

***63rd Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 18-21 October 2016***

Executive Summary

Programme on International Nonproprietary Names (INN)

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

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63rd Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

INTRODUCTIONS

The new Director of Essential Medicines and Health Products (EMP), Dr Sue Hill, introduced herself and welcomed all participants to the 63rd INN Consultation. She expressed her gratitude to the work done by the INN Experts and the WHO INN team, especially with the increasing number of applications for new INN being received and the new policies being developed for advanced therapies, vaccines and monoclonal antibodies.

Increased access to biotherapeutic products was recently identified as a global public health priority, articulated in resolution WHA67.21 of the World Health Assembly, which called on WHO to provide more support to member states on biotherapeutics. Dr Hill has therefore initiated a cross-departmental project on access to biotherapeutics. The aim is to bring all of the assets of the department – its policy development and health technology assessment work in addition to its normative and regulatory support work – to provide a comprehensive framework of support and advice to member states on biotherapeutics. The ongoing work on the BQ initiative will be an important consideration in the context of this holistic approach. To guide this work, a meeting of an *ad hoc* committee is being planned for Q1 of 2017.

WHO senior management has welcomed the drive and innovation of the INN Programme, which not only directs the science of nomenclature, but also fulfils the mandate of promoting, disseminating and advocating INN. The strength of INN, Dr Hill noted, was indeed their use and acceptance worldwide.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team thanked Dr Hill for her remarks and welcomed her to the 63rd INN Consultation. With the ongoing and increasing workload of INN which is reliant of the diligence of the Experts, he also expressed his gratitude to them.

The Chair, Dr Patience Holland, highlighted the innovative nature of the INN Programme, with its drive to move forward and being the first WHO committee to go paperless.

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

NOTES OF CONSULTATION

The Notes of Consultation of the 62nd INN Consultation was tabled and approved.

NOMENCLATURE of INN

During the 63rd Consultation, a total of 211 INN requests were discussed, including:

- 137 new INN requests, including 75 for biological substances
- 66 outstanding requests
- 8 previously selected proposed INN, against which a formal objection had been raised.

As a result of these discussions, 185 names were selected, which are planned to be published in List 117 of Proposed INNs (p.INN), while 15 requests were deferred for future discussion. Eight requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One application already had a published INN and 2 were withdrawn just before the Consultation. Five amendments are planned to be published in a forthcoming List of p.INN and 3 objections could not be retained. Two new stems/substems were selected and 2 suffixes were promoted to the pre-stem list.

Outstanding applications and objections

The Secretariat highlighted that formal objection to proposed INN (p.INN) by an applicant can result in many rounds of discussion, often with the application on hold. These take up considerable time and the Secretariat suggested that where the delay is voluntary on the part of the applicant, it should charge a fee after a set number of rounds of discussion. With some regulatory agencies, having an established non-proprietary name, e.g. a USAN, was a prerequisite for marketing, and if the applicant did not provide all necessary information, the application could be withdrawn.

INN rules provide for several options regarding formal objection. Where the INN Experts re-confirm a p.INN, the Secretariat would request the objector to withdraw the objection. If the objection is withdrawn the p.INN becomes a recommended INN (r.INN). Where the objection is not withdrawn, the p.INN remains a p.INN. Formal objections themselves have to be valid, for example, if an objection conflicts well-established INN rules, it would be invalid.

Review of use of *-anib* and *-tinib* stems

The *-anib* stem is for angiogenesis inhibitors, a pharmacological property that can be achieved via different modes of action. The *-tinib* stem is for tyrosine kinase inhibitors which constitute a true mode of action although there are many types of tyrosine kinases including one which is linked to angiogenesis inhibition.

The *-tinib* stem has limited value and indicates only that the drug is probably an antineoplastic. Substems of *-tinib* are also unlikely to be of use, except for EGFR inhibitors which present a common profile of side effects. In contrast the *-anib* stem is important, as inhibitors of angiogenesis have a common profile of side effects, especially cardiovascular effects. Consequently, where possible, preference should be given to use of the *-anib* stem.

Discussion focussed on how to deal with the vastly overcrowded *-tinib* stem. Changing from one stem (or suffix) to another should not be undertaken lightly, and especially not when a stem/suffix is in use for a marketed product, or when several INN have already been assigned with a particular stem/suffix. For example, for *-brutinib*, three INN have been assigned and this is probably too many now to assign an alternative stem when it is appropriate to use it. It remains however that *-tinib* is too large a category with several different substems, and if only one or two INN have been assigned with a particular *-tinib* substem, there should not be undue concern in creating a new stem.

The cancer pharmaceutical industry is now developing drugs no longer by histological subtype but by targeting mutations in e.g. EGFR, BRAF, and this would lead to a different clustering of anti-cancer drugs. Potentially, INN should follow this and group new drugs to kinases and not kinase inhibitors. Ultimately, when devising new names, there should be more serious consideration from the start as to whether a substance fits in the *-tinib* stem or is indeed first-in-class and should be assigned a standalone name that could be a future new stem, and the potential usefulness of that stem.

