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# 67th Consultation on

# International Nonproprietary Names for Pharmaceutical Substances

# Geneva, 23-26 October 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***

**67th Consultation on International Nonproprietary Names for Pharmaceutical Substances**

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**EXECUTIVE SUMMARY**

## INTRODUCTORY REMARKS

**Dr François-Xavier Lery**, Coordinator, Technologies Standards and Norms (TSN), opened the Consultation on behalf of the Assistant Director-General, Dr. Mariângela Batista Galvão Simão. He highlighted the importance of INN work and reported on recent significant events at WHO.

Progress in strengthening regulatory systems among Member States continues by advancing standards and norms, by pre-qualification, and by assisting quality control laboratories in the use of biological standards. Encouraging regulators to share expertise is a key element of the TSN strategy. Improving post marketing systems is also very important, especially for biosimilars. Pre-qualification of biosimilars is a key new project that was launched in July; alongside this the WHO will monitor access to biosimilars.

A resolution was adopted in May to harmonise the production and control of anti-snake venoms. These are made with antiquated technology in horses, but which remains state-of-the-art technology.

Among WHO's functions, the normative part is less visible and the INN work needs to be more visible at country level. With that, Dr Lery thanked the Experts for their hard work and wished them a good meeting.

**Dr Raffaella Balocco-Mattavelli**, Group Lead INN, welcomed all to the meeting, noting that there was a heavy agenda with 142 new requests, another new record number of applications. She expressed her gratitude to the Experts for their endurance and hard work in dealing with them.

## ELECTION OF CHAIR, VICE-CHAIRS and RAPPORTEUR

Prof. Sarel Malan was proposed and elected as Chair for the 67th INN Consultation. Dr Adrian Evans was proposed and elected as vice-chair for chemical substances and Dr Karin Weisser as vice-chair for biological substances. Dr James Robertson was proposed and elected as rapporteur.

**The Chair** thanked Dr Lery for his kind words, the INN Secretariat for its hard work, and the INN Experts for their time and energy spent on the work of the INN Programme; all this contributes to the safety of medicines and ultimately of patients.

## 66th EXECUTIVE SUMMARY

The Executive Summary of the 66th INN Consultation was tabled and adopted, with thanks to the rapporteur.

## NOMENCLATURE of INN

During the 67th INN Consultation, a total of 181 INN requests were discussed, including:

- 142 new INN requests, including 79 for biological substances
- 33 outstanding requests

- 6 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 170 names were selected, which are planned to be published in List 121 of Proposed INNs (p.INN), while 9 requests were deferred for future discussion. 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; one request of substitution could not be retained as it did not conform to the criteria.

Seven new stems/substems were selected, 3 suffixes were promoted to the pre-stem list and it was decided to review the descriptions of one pre-stem.

**Stem Book Update**

A new update of the Stem Book, the official WHO publication on INN stems, was tabled, the last update having been in 2013. Stems are common suffixes (occasionally prefixes or infixes) assigned to substances with a similar structure and/or mode of action, and are protected within the trademark arena by WHO Resolution 46.19. While this new update is likely to be quickly out of date, as before, addenda will be published when necessary.

Over the previous 5 years, over 1000 new INN have been proposed and has resulted in 35 new stems or substems, 6 for biological substances and the remainder for chemical substances. The most frequently used stems over these 5 years are *-mab* for monoclonal antibodies and *-tinib* for tyrosine kinase inhibitors. Many new pre-stems have also been created.

*In discussion*, the fate of stems no longer used was raised and the possibility of deleting them. However, the INN themselves may be active and even if not, they cannot be deleted for legal reasons, despite some poorly designed stems being criticised by trademark holders. It is feasible however to amend the definition of a stem.

## GENE AND CELL THERAPY – INVITED LECTURE

Prof. Guangping Gao, Professor of Microbiology & Physiological Systems, University of Massachusetts Medical School, and President-Elect of the American Society of Gene & Cell Therapy (ASGCT), was invited to address the INN Expert Group on the current and future state of gene and cell therapy.

In introducing gene therapy, Prof. Gao highlighted key components including identification of the disease mechanism and potential therapeutic gene, the design of the vector, how to identify and target the appropriate tissue and identification of an animal model that mimics the human disease.

Historically, following the first clinical trial of gene therapy with a retrovirus vector was in 1990 with the successful treatment of adenosine deaminase (ADA) deficiency, there was a period of progress with the development and use of other vectors including adenovirus, herpes virus and adeno-associated virus (AAV). However, following the death of a patient undergoing adenovirus vectored therapy through a severe adverse immune event in 1999, there was a hiatus in development. Nonetheless, progress eventually continued and by 2012 the first gene therapy treatment was licenced, followed by others in 2017.

