Group.

Prof Sarel Malan was proposed as new Chair of the INN Expert Group and was elected unanimously. Prof Malan felt it an honour to be Chair of the Expert Group and hoped that all members would provide him with support. He proposed that Prof Armando Genazzani continue as vice-chair for biologicals and that Prof Wai-Keung Chui gets elected as vice-chair for chemicals, and these were agreed by the Group. Dr Jim Robertson was proposed as rapporteur and this was agreed. The Chair welcomed Mrs Cooke to the meeting and looked forward to her input.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN), thanked Prof Malan for taking on the responsibility of the Chair and thanked all individual experts for their contributions on behalf of WHO. The INN agenda has grown enormously in recent years with a phenomenal number of INN applications, and when he mentions this to colleagues, they are surprised at the high level of work achieved. He noted that in addition to the new Chair, there were new Expert members, and that it was useful to refresh such Expert Committees as it helped with new ideas. Dr Wood was imminently about to retire from WHO and hoped that a successor would be in place soon to take over charge of the TSN team.

Dr Raffaella Balocco Mattavelli, Group Lead, INN Programme, joined with the others in welcoming all participants to the Consultation.

EXECUTIVE SUMMARY

The Executive Summary of the 63rd INN Consultation was tabled and approved.

NOMENCLATURE of INNs

During the 64th INN Consultation, a total of 161 INN requests were discussed, including:

- 109 new INN requests, including 55 for biological substances
- 49 outstanding requests
- 3 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 149 names were selected, which are planned to be published in List 118 of Proposed INNs (p.INN), while 2 requests were deferred for future discussion. Two applications were planned to be closed if the requested information is not received on time for review at the next INN Consultation. Four requests were rejected by the INN Expert Group, as the

substances did not conform to the criteria for INN selection. One INN application already had a published Recommended INN and two applications were withdrawn. One amendment was planned to be published in a forthcoming List of p.INN and one request of substitution could not be retained as it did not conform to the criteria. Four new stems/substems were selected, 6 suffixes were promoted to the pre-stem list and it was decided to amend the descriptions of two stems.

INN and the INN Procedure

The WHO Constitution requires it “to develop, establish and promote international standards with respect to biological and pharmaceutical products” and this has been accomplished for more than 60 years through WHO Expert Committees. Expert committees are official advisory bodies to the Director-General. They are established by the World Health Assembly (WHA) or the Executive Board (EB) and three such committees exist: the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (the ‘INN Expert Group’), the WHO Expert Committee on Specifications for Pharmaceutical Preparations, and the WHO Expert Committee on Biological Standardization. The committees are responsible for the development of WHO global standards and norms that are robust, durable and responsive to public health needs, and include written standards, measurement standards and INN. Reports from these committees get presented to the EB.

The latest amendments of the official ‘Procedures’ for INN were approved by the EB in 2004 and included the facility for substitution of an INN and the adoption of the name ‘the INN Expert Group’. Provisions were also made on submission of INN proposals to the Secretariat followed in turn by submission to the INN Expert Group, on giving notice of proposed INN by publication and by letters to Member States, on the submission of comments and formal objections to proposed names, and on the promotion of a proposed name to a recommended name. A new article, Article 9, provided in detail for the extraordinary circumstance of substitution of a recommended INN due to errors occurring in medication, prescription or distribution due to similarity with another name. Substitution requests require comments from all Member States, pharmacopoeia commissions and other interested bodies. Submitted comments get assessed by the INN Expert Group, the original applicant and the person making the proposal for substitution. Historically, requests for substitution have been extremely rare.

Provision of CAS

Clarification had been requested on when the CAS had to be supplied during an application for INN, specifically for high molecular weight substances. INN guidelines will be clarified that the CAS should be provided at time of submission only if it is available, but that it must be provided prior to publication of a new INN.

Promotion of Suffixes to Pre-Stems and of Pre-Stems to Stems

Common suffixes are generally promoted to pre-stem status when about three or more have been used in new INN. Pre-stems are generally promoted to stem status when about five or more have been assigned. As stems are protected from use in trademarks and other instances, there is an advantage in creating them as soon as possible; however, this has to be balanced by not inappropriately creating a stem after a few requests have been received in quick succession for the same new suffix, after which there may be no further requests for the suffix. The value of the pre-stem status (which is not protected) is to flag to applicants and to INN Experts of the existence of a new suffix which may be appropriate to an applicant’s application for INN.

