

78th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 18 – 22 March 2024 (hybrid face-to-face/virtual meeting)

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

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WELCOME and OPENING REMARKS

Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, opened the meeting and welcomed all participants on behalf of the Director General and Assistant Director General (ADG) who could not be present due to conflicting events at WHO. Dr Balocco highlighted how dependent the INN Programme is on the Expert Group, the Special Advisors and representatives from associated organisations and collaborating centres, and expressed her gratitude for the time taken by everyone both before and during the meeting. The meeting would be busy with 261 new requests of which 132 were biological and 129 were chemical, plus 22 outstanding requests and some objections to address. There will also be two closed sessions, one on gene and cell therapy, and one with the Chairs and Rapporteur to discuss how to better organise the workload.

Proposed changes to the Access to Medicines and Health Products (MHP) Division were announced. Dr Nakatani is the new ADG and three new departments are proposed: Health Product Policy and Standards (HPS) in which the INN and Classification of Medical Products (INN) Unit would be located, a Regulation and Prequalification (RPQ) department and an entirely new department of Innovation and Emerging Technologies (IET) that would include Local Production and mRNA Technology Transfer.

It was also announced that under the School of INN, pharmacy students at a pilot site university have been asked to design posters on INN as part of a competition. Dr Balocco invited all meeting participants to view these and vote on the best poster. The winner will be invited to visit WHO and to attend the World Health Assembly.

ELECTION of CHAIR, VICE-CHAIRS and RAPPORTEUR

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

Prof Malan took over as Chair of the meeting. He thanked Dr Balocco and his INN colleagues but gave a special thank you to the INN staff for the huge amount of work undertaken in preparing for this meeting, adding that everyone appreciated the effort required.

The Chair oversaw the election of Prof Menico Rizzi as co-chair for biologicals, Professor Vicente Rodilla Alamà as co-chair of chemicals, and Dr James Robertson as Rapporteur, following which he called for a Tour de Table given the number of new participants at the meeting.

NOTES of the 77th INN CONSULTATION

The Notes of the 77th INN Consultation were adopted without objection and the Chair thanked the Rapporteur for his clear and comprehensive report.

NOMENCLATURE of INN

During the 78th INN Consultation, 288 INN requests were discussed, including:

- 261 new INN requests, comprising:
 - 129 chemical substances
 - 120 biological substances (of which 36 had a chemical component)
 - 12 peptides
- 22 outstanding requests
- 5 objections

As a result of these discussions, 270 new names were selected, which are planned to be published in Lists 131 (COVID-19-related requests only) and 132 of proposed INN (p.INN). Four requests did

not fulfil INN criteria (No INN), one had been withdrawn by the applicant and 13 requests were deferred for future discussion.

One new stem/substem was selected, 2 suffixes were promoted to the pre-stem list and it was decided to review the description of 3 stems.

***Propagermanium* Structure**

The substance *propagermanium* is an old INN from Rec. List 31; the structure was first published in pList 63 in 1990 and revised a year later in pList 65. It comprises a 4-member ring with carboxy acids coming off either side and polymerised along each chain. However, recent X-ray crystallography has shown the published structure to be incorrect and a revised structure should be entered in the next pList. Both USAN and JAN agree with this but before re-publication, it will be sent out to the INN Experts for comment.

INN for Heterobifunctional Protein Degraders

Heterobifunctional protein degraders are proteolysis-targeting substances that eliminate and not simply inhibit target proteins. They consist of two ligands joined by a linker. One ligand binds to the protein of interest (PoI) while the other recruits and binds an E3 ubiquitin ligase. This leads to ubiquitination of the PoI and its subsequent degradation by the ubiquitin-proteasome system. Ubiquitination once started can continue without continued binding of the inhibitor and this allows for a very low stoichiometric concentration of the active substance. Also, this process takes place regardless of the position on the PoI where the inhibitor binds and not only at the protein active site. Conventional small molecule inhibitors typically bind directly to the active site, require a high affinity, and require a one-to-one stoichiometric concentration which is sometimes not easy to achieve.

An issue had arisen in that these degraders had been assigned INN using two different schemes. Where an established stem was available for the PoI binding moiety such as *-lutamide* or *-imod*, the infix *-deg(a)-* was added to highlight the protein degradation aspect, despite in some cases the presence of a thalidomide moiety. The alternative scheme that had been used was *-domide* for inhibitors with thalidomide moieties but only when no established stem for the PoI binding moiety existed.