During this time AAV moved into the front line of gene therapy although the prototypic AAV2 was of limited efficiency. This drove the search for alternative serotypes and AAV8, pioneered by Prof. Gao, became the first gene therapy drug to gain approval by the EMA. Currently AAV is the vector of choice for *in vivo* therapy whilst lentivirus vectors are the first choice for *ex*

*vivo* therapy and currently, more than 1,000 gene and cell therapy drug INDs are under review at the US FDA.

The genome of AAV vectors comprise AAV terminal repeats plus the gene of interest. Vectors are generated with a rep/cap (the two viral proteins) helper system and although the favoured genome is derived from AAV2, the capsid can derive from an alternative serotype to which the human immune system is not primed. The value of alternative AAV serotypes firstly is to overcome immune neutralisation by the host and secondly to allow targeting to specific tissues. AAV vectors also give very stable expression of the transgene, even up to 11 years in one animal model.

Prof Gao then focused on the use of gene therapy for gene replacement, highlighting success in treating patients suffering from Canavan disease, an inherited and fatal neurological disorder. Mutations in the asparto-acylase gene result in excess N-acetyl aspartate, which interferes with the growth of the myelin sheath of nerves. His research led to the development of an AAV9 vector for targeting brain tissue and using this to target and express functional asparto-acylase resulted in tremendous improvement in brain function and growth development of children with this condition.

AAV gene therapies are also being developed for gene silencing, for example to investigate the treatment of Huntington's disease in which there is an excess of glutamic acid, in gene addition for treating HIV infection using AAV to transport genes for broad spectrum anti-HIV antibodies, and finally for somatic gene editing using AAV vectors to deliver CRISPR gene editing technology.

Gene therapy may be the best and only chance of curing brain disease and Prof. Gao highlighted that after three decades of research, gene therapy had evolved from scientific fiction to clinical reality but that many challenges remain involving toxicity of cell therapy and improved tissue and cell type specificity.

## UPDATE ON ADVANCED THERAPIES NOMENCLATURE

The current naming scheme for gene therapy substances comprises a two-word scheme in which the first word pertains to the gene in question and the second word to the vector. The first word ends with the stem *-gene*; the second word ends with a stem appropriate to the vector. Cell therapy substances are assigned a one-word name with the stem *-cel*. No distinction is made between autologous and allogeneic cell therapy substances.

Substances for cell-based gene therapies, i.e. genetically modified cells, are given two-word names, in which the first word pertains to the gene in question and the second word to the type of cell. Thus, the first word is named with a *-gene* stem as for all gene therapy substances; the second word makes use of the *-cel* stem as for cell therapy substances. This scheme supersedes a previous scheme in which, for genetically modified autologous cells, the INN scheme assigned a two-word name only to the vector used to transfect the cell, and not to the cell. In contrast USAN assigned a one-word name to the modified cell, making use of the infix *-gen-*. For harmonisation purposes, the two-word scheme for 'cell-based gene therapies' as described above was agreed upon.

The INN Expert Group was informed of a further potential amendment to the naming of autologous cell-based gene therapy substances. Requests had been received for autologous cell-based gene therapies that share the same type of autologous cell. The question was whether or not the same fantasy prefix should be used for the second word, pertaining to the cell. The INN Group was informed that a WebEx conference had been held in June between experts from INN and the FDA at which four options had been considered: (i) provide different and

unique fantasy prefixes for the second word for each substance, (ii) provide identical fantasy prefixes for the second word, (iii) omit the fantasy prefix from the second, or (iv) substitute the fantasy prefix with a prefix that refers to the autologous nature of the cell substance, such as *auto-*. Given the nature of autologous cells, there was agreement to omit the fantasy prefix from the second word of autologous cell-based gene therapy substances; the fantasy prefix of the first word (gene component) is sufficient for the INN for the substance (gene plus cell components) to be unique. The use of *auto-* in place of the fantasy prefix was left as an option.

Similar scenarios with other gene therapy substances should be discussed. For example, when requests had been made for INN for gene therapies in which the vector components were identical, initially distinct fantasy prefixes were assigned to the second word. However, for more recent requests, the same fantasy prefix was assigned where the vector component was identical. In these cases, each INN was unique due to distinct fantasy prefixes of the first (gene-component) word.

*Following discussion*, the INN Expert Group agreed to drop the fantasy prefix from the second word of autologous cell-based gene therapy substances and replace it with the prefix *auto-*. For all other types of gene therapy substances, there was strong opinion to retain the second word fantasy prefix as there was potentially many different and distinct vectors. However, the use of the same fantasy prefix for identical vectors could continue.

