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79th Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 22-25 October 2024

Executive Summary

Programme on International Nonproprietary Names (INN)

Access to Medicines and Health Products Division (MHP)
Health Product Policy and Standards Department (HPS)
World Health Organization, Geneva

79th Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 22 – 25 October 2024 (hybrid face-to-face/virtual meeting)

EXECUTIVE SUMMARY

WELCOME and OPENING REMARKS

The 79th INN Consultation was opened by Mr Deusdedit Mubangizi, Director, Health Products policy and Standards (HPS), who welcomed all to the Consultation. He added his appreciation of the commitment and time that members of the INN Expert Group, the INN advisors, the observers from various institutions, his colleagues from the WHO Secretariat, and the WHO Collaborating Centres dedicated to the INN Programme, which was a testament to the collective drive to improve global healthcare and ensure access to medicines for all.

He highlighted how the INN system is much more than a global standard; it is a critical tool for driving down the costs of medicines and promoting their rational use. By providing clear, universally accepted names for medicinal substances, INN ensures that the right treatments are available when and where they are needed, improving access and supporting rational prescription practices worldwide.

Some recent achievements for the INN Programme were highlighted, including the publication of a *Lancet* letter on cell-based and gene-based substances, reflecting WHO's commitment to innovative therapies, and an INN paper analysing INN data over the years to be published in the Bulletin of the World Health Organisation under the title "*Disease foci of pharmaceutical research and development as reflected in applications for International Nonproprietary Names, 1953–2022*"[1].

It was noted that the Consultation would review 249 new INN requests including issues related to COVID-19 variants, advanced therapies and new chemical substances. These deliberations reflect the continuing innovation and collaboration of the INN Programme.

Significant progress of the SoINN initiative was commended, a project already recognized by pharmacy and medical students who will become the future generation of health professionals. Their involvement, along with the continued support of experts, will help to expand INN's reach and reinforce it as a global language of health.

In conclusion, the Director emphasised that the role of INN in global health was not just about naming substances, it was about improving access to treatments, ensuring their rational use, and driving down costs for patients everywhere, especially the most vulnerable. He expressed his confidence that the 79th Consultation will further solidify WHO's efforts to make a real impact on global health outcomes.

Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, thanked the Director for his supportive words and added her own welcome to the participants, especially those who had to travel long distance.

[1] DOI 10.2471/BLT.23.291203

ELECTION of CHAIR, VICE-CHAIRS and RAPPORTEUR

Professor Sarel Malan was proposed and seconded as chair of the meeting, and this was agreed.

The Chair then oversaw the election of Dr Akinola Adisa as co-chair for biologicals, Dr Adi Mester as co-chair of chemicals, and Dr James Robertson as Rapporteur.

The Chair highlighted that the work that goes on throughout the year is more than can be comprehended and thanked Dr Balocco, his INN colleagues and especially the INN staff for the huge amount of work undertaken in preparing for this meeting. A Tour de Table followed.

NOTES of the 78th INN CONSULTATION

The Notes of the 78th INN Consultation were adopted without objection and the Chair thanked the Rapporteur for his clear and comprehensive report.

NOMENCLATURE of INN

During the 79th INN Consultation, 281 INN requests were discussed, including:

- 249 new INN requests, of which 155 were for biological substances
- 27 outstanding requests
- 4 objections
- 1 request of substitution

As a result of these discussions, 263 new names were selected, which are planned to be published in Lists 132 (COVID-19-related requests only) and 133 of proposed INN (p.INN). Ten requests did not fulfil INN criteria (No INN), two had been withdrawn by the applicant and six requests were deferred for future discussion.

Four new stems/substems were selected, ten suffixes were promoted to the pre-stem list and it was decided to review the description of two stems.

Open Database of Proteins (ODP)

The final version of the ODP software has been published and is now accessible in IDMIS. The model itself, how the data is presented, and the importation of all data have been finalised with >1000 amino acid substances now fully integrated in IDMIS.

Users are first faced with a list of all available INN sequences that can be filtered e.g. by name or by a query search for a particular substance. Then for each substance, the available data can be accessed and for each chain of the protein will show, for example, S-S bridges, carbohydrate sites, and a description. Sequences can also now be subjected to a BLAST (basic local alignment search tool) for searching for similar sequences in the database. Results can be explored, presented in colour or in a graphic manner. Work is in progress on a manual for users.

The benefit to INN staff and Experts is that upon receipt of a new request for a protein, comparison with previous requests that used to be done manually can now be done easily and speedily electronically. With the database based upon structures, it does not include details of brand names although it may be possible to cross-link it with WIPO's global brand database, but the ODP itself would remain within WHO. As per WHO policy, it is available for public use.

A comment from the floor noted that it had been very useful to regulatory evaluators and that the BLAST option was very good.

Monoclonal Antibodies (mAbs)

The mAb working group discussed the ODP and its implementation for mAbs. Using the ODP, a mAb can be defined in a model with specific building blocks, that is, they are defined as a chain, with their INN number and a unique identifier, and mandatory data versus that which is optional can be identified. In this way, a mAb can be defined in the most generic way. All data can be interpreted by the ODP programme and a new model can be generated if necessary.