In discussion, it was agreed that inconsistent decisions on the use of the *-domide* stem had occurred. *-domide* derivatives are being used widely now as neoplastic agents and also in some cases to treat inflammatory disease, but as *-domides* are capable of being teratogenic, highlighting the presence of a thalidomide moiety was felt to be important. It was agreed that the stem should indicate the action of the substance rather than the possibility of adverse effects and so the decision was made to move away from *-domide* and to use *-deg-* as an infix/suffix in all cases for these protein degraders.

Revision of Working Document 21-520 on International Nonproprietary Names for Variant COVID-19 Vaccine Active Substances

In April 2021, in response to the rapid development of COVID-19 vaccines, the INN developed Working Document 21.520 on 'International Nonproprietary Names for Variant COVID-19 Vaccine Active Substances'. This announced that the assignment of INN for updated vaccines against SARS-CoV-2 Variants of Concern (VOC) would be expedited and that the usual fee would be waived. It also provided guidance on the structure of the name of a VOC.

In May 2023, the WHO announced that COVID-19 was now an 'established and ongoing health issue' which no longer constituted a *Public Health Emergency of International Concern* (PHEIC). In addition, since March 2023 there had been no further VOCs, only Variants Under Monitoring (VUM) and Variants of Interest (VOI). Consequently, at the 77th INN Consultation held in Geneva on 17-20 October 2023, the INN Expert Group recommended rescinding Working Document 21.520.

A revised version of 21-520 was tabled at this Consultation. The assignment of INN to COVID-19 vaccines would now follow standard procedures regardless of whether it is a VOC, a VOI or a VUM, and regardless of whether the request is to update a previous COVID-19 vaccine INN or a totally new request. However, at the discretion of the Secretariat, the procedure can still be accelerated by accepting requests after the official deadline has passed. Also, following the assignment of an INN, the standard procedure can be further accelerated by publishing the name in the forthcoming INN Proposed List. The earlier advice on the nature of the name for variant COVID-19 vaccine substances is also removed and the standard process of submitting appropriate names resumes. In the event of a major public health situation, further changes can be re-introduced. Fees for VOCs will no longer be waived and standard fees apply.

In discussion, it was queried if this revised document would apply only to COVID-19 vaccines. While the revision highlights COVID-19 vaccines, it was put forward that the document could be applied to other vaccines, such as for influenza, although the very short timelines that had been mooted for influenza may not be feasible. In the event of a new pandemic appropriate action can be taken, building on 21-520. Retaining flexibility was felt to be important.

Introduction of a Specific Infix for mRNA Vaccine Substances

A proposal to apply an infix such as *-va-* to INN for prophylactic mRNA vaccine substances was tabled, such that the suffix for these would be *-vameran*.

It was highlighted that prophylactic vaccines are designed to be immunogenic and since they are given to very large numbers of healthy subjects, the benefit-risk (B/R) ratio must be very high. In contrast, biological therapeutic substances are designed not to be immunogenic and are given to small numbers of patients to treat pre-existing medical conditions and so the B/R can be quite small. During the pandemic, there were many requests for INN for mRNA vaccine substances. There is now an increasing number of requests for mRNA substances encoding therapeutic proteins. Currently there is no distinguishing feature in INN for these two categories of mRNA substances; thus the proposal that INN for prophylactic mRNA vaccine substances get a discriminating infix, such as *-va-*. It was highlighted that the proposal was to introduce a *-va-* infix in INN for prophylactic vaccines only, and not additional infixes that could specify the nature of a therapeutic mRNA substance.

An important consideration was whether such an infix should also be used for therapeutic mRNA vaccines for treatment of chronic infectious disease or in cancer therapy. The mode of action of such ‘vaccines’ is also to induce an immune response but it was argued that the difference is in safety, as prophylactic vaccines must have an exceedingly high B/R ratio whereas therapeutic vaccines, intended for smaller cohorts of those already suffering from a disease, can have a considerably lower B/R. Consequently, the proposal was that *-va-* would be for prophylactic vaccines only.

It was added that previously, the EMA representative had informed the Experts that an mRNA vaccine manufacturer, in discussing INN with EMA, had requested a clear separation of therapeutic from vaccine mRNA. Also, at this consultation there would be a request for an mRNA encoding a therapeutic substance in which the applicant requested a specific infix to avoid health care professionals and patients misconstruing it as a vaccine.

There was extensive discussion of this proposal, during which four categories of mRNA substances were highlighted: (i) prophylactic vaccines against infectious disease, (ii) therapeutic vaccines to treat chronic infection (or the consequences thereof), (iii) ‘cancer’ vaccines in which an immune response is sought to inhibit the tumour, and (iv) therapeutic mRNA in which the mRNA encodes a non-immunogenic therapeutic functional protein. In the future additional categories may be identified such as for auto-immune disease.

