INN Working Doc. 18.439
July 2018
Distr.: PUBLIC
ENGLISH ONLY

66th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 1-4 May 2018

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

66th Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

ELECTION of CHAIR and VICE-CHAIRS

Prof. Sarel Malan was proposed and elected as Chair of this 66th INN Consultation, Dr Adrian Evans as vice-chair for chemical medicines and Dr Karin Weisser as vice-chair for biological medicines; Dr James Robertson was proposed and elected as rapporteur.

INTRODUCTORY REMARKS

Dr. Mariângela Batista Galvão Simão, Assistant Director-General for Drug Access, Vaccines and Pharmaceuticals, welcomed all participants and in particular newcomers to the 66th INN Consultation. She highlighted that Drug Access, Vaccines and Pharmaceuticals is a new WHO cluster that has hard core normative functions and five expert committees, of which the INN Expert Group is one of the oldest. The INN is essential to promoting generic prescribing and supports access to safe, effective and affordable medicines. Indeed, access to healthcare products features in the 13th general programme of work 2019-2023 which will be discussed and approved at the forthcoming 71st World Health Assembly. Dr Simão has been reinforcing the WHO commitment to access and to affordability and the work of the INN is fundamental to all this.

Dr Simão also noted that through generic names the INN is very visible but that establishing them is invisible work that people take for granted, not appreciating that the INN Expert Group is behind this. So, the WHO needs to do more about visibility of its committees, to increase the level of implementation of normative guidance, and to closely monitor policies and access to medicines, especially the increasingly complex new generation of biologicals. She also made clear that WHO had made a decision not to implement the BQ for the moment, pending monitoring of its impact on access in all WHO regional situations. The decision took into account what will work for all countries and not just some, and she thanked the Experts for their invaluable work on the INN Biological Qualifier recommendation.

For this Consultation, the Experts have a high workload of 137 new requests, and Dr Simão reminded them, especially new ones, that they were present for their own expertise and not representing any institute and that everyone is here to promote public health. Dr Simão expressed her appreciation of the Experts contributions and thanked the WHO INN team, especially Dr Raffaella Balocco (Group Lead INN), for organising the meeting and for leading the INN Programme and the medicines nomenclature globally, achieving outstanding results.

The Chair thanked Dr Simão for her comments and for taking time to address the Committee. He highlighted the diverse professional and social backgrounds, knowledge and experience of the INN Experts and that all were committed to serving public health at a global level and thanked them for that. The independence of the Group is also important and must be preserved and under no circumstances can it be influenced by any specific group or member state.

He acknowledged that the work done by the Committee is important and that its role in patient safety, generic prescribing and access to medicines should be recognised. The BQ project was undertaken on behalf of the safety of public medicine, and was achieved through a working group, then the Expert Committee, and then advice given to WHO, and the Experts remain ready to assist further with it.

He thanked the Experts for their work both at and outside of the meetings and expressed his appreciation of the amount of work that the INN Secretariat has to do between and prior to these meetings.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, informed the Experts of the need to apply general principles in assigning INN. Specifically, priority should be given to the suggestions of applicants and not to ignore the suggestions ranked lower in their list. Post meeting comments also play an important part, especially when alternative names to those requested by the applicant get proposed, so Experts were urged to check alternative names against trademarks and potential conflicts with proposed and recommended Lists. She reminded Experts that names should not be too long and to avoid creating too many new suffixes. At the previous Consultation, approximately 20 new suffixes were created and applicants often think that they are immediately new stems, probably for marketing purposes; however, this is not the case and there are proper procedures for creating stems. A balance between new stems and not having an appropriate stem is needed.

EXECUTIVE SUMMARY

The document "Notes of the of the 65th INN Consultation" was tabled and approved.

NOMENCLATURE of INN

During the 66th INN Consultation, a total of 172 INN requests were discussed, including:

- 137 new INN requests, including 85 for biological substances
- 23 outstanding requests
- 12 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 151 names were selected, which are planned to be published in List 120 of Proposed INNs (p.INN), while 7 requests were deferred for future discussion. One application has been closed since the requested information has not been received. One request was rejected by the INN Expert Group, as the substance did not conform to the criteria for INN selection. Four amendments were planned to be published in a forthcoming List of p.INN, 2 requests of substitution and 1 objection could not be retained as they did not conform to the criteria. Five requests were withdrawn prior to the Consultation.

Six new stems/substems were selected, 6 suffixes were promoted to the pre-stem list and it was decided to review the descriptions of 2 stems.

SCHOOL of INN

Since the last Consultation, the School of INN had met on two occasions. The 7th SoINN meeting was held in Gruyeres on 9-12 Jan, 2018 whilst the 8th meeting was held at WHO HQ on 30th April 2018.