## UPDATE ON MONOCLONAL ANTIBODIES

In 2017, it was decided to drop the 'source' infix from mAb INN as it had outlived its usefulness. However, the Description of the mAb still contains information pertaining to this infix, such as 'chimeric' or 'humanised', and this needed to be addressed. INN biologicals experts discussed this issue at a meeting in June 2018 with a consensus that the source terms should no longer be used in the Description as the source of a mAb was felt too complex to define with a single term and a fuller description of each domain would be required. It was also agreed that INN application forms should clarify the specific information that applicants should now submit, perhaps with examples, and that this should apply to all protein applications and not just mAbs.

In addition to the information that is currently sought for protein and mAb applications, the group emphasised the need for a simple graphical representation of antibody molecules as the amino acid sequence alone is not sufficient to understand the overall structure of the antibody. Applicants also need to make clear whether structural information on, for example di-sulphide bridges, is experimentally determined or assumed. Percentage similarities of closest match can continue to appear in the Description but with no conclusions being drawn from them. Experts need to devise an appropriate form and create a model Description, perhaps with a pre-existing mAb. It was acknowledged that getting a full set of data from applicants can be problematic.

The INN Expert Group was informed that The Antibody Society agreed with and fully supported this position. It was also brought to the Experts' attention that there is a huge number of formats of antibodies on the horizon, such as antibodies with variable domains with dual specificities, additional domains and appended Fab fragments. In addition, there are novel non-antibody proteins with binding properties on the horizon and a huge number of unique molecular scaffolds are available and being used for the development of new therapeutics. These may have multimeric formats, for example with five scaffolds linked in a row, with similar or different specificities and the INN Expert Group was warned to be prepared for INN applications for these highly complex molecules; for example, should each type of scaffold get its own suffix or should molecules that act identically but are based upon different scaffolds have identical target identifiers? It was emphasised that for all of these complex structures, the

amino acid sequence provides limited information and a diagram of the protein 3D structure would be necessary.

*In discussion*, the value of retaining the *-ta-* (for anti-tumour) and *-li-* (immunomodulatory) infixes was questioned given that the vast majority of mAbs contain one of these two infixes and that the function of the mAb would appear in the Description. There was probably some value in them but to bear in mind that dropping the infix would allow for shorter or more distinct fantasy prefixes.

## NAMING OF EXCIPIENTS

The INN Expert Group was informed of a draft document 'Guidance for Nomenclature on Pharmaceutical Excipients' being developed by the Chinese Pharmacopoeia Commission (CPC). Its purpose is to specify and harmonise pharmaceutical nomenclature of excipients and would assist regulators in assessing drug licensure. Naming of excipients should follow WHO INN and Chinese Approved Drug Name (CADN) principles; or where appropriate, reference should be made to Chinese Pharmacopoeia Names of Organic Compounds (PNOC) and Chinese Pharmacopoeia Names of Polymer Compounds (PNPC). The main considerations include a preference for chemical names, the use of prefixes or suffixes for those with multiple specifications, the route of administration where alternatives routes exist, following INN and CADN principles for optical isomers, racemates and geometric isomers, and by adding the number of water of crystallisation, when appropriate. Several individual classification schemes are being developed covering saccharides, cellulose, starch, grease, polymers, pre-mixtures, dispersions, hollow capsules, spheres and excipients from human and animal sources.

Current CPC guidance on excipients mainly refers to their classification and this new document is driven by drug safety and public health as excipients are complex in type, source and composition. Furthermore, the use of excipients is not directly related to the structure of the active ingredient and use may not be consistent where the same excipient is used in different products. The Commission will collaborate with state authorities and other stakeholders in this process whilst retroactive harmonization seems unnecessary and impossible.

**The status of excipient naming in other organisations was provided**

*The United States Pharmacopoeia (USP)* highlighted a recent workshop it held on excipient nomenclature attended by both regulators and industry. In the USA, nomenclature is driven by the FDA's inactive ingredient database and the USP is currently working on similar guidance. However, there are difficulties for nomenclature as much of the information concerning excipients is proprietary, not all of which gets fully disclosed.

*In the EU*, regulation of raw materials tends to be by pharmacopeia, which provides the requirements for excipients, although names tend to come from manufacturers. It is an overlooked area because of the amounts used and what they are used for. The European Pharmacopoeia has general monographs with some guidance on excipients but it is difficult to harmonise and develop specific monographs on excipients.

*In Brazil*, ANVISA is tackling excipients but finds it challenging with information being sought on a need basis. There is some regulation through the Brazil Pharmacopoeia, but this current exchange of information is important for ANVISA to improve its process.

*In Australia*, the TGA made progress in the harmonisation of excipient names two years ago but is aware that there is little worldwide harmonisation.

*South Africa* has no pharmacopoeia and so standardisation of excipient names and the development of monographs would be useful as much of their medicines are imported.

*In Tunisia*, national drug control makes use of the USP.