A comment from the floor wondered about the added value of creating the ODP when others already exist. In response, it was clarified that the ODP was developed not to re-invent the wheel but to provide a model specifically for INN Experts to easily check new applications and generate a description that would be the basis of the INN publication. It can be applied to mAbs and other proteins and prior to the ODP, the INN Programme did not have its own searchable database for biologicals.

New Monoclonal Antibody Formats

The well-used *-mab* stem for monoclonal antibodies has been superseded by four subdivisions of stems: *-tug* for normal mAbs, *-bart* for those with modified constant domains, *-ment* for fragments, and *-mig* for multi-functional proteins.

Many bispecific mAbs named under the *-mab* system are now approved biologics with many of them having traditional IgG formats. Those in late-stage development are now mostly named with the *-mig* stem and are in development for cancer treatment. Some bispecifics bind to two different antigens on the tumour cell, some bind to one tumour antigen and one soluble factor, many bridge to another cell, e.g. a T cell, while others bind a tumour antigen to a check point protein such as PD1. Essentially, all that can be combined are being combined but they should not necessarily be named with a *-mig* stem.

More advanced approaches include tri-specific proteins, for example, binding two factors on an NK cell plus a pro-drug, many of which are peptides. Yet others may bind in the presence of a soluble factor e.g. high ATP or low pH in the vicinity of a tumour. The more complicated are a mix of two proteins assembling on a tumour cell, one binding to tumour Ag 1 and one to tumour Ag 2, and only when they come together do they kill the cell; however, this is experimental and it is not known if they work in the clinic.

With the PROTAC (proteolysis targeting chimera) approach, one moiety binds to a tumour antigen linked to a moiety that binds to a membrane with the intention that they are internalised and degraded by the ubiquitin pathway. It is not clear if these should be *-migs* or *-degs*. Future developments look to direct to lysosomes as well as proteasomes.

Finally, there could be an avalanche of gene delivery vehicles that may encode any of the above and at the same time, co-express cytokines. It is not clear yet what the MOA would be and how to name them.

In discussion, it was discussed if it would be useful to describe the binding region of a mAb in the ODP; however, it may be difficult to recognise the binding region from the applicant's sequence. An alternative would be to use a system that uses Advanced Business Language (ABL) to describe graphical presentations and such drawings are already available.

Publication group

Names assigned at INN Consultations are the most visible part of the INN Programme. However, the substance behind the name needs to be uniquely defined with a full chemical name and/or description, plus a structure whenever possible. These definitions are translated into English, French and Spanish, and need to be presented in a consistent manner from list to list.

Definitions for newly named INN substances are created by members of the INN Publication Group (PG). Currently, 60% of INN consist of chemical substances, 25% of mAbs, 10% of cell-gene therapy substances, 5% of other proteins, and among these 10% are mixed chemical/biological structures, and so a wide variety of expertise, knowledge and experience is required by members of the PG.

Also, given the current large number of requests being handled at any Consultation (there were >250 at this 79th Consultation), the workload for publication gets shared, first by specialised subgroups of relevant experts and then by experts working in pairs, although sometimes 3-4 experts are required for combined chemical-biological structures. Publication experts also work with a technical officer from within INN HQ staff assigned to a specific subgroup of experts.

To assist in developing unique definitions, guidance has been provided to applicants detailing the type and extent of data required. The new ODP will also assist the publication experts. Creating accurate and consistent definitions can be very challenging with regard inorganic and organic structures, and interaction of classic organic chemistry with biologicals such as antibody conjugates.

There is also a separate Action & Use group as the mode of action is also an important part of the INN.

Bifunctional proteolysis-targeting substances (BPTS)

Bifunctional proteolysis-targeting substances (BPTS) are small molecule heterobifunctional degraders that co-opt the cells' ubiquitin-proteasomal degradation pathway by linking an E3 ubiquitin ligase to a target protein of interest (POI), prompting transport of the POI to the proteasome for degradation. They comprise three important elements, a POI ligand, a ligand for E3 ubiquitin ligase, and a linker between the two. A working group (WG) reported to the Consultation on how they should be named bearing in mind that this is an area that will expand considerably in the future.

The current naming scheme involves a fantasy name/the infix *deg(a)*/and a stem for the target, e.g. for an androgen receptor target the INN would be *fantasy-dega-lutamide*. As an alternative, the WG presented the following proposals.

First, use of a *-deg* suffix with a 1-letter approach for an infix, comprising a single consonant for the target, e.g. '*r'* for receptor, and a single vowel for the degradation type, e.g. '*e'* for E3 ligase; thus, the INN would take the form *fantasy-r-e-deg*. Another proposal was for a 2-letter approach for the infix, e.g. '*re'* for receptor and '*se'* for E3 ligase, thus names would be *fantasy-re-se-deg*. A third proposal was that the infix should be based upon pre-existing stems for the target, e.g. for *brutinib* targets, the name would be *fantasy-bru-deg*. Having *-deg-* as the suffix rather than an infix has the advantage of shortening the name, e.g. in the case of androgen receptors, the new name would end with *-luta-deg* rather than the previous *-deg-*

lutamide. The WG also recommended to abandon the use of the stem *-domide* for thalidomide derivatives or where there is no established stem for the target.