On-hold publications

There is a new tendency for some applicants, having accepted a proposed INN, to request that Secretariat postpone publication in the Proposed List, the reason perhaps being to withhold public disclosure of information pertaining to the substance until a further stage of its development has been reached. However, excessive postponement causes problems with procedures, data management and a risk of confusion when creating new names. Consequently, the Secretariat proposed to warn

applicants that a postponement can occur only once after which the name would be lost and a new application would be required. This proposal was accepted by the Expert Group.

SCHOOL of INN

A meeting was held in January to formalise the structure of and the way forward for the nascent School of INN (SoINN). Three subgroups were proposed: (i) an overarching steering committee that would handle communications and cooperation, (ii) a training subgroup, and (iii) a publications subgroup. Three additional INN Experts were invited to join the steering committee to spread the work and provide more input; other Experts were welcomed also, if they wished to participate.

A SoINN website will be created within the INN hub of the WHO website and a suggestion had been made to use Yoodle™ technology for online teaching. Infographics have been done and pages can be displayed at conferences. The first formal SoINN presentation will be given in September (2017) following an invitation to the FIP World Congress of Pharmacy and Pharmaceutical Sciences, in Seoul. A SoINN logo is needed and Experts were asked for ideas.

With regard to publications, the 'Guidance for INN' is being revised and the role of SoINN will be described. An article describing the survey performed in 2016 of students, academics and stakeholders on their familiarity with INN will be finalised shortly and will be published in WHO Drug Information. Following this, an article on the use of INN in teaching or on feedback from the survey was felt useful. A review on naming biological substances is currently being drafted and will include chapters on current rules of and considerations for gene therapy, vaccine-like, monoclonal antibody and biotherapeutic protein substances. A thought stimulating paper with a broad perspective on current problems in naming biological substances was also felt to be useful.

Work is in progress on a chapter that could be included in Goodman & Gilman's pharmacology textbook, incorporating ATC classification and the INN from each grouping. A further venture could be to prepare supplementary material for any pharmacology textbook that could be used by teachers. In that respect, the use of INN in teaching pharmacology is being introduced at pilot sites at the University of Piemonte Orientale, Italy, the University of the Western Cape, South Africa, and the National University of Singapore, starting with the next academic year. In terms of eLearning, this could be trialled on the annual course for industry, and ultimately would be available on the website.

UPDATE on MABS

At an *ad hoc* meeting on naming biologicals held in September 2016 and in a WebEx in March 2017, INN biological experts along with colleagues from the US FDA and USAN discussed the naming of mAbs, specifically to assess the current value of the two infixes, one for the target and one for the source of the mAb genetic sequence, with the intention of reducing the complexity of mAb names. From these discussions the biological experts agreed to drop the source infix as it does not convey information on immunogenicity and there is a need for more flexibility in creating mAb INN. Information on the source would instead be included in the Definition. In dropping the source infix, the vowels 'i', 'o' and 'u' immediately preceding the *-mab* stem should be avoided (as they allude to the source of the mAb). With regard to the target infix, it was felt that new and more specific target infixes should be sought. Further, the target infix could comprise the consonant only and could follow that of other substems in other schemes. Finally, it was noted that a very important factor would be dissemination of any new scheme.

In discussion, it was reinforced that communication of dropping the source infix was crucial, or the INN programme would be criticised for rushing through a major policy change that would have a major impact on manufacturers. It was also opined, however, that it was premature to drop the source infix, as many mAb INN have already been reduced in complexity by using one syllable for both the target (a consonant) and the source (a vowel) infixes, although humanised mAb names still need to be shortened, but for the moment it was still useful to know if a mAb is humanised.

With regard to target infixes, an expanded list of possible target infixes was tabled, some of which were revisions of existing infixes which had to be changed to avoid having the vowels 'i', 'o' and 'u'

preceding the *-mab* stem. However, an alternative opinion was that it was better to retain the current wide target range of infixes, e.g. immune, cancer, or cardiovascular.

In concluding the discussion, the Chair proposed the removal of the source infix from mAb INN, which was agreed by the INN Expert Group. It was also agreed to apply this new approach to names being assigned at the 64th INN Consultation on a case-by-case basis. Whilst applicants had submitted potential names taking into account a source infix, they have the opportunity to reject an alternative name that omitted the source infix. Changes to the target infix were not finalised at the meeting. For the US FDA, the derivation of new specific target infixes similarly remains a work in progress.