There was a strong opinion that mRNA whose encoded protein induces an immune response should be distinguished from those that do not, i.e. vaccine-like versus a therapeutic functional protein, and

so there was a general agreement to make use of a *-va-* infix. There was also opinion that this should go further and that from a safety point of view, prophylactic vaccines against infectious disease should be distinguished from therapeutic vaccines. Indeed, some Experts advocated four separate infixes for the above four categories of mRNA substances and indeed this was the ultimate general conclusion of the meeting, that *-va-* would be used in INN for prophylactic vaccine mRNA substances, and that infixes for the other three categories would be created but that the choice of the other infixes would be deferred for Experts to consider and suggest appropriate syllables.

Highlights of the discussion included:

- whether to follow a mechanistic (mode of action) approach versus an end-user (indicative) approach.
- that mRNA vaccine substances already named without a *-va-* infix were felt not to be a concern as the bulk of mRNA vaccine INN already assigned were for COVID-19 vaccines and most of these would fall by the wayside as the virus mutates and the vaccines are no longer effective and useable.
- that two previously named substances, the rabies mRNA vaccine *nadorameran* without the *-va-* infix and *acavameran*, an mRNA encoding an immunomodulatory therapeutic protein, would remain outliers.
- that any loss in flexibility in creating distinguishable names by having a 3-syllable suffix would be no worse than for many other pre-existing 3-syllable suffixes.
- whether there may be consequences of having no distinguishing infix for any mRNA substance.
- that some companies had expressed a desire for a distinguishing infix for therapeutic mRNA substances.
- that the infix *-va-* had already been used for three other vaccine substance classes.
- that the INN applies to the active substance within a vaccine and not to the vaccine itself.

Open Database for Proteins (ODP)

The Open Database for Proteins project is to gather together all INN protein information contained within a variety of different file formats, such as Word, pdf and others, into a structured database that supports an advanced search capability. There are four main objectives: (i) to assist INN Experts and the INN Team in analysing requests, (ii) provide an internationally certified database for registered INN proteins, that ensures the accuracy and reliability of the data, (iii) provide a structured protein database, including posttranslational modifications, for organised storage and easy retrieval of data, and (iv) to enable effective interaction with the database and advanced search facilities.

INN Experts will benefit from easy access to all relevant information for their comments on new INN requests, while the INN Team will have improved functionality of the different document formats encountered, can more readily assist the Experts and can update the database with newly published INN. Of the 889 protein substances being migrated from MedNet to the ODP, 70% have been validated and are now accessible. Of the remainder, 18% have .DOC files that require additional editing and for 12% the .DOC files are missing.

INN Experts were shown examples of the interface that appears online, data viewing and editing, including searching, multi-sequence alignment, clustering and pattern finding, and the types of reports that get generated.

First access of the database will be for the INN Experts after which the proposal is to make it publicly available in the SoINN website. A link will also be created, for example, for university use, at least to recommended INN.

School of INN (SoINN)

The SoINN Steering Committee (SC) met on Monday, March 18 for the 21st time. In examining the regulation of the SC, there was consensus to keep the composition of the steering committee small, and seven positions comprising three standing members (WHO INN Unit Head, WHO INN IT Technical Officer and Chairperson of the INN Expert Group) plus four rotational members (Chairperson of the SoINN, Scientific Working Group Coordinator, Education Working Group Coordinator, Stakeholders Coordinator) were approved. The rotational members are to be appointed for a renewable period of two or three years and the roles of the various members were discussed.

A new course in pharmacology using an alternative classification of drugs based on mechanism of action was proposed. There was a consensus among the SC members that this classification was of interest for chemical drugs but that for biological drugs the situation was much more complex. The SC therefore decided to postpone publication of this course pending a more in-depth examination of this classification.

As part of the INN friendly University project, a group of students from the Grenoble Faculty of Pharmacy produced a series of posters on the themes of ‘What is an INN and what is an INN used for?’. Ten posters were submitted. They were displayed in the hallway next to the meeting room and INN Group Experts were invited to vote on the best poster.

The SoINN pilot centres had met in Grenoble in May 2023. The Linguistics working group reported on meeting two groups of specialists, one in Italy and one in Grenoble. The Italian group's proposals concerned translations of the courses currently on the SoINN website. It was considered though that only a Chinese translation would be useful for the moment and its feasibility will be tested. Two proposals from the French group will be the subject of a future meeting to better specify their objectives. The Promotion working group met with the Association of Medical Deans in Europe (ADME) and representation of the SoINN at their next congress is being considered. The course and document ‘Learning Pharmacology by using ATC Classification and Stem’ has been updated and is currently being proofread. Updates on courses on biological medicines are being identified. The specifications for developing a course on anti-infectious substances were elaborated and the SC is currently looking for volunteer authors to draft this course. Volunteers from the INN Expert Group would be especially welcome. The Pharmacovigilance group has developed an agenda for its work and results are expected later this year and early next year.