Publications

A major focus of the group has been on drafting manuscripts for publication and the preparation of teaching and learning materials for the e-Platform. A first paper, entitled *'The Science of Nomenclature: INN as Global Language for Education and Practice'*, is finalized and awaiting WHO clearance for submission for publication. A second paper, *'The INN Global Nomenclature of Biological Medicines: a Continuous Challenge'* will shortly be submitted to WHO for clearance prior to submission for publication. An extensive paper, '*Learning Clinical Pharmacology with the Use of INNs and their Stems*' is well advanced; it is based upon ATC codes, will be included in the e-platform, will be used in the Deans Forum (see below) and will be added as an annex to the Stem Book. All articles are expected to be cleared through WHO by the end June 2018. The intended target audience for these publications includes both students and teachers.

An INN article has been prepared for the COIMS newsletter and following from this an information leaflet is being prepared for general distribution at, for example, pharmacology conferences.

e-Platform

Work has started on e-Platform teaching materials and will include courses on '*An introduction to INN*', '*Learning Clinical Pharmacology with the Use of INN and their Stems*', and '*Naming of*

Biological Medicines'. Courses will comprise modules with voice-over slides, a questions & answers component and an evaluation. A full draft of these courses is anticipated by Sept 2018. A small number of INN introductory slides which could be used by teachers is being developed for inclusion in the e-Platform.

A demonstration of the e-Platform was provided illustrating links to videos, an email facility, MedNet site access, and access to modules and courses. Step-by-step instructions on how to apply for an INN online is being developed. The e-Platform can probably go live in about 6 months and should be fully up and running by the end of the year.

Marketing & Publicity

Following from participation in the FIP 2017 annual congress in Seoul, where considerable interest was expressed on the SoINN, Dr Balocco-Mattavelli has been invited also to participate in the Deans Forum at the FIP 2018 annual congress in Glasgow, Scotland and anticipates making use of the teaching material being developed. In addition, the INN information leaflet could be distributed there.

INN staff presented the work of INN and the SoINN at the University of Grenoble where, again, much interest was expressed. The University has agreed to act as new pilot site for INN promotion and offered to be a contact point for francophone African Countries. Other pilot sites include the University of Piemonte Orientale, Italy and the University of the Western Cape, South Africa.

Dr Balocco-Mattavelli will make a presentation of INN and the SoINN in an education and training session of the forthcoming 2018 European Association of Faculties of Pharmacy annual conference in Parma, Italy.

Discussion

There was a recommendation that the SoINN be made visible to regulators, in addition to students and teachers.

Dr François-Xavier Lery, Coordinator, Technologies Standards and Norms (TSN), saw the SoINN as a highly important project and congratulated all those involved. He felt it important to reach out to all INN stakeholders and the SoINN project will contribute significantly to this, at the same time enhancing WHO's impact at the country level and improving implementation of WHO guidelines. He appreciated the involvement of ATC and highlighted other cross cutting issues such as the advanced therapies and the challenges they present, which should be discussed with the Expert Committee on Biological Standards; he would look into coordinating such cross-interactions and assist with implementation of the SoINN.

INTERNATIONAL PHARMACEUTICAL FEDERATION (FIP)

The International Pharmaceutical Federation is a global federation of 140 national associations representing over 4 million pharmacists, pharmaceutical scientists and educators. Its mission is to improve global health by advancing pharmaceutical education, sciences and practice thus enabling better discovery, development, access to and responsible use of cost-effective, quality medicines worldwide. Since 1997, TIP's policy on generic substitution is that where generic substitution is allowed, the responsibility for selection of the generic will be the pharmacist and where appropriate the use of generic names should be encouraged. This principle holds true but will be updated at its Sept 2018 Congress in Glasgow, Scotland.

The data presented by FIP at the Open Session concerned a 2017 voluntary survey of member organisations on INN prescribing and generic substitution. The survey revealed that amongst 72 territories representing 75-80% of the global population, INN prescribing is not mandatory in 55% of the countries, is mandatory in 37%, and for the remainder it depends on the 3rd party payer. The survey also revealed that where the physician has prescribed by brand name, pharmacists are obliged to dispense the branded medicine in only 5% of the countries, are obliged to dispense a generic in 17%, is voluntary in 22%, or depends on the 3rd party payer in 17% of jurisdictions. All-in-all, pharmacists have a right or the opportunity to select and dispense a generic medicine in 94% of jurisdictions. However, in many jurisdictions where the pharmacist is mandated to substitute,

prescribers still have the opportunity to disallow substitution, and also in these countries patients may refuse substitution.

Questions on measures to promote to use of generics, revealed that 20% of respondents had no measures in place and INN prescribing was not mandatory. The FIP sees this as a group that needs to consider such measures. But where there are measures to use generics (60% of respondents), the most extensive reason is where reimbursement is based upon the generic prices or where pharmacies receive some sort of financial incentive. Other measures to promote generic use include patients not having to pay in advance if generic, or public-sector tenders being restricted to generic medicines. Data from 38 countries concerning the market share of generics show an average of 51% but with a very wide spread. Interestingly, many countries with a high level of generic medicine use do not have mandatory prescribing which may indicate the success of pharmacy-centred policies to incentivise generic substitution.