The Antibody Society had recently contacted the INN Secretariat offering help in communicating any change to the mAb naming scheme and this would be followed up. Also, there should be a harmonised approach with the US FDA and USAN, which was endorsed by the FDA representative.

ADVANCED THERAPIES

Following a discussion with the US FDA and USAN via WebEx on descriptions for cell and gene therapies, a small working group with representation from INN, FDA and CBER, was established. The proliferation of documents on cell and gene therapies has culminated in a single INN document covering the naming schemes for all ‘*Advanced Therapies*’ –gene therapies, cell therapies and genetically engineered cell therapies. The group needs to establish a detailed list of what is required from applicants for the Definition of cell therapies.

The INN Experts were also asked by FDA/USAN to reassess the INN stance naming peptides used for ‘active immunisation’. Both INN and USAN do not consider these to be vaccines, and both agencies apply the stem *-motide* to them. However, whilst USAN will assign a name to specific mixtures of peptides in which the peptides cross-react as active substances, it was reaffirmed that the INN would not assign an INN to such mixtures.

The INN also affirmed that mRNA being used to transduce cells would be included in the Advanced Therapies document.

FUSION PROTEINS.

Fusions proteins are unique substances derived from a single novel gene created from two or more genes (or parts thereof) by recombinant technology. A fusion protein working group has been considering proposals made at the 63rd Consultation on naming fusion proteins and concurred that the best way forward was to assign the proposed new suffix *-fusp* to these substances. The new suffix would be used only where two or more distinct activities have been brought together in the fusion protein and where it is not clear which activity is the more important. The new suffix is not for conjugated proteins; nor would it be used where the fusion protein has a clear single action and the extra part is to increase the half-life. mAb-mAb fusions would probably be named with the *-mab* stem.

The working group also proposed that an infix comprising two letters to indicate the target would be useful. It was considered that an infix indicating the mode of action was not appropriate as this can change with time. Full details of a fusion protein would be provided in the Definition.

Of the two fusion proteins that were named with a *-fusp* suffix at the 63rd Consultation, one was accepted by the applicant and one was not; the applicant that did not accept the proposed name wanted to highlight the target infix more and was not against the *-fusp* suffix as such.

The Expert Group agreed to the introduction of the *-fusp* suffix and to name pending fusion protein applications using the new suffix. It was suggested that the SoINN would be a useful route to increase awareness of the new term.

BIOLOGICAL QUALIFIER UPDATE

Introduction of a Biological Qualifier (BQ) was recommended by the INN Expert Group to WHO at the 61st INN Consultation. WHO management responded with a request that a pilot study be

performed before implementation, to assess the impact of a BQ on the uptake of biotherapeutic medicines, especially biosimilars. Unfortunately, a glitch in legal processes held up progress, by which time new WHO management further stalled advancement by announcing that a WHO meeting would take place in early May (2017) to analyse access to biotherapeutics on a global basis from an holistic point-of-view. Participants to this meeting would be invited from WHO regional offices, other agencies, member states, patient associations and industry representatives. The meeting would examine the role of biosimilars globally, how to achieve greater market penetration at affordable prices, matters which were not an issue for the INN Group. The issue of the BQ would be on the agenda but would only be a small part of the discussion. Two members of the INN Committee would be invited to attend to support the BQ.

In preparation for the May meeting, the INN Secretariat had prepared a document on the BQ that would be included in the paperwork available to meeting participants. Also, an internal INN memo was drafted detailing the consequences of not adopting the BQ, viz., the absence of a global ID system for biotherapeutics and the proliferation of disparate national schemes, the continued use of Greek letters for glycosylated proteins with the certainty that they will run out, the potential for Greek letters being used inappropriately by national nomenclature agencies, and poor traceability, amongst others.

Both the Secretariat and Experts expressed their frustration at the sequence of events that had led to this situation and were despondent about the future of the BQ. With the US FDA having recently recommended the use of a similar (but distinct) coding scheme for biotherapeutics, it would additionally be an uphill struggle to have the BQ launched and established as a global identifier for biotherapeutics.