In discussion, INN Experts felt that since the mode of action is degradation, they agreed that the suffix should be *-deg*. It was also deemed important to show the target in the name and that this was not clear with the one-/two-letter infix approach, and so there was agreement that the third proposal was the best, making use of a *-deg* suffix with a clear and relevant infix for the target. However, it was also stated that the name needs to be simple and the length should be kept to a minimum, plus in creating target infixes, infixes for individual targets should be avoided and instead they should be grouped where possible under a single infix.

It was stressed that current names would not be changed.

Cell Therapy Working Group

The cell therapy working group (WG) recently published a letter in the medical journal The Lancet titled 'New WHO INN for cell-based and gene-based substances: timing, usage, and simplicity'[2]. The letter highlighted the complexity of defining cell-therapy substances, that INN users should avoid abbreviating the INN, and a recent revision of the cell therapy nomenclature scheme. Another recent publication was a review in Cytotherapy on 'The harmonization of WHO INN definitions for cell and cell-based gene therapy substances: when a name is not enough'[3] that focused on the issues surrounding INN Definitions of cell substances.

The WG had also made strides in shortening cell-based gene therapy INN by reducing the length of gene infixes from two/three syllables down to one whilst retaining adequate recognition of the nature of the gene. These new infixes would be used in gene therapy INN also.

INN are assigned to unique substances and too often applicants provide insufficient information to fully define their cell substance. Consequently, a revised annex on the information that cell substance applicants should provide to demonstrate uniqueness is being drafted and will provide guidance on the crucial elements needed to adequately describe their substance. This will include information on the manufacturing process as well as the cell substance itself.

This update is especially pertinent to tumour infiltrating lymphocytes (TILs) for which clearer information is especially needed. TILs are typically derived from a specific tumour, manipulated and expanded for clinical use. Currently, the definition for a TIL INN states the tumour type from which the TIL is derived; however, as new clinical data accrued, some applicants wish to expand the INN definition to cover additional cancer types and this continues to be discussed by the WG.

Infixes for mRNA substances

The meeting was reminded that at the 78th INN Consultation, four categories of mRNA substances were highlighted; prophylactic vaccines, therapeutic vaccines, cancer vaccines and substances for therapeutic use. It was also noted that there was agreement to use the infix

[2] DOI: 10.1016/S0140-6736(24)01858-0
[3] DOI: 10.1016/j.jcyt.2021.02.114

-*va*- alongside the suffix -*meran* for prophylactic vaccines and that infixes for other mRNAs would be assessed by an mRNA working Group (WG) before this 79th INN Consultation. At a WG meeting, it was proposed that the two categories of therapeutic vaccines and cancer vaccines be brought together since their mode of action is to raise an immune response to the encoded protein and the infix -*mo*- was suggested, aligned with -*motide* for peptides that are 'immunological agents for active immunization', thus -*momeran*. For therapeutic mRNA substances that encode functional proteins such as for enzyme replacement therapy, the infix -*te*- was suggested. Input from the IFPMA had also been sought, with support provided either for merging two categories into mRNA based immune therapies, or for maintaining four categories of mRNA substances including 'Cancer mRNA'. The WG itself had been inconclusive with regard the use of a -*mo*- infix but was in favour of having no infix for therapeutic mRNA substances.

In discussion, many Experts supported the -*mo*- infix as it made sense to distinguish between an mRNA that encodes an immunological agent for active immunization and an mRNA encoding a therapeutic protein, and that no infix for the latter class would be sensible, especially as such an infix does not exist for any protein INN, and both proposals were agreed.

Naming of Capsids and Virus-like-particles (VLPs)

The protein shell of a non-enveloped virus that surrounds the viral genetic material is known as the capsid and typically has a fixed structural form. Capsids consist of units called capsomeres containing one or more viral proteins that may or may not be covalently linked. Virus-like particles (VLPs) are particles that form in the absence of a viral infection by expression of the viral proteins that self-aggregate into a capsid structure. VLPs may also be enveloped particles where the viral proteins being expressed form by budding through a cell membrane.

The INN Programme has named capsid-based substances using the suffix -*cap*. These have been COVID-19 vaccine substances and also have a double infix -*co*- and -*va*-, thus having the suffix -*covacap*. A more recent INN request was for a VLP with a lipid membrane. It was determined that the -*cap* suffix was not suitable for enveloped particles and it was agreed to assign a new suffix -*vilp* to such substances. However, it was recommended that two infixes should be avoided to avoid creating overly long names and infixes for VLPs should be addressed on a case-by-case basis. It was also agreed that all proteins of a VLP or a capsid do not need to be of viral origin, or that the proteins of a VLP or capsid need be covalently bonded together. However, empty capsids or VLPs with no clinical significance by themselves are unlikely to be named. Where a capsid or VLP carries a specific clinically active payload, a two-word name may be appropriate; one word for the capsid/VLP and a second word for the payload. The nature of chemical linkers will also have to be taken onboard in a name. Not many capsid/VLP substances have been assigned INN to date but is anticipated that numbers will increase and that the complexity of the structures will increase also.