The next meeting of the pilot centres is planned for 30-31 May 2024 in Barcelona; the programme is currently being developed. The SC Chair highlighted the highly collaborative value of the group and the value of the SoINN in medical teaching.

The winner and runner-up of the poster competition were announced.

Dr Balocco informed participants that a second meeting running alongside the Barcelona SoINN meeting, was being planned with the University of Oslo on getting ADC into the classroom and for it to become a global standard for WHO.

COLLABORATORS’ UPDATES

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

This year is the 75th anniversary of the founding of the Council of Europe following the signing of the Treaty of London on 5 May 1949, and is based on the three pillars of democracy, human rights and the rule of law. 2024 is also the 60th anniversary of the European Pharmacopoeia and the EDQM.

On 17 November, 1963, the Council of Europe's Public Health Committee adopted the draft Convention on the establishment of legal, administrative and technical bodies of a European Pharmacopoeia. Shortly after, on 17 March 1964, the Convention on the Elaboration of a European Pharmacopoeia was adopted by the Committee of Ministers, and the first meeting of the Ph. Eur. Commission was held on 28 April 1964. The purpose was to create a common European Pharmacopoeia, with the aim of ensuring access to safe medicines, which is considered to be a basic human right. While this was originally a European initiative, the EDQM's activities reach beyond Europe, reflecting the global nature of medicines today. More than 120 countries worldwide accept European Pharmacopoeia standards, and world-wide experts contribute to the development of these standards.

A conference is being organised in June to mark the occasion of the 60th anniversary, which will be streamed and free to watch online. Further information on this event is available on the EDQM website.

Recommendations on modified INN are of interest to the Ph. Eur. since it uses INN in monograph titles and often needs to add a modifier. The Ph. Eur. needs to apply rules or guidance for this, and wants to ensure that they conform with those of the WHO. The last publicly available version was published in 2005, but a revised version 3 was circulated among the experts in 2012. Reference is still made to some of the guidance provided in the 2005 version some of which is revised in version 3 (e.g. retaining the active moiety at the start of the name); but the Ph.Eur. cannot refer to that document. The EDQM representative highlighted the importance of the guidance that comes from the INN group and the INN secretariat, and how much it is appreciated. Any news on the status of the INN document, or whether it is something that is remaining on pause for the moment, would be most welcome.

European Medicines Agency

The EMA publication 'Human Medicines Highlights 2023' provides a high-level overview of recommendations for new marketing authorisations. In 2023, 77 medicines received marketing authorisation of which 39 contained an active substance new to the EU. Among these was the first advanced therapy medicine to be authorised, which uses CRISPR/Cas9 gene-editing technology of patients' cells to treat transfusion-dependent beta-thalassemia and severe sickle cell disease. Two vaccines against respiratory syncytial virus, both recombinant with one also adjuvanted, were also approved. A new COVID-19 vaccine, Bimervax, was approved along with a number of updates of previously licensed COVID-19 vaccines. Two positive opinions for medicines for use outside of the EU were adopted; this procedure has also been used several times for WHO pre-qualification.

Highlights of the March CHMP meeting will be published shortly. In February, several new medicines were recommended for approval including two new influenza H5N1 vaccines, both containing the same active ingredient but with different indications, one for zoonotic infection and one for pandemic preparedness.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assesses the safety of products and highlights of its monthly meetings are published online. At its March meeting, it reported that available data do not support a causal link between mRNA COVID-19 vaccines and postmenopausal bleeding. At the February meeting there was a reminder of serious adverse reactions when the COVID-19 antiviral drug Paxlovid was taken together with certain immunosuppressants, due to drug-drug interactions. At the January meeting, the PRAC started a signal procedure to review data on secondary malignancies related to T-cells for the six approved CART cell medicines. Malignancies have always been considered a potential risk and are outlined in the risk management plans. PRAC is now reviewing all available evidence, including 23 cases of T cell lymphoma and leukaemia.

In discussion, there was a query on the approval of medicines by the EMA for use outside of the EU. This is Article 58 (of Regulation (EC) No 726/2004) which allows for an opinion on marketing approval to be given by the EMA for medicines to be used outside the EU. It has also been used for WHO pre-qualification, typically for HIV anti-virals and some vaccines. Occasionally the procedure has been run in parallel with an EU marketing authorisation request where the medicine is also to be used within the EU. The standards used for Article 58 submissions are the same as for medicines for EU internal use.