The Chair wished the Experts attending the meeting good luck in espousing the BQ. The report from the meeting would be considered at the next (October 2017) INN Consultation.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

Supplement 1 of BAN 2017 (published 2016) is in progress. In the UK there are two ways of legally naming a drug: INN and BAN. As both are part of legislation in the UK, the British Pharmacopoeia was able to choose how best to include entries for the BAN list; currently this was only done for substances that are in (or have been in) marketed products. For the BAN 2017 Supplement 1 there were forty-seven new entries that corresponded to new products that entered the UK market in 2016, twenty-one of which were biologicals. It was noted that more and more new biologicals were being taken through to market and now the ratio of small chemicals to biologicals was matching that observed in INN applications and the first gene therapy BAN was due for publication in the Supplement. The BP representative also noted the difficulty in including the sequence information in a hard copy format and requested information on an acceptable short hand that could be used.

International Union of Biochemistry and Molecular Biology (IUBMB)

Since the last meeting IUBMB has added 128 new enzymes, modified 44, and transferred 18. The modified and transferred entries are usually due to additional information becoming available.

International Union of Pure and Applied Chemistry (IUPAC)

Work continued on identifying corrections to the 2013 Blue Book (Nomenclature of Organic Chemistry). Very recently the first translation was published in Japan and IUPAC was very grateful to Japanese colleagues in flagging many possible corrections.

Names were agreed of four new elements: nihonium (Nh), moscovium (Mc), tennessine (Ts) and oganesson (Og).

The new definition of the SI unit of mass has been agreed by fixing Planck's constant, i.e. it will no longer use a reference specimen held in Paris.

Nomenclature of flavonoids is almost ready to go to press whilst recommendations on the numbering of phosphates and polyphosphates in phosphoryl transferase enzymes is *in press*.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs, Office of Standards and Guidelines Development within the PMDA is responsible for preparing the Japanese Accepted Name (JAN) and the Japanese Pharmacopoeia (JP). The JAN Expert Committee met 6 times in the past year, and 75 names were published. In April 2017, the drafts of Supplement 1 to the JP 17th edition will be reviewed at the committee on JP under the Pharmaceutical Affairs and Food Sanitation Council and will be posted on the MHLW website for public review and comment. After the public inquiry, the Supplement will be published this September with an additional 32 monographs.

United States Adopted Names (USAN)

The 2017 winter USAN Council meeting took place on January 12-13 in Coral Gables, Florida where names for 37 drug substances were reviewed and discussed. Seven new stems were approved and added to USAN's stem list. Policy discussions included biosimilar drug nomenclature, cellular therapy nomenclature revisions, monoclonal antibody proposed naming revisions and ISMP medication error reports. Twenty-seven INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 64th INN Consultation. USAN application requirements for cellular and gene therapies were updated and harmonised with the INN Programme.

Through March 2017 USAN staff will have processed, researched and made recommendations for 42 USAN applications and forwarded this information to the USAN Council for their review and selection. Also through March 2017, 36 USAN and 12 modified USAN will have been adopted for 2017. Revenue was realized for an additional 3 negotiations. Currently, there are 115 active USAN negotiations.

The 2017 summer meeting of the USAN Council is scheduled for July 13-14 in Chicago.

United States Food and Drug Administration (FDA)

In January 2017, the FDA published a final draft of guidance for industry on 'Nonproprietary Naming of Biological Products' and new draft guidance on 'Considerations in Demonstrating Interchangeability With a Reference Product'.

In the last two years, the FDA has approved four biosimilars: Sandoz's Erelzi (*etanercept-szss*), Sandoz's Zarxio (whose non-proprietary name was *filgrastim-sndz* but is now *filgrastim-blfm*, in accordance with the new rules that the 4 letter code should be random and not meaningful), Pfizer's Inflectra (*infliximab-dyyb*) and Amgen's Amjevita (*adalimumab-atto*). The FDA has also given a 4 letter code to Amgen's originator *filgrastim* Neupogen, whose non-proprietary name has been changed to *filgrastim-jcwp*.

The FDA has also contributed, via WebEx, to the INN and USAN discussions on a modified mAb naming scheme and on a revised scheme for cell and gene based therapies.

United States Pharmacopoeia (USP)

The 2017 version of the USP Dictionary of United States Adopted Names (USAN) and International Drug Names has been published and distributed in January.

In July 2016, USP launched a new version of its Food Fraud Database (FFD), a food fraud mitigation resource. The FFD is a continuously updated collection of thousands of food-fraud related records gathered from publicly available sources. The FFD features records that include ingredients that were adulterated, the identity of the adulterant, the method used to detect the adulterant, and whether the adulterant is hazardous to human health. Users can identify trends and vulnerabilities specific to ingredients of interest and receive updates as new records are added to the database. The FFD complements USP's ongoing compendial work in the foods area, as the organization continues to publish the Food Chemicals Codex (FCC), a compendium of internationally recognized standards for determining the purity and quality of food ingredients.