INN Stems in a German Educational Drug List

The German Institute for Medical and Pharmaceutical Examinations (IMPP) has created a drug list of around 450 active substances considered essential for medical student education and examination. The list contains INN names and stems, with the stems and their

definitions having been translated into German and will be published this year. The list will be available online for students and may also be useful for the INN group and the SoINN.

In discussion, it was noted that 450 drugs is a very large list, but that it would include all essential drugs. From the examples provided, it was also noted that not all INN were presented in full, for example heparin sodium was listed as heparin.

SCHOOL OF INN (SoINN)

The 22nd meeting of the SoINN steering committee took place the day preceding the 79th INN Consultation.

The composition of the Committee was reviewed. The Committee is composed of three permanent members due to their function within the INN group - the INN Unit Head, INN IT manager and INN Chair - while four additional members are appointed for three years, one of which is due to be appointed during the 79th Consultation.

A useful approach to learning pharmacology is the use of INN stems as a common basis for the pharmacological action and much of the SoINN meeting was devoted to the 'Stem in a Pill' learning programme. This requires the regular production of new chapters; twenty-five are currently finalized and gradually being made available on the SoINN website along with their translation into Spanish and French, since it is important that the SoINN remains a multilingual program. The content of the 'Stems in a Pill' programme itself needs to be easy to memorize and in this regard, a number of exercises were examined that could be implemented by the pilot sites.

The statistics of the SoINN website have revealed that the home page is the most visited page of all WHO websites. The content of the site is very comprehensive with the online courses being only part of it. However, it is difficult to measure its influence because the impact of a student connecting to an individual course is not the same as when a professor uses the courses for teaching and can thus reach a higher but unknown number of students. The courses would benefit from better exposure and various possibilities have been considered such as a letter to The Lancet and articles on the web such as Wikipedia. Ideas in this area are welcome and it was highlighted that the SoINN is open to ideas from the entire group of INN Experts.

Some courses have been updated recently and all the courses on the site correspond to current rules for developing INN, a fundamental aspect of the activity. No new courses are currently planned, although a course on ATC/INN classifications from the Oslo Collaborating Centre has been requested.

The second part of the SoINN meeting was opened to representatives of the pilot sites. The pilot site of the University of the Western Cape was a pioneer in the use of SoINN courses and is continuing with this teaching activity. The Barcelona University site is to provide broad information on INN during this academic year for a very varied audience including pharmacy students, dietetics students and nursing students. The Grenoble University site will renew its poster competition for its students and will make its poster rules available to other sites, while a research activity in linguistics is being set up. It motivated a doctor from the regional pharmacovigilance centre to participate in research work on INN and medication errors, coordinated by one of the INN Experts. The committee was also delighted to see posters on INN created by the students of the Faculty of Pharmacy of the International University for Science and Technology in Syria.

Finally, representatives from two candidate pilot sites were welcomed. The University of Sao Paulo, Brazil, will strengthen SoINN work in pharmacovigilance, whilst work at the University of Shanghai, China, is ongoing in translating SoINN courses into Chinese. This latter point has been a wish for a long time but was delayed by the Covid crisis and was excellent news.

Medication Errors

A SoINN project on medication errors caused by name confusion, making use of pharmacovigilance (PV) data in Germany and the EU, was presented. PV aims to improve drug safety by identifying adverse events and errors in the medication process and many authorities have specific medication error reporting systems, such as the AMTS initiative in Germany. Two approaches were used in the SoINN study; first, an analysis of reports on medications errors for monoclonal antibodies and antibody drug conjugates (ADCs) in EudraVigilance (the EU pharmacovigilance data base) and second, analysis of the German surveillance of (potential) medication errors due to 'sound-alikes' (AMTS initiative, BfArM) from 2012-2023.

The search of EudraVigilance for '*trastuzumab*' and 'medication error', identified seven preferred reporting terms, such as 'product name confusion' and 'product dispensing error' involving *trastuzumab* vs. *trastuzumab emtansine*. Consequently, in a second search of 'antibody drug conjugates' and the seven identified preferred terms, there were three cases of name confusion between *trastuzumab emtansine* and *trastuzumab*. There was no confusion reported in the use of the ADC *trastuzumab deruxtecan* and out of a total of 348 ADR reports using the seven preferred terms in Eudravigilance, there was only one other report of name confusion, that of a single case of confusion between *brentuximab vedotin* and *tisotumab vedotin*. This latter case was unusual in that the report arose from a clinical trial with *tisotumab vedotin* being part of the trial whilst *brentuximab vedotin* was an already authorised drug.