*At WHO*, a meeting was held in 2002 on 'Brainstorming on INNs and Excipients' from which technical considerations were developed; however, these were never openly published. Nomenclature of excipients was also discussed some time ago at a meeting with IPEC, at which it was decided that there was no great urgency in addressing this. However, following that discussion, it was mooted that perhaps it should be considered by WHO, which could liaise with a world forum of pharmacopoeia, the International Pharmaceutical Excipients Council (IPEC) and other experts to convene a discussion meeting.

*In conclusion*, the Chair recommended the WHO decide how to tackle this and volunteers were requested.

## KINASE INHIBITORS

A review of kinase inhibitors, developed by an INN Expert specifically for the INN Group, was tabled.

Protein phosphorylation is one of the most important regulatory mechanisms in the growth of animal cells and kinases can be subdivided into those that phosphorylate tyrosine residues, serine or threonine residues, or have dual specificity. In the human genome there are about 550 kinases of which nearly 100 are tyrosine-specific or have dual-specificity whilst the remainder are serine/threonine-specific. The development of inhibitors of kinases is a huge area in cancer therapy. In assigning INN, tyrosine kinase inhibitors are given names with the stem *-tinib*, or a further sub-division of it; for example *-citinib* is the substem for Janus kinase inhibitors. Many other stems and substems have been developed for other kinase inhibitors, for example *-lisib* for phosphatidylinositol 3-kinase inhibitors. However, many inhibitors have been assigned INN with no specific stem or substem. What is clear is that various stems are overloaded whilst many kinase inhibitor groups do not have a specific suffix.

The document listed INN for all kinase inhibitors according to mode of action and highlighted where the Group should give consideration to establishing a specific substem, or not. The INN Experts provided feedback for the assignment of INN to future kinase inhibitors.

## USE of INN in WHO MEMBER STATES

The INN Experts were updated on a questionnaire on assessing the use of INN in WHO Member States (MS).

Understanding the full implications of naming medicinal substances can play an important role in reducing costs and gaining access to high quality medicines, and an informal questionnaire on INN usage was developed and is on-going. Questions address the use of INN versus brand name in prescribing and adverse event reporting, while more general questions were posed on interchangeability, branding and the market share of innovator versus generic medicines.

To date, while only 46 MS had completed the questionnaire, this represented a majority of the world population. However, more responses especially from African and mid-Asian member states are needed. All respondents use INN to an extent, with three of them having their own parallel system, *viz.*, BAN in UK, JAN in Japan and USAN in the USA, although BAN and JAN adopt the INN when available.

Most MS allow prescribing with either brand name or INN. The use of INN is mandatory in only a few MS; similarly, the use of brand name is mandatory in very few MS. All MS allow generic substitution of small molecule drugs although some do not have clearly defined rules on this. Slightly less than half of the responding MS allow the substitution of biologicals (as

biosimilars) although interchangeability is generally limited. Finally, all MS reported that the INN appears on packaging but typically the INN font is smaller than the tradename.

*In discussion*, it was noted that Denmark uses an invented name only, although the INN is incorporated with the company name as the 'brand name'. It was also suggested that if there is a model country for interchangeability amongst respondents, this could be shared among all MS to help regulatory pathways; this could be useful although at present there is not enough data to understand fully what is going on.

As a footnote, Experts were informed that the questionnaire arose as a request from the DG about implementation of WHO norms and standards.

**SCHOOL of INN (SoINN)**

The SoINN group met the day before the 67th INN Consultation to discuss progress.

The online courses being developed are aimed at students and the pharmaceutical industry. Module 1 is an introduction to the science of nomenclature and acts as a foundation to modules 2 and 3, for biologicals and learning pharmacology with stems, respectively. At the end of each module there will be multiple choice questions for online assessment. Potentially, the courses could be adopted by colleges, and students could be provided with credits or certificates of achievement.

A manuscript has been developed also on 'Learning Pharmacology with Stems' and was recently published by WHO, both online and as a hard copy. Two further publications, on naming biologicals and on a general overview of INN, are awaiting clearance by WHO, following which they will be submitted elsewhere for publication.

A new presentation on stems and clinical pharmacology was made to the SoINN group and eventually will be published; it will serve as a complementary learning tool to Learning Pharmacology with Stems.

Interest in SoINN has been shown by a number of universities and the aim is to establish different pilot sites in different countries.

A presentation on INN and SoINN was given by the Secretariat at the Dean's Forum, held in Glasgow in September alongside the 2018 FIP World Congress. The talk was well received and provided a good opportunity to make contact with a variety of potential stakeholders for the SoINN. It also transpired that for the teaching modules to be attractive, students would need incentives to take part such as credits towards pharmacology qualification. FIP itself is also interested in participating in the SoINN, and INN Experts who attended the Congress re-affirmed that the presentation triggered a high level of interest from deans and heads of schools.