SCHOOL of INN (SoINN)

The Expert Group was informed of progress in the development of a 'School of INN' (SoINN), beginning with a preview of a cartoon video showing the use and value of INN. It was pointed out however that the choice of INN used in the video – *salbutamol* – was perhaps unfortunate as the USAN has a different name – *albuterol* – for this substance. Either the USAN can be used for the USA or a totally different INN used in the video. Whatever is decided, the intent is to make the infographics video available on the WHO website following final amendments.

An expert on educational technology had also advised the SoINN working group on making best use of WHO technical platforms, commercial platforms and the web in general. The group was advised that it would be overly ambitious to target everyone from the start and instead should target a subset, for example teachers, and then follow-up with industry buy-in and also practitioners.

Teaching materials should begin with publications in various media, covering awareness of the use of INN. The first could be the report of the recent survey conducted on INN awareness amongst practitioners and students in specific French and English speaking countries. Further publications

could involve pharmacological classes, groups of INN and INN construction, and on naming biological medicines, in educational journals or pharmacological textbooks.

The International Pharmaceutical Federation (FIP) is willing to assist and an INN educational presentation could be made at one of its conferences in 2017 and again in 2018. There would be a revised plan for the January 2017 INN training course. It was also suggested that the established model of WHO collaborating centres could be used to promote INN in different regions of the world although this would require volunteers e.g. in universities to establish this.

The full data set of 1074 responses of the survey into INN awareness had now been analysed and was being prepared for publication. The survey of lecturers and students revealed that the majority knew what an INN is but were weak on how they are constructed.

DUTIES, OBLIGATIONS and CONFLICTS of INTEREST

The meeting was addressed by two internal WHO experts, one on the duties and obligations of meeting participants to WHO, the other on conflicts of interest.

The INN Expert Group is a technical expert group governed by WHO regulations, and WHO relies on the contributions of such external experts to fulfil its work in public health. The Regulations state that expert members provide advice on a personal basis and not as part of an organisation; thus they should not seek or accept any instructions from any government or other authority, including their employer. External experts must respect the impartiality and independence of WHO, and perform their duties with the highest integrity with nothing that would call their work into question. Confidentiality is critically important and deliberations within a meeting must not be disclosed to any person outside the Group, including an employer. Experts agree to adhering to WHO rules and respecting confidentiality by signing a Memorandum of Agreement. Finally, it was pointed out that all rights in any work performed within an expert group belong to WHO.

Submission of a Declaration of Interest (DoI) form is also an important process for WHO. DoI forms are required when WHO requires expert advice at technical meetings, when WHO needs to reach a conclusion, provide advice, or support research. They ensure trust and the credibility of the work performed by experts. Completion of a DoI is to determine if any conflict of interest exists and external experts cannot contribute to expert groups until such a form is submitted, assessed and approved by management. Assessing DoI forms relies on full and complete disclosure. The types of interest to be declared include personal financial gain, family members with similar interests, and intellectual bias; any interest that may affect or be perceived to affect and create an advantage to the expert must be declared. Declaration of a potential conflict does not necessarily disqualify an expert member from contributing; occasionally there may be conditional participation, with a conflict publically disclosed and reported in the meeting report. Such an approach is no different from that of many similar organisations.

Two years ago, the WHO strengthened its rules on public disclosure, with any relevant interest being disclosed at the beginning of a meeting and reported, to ensure trust, integrity and transparency of the work done. Prior to the start of any meeting, a brief biography of each expert is now published on the WHO website for public consumption. The full DoI is not disclosed; these are available only to the meeting secretariat and the compliance and ethics office.

One Expert commented that advice had been sought from their own agency prior to a meeting in order to provide information to the INN Committee. This was deemed to be in order as long as the agency in question did not dictate to the expert how to assess or deal with certain matters. In addition, deliberations within WHO meetings are confidential and should not be disclosed to an employer. Even when deliberations are made public, the background to such deliberations must remain confidential.

With regard to funds obtained by educational (and other) establishments which are for the benefit of the university with no personal gain, Experts were informed that such funding should be disclosed so that WHO is aware of them. This might seem excessive but WHO is under close scrutiny from both

the press and the public, and as a rule of thumb, if an expert is unsure about a particular interest, it should be declared to let WHO manage the situation; disclosure does not mean exclusion.

AD HOC MEETING on BIOLOGICALS, SEPT 2016

Overview

In September, 2016, a group of INN biological experts met to review the current INN approach to naming specific classes of biologicals, to discuss whether existing policies and established nomenclature were applicable to emerging medicines, and to make recommendations for consideration at the 63rd INN Consultation. The biological experts reported back on the specific issues discussed including nomenclature for mAbs, cell therapies and vaccine-like substances.

With regard to the general background of the INN Programme, it was highlighted that nomenclature was driven by the science of the substances being assigned INN, this being especially true for biologicals. Also, whilst the INN Group has to adopt a global approach, each member state has its own legislative requirements and may choose to adopt a particular stance, or not. It was also acknowledged that much of the Committee's work goes to waste, as only 15-20% of the substances named ever get onto the market.