In the second approach of this exercise, out of 158 reports of potential medication error due to 'soundalike' drugs in Germany from 2012 to 2023, most (78%) involved brand name vs. brand name confusion; 13% involved brand name vs. INN, and only 9% involved INN vs. INN confusion. In cases where an actual medication error occurred between INN, some involved the same drug class (i.e. same suffix) and others involved a similarity in the fantasy prefix.

In summary, in EudraVigilance, only 2% of errors involving ADCs were based upon INN confusion, one between the ADC and the parental mAb and three between ADCs. It has to be noted though that there is a high rate of under-reporting in these databases. In the German 'sound-alike' study, only a minority of errors involved INN vs. INN confusion, with possibly a higher risk associated with the prefix rather than the suffix especially where the therapeutic action was different. Thus, the view often taken by INN Experts that the risk of confusion is less when indications differ needs to be re-considered.

COLLABORATORS' UPDATES

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since the 78th INN Consultation, the JAN Expert committee met twice from which 31 names were published, including one biosimilar. Supplement 2 to the Japanese Pharmacopeia (JP) 18th edition was implemented in June 2024, and the English version is under preparation.

The JP has also started a prospective pilot program with the United States Pharmacopeia (USP) to promote harmonization of pharmacopoeial standards for active pharmaceutical ingredients and formulation articles. *Dapagliflozin* Propylene Glycol Hydrate and its tablets have been selected as the articles for the pilot programme and the draft monographs are under public consultation on the JP website. Furthermore, JP has initiated a pilot harmonization project with the European Pharmacopoeia (Ph.Eur.). *Macitentan* and its tablets have been selected as the first candidates for this co-operation. The JP and Ph. Eur. will work jointly on bilateral harmonisation of these two monographs while taking the specificities of their respective regulatory frameworks into account. Discussions will include an overview of current and future possibilities and the challenges met when expanding the harmonisation of pharmacopoeial standards to both active substances and medicinal products. The lessons learned during this project may pave the way towards further strengthened co-operation between the two organisations and contribute to expanding the work of convergence of pharmacopoeial standards.

Lastly, the Pharmacopoeial Discussion Group (PDG), which brings together the Ph.Eur., the Indian Pharmacopeia Commission, the JP and the USP, along with the World Health Organization (WHO) as observer, held its annual autumn meeting in October 2024 hosted by the Ph.Eur. The next face-to-face PDG meeting will be hosted by the JP in Tokyo in 2025.

Therapeutic Goods Administration (TGA), Australia

In May 2023, the Australian Government announced reforms to the regulation of vaping products. These reforms are in stages over the course of 2024 and 2025 and change the way that vapes can be imported, manufactured, supplied and advertised in Australia. Vapes include vaping substances, vaping accessories and vaping devices and the TGA was given a central role in developing these reforms, the centrepiece of which is the *Therapeutic Goods and Other Legislation Amendment (Vaping Reforms) Act 2024* which commenced on 1 July 2024.

The Act prohibits the importation, domestic manufacture, supply, commercial possession and advertisement of disposable single use and non-therapeutic vapes but does not ban all vapes. Pharmacies may only sell vapes notified to the TGA as being compliant with the product standards and included in the list of notified vapes. Businesses must hold a relevant licence, permit, consent or other authority from a state or territory government or the TGA, or be otherwise authorised, to participate in the lawful supply chain for vaping goods. There are restrictions on advertising and a limitation on flavours available. Under 18-year-olds can only be supplied under prescription. The intent is to assist in preventing harm to children and help with smoking cessation. Additional information can be found on the TGA website.

Uppsala Monitoring Centre (UMC)

The UMC representative began their report with a comment that at a recent conference, someone asked why so many different names (referring to USAN and pharmacopeial names for example) were needed and why not only one. Interestingly, most of the audience voiced that the obvious answer was that they should apply the INN.

UMC itself is about to implement a tag showing if a substance name is an INN or modified INN in UMC's global dictionary to increase visibility and strengthen the recognition of INN. UMC continues to collaborate with WHO, regulators and industry, and in the Global IDMP Working Group (GIDWG) pilot projects, on the global IDMP identifiers. During the last year

the UMC together with other partners performed an end-to-end pilot with very good and encouraging results.

United States Adopted Names (USAN)

The 2024 summer USAN Council meeting took place on June 6-7, 2024, and was hosted by the USP in Rockville, Maryland. Names for 33 drug substances were reviewed and discussed. Seventeen new stems and infixes were approved and added to USAN's stem list. Meeting topics discussed included: Negotiations Update, USAN website metrics, the March 2024 INN Consultation, ISMP and FDA's medical error reports, a USP update and key monoclonal antibody nomenclature statistics.

Thirty-eight INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 79th INN Consultation.

From April through September 2024, USAN staff processed, researched, and made recommendations for approximately 117 USAN applications and forwarded this information to the USAN Council for their review and name selection. Through October 2024, 252 USANs were adopted for 2024 while revenue from 9 other applications was also realized. Currently, there are approximately 200 active USAN negotiations.

The 2025 Summer meeting of the USAN Council is tentatively scheduled for June 5-6, 2025, most likely in Washington, D.C., hosted by APhA.