Under the Medicare Prescription Drug Improvement and Modernization Act, USP is charged with establishing and maintaining a list of categories and classes of drugs that may be utilized by prescription drug plans in the U.S. healthcare system. Through the work of the volunteer Healthcare Quality & Safety Expert Committee, USP issued the most recent version of the Medicare Model Guidelines (MMG) v7.0 in February 2017.

WHO Collaborating Centre for Drug Statistics Methodology

The remit of the WHO Collaborating Centre for Drug Statistics Methodology is to classify drugs according to the Anatomical Therapeutic Chemical (ATC) classification system and assign the Defined Daily Dose (DDD). It is based in Oslo, in the Department of Pharmaco-epidemiology at the Norwegian Institute of Public Health and is a global WHO centre. The main purpose of the ATC/DDD system is as an international language for drug utilization monitoring and research to improve quality of drug use and to group drugs to facilitate retrieval. It is recommended by WHO as the international standard for drug utilization studies. Substances assigned an ATC code in the ATC/DDD system include new chemical entities for licensing, preferably in more than one country, and well-defined chemical entities used in a variety of countries, preferably with an INN. Some well-established herbal medicines are included but traditional herbal or homeopathic medicines are not.

Substances are classified according to their main therapeutic use and if there are several indications, the main one is used. Products having two or more active ingredients have separate 5th level codes. ATC codes are not assigned until a marketing authorisation application has been submitted in at least one country. The INN is the preferred name for the active substance although where no INN exists, the USAN, BAN or accepted chemical name can be used. Where an INN has been applied for but not yet assigned, assignment of an ATC code would be postponed.

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The Centre tries to have the DDD available as soon as possible after licensure. Centre staff also use the system in their work on drug use in Norway; for example, the national strategy to lower the level of antibiotic use can be tracked by assessing the DDD/1000 inhabitants/day.

The Centre publishes an ATC index and guideline for ATC classification and DDD assignment, which get updated annually. International workshops are organised by the Centre with a course held in Oslo every year. Staff attend other WHO and international meetings, and interact with other agencies including the EMA, INCB (International Narcotics Control Board) and ESAC-net (European Surveillance of Antibiotic Consumption). The Centre has established an ATC system for veterinary use and interacts with the EMA/ESVAC project on the collection of data on use of antimicrobial agents by animal species and on technical units of measurement (DDDvet). A more recent project is the development of an ATC/DDD toolkit for drug utilization monitoring studies¹.

The Centre intends to make ATC/DDD accessible as Open Data, and plan to develop ATC/DDD webinars to reduce travelling time and budgets.

World Customs Organisation (WCO)

The World Customs Organisation is an independent intergovernmental organisation established in 1952 and based in Brussels. Its 181 members process >98% of all international trade and is recognised as the voice of the global customs community.

The International Convention on the Harmonized Commodity Description and Coding System (known as the Harmonized System or the HS) is one of the most successful instruments ever developed by the WCO. It is a multipurpose goods nomenclature used by more than 200 countries and customs or economic unions as the basis for customs tariffs and for the compilation of international trade statistics.

The HS is also used by other organisations, including the private sector, for many other purposes such as trade policy, rules of origin, monitoring of controlled goods, internal taxes, and economic research and analysis. Governments and businesses use the HS as a unique way of identifying and coding

¹ <http://www.who.int/medicines/regulation/medicines-safety/toolkit/en/>

merchandise in order to facilitate international trade and customs regulations and applications. The HS is, therefore, an important instrument not only for the WCO but also for all institutions, public or private, involved in world trade.

The HS classification of INN products is important for proper application of the WTO Agreement on pharmaceutical products as each government will eliminate customs duties on the products. The WCO HS Committee has now decided the HS classification of almost four thousand INN products.

The HS is also used to protect society and the environment by facilitating the monitoring and control of trade of dangerous substances. For example, the 2017 HS amendment assigned new HS codes to 33 chemicals as requested by the Organisation for the Prohibition of Chemical Weapons (OPCW) in order to enhance effectiveness of their control and monitoring among members. Further, new HS codes for antimalarial commodities, such as long lasting insecticidal nets, antimalarial pharmaceuticals, insecticides for indoor residual spraying, and rapid diagnostic test kits, have been inserted in the HS, in order to facilitate customs classification and entry of these life-saving products into commerce.