It was noted that names for biologicals are more complex, reflecting the structure of the substances, with greater use of sub-stems and of two-word names. What is also clear is the significant rise in the proportion of applications for INN for biologicals, rising from less than 20% in 2002, to 50% by 2016, and the WHO working document 'INN for biological and biotechnological substances (a review)' (the 'BioReview') has been updated regularly following such specific INN meetings on biologicals.

mAbs

INN applications for mAbs have increased especially and an algorithm was presented showing the number of unique names that could be created depending on the number of sub-stems and the overall number of syllables used. From this it could be extrapolated that the INN Programme will run out of usable names for mAbs within a couple of years. The current mAb naming scheme comprises a *-mab* stem, two infixes, one to designate the target and one to designate the species, and a random prefix. An assessment of assigned mAb INN reveals that the vast majority make use of only two of the target infixes and only two of the origin infixes. Dropping one of the infixes would provide more options but would still result in eventually running out of names. Dropping both infixes altogether and use of the *-mab* stem alone with a random prefix would achieve maximum flexibility. A reasonable and logical proposal by the Antibody Society that involved the creation of an alternative species infix was considered not to enable the Expert Group to devise the volume of unique names required in the foreseeable future. There was no general consensus on the way forward although removal of the source infix was favoured.

In a follow-up teleconference with the US CBER, it was expressed that CBER desired to drop the species infix, and furthermore CBER disagreed with the current species infix calculation, maintaining that the J-region should be included. CBER also had a view that the target infix should be more specific, although in reality this would be difficult as sponsors typically modified and expanded the indication.

During the Consultation, given that the species infix was becoming clinically less relevant with no direct correlation between species and safety profile, including immunogenicity, many Experts were in favour of dropping it. Indeed, there was some evidence that sponsors were using the species infix to enable marketing. However, there being no firm recommendation from the *Ad hoc* meeting and no agreement during the Consultation on the way forward, it was proposed that a small working group be set up to finalise a new mAb scheme, and to review information to be included in the Definition in a standardised, possibly computer-readable, manner.

Fusion proteins

Fusion proteins are new entities derived from one nucleotide sequence and are unique single substances. At the *Ad hoc* meeting, there was no consensus regarding assigning one or two word names to fusion proteins although opinion favoured one word. If the name comprises one word only, further deliberation was needed on how to devise short names. The possibility of a new stem specific for fusion proteins was mooted. For conjugated proteins, the current policy of a two word name should remain. In contrast to a conjugated mAb, when a fusion protein contains a mAb, there should be no requirement for a separate INN for the stand-alone mAb.

Glycoproteins

Nomenclature for glycoproteins should continue with the current policy, i.e. the use of Greek letters with the first name being assigned *alfa*. For mAbs, Greek letters are assigned only to the second and subsequent mAb with an identical amino acid sequence, beginning with *beta*.

Cell therapies

The *Ad hoc* group agreed that there should be alignment of nomenclature for advanced therapies. There was also agreement that names had too much scientific content and were too long as a result. Furthermore, a modified application form for cell therapy applications is needed that requests information to be used in the Definition and omits requests for CAS numbers and structure.

Genetically modified autologous cell therapy had previously been considered by INN to be *ex vivo* gene therapy (in parallel with the EU definition) whilst USAN had named such substances as cell therapy. Consequently distinct INN and USAN had been assigned and applicants were unsure of the situation. The recommended solution was to retain the one-word scheme for cell therapies (non-genetically modified), retain the two-word scheme for gene therapies, and introduce a two-word scheme for genetically modified cell therapies, where the first word identifies the gene (as in Gene Therapy (GT) nomenclature) and the second word identifies the cell. It was recommended however, to keep the second word short by omitting the vector infix and having a random prefix followed by the cell type only. This two-word rule would be applied to both autologous and allogeneic genetically modified cell therapies

There was also a strong recommendation to improve the information received from applicants defining the cell types, to standardise cell descriptions and develop key words for Definitions as different names were being assigned to substances with similar definitions.

Vaccine-like substances

At present, vaccines were not included within the INN system with the WHO Expert Committee for Biological Standardisation (ECBS) having a system in place for naming prophylactic vaccines for infectious diseases. Consequently, the *Ad hoc* group considered that this *status quo* should be maintained. However, although the INN Programme had not received any requests for INN for defined recombinant proteins used as active substances in vaccines, it could continue to assign these INN upon request. Defined recombinant nucleic acids (used as active substances in vaccines) similarly could be assigned INN. Vaccine-like substances for anti-cancer immunotherapy, such as oncoviruses, can be handled within existing INN policies and the *Ad hoc* group recommended that INN could be assigned to engineered live viruses and bacteria.

The Future Environment

In concluding the feedback from the *Ad Hoc* meeting, a variety of viewpoints from industry were presented that would require future consideration. These included: how would the 'target' infix be assigned to engineered mAbs that recognise two different targets? If a mAb was present in a fusion protein to target a cytokine or an enzyme to a specific tissue, and a two word name was applied, use of the stem *-mab* in one of the words may cause confusion. Where proteins were conjugated with more than one kind of small molecule or payload, might the names of these substances comprise multiple words? How would micro-organisms that secrete therapeutic antibodies and being used

directly as a therapeutic get named? What naming scheme would apply to platforms such as bacteria, viruses or particles that carried one or many antigens/neoantigens to induce an immune response?