International Union of Pure and Applied Chemistry (IUPAC)

The third version of the pdf format of IUPAC's Blue Book (Nomenclature of Organic Chemistry IUPAC Recommendations and Preferred Names 2013) that incorporates improvements and recent corrections, is available at:

<https://iupac.qmul.ac.uk/BlueBook/PDF/BlueBookV3.pdf>

The most significant change is a revision of the definition of a cyclophane. This is unlikely to affect any existing INN names but does eliminate a problem that had been recognised.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since the last Consultation, the Japanese Approved Names (JAN) Expert committee has met three times, and 28 names have been published, including three COVID-19 related substances and one biosimilar.

Supplement 2 to the Japanese Pharmacopoeia (JP) 18th edition is now under preparation and should be implemented in June 2024.

The JP has also initiated a prospective pilot programme with the USP to promote harmonization of pharmacopoeial standards for active pharmaceutical ingredients and formulation articles. The programme is part of the activities of the memorandum of cooperation (MOC) between the USP and the Japanese Ministry of Health, Labour and Welfare (MHLW)/Pharmaceuticals and Medical Devices Agency (PMDA), and takes place outside of the Pharmacopoeial Discussion Group (PDG) process for harmonization of excipients and general chapters. Dapagliflozin Propylene Glycol Hydrate and Dapagliflozin Propylene Glycol Tablets have been selected as the articles for the pilot program.

<https://www.pmda.go.jp/files/000264989.pdf>

Therapeutic Goods Administration (TGA), Australia

Two TGA representatives attended the Consultation in person. This is the first time there has been the opportunity for two people to attend and the INN secretariat was thanked for providing all the necessary support to secure approval from TGA for their attendance.

The ACCESS Consortium comprises therapeutic goods regulators from Australia, Canada, Switzerland, Singapore & UK. It was reported that the Access Consortium working group for new active substances had established an aligned process for priority review, which includes the decision on priority status. The priority pathway aims to achieve a shorter timeframe to approval for any new active substance that diagnoses, treats or prevents a condition that is serious, life-threatening or severely debilitating and for which no other treatment is currently registered and marketed in participating jurisdictions for the proposed indication.

Flexible working arrangements continue at the TGA for the foreseeable future.

United States Adopted Names (USAN)

The 2023 winter USAN Council meeting took place on December 8, 2023. Names for 33 drug substances were reviewed and discussed. Nine new stems and infixes were approved and added to

USAN's stem list. Two stem definitions were revised. Meeting topics discussed included: a negotiations update, USAN website metrics, the October 2023 INN Consultation, ISMP and FDA's medical error reports, and an INN cellular and gene therapies revised nomenclature report.

Twenty-seven INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 78th INN Consultation.

From September 2023 through February 2024, USAN staff had processed, researched, and made recommendations for approximately 127 USAN applications and forwarded this information to the USAN Council for their review and name selection. Also through February 2024, 53 USAN had been adopted for 2024 whilst currently, there were approximately 190 active USAN negotiations.

The 2024 Summer meeting of the USAN Council is scheduled for June 6-7, 2024 and will be hosted by USP.

United States Food and Drug Administration (FDA)

The second 10-year term of the current FDA-USAN liaison representative ends this year. The FDA has identified a replacement which will be formalised in September. This new FDA representative is likely to attend the INN Consultation in October. The current representative expressed his honour to have participated in INN Consultations for the past 20 years. He has been very impressed by the work of the INN Programme and has found it valuable to have made new professional friends. He was grateful for being able to participate and had enjoyed every bit of it.

The Chair felt he was being modest and that it would really need two people to try to replace all the knowledge that the FDA representative had built up and his great memory of pharmaceuticals that everyone would like to have.

United States Pharmacopoeia (USP)

The USP representative reported on two ongoing USP projects. For one project, on detecting and controlling impurities, the USP is preparing, packaging and selling impurity reference standards for manufacturers, and there has been great interest in this. In this regard, taking note of the M7 ICH guideline on control of DNA reactive (mutagenic) impurities in pharmaceuticals, USP is currently working on nitrosamines and providing diluted solutions for analytic purposes. The other major USP project involves analysing the pharma supply chain in order to react to potential drug shortages. This involves machine learning, which is basically software that analyses what the outcome might be after major storm damage to pharmaceutical facilities e.g. as happened in Puerto Rico in 2017. The software is being designed to react to such situations and predict shortages in advance.