United States Pharmacopoeia (USP)

The USP is a scientific nonprofit organization founded in 1820 that sets quality standards for medicine, food ingredients and dietary supplements. It works closely with the Japanese, European and other pharmacopeias in harmonisation, and also with the USAN. The USP has a small molecule programme that plays a pivotal role ensuring quality, safety, and efficacy of chemically synthesised drugs used by millions of patients worldwide and by providing this essential standard, USP supports the pharmaceutical industry in meeting regulatory requirement and in safeguarding public health. The small molecule programme is responsible for developing new monographs and revising existing monographs for example from titration assays to newer methodology such as HPLC.

Over 200 new pharmaceutical analytical impurities (PAI) have been added to the USP catalogue increasing the number of PAI and reference standards to 550 covering 130 active pharmaceutical ingredients across 20 therapeutic areas. As a leading provider of official reference standards, trusted by thousands of manufacturing and regulatory bodies around the world, USP offers PAI material to support impurity-related needs for product development.

USP is also supporting manufacturers and regulators with science-based solutions for testing, assessing risk and identifying potential sources of nitrosamines. USP General Chapter 1469 'Nitrosamine Impurities' provides information on developing testing methodologies to detect and measure nitrosamine impurities in drug ingredients and drug products.

World Customs Organisation (WCO)

The Scientific Sub-Committee (SSC) of the World Customs Organisation (WCO) convenes every January and examines, among other issues, the Harmonized System (HS) classification of INN. In this regard, the last SSC meeting dealt with the examination of proposed lists 128 and 129. Meanwhile, work on the new proposed lists 130 and 131 has already started and the

forthcoming SSC meeting will examine, among others, these two new lists. It will review the classification of all INN with the stems *-golix* and *-relix* to ensure that all of them have been classified in a consistent manner. It will continue with the examination of the classification of *pegmispotide* (INN), as it was not concluded at the previous session. Another examination will be that of a possible amendment to the Explanatory Note to the HS heading of "antibiotics" (29.41) to clarify the difference between antibiotics and antibacterials, especially taking into consideration the information that, in the future, the term "antibiotics" might not to be used for INN.

The WCO continues to look forward to discussing classification of new INN substances that the WHO will submit to the future sessions of the SSC. Finally, the WCO Secretariat expressed its appreciation for the ongoing and valuable technical advice provided by the INN technical officers to the SSC with respect to the examination of INN classification.

WHO Collaborating Centre for Drug Statistic Methodology, Olso

The WHO International Working Group for Drug Statistics Methodology will meet in Geneva the week following the 79th Consultation, at which about 60 applications for new ATC will be discussed. Half of the applications refer to substances of the 1st level: A, alimentary tract and metabolism products, and L, antineoplastic and immunomodulating agents. Most of the requests for ATC codes come from Europe and USA, and WHO is working on expanding this standard to make it more globally acceptable, available and usable. Fifteen applications for new DDD will also be discussed at the meeting.

The working group on DDD for cancer drugs will also report to the meeting. This is a collaboration with the European Society for Medical Oncology (ESMO) and many groups that work on antineoplastics at different levels, including the WHO Essential Medicines List and the INN Programme, to try to establish DDD for cancer drugs. This is a long-standing project which will be approved during the meeting.

The Centre is preparing a small online course on fundamentals for the ATC/DDD methodology for the SoINN platform.

The European Pharmaceutical Market Research Association (EPHMRA) - WHO Harmonization Committee meeting, was arranged as a virtual meeting on 24-25 April 2024, while the annual International ATC/DDD course was held in Oslo on 13-14 June 2024, as a face-to-face meeting.

World Intellectual Property Organisation (WIPO)

There are similarities between the work of the INN and that of trademark examiners in IP offices, particularly in how any similarity of requested names with previously adopted INN gets assessed. In trademark law, some of the same principles are applied, for example, some expressions encountered in proposed INN at this Consultation were deemed inappropriate as they could offend moral principles or could raise doubts about a product's qualities, and if such expressions appeared in trademarks, they would similarly not be acceptable. However, an important distinction was highlighted; once an INN is proposed, it is unique and internationally recognized, while a registered trademark is territorial and has its legal effect only in the country where it has been registered. Thus, producers or pharmaceutical companies often file trademarks applications only in countries where they intend to market their products.

WIPO has informed its Member States on October 2023, and April 2024, that INN Lists number 90 and 91 of Recommended INN have been published, and those names have been successfully integrated into WIPO's global brand database for the use of examiners by its Member States.

CLOSE of MEETING

The Chair thanked everyone for their work and contributions throughout the year highlighting that it contributed to a very good learning opportunity, and closed the meeting.

Dr Balocco thanked her in-house team especially the administrative staff who tend to remain in the background. She also thanked the Chair for his excellent work in leading everyone through this meeting.

Next meeting

The 80th INN Consultation will be held in Geneva on 17-21 March 2025.