The WCO normally invites a member of the INN Secretariat to its meetings and very much appreciates the excellent cooperation it has with the WHO.

CLOSE OF MEETING

In closing the meeting, the Chair thanked all participants for their time and efforts contributed both before and during the Consultation, and acknowledged also the support provided by the INN Secretariat. In return, the Chair was congratulated on his exemplary chairing of the meeting.

Next Meeting

The 65th INN Consultation will take place in Geneva on 17-20 October, 2017.

Open Session to Stakeholders

64th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 4 April 2017

The meeting was opened and participants welcomed by Prof Sarel Malan, acting Chair, INN Expert Group. He particularly welcomed Dr Emer Cooke, the new Head of WHO's Regulation of Medicines and other Health Technologies (RHT) and Dr David Wood, Coordinator of WHO's Technologies Standards and Norms (TSN) for whom this would be his last meeting before retirement.

Dr Cooke summarised her previous positions at the EMA, the EU Commission and the Irish drug authority. She admitted being a novice with INN, expressed admiration for the WHO INN team, and looked forward to hearing the views of stakeholders. Dr Wood also extended a warm welcome to all stakeholders and welcomed their feedback which helped the INN Experts make decisions. Dr Raffaella Balocco Mattavelli, Group Lead INN Programme, added her welcome to and appreciation of the views of all stakeholders.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Association for Accessible Medicines (AAM)

The AAM, formerly the GPhA, had not been able to attend in person and instead had submitted a statement which was read out by the Rapporteur, Dr J Robertson, and which is summarised below.

The AAM and its Biosimilars Council have had a dialogue with the WHO INN Experts via the Open Session for the past five years. While conflicting schedules did not allow them to present views in person at this meeting, they felt it important to continue their interactions on the important topic of the proposed Biological Qualifier (BQ) and appreciated this opportunity to do so.

Since the last INN Stakeholder meeting in Oct 2016, the US FDA had finalised a naming guidance and conflicts with the WHO's BQ was causing AAM great concern. The AAM affirmed that a biosimilar that has demonstrated biosimilarity to the reference product should share the same INN. However, it felt that the BQ and other random/without meaning suffixes, such as the FDA's Guidance, will introduce complexity and increase risks of confusion on prescribing, dispensing and substitution. As such, AAM firmly believes that a consistent international standard is needed that will apply to all biologic and biosimilar products in all markets, a standard that must be applied retroactively and prospectively.

The primary reasons behind its concerns were:

Pharmacovigilance: whilst it had been stated that a suffix is required to effectively track/trace products when adverse events occur, it was not clear to AAM that the BQ or the FDA's approach would effectively address the stated goal of improved pharmacovigilance. Additionally, AAM was concerned that two different naming conventions would result in added confusion.

Since WHO had not provided any details to measure the burden imposed by the BQ on all stakeholders, AAM requested that WHO fully evaluate these burdens. AAM believes that collection of such data will help WHO better understand and make necessary adjustments to its BQ.

It appeared to AAM that WHO had no concrete plan to apply the BQ to new biological products or to biological products currently on the market. Consequently, AAM requested that WHO assign suffixes to biologics seeking approval, and that reference products approved without a suffix get addressed in any final documents.

Finally, the AAM expressed concern about the lack of clarity surrounding the non-proprietary naming convention that will apply to interchangeable biological products in the US, especially where suffixes

change when a product is approved from biosimilar to interchangeable as this could mislead doctors and pharmacists to conclude that a product 'had changed'. While only the US has the interchangeable pathway, it urged WHO to consider this matter also in any final documents.

Alliance for Safe Biologics Medicines (ASBM)

The ASBM is an organisation representing patients, physicians and pharmacists dedicated to acceptable policies for biosimilars for patient safety.

The Alliance has conducted a variety of surveys on biosimilars over the past five years with the most recent being in Australia, whose data has recently been shared with the Australian TGA and other interested parties. In Australia, there is significant use of INN to identify medicines in both patients' records and for pharmacovigilance; in contrast, batch numbers were not consistently used in AE reporting. The Australian data were consistent with other worldwide surveys in that physicians value having distinctive names and disagree that it would result in confusion.