The key take-home message of the survey was that pharmacists can play a substantial role in maintaining the financial health of patient care by dispensing generics where possible

UPDATE on ADVANCED THERAPIES

The INN Programme recently adopted a new naming scheme for genetically engineered cells in agreement with USAN/CBER. Such substances will be termed cell-based gene therapies and will be given a two-word name, with word 1 pertaining to the gene being transduced into the cell and word 2 would pertain to the cell being transduced. The structure of word 1 would be the same as that for gene therapies and the structure of word 2 would be the same as that for cell therapies. This harmonised scheme is applicable to both autologous and allogeneic therapies, and replaces the concept previously held by the Expert Group that cells transduced *ex vivo* were purely gene therapies and not cell therapies.

At the 65th INN Consultation, applications for cell-based gene therapies involving the same cell types were considered. One applicant applied for two INN for two distinct genes carried on lentivirus vectors but targeting the same autologous T cell population. A second applicant also applied for two INN for two distinct genes also carried on lentivirus vectors and in this case targeting the same autologous stem cell population. The dilemma facing the INN Experts was where the same cell population is involved should word 2 have the same fantasy prefix? In considering this, it was noted that in the near future the characterization and purification of cells will develop rapidly, making initial descriptions obsolete.

A further four options were posed to the Experts concerning names for cell-based gene therapies. First was that the current new scheme should stand as is with each word having a unique fantasy prefix. The second option was that the fantasy prefixes for words 1 and 2 should be identical, as it refers to the same therapy. Third, word 2 should not have a fantasy prefix at all, as the INN is made unique by the fantasy prefix of the gene component; the second *-cel* word would simply refer to the overall substance. Fourth, as a variation to option 3, the fantasy prefix of word 2 could be substituted with a prefix that refers to the autologous or allogeneic nature of the substance, i.e. *auto-* or *allo-*.

A not dissimilar situation arises with gene therapies for which there have been applications for INN for substances bearing distinct genes of interest carried on identical backbone vectors. In some cases, word 2 has been given a unique fantasy prefix whilst in other cases, generally more recent applications, the same fantasy prefix has been given to where an identical vector backbone is present.

In discussion, there was a groundswell of opinion that of the four options presented the use of a fantasy prefix for word 2 of cell-based gene therapies was somewhat illogical and that the fourth option made more sense. There was also some concern that giving the same fantasy prefix for word 2 where the same cell population is targeted could provide some applicants with a proprietary prefix. Getting rid of the fantasy prefixes altogether, or at least ensuring it is unique in all cases, would overcome that concern. An opinion from the American Society of Gene and Cell Therapy had also been sought and was that the cell word should, in principle, be the same but that autologous cells should be distinguished from allogeneic cells.

This alternative approach to cell-based gene therapy naming needs to be discussed with USAN/CBER/FDA to maintain harmony and the INN Secretariat would arrange a WebEx meeting with them. In the meantime, pending INN applications for cell-based gene therapy INN were put on hold. The USAN representative similarly felt that USAN should impose a moratorium on these until this issue was settled.

It had also been mooted that applicants for cell-based gene therapy substances should be required to apply for a separate INN for the gene vector used to create the modified cell; however there appeared to be no real justification for a separate INN for the vector.

A difference concerning the fantasy prefixes for word 2 for cell-based gene therapy versus those for plasmids or viral vectors was highlighted. The sequence of vector backbones is defined and gets published, and another company could create the same vector backbone and insert the same or a novel gene and so there is a need to have a provision for defining a specific vector backbone. Also, there were safety issues with some viral vectors in the past so there is merit in having a fantasy prefix for word 2 for them. The consensus was that word 2 for gene therapy vectors should have a fantasy prefix but that where the same vector backbone was present, the same fantasy prefix would be used.

The ANTIBODY SOCIETY

In December 2017, Dr Raffaella Balocco-Mattavelli, Group Lead INN, attended the Annual Antibody Engineering & Therapeutics Conference in San Diego, USA to explain INN and the issues surrounding the new naming scheme for mAbs. Amongst the experts present expressing an interest was Prof Andreas Plückthun of The Antibody Society, who was invited to this INN Consultation to discuss mAb naming. Prof Plückthun agreed that the previous scheme has led to some strange behaviour, with some mAbs being engineered either to avoid a specific INN or to obtain a specific name.

The Antibody Society is an international non-profit association representing individuals and organizations involved in antibody R&D. It addresses issues of interest to members including standards, quality control, education, publishing and the scientific and financial support of conferences. Two recent Society publications specifically address mAb INN infixes[1].

The original scheme for naming mAbs included a source substem to indicate a mouse, chimeric, humanised or human source of the mAb. A 2014 revision of the scheme attempted to overcome inconsistencies in assigning the source with a sequence-based definition but maintaining the same infixes. Unfortunately, this led to further inconsistences and in some cases of companies manipulating data to obtain a 'humanised' name. With a huge expansion in technologies for creating mAbs, Prof Plückthun stated that the Antibody Society very much welcomed the recent decision made by the INN to drop the source infix.

