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70th Consultation on

International Nonproprietary Names for Pharmaceutical Substances

Geneva, 20-24 April 2020

Executive Summary

Programme on International Nonproprietary Names (INN)

INN Programme and Classification of Medical Products Unit
Health Products Policy and Standards Department (HPS)
Access to Medicines and Health Products Division (MHP)
World Health Organization, Geneva

70th Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

OPENING OF MEETING

The meeting was opened by *Dr Clive Ondari*, acting Director, Essential Medicines and Health Products (EMP), who welcomed the family of INN experts. The Consultation was held as a virtual meeting held under challenging circumstances due to the ongoing pandemic and thanks were due to the secretariat working off campus and to the INN IT officer coming into HQ to make the meeting a reality. He highlighted increasing demands on the INN Programme with a tremendous increase in the number of applications, and acknowledged the letter addressed by the INN Expert Group to the WHO management highlighting the excellent work done by the INN secretariat and the need to ensure that proper and sufficient resources are allocated. Dr Ondari noted that WHO management is fully behind maintaining high levels of standards and enhancing the programme. As a consequence, structural changes have been made to the leadership of the programme in recognition of the prominence of the work and to assure maintenance of the work. Dr Ondari acknowledged the excellent work that has been done by the whole INN team in the weeks and months prior to the meeting in anticipation of the huge work load involved.

ELECTION OF CHAIR, VICE-CHAIRS and RAPPORTEUR

Prof Sarel Malan was elected as Chair of the meeting; Dr Menico Rizzi was elected as the vice-chair for biologics and Dr Adrian Evans was elected as the vice-chair for chemicals. Dr James S Robertson was elected rapporteur.

INTRODUCTORY REMARKS

The *Chair* thanked all for their confidence in him and looked forward to the challenge of chairing the meeting through WebEx; he would endeavour to be as effective as possible and not to stifle conversation.

Dr Raffaella Balocco, Head, International Nonproprietary Names Programme and Classification of Medical Products Unit, also welcomed participants and briefly ran through procedural aspects of holding the meeting by WebEx.

Given the presence of several new members, the Chair called for a *tour de table* of introductions.

69th EXECUTIVE SUMMARY

The Executive Summary of the 69th INN Consultation was tabled and adopted, with thanks to the Rapporteur.

NOMENCLATURE of INN

During the 70th INN Consultation, a total of 190 INN requests was discussed, including:

- 157 new INN requests, including 76 for biological substances
- 30 outstanding requests
- 3 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 182 names were selected, which are planned to be published in List 124 of proposed INN (p.INN), while 5 requests were deferred for future discussion and 2 were withdrawn. One request was rejected by the INN Expert Group, as the substance did not conform to the criteria for INN selection. One amendment was planned to be published in a forthcoming List of p.INN; one request of substitution could not be retained as it did not conform to the criteria.

Three new stems/substems were selected, 5 suffixes were promoted to the pre-stem list and it was decided to review the descriptions of 2 stems/pre-stems.

CELL THERAPY SUBSTANCES

The INN Secretariat reported on a meeting held at WHO in February on cell and gene therapy products that was attended by representatives from CBER, EMA, TGA and other regulatory bodies. A presentation on INN was well received and it was acknowledged that harmonisation of cell definitions was highly important. A white paper is to be drafted to be shared by all regulators covering regulatory issues for cell and advanced therapies. INN will be featured and reliance on the cell definition will be highlighted.

Participants were then updated on recent discussions on cell therapy substances within the INN Programme. A few INN Experts and cell therapy advisors held a short meeting in December and a two-day meeting in March, both via WebEx, to revise the cell therapy application form and to discuss cell definitions. The form now requests much more comprehensive information on the cell therapy substance, especially on the source of the cell, the manufacturing process and the characterisation. A new request is that for substances claiming to be stem cells, information must be provided to demonstrate that the cells are capable of self-renewal, are unspecialized, and the population can give rise to a number of specialized cell types. For those claiming to be stromal cells, data must be provided to demonstrate the claimed cell functionality. The cell experts felt that these data were essential features to be reported. Information requested on genetic manipulation is relatively unchanged; the one new point concerns sequence alignment of similar novel and pre-existing vectors to determine if the new vector platform is the same or different. Overall, the cell experts felt that since cell processing is becoming more stable and defined, the new requested information should more reflect the process, and this would give more confidence in naming.