In concluding the feedback session, the Chair thanked the biological experts for their contributions and noted that there was plenty to discuss in future deliberations.

BIOREVIEW

An update of the working document 'INN for biological and biotechnological substances (a review)' (the 'BioReview') was presented. The 2016 version contained a new 'General policies for pegylated substances' (Section 2.5), a new 'Summary of INN assigned to immunomodulators, both stimulant/suppressive and stimulant' (Section 3.18), a new annex with a 'List of INN for pegylated substances' (Annex 3), whilst the BioReview had been updated with INN from proposed List 114.

Other changes included revision of 'Introduction' and 'Current Challenges', removal of the section on 'Pharmacological classification of biological and biotechnological substances', and revision of the sections on 'General policies for vaccines', 'Monoclonal antibodies' (organized by target), 'Peptide vaccines/recombined vaccines' (renamed to 'Vaccine-like substances'). The previous Annex 1: 'List of INN for composite proteins published' had been divided into two annexes: Annex 1: 'List of INN for fusion proteins' and Annex 2: 'List of INN for conjugated proteins', whilst bi-specific monoclonal antibodies had been removed from these lists.

Planned changes for the next version would include recommendations from the recent *Ad hoc* meeting on Biologicals, a new section on advanced therapies incorporating cell, gene, and genetically modified cell therapies and vaccine-like substances, plus a review of general policies for fusion proteins, a new section on conjugated substances, and a review of the general policies for mAbs.

ISBT 128 and CELL THERAPY NOMENCLATURE

The ICCBBA (International Council for Commonality in Blood Banking Automation) is responsible for the management and development of the ISBT 128 Standard, the global information standard for Medical Products of Human Origin (MPHO). It is a not-for-profit nongovernmental organization in official relations with the WHO. WHO began the MPHO initiative in 2013 with the WHA requesting WHO to work with Member States on a global consensus on issues such as ethical principles and traceability. MPHO's include blood, cell, tissue, milk and organ products, and the objective of ISBT 128 is to provide global standards to support their traceability. It recognizes that one donor may be the source of many types of MPHO and that effective traceability must ensure all products derived from one donor could be traced internationally. It is a well-established standard, currently used in licensed facilities in 80 countries, and the product database included 45 cell therapy classes and 1,700 products. It involved a barcode system that includes the product code along with the donation number, which is highly important for traceability.

The label on cell therapy products assigned an INN will have two names, the brand name and the INN. Those also assigned an ISBT code will also show an ISBT name. Having three names on the label is not good practice so the ISBT proposal is to incorporate the INN into the ISBT 128 code, with the INN being treated as a new class within the non-proprietary category of the code. It will also be important to harmonise naming to avoid ISBT and INN creating distinct names, with the same holding true for INN and USAN.

In discussion, it was highlighted that some products may have a USAN but no INN, but where both existed harmonisation was being sought. It was also felt that the ISBT code and the INN served different purposes, with traceability for virus safety reasons being important for ISBT and not covered by INN, and so the benefit of having the INN within the code was not clear.

POSSIBILITY of a COMMON NEW STEM for FUSION PROTEINS

A proposal was tabled that a unique stem for fusion proteins gets created, such as *-fusp*, *-ftin* or *-fep*, which could be broadened for example to *-zafusp* where '-z-' would indicate an enzyme, and '-a-' would indicate an antibody. An alternative could be a combination of the pre-existing stems *-mab* and

-ase, to give *-mabase* (where the fusion comprises a mAb and an enzyme, which is likely to be the majority of cases), although it was stressed that the use of two strong stems in one word could cause confusion in prescription.

The INN Group firstly further discussed a one versus a two-word name. For a (mAb-enzyme) fusion protein, it was deemed difficult to define which moiety comprised the principal activity; for many it would be the enzyme that was the primary active component, although without the mAb moiety, it would not be targeted and thus exert its activity in a more defined manner. Two-word names would provide more flexibility; this could be especially important as fusion proteins became more complex. Feedback from industry would be needed.

To minimise prescription errors, a one word name would be better. For example, errors could arise where the same mAb was used in more than one different fusion proteins with distinct enzyme activities. Further, with a one word name, it would be easier to add a Greek letter for glycosylated proteins or an additional word for conjugated fusion proteins. A simple name would be more user-friendly; fusions are single protein entities and full information regarding the protein could be incorporated in the Definition. There had been near misses from patients not remembering long complex names for their medicines.

The name needs to flag that an enzyme (or other) activity was being presented in a different manner; the clinician was unlikely to note that it was a fusion protein. The stem *-ase* remained important and should not be masked by the use of a single letter ‘-z-’. Possibly, *-fusp* could be used for mAb fusion proteins only and alternative distinct stems could be created for other fusions.

Ultimately, many Experts leant towards a one word name, although there was by no means agreement on the use of a *-fusp* stem. To move ahead, the Chair proposed that the *-fusp* stem is trialled for two outstanding requests while new requests for fusions got deferred, and that the discussion continued at the planned Consultation in April 2017.