The next meeting of the SoINN will be in November in Madrid, hosted by AEMPS, to finalise the courses and consider the next steps. It was highlighted to participants of the Consultation that SoINN is not a closed group and anyone with an interest is welcome to join. A future task is to translate the course into other languages. Finally, it was suggested that those Experts who interact with Universities could begin advertising the existence of the SoINN to universities.

There followed a demonstration of the SoINN e-platform.

**COLLABORATORS' UPDATES**

**European Directorate for the Quality of Medicines (EDQM)**

While the main publication of the EDQM is the European Pharmacopoeia, this month saw the release of the first two draft monographs on a new website for the European Paediatric

Formulary (PaedForm). The purpose of this new formulary is to provide a collection of formulations for extemporaneous preparations that are specifically intended for children, and that are currently described in formularies of individual member states. The non-mandatory monographs will be available free-of-charge and allow clinicians to formulate such preparations where a licensed medicine is not available. Unlike Pharmeuropa, these draft PaedForm monographs are open to all users to provide comments in order to encourage as much input as possible from around the world.

Other publications from the EDQM include a guide for parents on umbilical cord blood banking and its therapeutic value, in order to allow them to make an informed decision on whether or not they wish to participate. It includes information on what umbilical cord is, what it can be used for and the difference between public and family banks.

The EDQM has also published the 1st Edition of its guide to Safer Tattooing, which provides an overview of the current knowledge and challenges related to the toxicology of inks used in tattooing. Also available are guides to blood, tissue and organ donations. Finally, a flyer is available that outlines the ways in which the EDQM is involved in trying to solve the challenges around the quality control of gene therapy products (for example its coordination of the network of Official Medicine Control Laboratories), showing how the products that are named here by the INN experts are then overseen when on the market.

**International Union of Biochemistry and Molecular Biology (IUBMB)**

The IUBMB oversees enzyme nomenclature which started in 1961. The nomenclature categorises enzyme reactions and not the proteins themselves and now lists 6,200 characterised enzymes.[1] The seven Enzyme Commission (EC) categories are: EC 1, oxidoreductases; EC 2, transferases; EC 3, hydrolases; EC 4, lyases; EC 5, isomerases; EC 6, ligases; and EC 7, translocases. EC 7 was only recently created and comprises the least number of enzymes although many are in preparation and with it being a growing area, many more are expected. Its enzymes had not necessarily never been categorised before, it was that many did not fit any other category.

Categories are further subdivided into 3 sublevels such that codes generally comprise 4 sets of digits, e.g. EC 1.1.1.34, where EC 1.1 is for oxidoreductase enzymes acting on the CH-OH group of donors, EC 1.1.1 with NAD+ or NADP+ as acceptor, and EC 1.1.1.34 for the specific enzyme reaction catalysed by hydroxymethylglutaryl-CoA reductase (NADPH).

**International Union of Pure and Applied Chemistry (IUPAC)**

IUPAC has now published the Nomenclature of Flavonoids (IUPAC Recommendations 2017)[2].

**Pharmaceuticals and Medical Devices Agency (PMDA), Japan**

The Division of Pharmacopoeia and Standards for Drugs, Office of Standards and Guidelines Development within PMDA is responsible for preparing the Japanese Accepted Names (JAN) and the Japanese Pharmacopoeia (JP). From April to September of 2018, the JAN Expert Committee met 3 times and 24 names were published including 3 biosimilars; 2 biosimilars of *trastuzumab* and the first biosimilar of *agalsidase beta*.

In September 2018, the English version of Supplement 1 to the 17th Edition of JP became available and can be downloaded from the PMDA website for free

[1] http://www.sbcs.qmul.ac.uk/iubmb/enzyme/

[2] Pure & Applied Chemistry, 2018, 90, 1429-1486. https://doi.org/10.1515/pac-2013-0919

(http://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0019.html). Supplement 2 is scheduled to be published next May. After publication, JP will contain over 2000 monographs.

**Therapeutic Goods Administration (TGA), Australia**

Australia's regulatory framework for therapeutic goods is undergoing a number of changes in response to the Review of Medicines and Medical Devices Regulation. These reforms aim to ensure the availability of products that meet Australian standards for safety, quality and efficacy. Progress has been made in establishing expedited submission pathway for prescription medicines, developing enhanced orphan medicines criteria as well as promoting international work-sharing and the use of comparable overseas regulators' report. Generics medicines reform is also ongoing to improve their market authorisation process.

The TGA is collaborating with other government agencies to strengthen national regulatory authorities around the Pacific rim. Currently 5-6 countries are involved and the activities include enhancing regulatory processes and medicines testing programmes. Finally, reporting medicine shortages to the TGA will be mandatory from January 2019. Inter alia, the aim of this initiative is to facilitate more proactive, timely and transparent management and communication about medicine shortages for the benefit of Australian consumers and health professionals, as well as for medicine sponsors.