Uppsala Monitoring Centre (UMC)

The UMC reported that it is heavily involved with global substance work with regards to the ISO IDMP standards (Identification of Medicinal Products), both within ISO and within the global IDMP working group, collaborating with INN amongst others. The UMC is also working more intensively with regulatory authorities and other stakeholders in Latin American countries resulting in an increased demand in translation, especially in Spanish and Portuguese.

World Customs Organisation (WCO)

In January 2024, the 39th Session of the Scientific Sub-Committee of the WCO took place and examined, among others, the classification of the 419 substances of INN Proposed Lists 128 and 129. Classification was agreed for all these substances except for *pegmispotide* (INN).

At its March 2024 meeting, the Harmonized System Committee (HSC) of the WCO approved the above classifications and took note that the Scientific Sub-Committee would review the classification

of the INN products with the stems *-golix* and *-relix* and continue with the discussion of the classification of *pegmispotide* (INN) at its next Session.

The Scientific Sub-Committee further examined the pending classifications of *imlunestrant* (INN), *sirpefenicol* (INN) and *efrilacedase alfa* (INN) from INN Proposed List 126. The HSC agreed on the classification of *efrilacedase alfa* as an enzyme, in subheading 3507.90, and decided to classify *imlunestrant*, as an antihormone, in subheading 2937.23.

With respect to the classification of *sirpefenicol* (INN), the HSC decided to classify it in the antibiotics heading, 29.41. The Committee took note that the next Scientific Sub-Committee Session would discuss a possible amendment to the Explanatory Note to the heading of ‘antibiotics’ to clarify the difference between antibiotics and antibacterials, especially taking into consideration the information that maybe in the future the term ‘antibiotics’ might not be used for INN.

The HSC also reviewed the classification of the INN substances of the ‘-cholic acid’ group and agreed with their prior HS classification.

The WCO expressed its appreciation for technical advice that the INN Team provide to its scientific subcommittee.

WHO Collaborating Centre for Drug Statistic Methodology

A meeting of the ATC/DDD Working Group took place in Oslo in the week before this Consultation. About 30 applications for new ATC codes were discussed, with half of the applications being for substances belonging to the ATC first level L, antineoplastic and immunomodulating agents. Eight applications for new DDDs were also discussed.

In January 2024, the Centre published its annual ATC/DDD Index plus Guidelines for ATC classification and DDD assignment, in both Spanish and English.

The Centre has also published the 2024 ATCvet Index and the Guidelines for ATCvet classification, which is closely related to the human ATC system.

The Centre is developing a short online course on ATC/DDD in collaboration with the School of INN and the annual international ATC/DDD course is to be held in Oslo on 13-14 June 2024.

CLOSE of MEETING

Before the end of the 78th INN Consultation, Dr Yukiko Nakatani, the new Assistant Director-General (ADG) of Medicines and Health Products, addressed the meeting, expressing her gratitude to the INN Expert Group, especially as INN are not simply names but are used for access to quality pharmaceuticals in LMIC (low-and-middle-income-countries), in registration, in pharmacovigilance, in procurement and for insurance health services. The ADG also highlighted the ongoing work of the WHO’s INB (intergovernmental negotiating body) to draft and negotiate a WHO convention, agreement or other international instrument on pandemic prevention, preparedness and response. She congratulated the Chair in coordinating discussion, Dr Balocco and the INN Team in coordinating the meeting, and all participants for their hard work. The ADG noted that Dr Balocco is the expert in INN and in communication in getting you all here and she looked forward to getting to know everyone.

The Chair thanked the ADG for her comments and agreed that Dr Balocco and the INN Team do exceptional work between and for the meetings, and thanked the ADG for noticing and making comment on that.

In closing the meeting, the Chair thanked all Experts for their contributions, especially those online for whom it has meant very early mornings or late evenings. He additionally acknowledged the exceptional work of the secretariat.

The Chairs and Rapporteur were thanked by Dr Balocco for their work during the meeting.

Next meeting

The 79th INN Consultation will be held in Geneva on 21-25 October 2024.

OPEN SESSION for INN STAKEHOLDERS
78th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances
(a hybrid virtual and face-to-face meeting)
WHO Headquarters, Geneva, 19 March 2024

The Open Session for Stakeholders held in conjunction with the 78th INN Consultation was opened by Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, who gave a warm welcome to all, both those present in the meeting room and those joining online. She emphasised the importance of these sessions for stakeholders during which they can present their case directly to the INN Experts, following which there will be considerable discussion in the closed session of the 78th INN Consultation. Dr Balocco also requested that although the session is described as Open, it is open only to those present at the meeting and all matters discussed should remain confidential until the meeting report is published.