BIOLOGICAL QUALIFIER UPDATE

The new Director of EMP appreciated that biologicals were an important issue, but that various aspects were spread across WHO departments and not restricted to the INN Programme. In taking into consideration WHA resolutions on biologicals including greater access for Member States, she had set up a small group from various sections to discuss biologicals at a holistic level. The group had already met a few times but a major meeting was planned for February 2017 with additional participants. The focus would be on access although the BQ discussion would be an important item on the agenda as this could have a significant impact on access.

This did not prevent the INN Secretariat from proceeding with regulators in developing a BQ pilot scheme although the Secretariat was not at liberty at the 63rd Consultation to say with which regulators it was in discussion. Memoranda of understanding (MoU) were being set up with specific regulators and others had expressed an interest. The Director was in agreement with this dialogue and had already signed the first MoU. The software necessary for the project had been developed and ready to be used.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

BP 2017 was published in August 2016 with 29 new monographs and 127 revised. The BP was also following ICH Q3D for elemental impurities. BAN 2017 was published and contained 29 new entries involving those INNs on the UK market.

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

The 9th edition of the European Pharmacopoeia had been published in early 2016. Changes included deletion of tests for heavy metals following implementation of ICH Q3D, Guideline for Elemental Impurities. The draft general chapter 5.20. Chemical imaging, was also published in *Pharmeuropa* in

2016. This publication contained recommendations to assess the performance of chemical imaging systems, e.g. mid-infrared, near-infrared and Raman spectroscopy.

Pharmeuropa 28.4, the list of draft monographs out for comment, included a draft monograph for *infliximab*; with comments due by the end of 2016. This was the first monograph for a monoclonal antibody, and the commenting period would form part of the pilot phase for such monographs. It had also come to light that certain regions were using monographs to try to demonstrate bio-similarity instead of a proper biosimilar exercise, which was clearly not the intention of a pharmacopoeial monograph.

Finally, work had started on the preparation of a paediatric formulary, the aim of which was to provide a compilation of appropriate extemporaneous formulations for paediatric use, where no licensed product was available. Formulations from existing national or regional formularies would be selected and evaluated, making them freely available in order to help fill the gap until approved medicines were available.

European Medicines Agency (EMA)

The Name Review Group of the European Medicines Agency had met six times in the past year and considered around 350 names.

A review of EudraVigilance data for biologicals was currently underway to measure identification of biologicals in ADR reports received from European clinical practice between 2011 and 2016. The focus of the study was biologicals for which two or more products shared the same INN (biosimilars or related biologicals). More than 50,000 reports were included in the study and the results were reassuring. The exact product could be identified in approximately 93% of the reports, but as the reports were still being reviewed this was considered to be a conservative figure. The final figure was expected to be similar to previous studies for earlier time periods (around 96%).

Ministry of Food and Drug Safety (MFDS), Republic of Korea

Currently, the use of INN for pharmaceutical substances was not required by national legislation in Korea, but in accordance with the Regulation on Product Approval and Review of Medicines and Biopharmaceuticals, a Korean product name may be assigned according to the Guideline for Drug Nomenclature administered by the MFDS. An English name may be given according to the INN or the Guideline for Drug Nomenclature. The Guideline for Drug Nomenclature was established by the Department of Pharmaceutical Review in June 2010 and subsequently revised in December 2015. This guideline covered part of the naming rules for biopharmaceuticals (mainly biotherapeutics). The INN information book for therapeutics published in April 2009 was a useful reference.

In Korea, approval was granted to a brand name, not to pharmaceutical substances, so naming pharmaceutical substances based on drug nomenclature was not mandatory. However, MFDS is committed to promoting international harmonization through, for example, the Guideline for Drug Nomenclature which was developed based on the WHO INN system.

MFDS has no plan to introduce the BQ scheme yet, because it is implementing a traceability system through pharmacovigilance. However, it will monitor the developments of the BQ system and consider its necessity.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs within the PMDA was responsible for preparing the Japanese Accepted Name (JAN) and the Japanese Pharmacopoeia (JP). The JAN committee met four times from April to September 2016, from which 35 names were published. The 17th edition of the JP was published in March 2016, the English version which could be downloaded from the website was made available for free in August 2016.

The International Meeting of World Pharmacopoeias was held in Tokyo in September 2016, hosted by WHO, the Japanese Ministry of Health and PMDA. Immediately following this, the JP held its 130th anniversary symposium, also in Tokyo.

United States Adopted Names (USAN)

The 2016 Summer USAN Council meeting took place on July 21-22 at the American Pharmacists Association Headquarters in Washington D.C., where names for 42 drug substances were reviewed and discussed. Nine new stems or infixes with existing stems were approved and added to USAN's stem list. Policy discussions included biosimilar drug nomenclature, cellular therapy nomenclature revisions for genetically manipulated cells, monoclonal antibody proposed naming revisions and ISMP medication errors reports.