**United States Adopted Names (USAN)**

The 2018 Summer USAN Council meeting took place on July 12-13 at USP Headquarters in Rockville, Maryland, where names for 32 drug substances were reviewed and discussed. Thirteen new stems and infixes were approved and added to USAN's stem list, 3 stems were revised and 2 stem definitions were revised to harmonise with the INN Programme. Policy discussions included advanced therapies nomenclature, an introduction to phonetic and orthographic computer analysis (POCA) and a review of revisions made to USAN sponsored INN applications. Twenty-nine INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 67$^{th}$ INN Consultation.

Through October 2018 USAN staff will have processed, researched and made recommendations for 158 USAN applications and forwarded this information to the USAN Council for their review and selection. Also through October 2018, 94 USAN will have been adopted for 2018 while revenue was realised for two additional negotiations. Currently, there are 174 active USAN negotiations.

The 2019 summer meeting of the USAN Council is scheduled to take place on July 11-12 at the American Pharmacists Association headquarters in Washington D.C.

**United States Food and Drug Administration (FDA)**

The FDA has approved several new biologics with the 4-letter suffix, not only biosimilars but also new innovative biologics, although the recently approved *lanadelumab* does not seem to have a suffix.

Drug shortage has occurred mainly with IV fluids, for example, some facilities have had to shut down following hurricane damage and then to maintain supplies foreign facilities have had to be approved.

**United States Pharmacopoeia (USP)**

USP helps ensure the quality of medicines, from the time they are named and manufactured until the time they are taken by a patient.

To address emerging needs, USP is enhancing informatics capabilities to establish a robust digital presence in drug nomenclature, quality of medicines, and drug classifications. As examples, USP is currently collaborating with the FDA and NCATS to leverage the capabilities of the Global Substance Registration System (G-SRS) platform. Under a cooperative research and development agreement (CRADA) with the FDA, USP is submitting drug impurity information that can be leveraged by digital platforms to programmatically query impurity profiles for active pharmaceutical ingredients. This collaboration will assist agencies in registering and documenting information about substances found in medicines as it aims to provide common identifiers for all of the substances used in medicinal products, utilizing a consistent definition of substances globally, including active substances under clinical investigation, consistent with the ISO 11238 standard.

Separately, USP has installed an internal instance of the G-SRS platform that can be used to provide a source of truth for common chemical data elements (molecular weight, structures, nomenclature, etc.) for USP publications, such as the USP Dictionary of USAN Names, in the near future.

As a standard setting organization, collaboration with stakeholders is key, and USP welcomes input and participation. Signing up to USP updates is encouraged, as is participating in USP's Inaugural Pharmaco-informatics workshops that will take place in April 2019.

## IDMIS UPDATE

INN Experts were informed that with some new computer equipment within the INN Programme, some applications may not work initially; however, the advantage is that all users will now use the same interface as within the INN Programme itself. In this way also, the IT manager can help individual Experts by installing an application directly onto their laptops. There will also be a link in the main page of the system, one for INN files and one for personal documents. The IDMIS interface itself will stay the same but hopefully will be faster.

## CLOSE OF MEETING

The Chair closed the meeting and thanked everyone for their interesting input and observations, and all the help provided. For those wishing to learn more about the IDMIS platform, an IT clinic would be held following the close of the meeting.

Thanks were proffered to the Chair for the diligent chairing of the meeting over four days of fruitful discussion.

### Next meeting

The 68$^{th}$ INN Consultation will take place in Geneva at WHO HQ on 2-5 April 2019.

**SESSION for INN STAKEHOLDERS**

**67th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances**

**Geneva, 23rd October 2018**

## OPENING REMARKS

**Dr François-Xavier Lery**, Coordinator, Technologies Standards and Norms (TSN), opened the Open Session on behalf of the Assistant Director-General, Dr. Mariângela Batista Galvão Simão. He reminded participants that material presented and discussion at these sessions was confidential until published by WHO.

Dr Lery pointed out that in WHO's general programme of work over the next 5 years, universal access to affordable medicines is a key element and that the normative work on harmonised naming, being a core function of WHO, is a significant part of that. Dr Lery also highlighted the WHO Global Policy Group's new transformation agenda that impacts all departments and was pleased to report that the work of the norms and standards unit at country level is consistent and solid, whilst what the unit delivers, including the INN Programme, is having an impact on public health. In addition, work place values and respect for staff and for patients are also targeted. He stressed that the work done by INN, including good practices like the SoINN, is fully in line with the transformation agenda for establishing standards.

**Dr Raffaella Balocco-Mattavelli**, Group Lead INN, also welcomed stakeholders to the Open Session. The INN programme is the normative function of the WHO for naming substances. It has been doing this for 70 years and 10,000 INN have been assigned; all this requires good collaboration with INN stakeholders. To maintain a full and open dialogue with all stakeholders, stakeholders are bound to a confidentiality agreement, and any work presented is fully protected.