The Antibody Society also very much welcomed the INN Programme's proposed extensive description of mAbs but emphasised that more extensive detail should be provided for the IG class, subclass and format, and a more precise and detailed description of the nature of the sequence of the construct should be obtained.

In summary, The Antibody Society sees the INN mostly as a discriminator and much less of a descriptor of a very complex biological. The description needs to be upgraded and critical information needs to be requested from the applicants, and even although the sequence is provided, it should be combined with detailed information to highlight all relevant engineered features. Prof. Plückthun noted that the IFPMA was proposing something similar.

[1] Jones, T. D. et al., *mAbs* **8**, 1-9 (2016); Parren, Carter, and Plückthun, *mAbs* **9**, 898-906 (2017).

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

The BP sits within the Inspection, Enforcement and Standards Division of the Medicines and Healthcare products Regulatory Agency (MHRA). Gerald Heddell, the previous director of the Division, had recently retired, being replaced by Samantha Atkinson, the previous Secretary and Scientific Director of the BP.

The BAN programme publishes a full consolidated edition every 5 years alongside annual supplements. The BAN 2017 Supplement 2 is being finalised and will be published in August 2018 with an effective date of 1 January 2019. Twenty-two new BANs have been included in the publication, comprising 7 biological and 15 chemical names. These were selected as new active pharmaceutical ingredients in medicines that were new to the market in the UK.

The BP 2019 is in the final stages of the publication process and, again, should be published in August 2018 and have the effective date of 1 January 2019.

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 last fiscal year, and 58 names were newly added. During this half year, 2 biosimilars were added (infliximab (Genetical Recombination) [infliximab Biosimilar 3] and trastuzumab (Genetical Recombination) [trastuzumab Biosimilar 1]. Supplement I to the JP 17th edition was finally published on December 1, 2017. The texts were translated into English and will be finalized soon. Meanwhile, the drafts for the next supplement have been prepared.

Therapeutic Goods Administration (TGA), Australia

The TGA consultation on biological medicines nomenclature is now completed and the active ingredient of biosimilars will continue to use the ABN (Australian Biological Name) without a specific suffix. This keeps Australia in line with the European approach whereby the active ingredient in a biosimilar medicine and its reference medicine are given the same INN. Biosimilar medicines are required to have a trade name clearly distinguishable from all other products, especially the reference medicine and other biosimilar medicines. The trade name is mandatory for pharmacovigilance/adverse event reports.

With regard to cell and tissue therapy products, the TGA has yet to finalise its naming policy. The TGA is busy implementing several recommendations in a government review (Medicines and Medical Device Regulation Review) of three years ago, for example for expedited pathways to pre-market approval.

United States Adopted Names (USAN)

The 2018 winter USAN Council meeting took place on January 18-19 in Florida where names for 35 drug substances were reviewed and discussed. Eight new stems were approved and added to USAN's stem list and one stem definition was revised. Policy discussions included a biosimilar drug nomenclature update, USAN Process Flowchart review and ISMP medication error reports. Thirty-eight INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 66th INN Consultation.

The USAN Programme is in the process of installing FDA's Phonetic and Orthographic Computer Analysis (POCA) programme. It is a software tool that uses an advanced algorithm to determine the orthographic and phonetic similarity between two drug names. It will be operational soon at USAN.

Through April 2018 USAN staff will have processed, researched and made recommendations for 82 USAN applications and forwarded this information to the USAN Council for their review and selection. Also through April 2018, 44 USAN and 8 modified USAN will have been adopted for 2018. Revenue was realised for one additional negotiation. Currently there are 149 active USAN negotiations.

The 2018 summer meeting of the USAN Council is scheduled to occur on July 12-13 at USP Headquarters in Rockville, Maryland.

United States Food and Drug Administration (FDA)

The FDA representative appreciated being present at INN Consultations and found the tripartite discussions between the INN, USAN and FDA highly useful, such as continued discussion to fine-tune the scheme for cell and gene therapies. In 2017 no further biosimilars were approved and the total remains at nine, although three gene therapy products were approved. At this time the FDA has not yet started asking manufacturers of innovator drugs to apply suffixes. It was highlighted that the suffixes are only used for the drug product and not the drug substance. Also, that the USAN is not changed by the new rule, it is the core name comprising the brand name, USAN and dosage that is changed. The 4-letter suffix appears hyphenated between the USAN and the dosage form, and so is connected as much to the dosage form as it is to the USAN, but it does not constitute a change to the USAN.

The FDA representative also noted that of the nine approved biosimilars, only three had been launched and so it was not yet known whether the use of the suffix was creating an impediment to the uptake of biosimilars compared to innovator products, which do not yet have a 4-letter code.

United States Pharmacopoeia (USP)

USP is currently evaluating the use of the G-SRS platform as a means to curate and maintain information related to chemical substances, such as name, molecular weight, structure, as well as impurities. USP is working with FDA and EMA to better understand how the technology platform can improve scientific collaboration and accuracy of chemical information.