Thirty-five INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 63rd INN Consultation. Through September, 2016 USAN staff would have processed, researched and made recommendations for 127 new USAN applications and forwarded this information to the USAN Council for their review and selection. Also through September 2016, 92 USAN, 18 modified USAN and 5 revised USAN would have been adopted for 2016. Revenue was realized for an additional 12 negotiations.

The 2017 winter meeting of the USAN council was scheduled to occur on January 12-13 in Miami.

United States Food and Drug Administration (FDA)

The US FDA recently approved two more biosimilars, Amjevita (*adalimumab-atto*), a biosimilar to Hospira (*adalimumab*), and Inflectra (*infliximab-dyyb*), a biosimilar to Remicade (*infliximab*). Recently, the FDA representative, during a Webex meeting with the INN Secretariat and some INN Experts, indicated support for a modified mAb naming scheme in which 1 or 2 infixes get deleted. The FDA looks forward to having further Webex meetings with WHO to discuss harmonisation of BQ suffixes and also to reach more formal conclusions on modifications to schemes for gene therapy, cell therapy and monoclonal antibodies.

United States Pharmacopoeia (USP)

As a global organization, the USP also continued to expand its activities; for example, within the food safety area, it had developed a growing food fraud database to track incidents of economically motivated adulteration in the global food supply.

In another active arena, the USP continued to revise and develop standards for pharmaceutical compounding. Recognizing the need for individualized therapies for patient groups such as pediatric patients, the Compounding Committee was developing monographs for compounded formulations.

Finally, the Nomenclature and Labeling committee recently approved the name for new dosage form that had grown in popularity within the dietary supplement category – chewable gels. Although some had referred to this delivery format as “gummies,” the confectionery-related nature of that category and concerns about children's safety counsel the use of different terminology to describe health care products.

These efforts, among many others, reflect the USP's continued commitment to the development of public standards.

CLOSE OF MEETING

The Chair closed the meeting, thanking all participants for their time and efforts contributed both before and during the Consultation, and acknowledged also the support provided by the INN Secretariat.

Next Meeting

The 64th INN Consultation will take place in Geneva on 4-7 April, 2017.

Open Session for INN Stakeholders
**63rd INN Consultation on International Nonproprietary Names (INN) for
Pharmaceutical Substances**
Geneva, 18 October 2016

Dr David Wood, Technologies Standards and Norms Team Coordinator, welcomed stakeholders to the Open Session of the 63rd INN Consultation. At these sessions, INN users are invited to provide feedback, either in the form of general comments on policy matters, or regarding individual applications for an INN. INN Experts were also welcomed and thanked for their contributions to the INN Programme. The increasing number of new applications suggested that the innovation pipeline is strong, and this was good news for public health. For the United Nations, access to pharmaceutical products is a key part of its sustainable goal of access to a wide range of health care by 2030. Having non-proprietary names in place is an important part of that goal.

Dr Wood also informed stakeholders and Experts that a new director of Essential Medicines and Health Products, Dr Sue Hill, had recently been appointed, bringing new energy and enthusiasm.

Dr Raffaella Balocco-Mattavelli, INN Lead, also gave a welcome to stakeholders and INN Experts. She also acknowledged her INN team, without whom the meeting could not take place.

Dr Patience Holland, INN Chair, welcomed stakeholders on behalf of the INN Experts. The Open Session provides an opportunity for the Experts to learn what is new, what topical issues are, and how to find solutions. She also highlighted to stakeholders that all information presented and discussed at the meeting was strictly confidential until the meeting report was adopted and made public.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologics Medicines (ASBM)

Since it was four years ago that the issue of naming biosimilars globally was first raised by INN, the ASBM stressed the need to act, especially since there had been a great increase in biosimilar approvals, from 24 to 52, in that four year period, and that more than 40 biosimilars were in development worldwide for seven key biologics. The ASBM was very appreciative of the INN committee for its care, openness and fairness, but urged the Committee to finalise a policy as the danger in delaying creates a policy vacuum. There is no other entity with the gravitas and the experience to solve this global challenge and WHO leadership is awaited by regulators worldwide supportive of the WHO's efforts. BQ implementation will particularly aid countries with no strong pharmacovigilance system for biologics. In urging action, the ASBM understood the challenges, e.g. mergers and acquisitions; however, to date no biosimilars had been sold to another party after approval. In mergers, biosimilars had not lost their corporate identity and so can retain their original BQ; concerns were unwarranted and slight changes can be accommodated. Since the previous (62nd) INN Consultation, the US FDA has approved two more biosimilars, assigning potentially BQ-compatible 4-letter random suffixes and it was repeated that the INN needs to act soon.

ASBM surveys have cumulatively obtained opinions of about 2,500 clinicians. In its most recent survey, of Australian prescribers, more than three-quarters were of the opinion that the TGA should insist upon distinct non-proprietary names for all biosimilar and biologics

medicines it approves. These results were consistent with other surveys of physicians worldwide and highlight the need for global consistency led by the WHO. Also, the ASBM remained supportive of meaningful rather than random suffixes as surveys showed that clinicians worldwide support a manufacturer suffix.