**The Chair, Prof Sarel Malan** similarly welcomed all participants and requested stakeholders to provide all information felt relevant. Ultimately, decisions may not go in the preferred direction, but sound science and logic should be the basis of presentation and arguments.

## PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

### Alliance for Safe Biologic Medicines (ASBM)

ASBM has been a frequent participant in the INN Open Sessions, campaigning for the introduction of the Biological Qualifier (BQ). The BQ was first developed by the INN in 2014 and despite extensive discussion has not yet been implemented and ASBM wanted to know why as it was now even more urgent, with many more biosimilars now on the market. ASBM listed several factors it had heard over many Open Sessions as to why the BQ should not be adopted and proceeded to debunk each one.

There would be no redundancy, and the use of distinguishable names was particularly important in developing countries with no pharmacovigilance system. The four-letter suffix design would create more than enough codes for the foreseeable future. With application of the BQ to all biological medicines, including retrospectively, access would not be impeded. A US marketed biosimilar with a four-letter suffix has the same market share as an EU equivalent with no suffix code; so uptake is not being impeded. Delay is costly, not implementation, plus

cost should not override patient safety. ASBM has demonstrated that a web-based tool could readily and easily handle implementation whilst worldwide surveys conducted by ASBM show robust support for distinct names including by regulators.

ASBM was critical of the lack of further information on the status of BQ implementation plans and data gathering, and suggested that WHO was simply delaying implementation. The ASBM itself has held discussion forums with stakeholders, including regulators from USA and Canada who voiced support for a BQ system but would prefer WHO to take the lead. Following the forum held in April 2018, a white paper prepared for ASBM by Scientific American and Nature: Biotechnology reporters, who moderated the forum, outlines the need for and benefits of distinct naming.

Stronger support for distinct naming was voiced at a second forum held in July 2018, attended by regulators and additional Canadian patient groups, whilst a third forum is planned for December 2018.

The Chair-Elect of the International Associations of Patients' Organizations, an ASBM Steering Committee member, further highlighted that patient groups, in addition to regulators, overwhelmingly support distinct naming and are frustrated at the lack of WHO action. Such groups support biosimilars, want new treatment options with lower costs, and good pharmacovigilance. Patient groups are also concerned that health and safety progress is being blocked by a few regulators.

*In summary*, the ASBM knows that global physicians and patient communities strongly support distinguishable names. The US FDA and Health Canada agree with this and in the absence of WHO action, are working together on a regional system, whilst other regulators have changed course or failed to act whilst waiting for WHO action. The ASBM concluded by urging the WHO to listen to stakeholders, to assume leadership and implement the BQ.

**Gastrointestinal Society**

The Gastrointestinal Society is a Canadian registered charity that provides evidence-based information on all areas of the gastrointestinal tract.

It is overseen by gastro-enterologists and physicians, and supports the use of biosimilars for all gastric diseases, especially inflammatory disease. The Society has been publicly engaged in biosimilars and has called for distinct naming of them since 2013. Canadian patients are very aware of their medications, about switching and issues with travelling, and they see a unique name as very important.

The Society has discussed this issue with Health Canada (HC) which has been supportive of the WHO's BQ, and agree with HC on the need for an international consensus. The Society has conducted its own survey of inflammatory bowel disease medications, including questions on non-proprietary names, with an overwhelming majority in favour of them. At a recent biosimilars meeting in Toronto, WHO leadership on naming was high on the agenda. The Society remains in close communication with HC and is aware of HC's presence at the forums held by ASBM on distinct naming and of the HC support for this. As further evidence of the need for distinct naming, the Society referred to two published studies on therapeutic responses following switching from originator to biosimilar and in conclusion, with a world of mobile populations, it emphasised the need for unique INN.

*Dr François-Xavier Lery*, highlighted that the WHO was aligned with stakeholders on the need for improved pharmacovigilance systems. He also stated that the WHO had put the implementation of the BQ on hold pending the availability of further data.

This was reinforced by Dr Raffaella Balocco-Mattavelli who added that following a WHO meeting on access to biosimilars in May 2017, data was to be gathered by WHO units outside of the INN Programme on the potential impact of a BQ on biosimilar access and price.

**PRESENTATIONS on INN ASSIGNMENTS**

**MetrioPharm AG**

MetrioPharm is developing MP1032 as an anti-inflammatory drug. It is a small molecule that is used in chemical procedures but so far not as a medicine. Administered orally, it has been extensively tested and has a very good safety record. The company sees it as a future OTC drug for a wide range of anti-inflammatory indications. Since MP1032 is an immune modulating drug, several names had previously been suggested with the *-imod* stem, for immunomodulators, although the company would be open to alternative suggestions. The earlier applications for an INN for this drug had been turned down by the INN Committee.