Zydus

Zydus, based in India, had developed compound ZY-19489 in collaboration with MRC Delhi for prevention of malaria. The substance had completed phase 2 trials and the company was ready to begin phase 3 development. In 2022, an INN request was submitted. However, as none of the company's submitted names could be retained, the INN Expert Committee proposed the name *sutidiazine*, which was accepted by the company. Unfortunately, an objection was raised to this based upon its similarity to *sulfadiazine* (4)(3), which came as a surprise to the company as *sutidiazine* had been proposed by the INN Committee. The company attended the Stakeholders Session to argue for the retention of *sutidiazine*.

The *sulfa*- prefix is a stem representing anti-infectives, sulphonamides; neither *-diazine* nor *suti*- are stems, and *sutidiazine*, not being an anti-infective, was felt to be novel and distinct from *sulfadiazine*. Diazines are heterocyclic rings incorporating two nitrogen atoms, and exist in nature with properties that include diverse pharmacological activities, flavours and fragrances. The company had wondered if the objection was based upon pronunciation but found no phonetic similarity between *sutidiazine* and *sulfadiazine* in French.

The name *sutidiazine* has already been used in articles and by independent reviewers, and appears in a WHO Inventory of the ten small molecules with the most potential. With the substance in clinical development, the company is concerned that with an alternative *-diazine* name proposed by the INN Committee, there may be a further objection and another year would be lost in the development of this important therapeutic drug. A French physician colleague confirmed that it is not similar sounding in French and so the company felt that there was no strong reason to reject *sutidiazine*.

Dr Balocco confirmed that the objection was based upon the pronunciation in French. The INN Committee cannot overrule the objection but it can approach the objector. It was appreciated that development of this drug had been made out of goodwill for global health and malaria prevention, and it would be good not to change the name. There are a number of French speakers on the Committee who will assess not only the pronunciation but in writing also, and all this will be taken into consideration during its deliberation.

Zydus thanked Dr Balocco and expressed its hope for a favourable decision.

Diamyd Medical

The enzyme glutamic acid decarboxylase 65 (GAD65) catalyses glutamate to gamma-aminobutyric acid (GABA), mostly in neurons and pancreatic beta cells. GAD65 is also a major autoantigen in Type 1 Diabetes in which the immune system mistakenly targets and attacks the insulin producing beta cells of the pancreas via GAD65. Anti-GAD65 autoantibodies are commonly found in the blood of Type 1 diabetics and are used as diagnostic markers of the disease.

Diamyd's drug product (GAD2) is a recombinant GAD65 (rGAD65) adsorbed onto aluminium hydroxide for direct inoculation into lymph nodes to regulate auto-immunity in diabetes. The GAD2 product has no enzyme activity and the basis of its action is the linear structure of the protein and how it is processed by the histocompatibility complex. Thus, the company felt that for an INN, the common stem *-ase* for enzymes was inappropriate and that the stem *-imod* for immunomodulators, or an entirely novel suffix, would be more appropriate. If a name with an *-ase* stem is assigned, there is a risk of off-label use as an enzyme replacement therapy that would be in-efficacious and unsafe through inappropriate dosing and incorrect route of administration. Data were presented showing the immunomodulatory effects of rGAD65 with strong induction of anti-GAD65 antibodies following direct inoculation into lymph nodes that leads to proliferation of novel tolerogenic GAD-stimulated T cell responses.

In summarising, the company stressed that its rGAD65 product has immunomodulatory but no enzymic activity, and that the stem *-ase* would be inappropriate with *-imod* better reflecting the properties of this product. The company expressed its willingness to provide any further support of this request.

In discussion, upon being highlighted that INN refers to the active substance and not the final product, the company acknowledged that the protein is active before adsorption to alum. It believed that most of the adsorbed protein was intact but had no data on whether the protein would regain enzymic activity upon de-adsorption from the alum.

Revolution Medicines

Revolution Medicines (RevMed) has an extensive portfolio of a new class of Ras inhibitor, called RAS(ON) inhibitors, and with two requests for these new substances, the company attended this Open Session to request a modification of the *-rasib* stem to *-rasonib* or *-onrasib* for their substances, as all current *-rasibs* are RAS(OFF) inhibitors.

Ras proteins are small GTPases that serve as regulators of many signalling cascades involved in diverse cellular processes. Activating mutations in Ras are found in about one-third of cancers and relate to a single mutation, typically at codon 12, 13 or 61. The Ras(ON) state is characterised by Ras being GTP-loaded, whereas the Ras(OFF) state is characterised by Ras being GDP-loaded; it is the Ras(ON) state that stimulates cell growth and survival effectors.