Pharmacists similarly agree on distinguishable names, shown by surveys and at continuing education courses. Prescribers and pharmacists also concur in preferring a meaningful over a random suffix. However, ASBM felt that it was more important to have a distinguishable name, whether meaningful or not, and that seeking perfection should not stand in the way of implementing what is essentially a good system. The ASBM also noted that objections and concerns raised to the BQ could be addressed during implementation.

The ASBM went on to demonstrate a novel database – SuffixDB – constructed from all possible 4 letter suffixes. The database provides for a web-based method of readily pre-defining BQ compliance for both biosimilar manufacturers and regulators, and establishes a reliable way of avoiding conflicting suffixes. It is a Cloud™ based site that helps search for compliant suffixes and was offered to the INN as an example for potential BQ implementation. It can also provide a checksum with a 32 bit cyclic redundancy check.

In conclusion, the ASBM highlighted that the BQ would be a solution to the global problem of biologic naming, and that it has continued and growing support, both empirical and anecdotal, among healthcare providers and regulators. SuffixDB provides a proof of concept of the workability of the BQ system and WHO was urged to move forward in implementation of the BQ to avoid proliferation of national schemes.

Medicines for Europe (MfE)

MfE is a trade association of manufacturers of generic medicines. The MfE representative highlighted the current biologics naming conventions being used in the USA, EU and Japan. The US FDA has agreed its final guidance although final government approval remains pending. It was noted that the 4-letter US scheme is incompatible with the BQ with the only common feature being 4 letters. Beyond that there are differences in the potential use of numerals and vowels, the application of the US scheme to blood, vaccines and gene and cell therapy products, the application to the active ingredient versus the final product, and others. These differences would result in more confusion. It was also estimated that implementation of the US scheme will cost >\$500 million, placing a huge burden on manufacturers and ultimately health plans. In the EU, data show a very high level of traceability using its preferred approach of use of tradename and batch number, whilst Japan has its own specific naming convention for biosimilars. A BQ would come on top of the above systems. It was also highlighted that with only three exceptions, (epoetin zeta, kappa and lambda) the same INN for the reference product and biosimilar is used globally.

It was further pointed out that the International Pharmaceutical Regulators Forum supports ISO IDMP Implementation, a suite of ISO standards for data elements, formats and terminologies for the unique identification of and the exchange of information on medicines.

In summary, the opinion of MfE was that the BQ was likely to cause and increase confusion, especially now that the FDA had established its alternative scheme. If the BQ were to move forward, it should be done cautiously, involving a pilot scheme and rigorous regulatory impact assessment. Overall, the WHO approach to improve access to and use of biosimilars should be holistic, taking into

account improving an understanding of biosimilars, regulatory capacity building including pharmacovigilance activities, learning from pioneering regions, and understanding and implementing tools tailored to identified hurdles.

Dr Wood, Coordinator, TSN, highlighted that WHO was indeed adopting an holistic approach to increasing future access to biotherapeutic products, and a meeting of interested parties and experts on 2-3 May (2017) would assess what immediate actions are needed for the 2030 sustainability plan. INN will be represented at the meeting as well as ECBS and Essential Medicines List experts.

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

Whilst the IFPMA was represented at the meeting, it had nothing more to add regarding the BQ beyond the views it had previously stated supporting it and urged WHO management to implement the Recommendation of the INN Expert Group.

PRESENTATIONS on INN ASSIGNMENTS

Cadila Healthcare

Cadila Healthcare petitioned for a corrected stem for *saroglitazar*, the proposed INN of a new chemical entity discovered and developed by the company. The company had realised in hindsight that the *-gli-* infix is indicative of anti-hyperglycaemics, whereas *saroglitazar* is not predominantly a diabetic drug. The drug is the only *-glitazar* on the market and has been approved for treatment of diabetic dyslipidemia and hypertriglyceridemia but is not useful for treatment of diabetes. Furthermore, it is chemically distinct from *-glitazones*, *-fibrates* and all other *-glitazars*.

Saroglitazar is predominantly a PPAR α agonist with anti-dyslipidemia effects and a favourable liver profile, and the company has concerns that it may be wrongly prescribed for diabetic patients. In contrast, all other *-glitazars* share PPAR γ activity with common side effects such as weight gain and oedema; *saroglitazar* does not show these same side effects. Furthermore, *saroglitazar* has no hypoglycaemic effect and is not expected to have benefit for diabetics.