Pharmacists have a history of avoiding look-alike/sound-alike names, and a great majority feel that distinguishable names for biologics should be used, which is in contrast to that of US Pharmacist Associations. Furthermore, in surveys of pharmacists, there was a consistent and clear majority with a preference for a meaningful name with little support for a random suffix. Current opinion supported that now is the time for WHO to implement a scheme for distinguishable non-proprietary names for all biologics.

Global Alliance for Patient Access (GAfPA)

Within the USA, the Alliance for Patient Access (AfPA) comprises a national network of physicians whose mission is to ensure patient access to approved therapies and appropriate clinical care. It achieves this through educating physicians on policy priorities and training them to be effective advocates for their patients. It works closely with the Global Alliance for Patient Access (GAfPA) and with other physician/patient initiatives and medical societies. The Alliance engages with policy makers globally across many different disease states, and much of the work is focussed on biologic therapies including biosimilars. With patient organisations anxious to understand these new medicines, it provides training, educational materials and advocacy.

The GAfPA's biologics viewpoint reflected the WHO's BQ in that it supported naming policies that reflect inherent differences between biologics and biosimilars. Distinguishable names would benefit patients through robust pharmacovigilance. Upon switching from a biologic to a biosimilar, patients need to be assured of their efficacy and safety, and as more and more patients have access to biosimilars, data that assures robust pharmacovigilance was needed and the Alliance believes that the BQ will achieve this.

The Alliance's educational work includes briefing patients through conferences, white papers and web-based info-graphics which are easily accessed and user friendly. Information is provided in several languages and the Alliance will soon release a video in Spanish, outlining the BQ proposal and urging regulators to adopt it. The Alliance wants to increase confidence amongst physicians and patients that when switching to biosimilars, a robust pharmacovigilance system is in place by promoting a truly global naming system that distinguishes biologics from biosimilars.

GAfPA's view is that the WHO BQ would provide distinct INN that reflect subtle but potentially meaningful differences among biologics and biosimilars, that it will facilitate pharmacovigilance and that it will give physicians confidence in their ability to precisely prescribe, administer and monitor these treatments.

Generics Pharmaceutical Association (GPhA)

GPhA's presentation focussed on convergence of the proposed WHO BQ and the US FDA's draft guidance on biosimilar naming. The WHO 'biological qualifier' proposes a consonants only 4-letter non-meaningful code with an optional 2-digit checksum. It would follow the INN but not be part of it. It would be assigned by WHO, be voluntary, and be applied to all biosimilars/biologics. It remains unclear if it would be applied retrospectively including to reference products. The FDA draft scheme also comprises a 4-letter non-meaningful code, but with vowels and consonants, and no-checksum. It would be attached to the USAN/INN via a hyphen. It would be assigned by the FDA with input from the applicant and it is not

voluntary. The FDA has approved four biosimilars along with 4-letter suffix codes. In the FDA system, the 'proper' name for a product would be the 'core' name (USAN/INN) plus the 4-letter suffix.

With these differences between the BQ and FDA draft schemes, convergence would limit confusion. The FDA will assess the impact of its scheme on pharmacovigilance over the next four years. GPhA recommended that the BQ scheme is not implemented until consensus has been reached between FDA and WHO, and that due to the increased risk of confusion regarding prescribing, dispensing and substitution with attached suffixes, the identified systems should be independently tested to ensure they improve identification and reduce safety risks.

The GPhA presented a substantial list of questions on the proposed BQ pilot scheme to the INN Committee, including on the inclusion of the FDA suffix in the pilot scheme, on the assignment of identical FDA and BQ codes, and on the application of the BQ to innovator products.

The Chair was appreciative of the GPhA's comments and questions, and noted that the WHO was addressing such questions with all WHO member states and not just the US FDA.

In discussion, the FDA representative noted that the attached suffix would only be part of the product name, as it only labels products, and there was no intention to modify the name of the drug substance. The BQ, whilst not part of the INN, could however be on the product label. The FDA also needed to work with the USP on harmonising monographs, as the USP title becomes the official name of an FDA approved product. For example, for a specific biologic/biosimilar with two different names because of two different suffix codes, it is not yet clear how this would work with the USP monographs. However, many monographs are not published until the product has been on the market for several years.

Medicines for Europe/Biosimilars Medicines Group

Medicines for Europe highlighted recent developments relevant to the debate on the proposed WHO BQ. First, the new EMA Good Pharmacovigilance Practice chapter for Biologicals, which came into effect in August 2016, highlights that the information to be provided when reporting suspected adverse reactions includes the product name and batch number. Second, the EU Falsified Medicines Directive is in implementation phase and includes the use of a 2D data matrix code in which the batch number is a key element. Any additional element such as a BQ should be avoided to avoid confusion. Third, implementation of ISO IDMP standards is ongoing within the EU (covering also the unique identification of substances). This is a complex but important development, going beyond the EU,. Abbreviated regional testing was performed by the ICH Parties to guarantee interoperability across regulatory and healthcare communities Medicines for Europe also presented a series of important questions with regard to the BQ pilot scheme including the extent to which a limited number of prospective approvals can provide sufficient data to evaluate the scheme, when the retrospective application of the scheme be addressed, how local pharmacovigilance systems will be taken into account, the interoperability of the BQ with other systems, and how the US FDA suffix (at product level) would fit into a pilot scheme. Other areas under question were the criteria for evaluating the impact on access to medicines, the organisation of the pilot scheme and how the added value would be assessed.