World Customs Organization (WCO)

2018 is the 30th anniversary of the WCO's Harmonised System for product nomenclature. It is used by more than 200 countries as a basis for their customs tariffs and is one of the most useful tools developed by the WCO. In 2017, it classified more than 200 INN substances from INN p.Lists 115-117. However, it is still discussing how to classify cell therapy products as some are derived from human or animal blood and some directly from tissue cells; consequently, the WCO may need more clarification from the INN. The recent p.List 118 also contains some *-fusp* (fusion protein) products that initially caused confusion, and the descriptive part was needed to understand these. The WCO is not expert in these areas and looks forward to further cooperation with the INN Programme to assist the work of the WCO.

CLOSE OF MEETING

Dr Balocco-Mattavelli reminded the Experts that the Consultation would not be formally closed until post-meeting comments have been posted by the Experts via IDMIS.

The Chair thanked everyone for their hard work, their passion and their ability to compromise. He also thanked Dr Balocco-Mattavelli and the INN team for their considerable work and closed the meeting.

Congratulations were proffered to the Chair for a successfully led meeting.

Next meeting

The 67th INN Consultation will take place in Geneva on 23-26 October 2018

Open Session to Stakeholders

66th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 1st May 2018

OPENING REMARKS

The Open Session for Stakeholders adjoining the 66th INN Consultation was opened by Dr François-Xavier Lery, Coordinator, Technologies Standards and Norms (TSN), who welcomed all to the meeting.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, expressed her pleasure in seeing stakeholders face-to-face after corresponding with them. She reminded participants that whilst the session is open to the stakeholders present at the meeting, all material presented and discussed during the meeting was confidential until the report was approved and published.

Ms Emer Cooke, Head, Regulation of Medicines and other Health Technologies (RHT), similarly welcomed stakeholders and was pleased for WHO to host this session. She expressed her appreciation of the work of the Expert Group and the interest of stakeholders and the information they bring to the meeting.

The Chair, Prof. Sarel Malan, thanked Dr Balocco-Mattavelli for the work performed beforehand in setting up the meeting, and felt it a privilege to listen to the independent scientific expertise of stakeholders as decisions should be based on good science to the advantage of patients.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologic Medicines (ASBM)

The ASBM is a growing global network of stakeholders working to keep patient safety at the forefront of biosimilar policy discussion. It is comprised of more than 130 organisations in six continents representing mainly patient groups but also physicians and pharmacists. The ASBM has attended many INN Open Session meetings, presenting the perspectives of physicians, patients and pharmacists worldwide, much of it gleaned from surveys of biologics prescribers in twelve countries.

The ASBM reported that in April 2018, it organised a Forum on International Harmonization of Biologic Nomenclature, attended by a variety of national regulators, pharmacist groups and patient advocacy organisations, but with no industry representation. The Forum was cosponsored by Scientific American and Nature: Biotechnology whose reporters will publish a white paper on the meeting. Themes explored included an appropriate naming convention that could be adopted globally, how naming harmonization could lead to better global safety monitoring and what the associated costs might be.

There was strong agreement that biosimilars are critical to increasing patient access to biologic therapies and to controlling health costs, and that a unique and harmonized nomenclature is critical to building confidence in their safe use by promoting better pharmacovigilance (PV), especially in countries with less-developed PV systems. WHO has led global naming harmonisation and such leadership was felt to be essential to avoid the proliferation of different systems worldwide. However, in this instance, it was felt that leadership in determining global naming was lacking as there was already evidence that systems are diverging, e.g. the Australian TGA was initially supportive of WHO but has now reversed itself whereas in contrast the US FDA has implemented a similar system to the BQ, with 4-letter suffixes. Health Canada remains supportive of distinct names and of international harmonization and is to announce its plans later in 2018. .

At the Forum, FDA representatives assured participants that the US suffix-based naming system will provide the strong PV and data collection required to increase confidence in the safe use of biosimilars. The Health Canada representative echoed these thoughts and noted that a further benefit

of an international naming system vs. country-specific naming systems is the tremendous value of tracking the use of biosimilars in large populations across many countries.

Contrary to arguments with no empirical evidence that globally harmonised names for all biologics will impede access to biosimilars, ASBM believes, in line with FDA and Health Canada, that distinguishable names will increase access to biosimilars. It repeated its assertion that WHO is the only organisation that can provide a lead in global harmonisation and the ASBM continues to support the BQ system. The success of the Forum has led them to organise a follow-up meeting for additional stakeholders and regulators and hope that WHO will participate also.

International Generic and Biosimilar Medicines Association (IGBA)

The International Generic and Biosimilar Medicines Association (IGBA) is committed to promoting generic and biosimilar medicines worldwide and consists of a number of associations such as the Canadian Generic Pharmaceutical Association (CGPA-Canada) and the Indian Pharmaceutical Alliance (IPA-India). It is legally incorporated in Switzerland, is an Assembly Member of ICH and maintains dialogue with various global, international and national bodies.