OPEN SESSION for INN STAKEHOLDERS

79th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

WHO HQ, Geneva, 22 October 2024

Dr Rafaella Balocco, Unit Head, INN Programme and Classification of Medical Products, welcomed participants both those in the room and those in virtual attendance. She highlighted that this Open Session was open only to those present and that all data presented and discussed should be treated as confidential until the report of the meeting is made public.

She gave the floor to the Chair, Professor Sarel Malan who looked forward to the data that the visitors would present and noted that discussion of data would continue in the closed session of the INN Experts in the 79th INN Consultation.

Aflofarm Farmacja

Aflofarm Farmacja Polska attended the Stakeholders session to lobby for a change to a recommended INN, *cytisinicline*, under Art. 9: Procedure for the selection of recommended international nonproprietary names for pharmaceutical substances, Annex 1 [International Nonproprietary Names: revised procedure (EB115/11 2004)], with the proposal to change it to the commonly used name for this substance – cytisine.

Cytisine is of plant origin and has been marketed in Europe since 1964 for smoking aversion therapy. Its chemical structure is similar to that of nicotine, another plant-based alkaloid, with both belonging to the same ATC group and having similar mechanisms of action. The synthetic substance *varenicline* is also in this ATC group but has a different structure.

The reasons for a request of INN change were presented. First, the name should be consistent with for example nictotine, and have an *-ine* suffix; second, changing the INN to cytisine would be in accordance with the policy of the INN programme not to select names for those substances that have a long history of use for medical purposes under well-established names; then, the current INN causes confusion as it not clear that cytisine and *cytisinicline* are the same substance and a PubMed search for 2024 shows 1038 results for cytisine and only 35 for *cytisinicline*; furthermore, cytisine is used in a 2024 WHO guideline for tobacco cessation and is used in various national guidelines; finally it is patient friendly in all EU countries, appearing on marketed packs since 1964.

Aflofarm is fully dedicated to improving public health worldwide and contribute to decreasing the number of smokers. The current INN impedes development of this effective treatment and this could be eliminated by re-naming the INN with the well-known and non-confusing cytisine.

In discussion, Dr Balocco, highlighted that changing an INN under Article 9 is not straightforward. If the Expert Group accepts this request, all 194 WHO member states would have to be informed in writing and all have to agree that the request is agreeable. The application for the INN *cytisinicline* had come from a separate nomenclature body and was assigned taking into account other names in use.

SciencePharma

The second representation, from SciencePharma, was similarly to request changing the INN *cytisinicline* to the more commonly used name cytisine, used for smoking cessation.

SciencePharma highlighted that cytisine is a plant alkaloid; many of the well-known plant-based alkaloids used in medicine have the -ine suffix including morphine, caffeine and nicotine, and some are named by adding -ine to the plant name of origin, for example, nicotine is derived from nicotiana *sp*. and cytisine from cytisus *sp*. The WHO Collaborating Centre has assigned an ATC code to cystisine, and the INN of this should align with nicotine, which also has an ATC code.

SciencePharma similarly highlighted that a PubMed search reveals 1038 results for cytisine and only 15 for *cytisinicline*, with half of the latter INN arising from one source. In Europe, 16 marketing authorisation holders have authorised cytisine products in 22 countries and according to WHO data it is available in a number of other countries worldwide. In packaging, both cytisine and *cytisinicline* as the active substance, commonly appear, which is confusing. In national and international guidelines for smoking cessation, cytisine is the name that commonly appears, with the INN *cytisinicline* only being mentioned in passing.

It was also re-iterated that according to WHO policy itself, the INN programme should not select (alternative) names for those substances that have a long history of use for medical purposes under well-established names. Clearly, the name cytisine follows this and other points in the assigning of an INN. With cytisine having been marketed for 60 years and commonly used globally in scientific fields and in pharmacies, SciencePharma urged the Expert Group to re-assign cytisine as the INN to avoid complications.

In discussion, it was acknowledged that an ATC code is a WHO code as they are assigned through the WHO Collaborating Centre in Oslo. It was also re-iterated that the original request for the INN came from a national nomenclature body and *cytisinicline* was accepted as the INN. Now the Expert Group has to decide upon the solution but taking into account that greater problems may be created.

Rivus Pharmaceuticals

Rivus Pharmaceuticals introduced a new class of medicines, that of controlled metabolic accelerators (CMAs) that increase metabolic rate, reduce obesity and associated cardiometabolic disease. When patients come off current anti-obesity drugs, they regain weight quickly, mainly as adipose fat, a root cause of metabolic disease. These effects could be overcome with CMAs.

Rivus is in phase 2 trials with HU6, an orally delivered CMA comprising a dinitrophenol (DNP) conjugate that activates mitochondrial transporter adenine translocase (ANT). This relieves the extreme proton gradient that has developed in the mitochondrion intermembrane space due to excess fat and glucose with a resultant increase in their oxidation. There is an historic challenge in using a DNP-based drug but the conjugate confers improved tolerance and safety, and more than 400 patients with high BMI treated with HU6 have shown no evidence of elevated body temperature or adverse kidney effects even with high doses. The company's most recent trial in heart failure patients has shown safety to date has been excellent and trials are being extended across a broad range of indications.