Medicines for Europe recommended that ISO IDMP standards be implemented first by those countries involved in their development and that the implementation of the BQ scheme and the impact study is decoupled. The organisation again called for a moratorium of the provisional implementation of the BQ scheme and for further international exchange and

dialogue; implementation without a prior regulatory impact assessment could contribute to a proliferation of different identifiers . Finally, a prior impact study in every “BQ volunteering country” in line with the WHO draft GRP guidelines is essential to ensure that, the BQ does not lead to any confusion or medical errors in the global healthcare arena.

In discussion, it was highlighted that ISO standards have to be adopted globally to be useful. For example, the ISO standard on how to present dates on documents has never been adopted globally, and in reference to the 2D matrix code on packaging, the BQ could be included with very little problem as it takes very little space within the code.

It was acknowledged that the Australian regulatory authority would publish an impact statement on implementation, but it remained unclear how other countries might implement the BQ. Meeting participants were informed by the Secretariat that discussions on BQ implementation with individual regulatory authorities were ongoing but remained confidential.

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Medicines for Europe also presented a series of important questions with regard to the BQ pilot scheme including the extent to which a prospective study can provide sufficient data to evaluate the scheme, how local pharmacovigilance systems will be taken into account, the interoperability of the BQ with other systems, and how the US FDA suffix would fit into a pilot scheme. Other areas under question were the criteria for evaluating the impact on access to medicines, the organisation of the pilot scheme and how the added value would be assessed.

Medicines for Europe recommended that implementation of the BQ is firstly by those countries implementing ISO IDMP. The organisation again called for a moratorium on implementation of the BQ scheme and for further international exchange and dialogue; implementation without a prior impact assessment on regulators could contribute to a proliferation of different qualifiers. Finally, a prior impact study is essential to ensure that prior to any provisional implementation scheme, the BQ does not lead to any confusion or medical errors in the global healthcare arena.

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PRESENTATIONS on INN ASSIGNMENTS

AMGEN Biosimilars

Amgen expressed its concern regarding the lack of implementation of the Greek letter policy for mAbs (no Greek letter for the first application, the use of *beta* and further Greek letters for additional applications for a mAb with the same amino acid sequence where there are glycosylation differences). Amgen had approached the INN at its Open Session two years ago to request clarification at which time it had illustrated the need for application of the policy by reference to the distinct critical quality attributes (afucosylation profiles) of an originator and two biosimilar mAbs.

In this session, Amgen presented Australian data on the high level of ambiguity (41%) on attributing AERs to a specific product where the same INN was assigned (*filgrastim*), versus the low level of ambiguity (5%) when distinguishable non-proprietary names were available (*epoetin 'alfa', 'beta', 'lambda'*). Amgen further noted that in 2015, WHO reaffirmed its Greek letter policy, although Amgen currently remains unable to secure recommended INN for several follow-on mAbs. Furthermore, Amgen is aware that two second versions of originator mAbs had proposed INNs including Greek letter second words.. Furthermore, despite glycan differences, several licensed biosimilars do not have a distinguishable INN, whilst others do. It is not clear under what circumstance distinguishable INN are assigned.

As a sponsor of both biosimilar and originator biologics, Amgen reiterated its 2014 request for access to differentiate non-proprietary names. Several drug agencies are interested in approving these biologics using distinguishable non-proprietary names but are awaiting WHO's decision on a recommended INN. The INN Programme needs to follow its reaffirmed policy for the Greek letter option, or fully implement the BQ programme of which Amgen is fully in favour.

The INN Secretariat responded that some proposed INN for mAbs had not yet been promoted to recommended INN because official objections had been received, but that these objections could not be upheld, and so the names are likely to become recommended INN; these will be considered during the 63rd Consultation.

The Chair added that with respect to differences in glycan structure, the INN Committee often do not receive sufficient data from applicants for the Experts to decide whether a new Greek letter is warranted.

Biogen

Biogen's representation was similar to Amgen's in requesting the assignment of '*beta*' to its new version of the mAb *daclizumab*. The new version (Daclizumab HYP) is being manufactured from a new production cell line and under a new manufacturing process. This had resulted in a distinct and consistent glycosylation profile, markedly different from the version of *daclizumab* previously marketed by Roche (*Zenapax*). *Daclizumab beta* had indeed been originally assigned by the INN Experts to Biogen's mAb in May 2015, but the Company was informed in February 2016 that there had been an official objection to the use of '*beta*' as the Greek letter should not be used to indicate glycosylation differences for mAbs. Biogen emphasised that this appeared to be inconsistent with published WHO policy and respectfully requested that *daclizumab beta* was re-assigned.

The INN Secretariat assured Biogen that this would be discussed during the plenary Consultation.

CLOSE OF SESSION

The Chair thanked the Stakeholders for their contributions to the Open Session and closed the meeting.