RAS(ON) inhibitors differentiate from (OFF) inhibitors through rapid target engagement and insensitivity to adaptive resistance. The Company's RMC-6291 product is a first-in-class RAS(ON) inhibitor quite distinct from RAS(OFF) inhibitors. Clinically it induces responses in non-small cell lung cancer (NSCLC) patients whose cancers had progressed on a RAS(OFF) inhibitor while its other RAS(ON) inhibitor (RMC-6236) has delivered promising clinical results across diverse Ras mutations in pancreatic ductal adenocarcinoma (PDAC). The importance of differentiating between RAS(ON) and RAS(OFF) inhibitors is also reflected in the scientific and clinical literature. Thus, the Company requested the INN Experts to consider a new stem to distinguish RAS(ON) from RAS(OFF) inhibitors or at least some means of differentiating the two.

In discussion, the company added that RAS(ON) and RAS(OFF) inhibitors had distinct modes of action with its own molecules binding in a pocket of the target distinct from the mutations that

characterise tumorigenic forms of Ras. It also added that with regard adverse effects, RAS(ON) inhibitors are quite well tolerated with a much better safety profile than RAS(OFF) inhibitors, with minimal side effects and an especially low level of hepato-toxicity.

Alliance for Safe Biologic Medicines (ASBM)

The ASBM promotes clinical trials and supports patient safety but has discovered that clinical trials are expensive, time consuming, and that the public and administrators are frustrated by a lack of available important medicines. The balance between safety and speed in clinical assessment should lean towards safety with alternate approaches to increasing speed. The approval pathway for originator products relies heavily on expensive and time-consuming clinical trials to demonstrate safety and efficacy but for biosimilars an abbreviated pathway has been created that relies much less on clinical trials and more on analytics. With fewer clinical trials for the approval of biosimilars, the importance of pharmacovigilance (PV) is increasing. However, many biosimilars share the same non-proprietary name and the brand name is often missing in adverse drug reaction (ADR) reports, in some countries in almost 40% of cases.

In addition to the abbreviated pathway, there are several initiatives to re-evaluate (de-emphasise) clinical trials. For example, following a recent FDA meta-analysis of safety outcomes when switching between biosimilars/originators, no difference in safety profiles or immunogenicity rates between switched and non-switched patients were found. Consequently, the FDA supports reducing the burden of switching studies in clinical studies which in turn would reduce the time and cost of development. Reducing regulatory oversight has also become political. In the USA, a US senate bill is under review that would restrict FDA flexibility in requiring switching studies and shift responsibility from the regulatory agency to a political committee because of drug costs. Also, in the EU, the EMA has published a concept paper soliciting comments to develop a ‘tailored clinical approach’ in biosimilar development with regard to the role of clinical data. It recognizes that there may be the potential to waive certain clinical data requirements even for complex biosimilars such as mAbs based on solid evidence of quality comparability.

The ASBM intends to defend the role of clinical data in biosimilar approval and this trend toward de-emphasis of clinical data in biosimilar approval also makes strong post-marketing pharmacovigilance all the more important. In this respect, the ASBM re-iterated its support for the INN’s Biological Qualifier (BQ) which it believes remains supported by the INN Group.

The benefits of a WHO led distinct nomenclature standard remain clear and would benefit the least economically-developed countries of the world. The meeting was reminded of previous ASBM studies that show strong support for distinct naming including regulators in large and small countries. Some regulators have adopted their own specific naming system and some who initially supported the BQ have initiated their own system would be happy to adopt a WHO global standard.

ASBM remains determined to advance the INN’s BQ for distinct names. Last October the ASBM proposed to define support for distinct biologics nomenclature. To that end, it will gather statements of support from national regulatory authorities worldwide, through a letter designed for that purpose. ASBM will share the resulting statements of support in conjunction with the 2024 ICDRA Meeting in New Delhi, India.

In summary, as the INN Group still supports its recommendation for distinct suffixes, as strong support for distinct naming remains amongst regulators and as lead regulators push for reduced emphasis on clinical trials in biosimilar approvals and stronger biologic pharmacovigilance becomes increasingly important, ASBM is determined to advance the proposal by working with the WHO and other National Regulatory Authorities worldwide to collect statements of support, in conjunction with this year’s ICRDA meeting.

Dr Balocco thanked the ASBM for its presentation and noted that while a position from WHO management is awaited, a presentation reaching out to the Assembly would be good, and perhaps regulators could propose this topic for discussion at the WHA.

Dr Balocco thanked all stakeholders for their presentations noting how useful these are for the Experts, and called the meeting to a close.