Chemically, MP1032 is the sodium salt of luminol which is used as a luminescent tool for blood stains, in schools, and in forensics. Luminol is sold widely on the internet but is of questionable quality; it has poor bioavailability, is unstable, and under normal production procedures can be contaminated with genotoxins and heavy metals, all of which makes luminol unfit for clinical use. MP1032 however is a form of the substance that is suitable for medicinal use but there could be confusion if the name luminol is used as the INN. Luminol and very similar terms are also used as trademarks and if the term luminol were used for the INN there would be confusion with non-GMP material which is usually contaminated with hydrazine and heavy metals. Furthermore, luminol is not listed in a pharmacopoeia as it is not associated with a medicinal product, and so one more reason for confusion if the name luminol is used.

The company highlighted that whilst substances such as morphine glucuronide (an analgesic) and fluorescein lisicol (a diagnostic reagent) have not been given INN, the danger of confusion for these substances is low whereas for luminol it would be high.

In conclusion, the company requested the INN Committee to reconsider its position in not assigning an INN to this substance, to avoid trademark infringement, confusion, fraud and safety concerns.

*In discussion*, the company went on to explain that it is the specific three-dimensional crystalline state of their substance that confers stability and distinguishes it from freely available non-GMP material and not simply purity. However, INN Experts remained hesitant that it could not be called luminol, which could not be adopted as an INN as it is already a trademark and suggested that control of their specific form of luminol would be by medicines regulatory authorities.

**F. Hoffmann-La Roche Ltd**

An INN is being requested for an anti-cancer treatment using an RNA molecule that expresses unique neo-antigens corresponding to an individual patient's tumour. The drug is unique to each patient and is expected to elicit a tumour specific response. Comparison of DNA sequence data from the patients' normal tissue versus the specific tumour is used to identify mutations unique to the tumour. Based upon such data, up to two DNA templates encoding up to 20 tumour-specific neo-epitopes are created and messenger RNA transcribed *in vitro* as the drug substance. The bulk of the RNA molecules comprise the coding regions for up to 20 neo-antigens, while constant parts at the 5' and 3' ends enable and enhance translational efficiency

and stability of the molecule. Thus, each RNA molecule is unique to a specific patient's tumour, although the manufacturing process is constant.

The messenger RNA is targeted to antigen presenting cells using a liposomal formulation, and the expressed protein, after processing, gets presented on MHC class 1 and 2 molecules to generate CD8+ and CD4+ T cell responses specific for the tumour.

This platform is but one of many being developed in the field of patient specific medicines. Even with unique patient specific sequences, the company felt that the common manufacturing process and common structural backbone sequence suffice for an INN to be assigned. Indeed, the Committee for Advanced Therapies of the EMA considers that the RNA falls within the definition of a gene therapy medicinal product. Two precedents for assigning INN to RNA were highlighted. First, small interfering RNAs, although small compared to this anti-cancer RNA drug substance, have been assigned INN. Second, an mRNA vaccine against rabies was assigned the INN *nadorameran*, although it is not defined as a gene therapy substance.

Guidance for INN nomenclature for gene therapy substances recommends a two-word name and the company suggested a *-limo-* infix such that for first word *-limogene* was appropriate. For the 2nd word, RNA has not yet been assigned a suffix and so a new suffix *-codran* was proposed.

This presentation prompted considerable discussion and the following information was provided. In general, each neo-epitope is about 27 amino acids in size with the tumour specific mutation in the middle. It was acknowledged that the neo-epitopes are already present in the patient's tumour but that expressing them from the RNA molecule as described enhances an immune response against them. Beyond the RNA itself, which can stimulate a non-specific immune response through Toll-like receptors, there is no other component that would impact the immune system.

It was mooted that rather than using *-limo-* as the infix, which is over-used, a new approach warrants a new infix.

The INN Experts were interested in knowing exactly what was being administered to the patient as it would be impossible to apply for and assign a new INN for each patient. Thus, it was mooted that rather than have an INN for a substance that will vary from patient to patient, and rather than have an INN for every patient, one approach may be to identify the most common mutations and apply for INN for say each of the most common 10 tumour epitopes. However, amongst the hundreds of neo-epitopes now sequenced, the company had found no common epitope and the strength of the procedure is the individuality of the approach. Also, the common backbone of the RNAs does not exist as a separate entity at any stage and the patient specific portion is always in the middle part of the molecule.

The INN Experts asked how the sequence data is stored and whether it will be made publicly available. The company replied that the data is patient specific which is private patient data and ownership is an ethical as well as legal issue still being studied.

The company thanked the experts for their interesting questions and added that clinical trials had been approved in the USA, Canada, and various EU member states.

## CLOSE OF MEETING

In closing the Open Session, the Chair expressed his thanks to all stakeholders for their attendance and for adding value to the forthcoming discussions of the INN Group.