IGBA maintains that successful traceability and identification are possible without an additional identifier and that unique identification can be achieved either through the brand/invented name, or via the INN plus the name of the marketing authorisation holder (MAH), noting that it is the MAH that is responsible for pharmacovigilance (PV). It is the worldwide implementation of WHO standards and the strengthening of national pharmacovigilance systems, and not an additional identifier, that will support patient safety and public health.

IGBA commented on various regional situations. In the EU, an EMA guideline requires that the product name and batch number are included in adverse event reports of biological medicines and Eudravigilance data suggest continuous robust levels of product identification of biologicals from European clinical practice. For example, an ongoing EMA study shows that 95.5% of ADR reports were unambiguously attributed to the product dispensed, noting that this data had been gathered before 2D barcoding was fully in place. IGBA welcomed the Australian government's decision to continue with its naming convention for biological and biosimilar medicines using the Australian Biological Name without an added suffix, and to strengthen adverse event reporting by requiring the product name and INN in AE reporting, bringing it into line with the EU system. In the USA, more than 75 biologic products share INN with no PV concerns. The FDA has approved 9 biosimilars to date, all with a 4-letter suffix, but no timelines are available for applying suffixes to reference products already on the market. To date, US PV safety databases are not implemented to track 4-letter suffixes and there are no reports of problems in differentiating safety reports for biosimilars from their reference products. Overall, IGBA finds no evidence whatsoever from the U.S. that suffixes will improve safety reporting.

A recent systematic review of 3 biosimilars (*epoetin alfa*, *somatropin* and *filgrastim*) representing 350 million patient days of treatment worldwide showed that in the majority of cases, AE reporting was by brand name and thus attributable to a specific medicine; where a brand name was not available the INN plus the MHA holder would identify the medicine. Inclusion of a batch number would be an enhancement.

WHA Resolution 46.19 requests member states to encourage manufacturers to rely on their corporate name and the INN, rather than on trademarks, to promote and market multisource products introduced after patent expiration, and national regulatory authorities should be encouraged to request the INN plus the MAH are used in AE reports. The consistent use of batch numbers in reports should also be promoted.

In summary, IGBA believes that unique identification is possible through existing tools and that a differentiator, introduced via a suffix-based naming system, does not provide any greater assurance of product quality or ensure its safety.

National Council for Prescription Drug Programs (NCPDP)

Via WebEx

The National Council for Prescription Drug Programs (NCPDP) is a not-for-profit, ANSI-accredited, standards development organization with over 1500 members across the US healthcare industry. With its broad industry membership, it has an obligation to be non-biased.

The NCPDP noted that the rational of the WHO BQ proposal aligns with the US FDA system of suffixes for biological names. However, it remains opposed to these schemes; it believes them to be unnecessary and will lead to greater confusion and errors. Analyses by NCPDP members reveal that implementation would cost billions of dollars across the healthcare system, have additional indirect costs, and will impact patient safety and drug availability. This is because numerous elements of national healthcare systems would need to be modified such as both paper and electronic healthcare record collection, label generation and electronic drug selection processes. All such systems would need to be updated and qualified for a suffix and patient safety could be compromised during this process. In detail, NCPDP members estimate it will take 40-50 hours of work per drug and if a facility were using 1,000 products it will require tens of thousands of hours in reprioritized work effort and millions of dollars in added cost to implement these changes. The cost of this in the USA alone would be staggering never mind the disruption to existing processes, the confusion it will cause and the potential for errors. Also, addressing all of the elements identified will divert resources from other local healthcare needs whilst retroactive application will be hugely disruptive and will undermine national objectives, e.g. to implement safe pharmacovigilance. Furthermore, the impact would be worldwide and not only within the USA.

NCPDP further highlighted that the WHO BQ proposal is quite different from the FDA biologics naming scheme. What the NCPDP would like is global alignment, maintaining the INN system as is. It sees no data to support a new biologics naming convention and has concerns about its impact on patient safety. Clearly, the NCPDP does not support the BQ proposal.

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The IFPMA has presented at numerous Open Sessions on the BQ and attended this meeting to reiterate its support for the BQ and for a pilot scheme. In this presentation the IFPMA focused on pharmacovigilance and the need for accurate product identification. Under good professional practices physicians should prescribe by INN, but in doing so the patient will receive an active substance regardless of the manufacturer. A consequence of this would be a reduction in the ability to trace specific products and given the complexity of biological medicines and a desire to distinguish products for reporting purposes, this lack of traceability is undesirable. However, various tools exist to facilitate pharmacovigilance (PV) for biologicals such as use of INN accompanied by brand name or batch number, although only the EU has legislation that specifically addresses PV requirements for biological medicines. To promote global health and provide accurate traceability the BQ is a useful tool to enhance traceability even for regions that lack infrastructure for PV systems.