In summary, it was emphasised that HU6 does not cause historical DNP toxicities and should not be confused with DNP on the black market; the conjugate HU6 can be given in very high doses with no issues. Several companies are now targeting the same pharmacology and Rivus called for a unified nomenclature for metabolic accelerators to describe molecules that activate mitochondrial carrier proteins.

The company was queried as to whether they had observed any interactions with compounds that uncouple phosphorylation e.g. aspirin; Rivus responded that there had been no indication of any untoward interaction.

Nurix Therapeutics

Targeted degraders comprise a new era of drugs with a novel mechanism of action. They are functionally distinct from kinase inhibitors that bind stoichiometrically to the target protein either to the active site or allosterically. In contrast, degraders bind to the target protein in a sub-stoichiometric manner and eliminate protein through covalent modification with ubiquitin, triggering proteasomal degradation.

At the 78th INN Consultation, Nurix's NX-5948 degrader was assigned the INN *bexodegbrutinib* which was rejected by the company as their drug does not function as a tyrosine kinase inhibitor. Data were shown that in contrast to a Bruton's kinase inhibitor such as *ibrutinib*, NX-5948 degrades the kinase target, does not block kinase signalling, that one molecule can degrade multiple target proteins, that very low levels of the free degrader drug are required compared to direct inhibitors, and that degraders are less susceptible to resistance mutation than kinase inhibitors. The company considered that degradation was a special type of inhibition and that the stem *-tinib* (or *-brutinib*) was not appropriate for degraders.

Targeted protein degraders are a rapidly expanding modality that requires new INN. The stem *-degbrutinib* does not adequately cover these substances and a name with *-deg-* and *-ib* is not adequate. Following INN guidance, the company proposed the infix *-bru-* to indicate their effect on tyrosine kinase and *-deg* as the suffix, thus *-brudeg* would be the new suffix.

Dr Balocco acknowledged that there had been several meetings of a working group to find the best solution possible and that the presentation was indeed useful.

Alliance For Safe Biologic Medicines

This was the ASBM's 24th appearance at the INN Stakeholders session to advocate for distinct biologic nomenclature and international harmonization. It was also the 10th anniversary of the INN's Biological Qualifier (BQ). Noting this, it was highlighted that ten years ago the EMA had approved only 18 biosimilars, Canada two and USA one. Today these three countries together have now approved 237 biosimilars. This increased proliferation is paralleled by an increased emphasis on cost savings and it was estimated that there had been a cost savings of 50 billion euros in the EU and $36 billion in the US. The ASBM is concerned that this is being paralleled in the US by decreased emphasis on clinical data and an increased emphasis on biosimilar substitutions by pharmacists. In late 2023, the EU's EMA issued a concept paper highlighting that there may be a potential to waive certain clinical data requirements even for complex biosimilars such as mAbs based on solid evidence of quality comparability. A similar situation exists in the USA with the FDA having recently published draft guidance that switching studies may no longer be necessary. Even more recently, the US government is looking to introduce a bill that would declare all biosimilars interchangeable; this would remove the authority of the FDA to consider clinical

switching studies. An ASBM of survey physicians found that only 11% support all biosimilars being declared interchangeable with the vast majority believing that switching studies increase their confidence in biosimilars. The ASBM is opposed to this erosion of data standards and has submitted comments to EMA and also to the FDA on their Biosimilar Red Tape Elimination Act.

These trends emphasize the importance of improved post-market surveillance and reliance on real-world evidence, which requires better biologic pharmacovigilance (PV) and international harmonization. A global IDMP (Identification of Medicinal Products) working group was set up in 2021 to enhance safety and pharmacovigilance, improve medicine capacity and improve international sharing of medical product information. The Group comprises regulators worldwide including the EMA, Health Canada and several other medicines organisations, and projects of the Group interface with a variety of SMEs including the WHO INN. However, the ASBM questioned whether the standards as applied to chemical medicines would be fit for complex biological proteins. The ABSM highlighted that the INN Group had already developed an answer – the BQ, but which has not been implemented but neither has it been withdrawn, and many regulators support distinct biologic naming and/or the BQ. ASBM is now working also with GaBi (Generics and Biosimilars Initiative) on a questionnaire for regulators worldwide on support for the BQ and will share the data at the next INN Consultation.

Dr Balocco thanked the ASBM for its comprehensive presentation that shows the INN Group were correct in developing the BQ. She added that she did not know why WHO management had not adopted it. Dr Balocco had been at an IDMP meeting and had raised the same issues regarding the treatment of biologics as chemicals. She acknowledged that a number of regulatory authorities were onboard with the BQ but also that others were not. Substances need to be clearly defined; the IDMP is a way to group substances and not identify them, and is not even in line with ISO standards. Also, the IDMP does not list excipients; she did not know why, e.g. for mRNA vaccines the active substance is the mRNA but there are those who wish to include the lipid carriers.

With no further comments arising, the Chair thanked all speakers for their contributions. All data presented will be taken onboard by the INN Experts and with that he closed the meeting.