Feedback from doctors suggested that they are reluctant to use it for diabetes, but because of the *-glitazar* stem, many doctors and patients believe that it might have a hypoglycaemic effect and so doctors tend to prescribe higher doses to achieve an anti-diabetic effect; this could lead to safety issues. A large number of CME programs in India have been targeted to educate doctors that *saroglitazar* is not a diabetes drug, but to no avail. Hence the request to change the infix/stem, for example, to a *-fibrinor* stem.

The INN Expert Group will discuss this application during the plenary Consultation but as a general comment, it was noted that an INN is given based upon the data supplied at the time of the application and that to change an INN is a long complex process with agreement being required from all WHO member states.

Biocad

The Biocad computational biologist discussed humanisation vs germinalization of mAbs with the intent of convincing the INN Experts that the homology values of antibodies with V gene germline have no real significance and that creating an antibody with improved selectivity will not necessarily make it humanised. Further, plotting the light chain framework region's (FR's) identity versus heavy chain FR's identity shows chimeric and humanised antibodies intermixed, suggesting that FR is not involved in the selection step. Consequently, it was proposed that applications for INN for mAbs should be supported by T cell analysis, in vitro or in silico, rather than by reference to homology data. In summary, stem CDR1-CDR2 loops have to be matured as much as possible to reduce the risk of cross-reactivity. Light and heavy FR's need to be very similar and T cell epitopes should play a more important role in assessing immunogenicity. Finally it was proposed that a double infix could be used for fusion Ab constructs.

Scynexis

Scynexis has developed a novel class of anti-fungals and petitioned the INN Experts for a new stem for its novel anti-fungal to replace the *-fungin* stem in the name *ibrexafungin* already proposed by the Experts. Substances with the *-fungin* stem are echinocandins, a class of structure represented by six amino acid cyclic structures linked to lipid, and can only be given *i.v.* In contrast, *ibrexafungin* was developed for oral administration, is a triterpenoid, and is chemically and biologically different from echinocandins.

Although *ibrexafungin* acts upon the same enzyme, $\beta(1-3)$ -glucan-synthase, as echinocandins, it has a different mechanism of inhibition and is believed to bind to the enzyme at a different site. This results in fungal strains that are resistant to echinocandins being highly sensitive to *ibrexafungin*; indeed, combinations of echinocandins and *ibrexafungin* have additive activity. A different inhibitory mechanism is also supported by the observation that when specific changes in the amino acid sequence of the enzyme are introduced, they have a differential effect on the inhibitory activity of echinocandins versus *ibrexafungin*.

From a clinical point of view, doctors could erroneously assume that hypersensitivity and cross-resistance would be the same as for echinocandins, whereas it is not. Having a new stem would make it clear that *ibrexafungin* represents a distinct family from *-fungin* substances.

In discussion the Experts expressed an interest in any available crystallography data to assess if binding of *ibrexafungin* versus echinocandins was indeed mutually exclusive or merely competitive; however, it transpired that making a crystal of the enzyme would disrupt the active site 3D structure.

Hoffmann La Roche

CAS registration of a drug substance is required for INN applications and Hoffmann La Roche lobbied the INN Experts for a delay in the timing of the submission of the CAS for large molecules.

CAS is typically assigned automatically to a small molecule whenever the structure appears in any publication. This is not the case for large molecules as the required data is not usually in the public domain until the company itself publishes it. Since INN applications require a CAS, registering a structure with CAS results in immediate publication of the structure in the public domain. This is fine for small molecules as various sources of structural data will typically already exist. But for large molecules, e.g. proteins, only the company will be privy to the structure and early publication by CAS could provide competitors with proprietary information earlier than need be.

The INN guidelines in this respect are not clear. They state that if a CAS has been issued, then it should be included in the INN application. However, “*If no number has yet been assigned, the manufacturer should obtain the CAS registry number from Chemical Abstracts Services for publication in the INN lists*”. It is this latter statement that requires clarity and the Roche proposal was that for large molecules, filing of CAS registry numbers should accompany the letter of acceptance of the selected INN, and not with the initial proposal submission, i.e. at the end of the process rather than the beginning. The INN Experts had sympathy with this request although noted that knowledge of the structure was essential for assignment of an INN; however, validation of the structure published in the INN definition through CAS was certainly required prior to publication of INN in the proposed Lists. The issue would be discussed during the 64th Consultation.

CLOSE of OPEN SESSION

In closing the Open Session, the Chair thanked all participants for their information and comments.

The next Open Session will take place in Geneva on