Data from regional PV systems were presented. In the EU, the level of non-attribution of adverse event (AE) reports for *infliximab* continued at 20% despite the introduction of Good Pharmacovigilance Practices. In Australia, where there is a shared non-proprietary name, e.g. *filgrastim*, there was 36% ambiguity in AE reporting whereas for distinguishable non-proprietary names such as for *epoetin* with a Greek suffix, mis-attribution was almost non-existent. In Japan, the level of brand name prescribing for *infliximab* runs at approximately 75-80% leaving 20-25% of reports using the INN only. However, following the introduction of an *infliximab* biosimilar and the use of a distinguishing non-proprietary name, the level on mis-attribution is significantly reduced. Hence, having an extra handle helps reduce mis-attribution.

The IFPMA also finds no evidence that a BQ would impact market uptake. The factors impacting uptake are complex and it is not clear that any particular factor preferentially impacts access. Ultimately, a BQ pilot study as was mooted by WHO a couple of years ago would provide an opportunity to generate empirical evidence regarding the impact of a suffix. Nearly three-quarters of

the world's population may be subject to substandard PV systems and distinguishable naming (e.g. through use of a suffix or biological qualifier) may aid in accurate product traceability in regions with weaker PV systems.

The IFPMA remained supportive of the concept of a BQ, that it could improve PV systems, and importantly would avoid a proliferation of national or regional alternatives. Consequently, the IFPMA strongly encouraged WHO to implement a BQ programme although it would be up to individual health authorities to adopt or not.

Third World Network (TWN)[2]

(via WebEx)

Based in a developing country, the Third World Network expressed concern about the impact the BQ may have on access to affordable bio-therapeutics. In introducing its arguments, it highlighted that WHO's approach to the BQ should be informed by science and by the WHO's mandate to ensure the highest available standard of health and science. Such rights should not be compromised and any recommendation should take into consideration WHA 67.21 which acknowledges that similar biotherapeutic products could be more affordable and offer better access to treatments of biological origin, while ensuring quality, safety and efficacy.

TWN felt that the initial idea of the BQ emanated from a need to distinguish follow-on biological products from the originator medicine. However, it noted that regulatory science had developed to the point that it supports an abbreviated licensing pathway without comparative clinical trials as studies show that they are similar with not much difference. Furthermore, a 2006 informal consultation recommended to the WHO INN Expert Group, that no specific process should be introduced for naming biosimilars.

Following the initial 2012 BQ proposal, the debate changed in 2013, with the BQ focusing on all biotherapeutics and not only on biosimilars; it also de-linked the BQ from the INN and was to be voluntary. The purpose of the BQ was to aid prescribing and dispensing of medicines, pharmacovigilance and the international transfer of prescriptions, but the TWN does not believe these reasons are sound enough to introduce the BQ.

The TWN feels that the BQ primarily targets interchangeability and competition of biosimilars, that it will enhance the regulatory burden and that by having a BQ for every single biotherapeutic product, it goes against the fundamental principles of INN. The conclusion of the TWN was that there are no convincing reasons, no scientific basis for the BQ, that it would affect affordable access and that WHO should call off its plan to introduce a voluntary BQ system. The TWN presentation ended with a call to publicise an internal memo on the consequences of having a BQ.[3]

In response to these presentations, Ms Emer Cooke, Head RHT, stated that it was important to make clear that WHO had made a decision not to implement the BQ at this time, and that the WHO needs to continue to collect more information to make an informed decision. The WHO is listening very carefully to what stakeholders are saying but needs more time and more data before implementing a BQ.

PRESENTATIONS on INN ASSIGNMENTS

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The IFPMA took the opportunity of this Open Session to discuss further the naming of monoclonal antibodies (mAbs) and the removal of substem B, the 'source' substem. The historical naming of

[2] http://www.twn.my/

[3] The memo referred to was mentioned in the Executive Report of the 64th INN Consultation and was a BQ document from the INN Expert Group to WHO management to help the deliberations of management. Not all documents from the INN Secretariat are placed in the public domain, but if management agreed, this memo could be made public.

mAbs involved the use of a source infix, viz., *-o-* for mAbs of mouse origin, *-xi-* for chimeric, *-zu-* for humanised and *-u-* for human. In 2017, the INN Expert Group announced the dropping of the source infix for new mAb names, relying on the Description alone to provide this information. This prompted the IFPMA to question the value of the single word source descriptor within the Description, as is currently the case, as the source of a mAb is more complex than the final sequence and may not be accurately described by a single word. Consequently, the IFPMA proposed slightly more extensive wording to describe the source of the sequence. Five initial categories were envisaged:

- Human antibody derived from human B cells
- Human antibody derived from transgenic animal
- Human antibody derived from synthetic *in vitro* libraries
- Engineered antibody derived from a non-human parent
- Chimeric antibody with non-human variable domains

Thus, a mAb currently defined as 'homo sapiens' would more usefully be described as, for example, 'human antibody derived from a synthetic *in vitro* library'. It remains important to retain the sequence of the mAb and to relate it to the human genome, but the percent homology to the nearest human germline sequence used in the Description would be for information purposes only and would not be used to modify the source description.

The categories suggested are flexible and new ones could easily be created, for example for bispecific antibodies or engineered domains.

In discussion, there was a favourable response from INN Experts.

Cytomx

Cytomx attended the Open Session to request that INN Experts introduce a common distinguishable infix between the prefix and target infix for mAb prodrugs. The approach being developed by Cytomx for modifying a mAb is the addition of a 'mask' onto the light chain via a protease-cleavable linker; the mask blocks the CDR site until activated within the body. Other approaches are also possible. Such mAb prodrugs are designed to produce clinically meaningful differences compared to their parent mAbs by altering key biological properties, such as antigen binding affinity, pharmacodynamics and pharmacokinetics.

A significant attribute of such mAb prodrugs is an improvement in the safety profile compared to the naked parent mAb; however, mis-prescribing or mis-dispensing of mAbs versus mAb prodrugs could end up causing patient harm. An INN mAb prodrug infix would alert the medical community to product distinction, which could reduce the risk of product confusion during medical use and help prevent medical errors. Such an infix could take the form of *-pro-* or *-masc-* and would offer a class distinction for this growing class of mAbs.

In discussion, the INN Experts found the presentation interesting and acknowledged the value of these new mAbs but questioned the need to flag them with a new infix as the feature will be noted in the mAb Description; also, other types of mAb prodrugs have been around for some time. Given the previous presentation from IFPMA, INN Experts felt that they needed to consider carefully what is useful within the name and what should be in the Description. Cytomx highlighted that many companies are now developing masked mAbs with many different combinations and re-iterated the serious risk of medical errors through mis-prescribing.

Mundipharma Research

Mundipharma Research attended the meeting to request a differential terminology for Sigma 1 receptor antagonists. Two distinct sigma (σ) opioid receptors, σ1 and σ2, were first recognised in the early 1990's. Sigma 1 has been well characterised and is a unique protein with no structural homology to any known human protein including σ2. It is a stress-regulated molecular chaperone or modulator of cellular signalling located at the mitochondria-associated endoplasmic reticulum

membrane and is differentially affected by agonists and antagonists depending on its oligomeric state. Much less is known about the σ2 receptor.

Several drug substances that interact with σ1 and σ2 have been named with the *-mesine* stem but there is no differentiation between agonists or antagonists. Agonists and antagonists of σ1 receptors mediate opposing biological effects and several are under development by various pharmaceutical companies: agonists are being developed for neurodegenerative or neurodevelopmental conditions while antagonists are being investigated for neuropathic pain and oncology indications. Development of σ2 agonists/antagonists is less well advanced and here it is the opposite; antagonists are being investigated for neurodegenerative conditions while agonists are under investigation for neuropathic pain and oncology indications.

Clearly, σ1 and σ2 receptors have evolved differently and with the divergent biological activities of σ1 agonists and σ1 antagonists, if the same stem is used for both agonists and antagonists it will be a source of confusion and may even present a risk to patient safety. Consequently, Mundipharma Research requested the INN Experts to consider new stems, such as *-sigtor*, *-sigetor* or *-sigemod* to enable differentiation of σ1 receptor agonists and antagonists and prevent confusion and medication errors when products become available.

Nektar

Nektar has been negotiating with the INN Expert Group since 2013 for an INN for its pegylated form of oxycodone. Following various rebuttals by Nektar of suggested names with an *oxy-* prefix for safety reasons, agreement was reached in 2016 on *loxicodegol* and published in Proposed List 117. However, a 3rd party objection was received by WHO stating that the relationship between the proposed INN and oxycodone should be prominently featured in the non-proprietary name to protect patient safety. Consequently, in Feb 2018 USAN suggested oxycodagol but due to Nektar's continued safety concerns with the *oxy-* prefix, it countered with pegoxycodol.

Nektar's safety concern is that the dose for its pegylated version is 10-fold higher than for oxycodone and thus there is a serious risk of fatal overdosing if a pharmacist mistakenly dispenses oxycodone in place of the pegylated form and it feels that the concerns raised by itself and the objector are overcome with the suggested pegoxycodol.

This is supported by a survey of healthcare practitioners in the USA and in the EU that demonstrated that over three-quarters of those surveyed felt that oxycodagol could be mistaken for and filled with oxycodone compared with less than half believing that pegoxycodol may be mis-filled with oxycodone. With Nektar's compound being a pegylated form of oxycodone, the rational for the name pegoxycodol is clear and the opioid component is prominently displayed within the name.

Consequently, Nektar urged the INN Committee to adopt the name pegoxycodol; this name addresses the major concern of transparency and patient safety related to the opioid nature of the molecule and the *peg-* prefix significantly reduces the risk of dispensing errors with oxycodone.

CLOSE OF MEETING

The Chair expressed his thanks to all stakeholders for their attendance at this Open Session and closed the meeting.