The INN Experts welcomed the new application form and given the extent to which applicants may modify their process, it will make them consider carefully what they are asking of the INN.

The Secretariat added that the activities of the INN cell therapy working group are very important and this new information will become part of the white paper arising from the February WHO meeting. The work of INN will help regulators and others in harmonising the definition of cell substances. Several organisations already use INN descriptions in their work and note the importance of this.

In discussion, it was highlighted that distinguishing stem cells from stromal cells remains problematic. If the applicant can demonstrate differentiation, even *in vitro*, that is sufficient to call it a stem cell. Stromal cells are distinguished by having the ability to release molecules that affect its environment and applicants can provide data on this. However, stem cells may also exhibit stromal properties and the mechanism of action can help provide the best definition of the substance.

It was mooted that it would be valuable to publish the conclusions of the expert advisors to disseminate cell INN and educate academic and other developers of cell therapies. The Secretariat responded that first the new procedure would have to be endorsed by the INN Expert Group and then published on the INN website; but ultimately it would be good to publish it to increase dissemination.

SCHOOL of INN (SoINN)

The School of INN was launched last October (2019) and was highly appreciated by the WHO Director General (DG). Successful webinars have been held, directed at different stakeholders including those from academia, industry, patients and WHO staff. Further work has continued with various collaborators and groups, including the Universities of Grenoble, France and Alcalá, Madrid, and the Spanish Medicines Agency (AEMPS), all of which are involved in translating the online courses into French (Grenoble) and Spanish (Alcalá and AEMPS). Work is also underway to transliterate the courses into Chinese (with Fudan Shanghai University, China) and Arabic (with the University of Monastir, Tunisia). A meeting of various university stakeholders piloting the SoINN, which was to be held later in 2020 in Italy has been postponed until 2021 due to the ongoing pandemic.

A project called 'Stem in a pill' is progressing, but slowly. Stems are being categorised into pharmacological classes and 14 classes have been completed to date. The project would benefit from additional clinical pharmacological expertise input.

Finally, data were presented on the statistics of access to the online SoINN platform. Since October, when the platform was launched, the site has had >4,000 visits from almost 3,000 unique visitors, accessing >90,000 pages, although the number of visits has been gradually decreasing since it was launched. The greatest use has been by students. A French version is being added to the site and a search tool should increase the number of visits to the SoINN.

COLLABORATORS' UPDATES

European Medicines Agency (EMA)

The European Medicines Agency (EMA) is now established in Amsterdam in The Netherlands. The intention is to gradually reactivate activities that had been put on hold during the relocation, e.g. guidelines. However, in view of the Covid-19 pandemic priorities are being continuously evaluated and a significant amount of resource is being directed towards supporting developers of Covid-19 vaccines and treatments, and to ensure the supply of medicines. The agency is also currently going through a reorganisation to ensure best use is made of available resources and make the Agency better prepared for future challenges, such as new technologies. During the relocation period, focus was on core business, e.g. evaluating marketing authorisation applications (MAAs) and providing scientific advice (SA). In 2019, 117 MAAs were received, representing a 40 % increase, alongside 674 scientific advice procedures. Thirteen MAA for biosimilars were received bringing the total biosimilar MAAs received to 103, with 55 currently approved.

With regard to advanced therapy medicinal products (ATMPs), in 2019 there were two MAAs received, bringing the total number of ATMP applications to 26. However, only 9 of these correspond to current, valid MAs, indicating a relatively high number of negative opinions or withdrawals; four ATMPs are currently under review and one is awaiting the European Commission's final decision. As part of MA evaluations, the Agency also assesses whether ATMPs are considered to be new or known active substances and about 70 requests for classification of ATMPs were received in 2019. A good dialogue with the INN Programme is

desirable to ensure harmonisation where possible (i.e. that a unique INN is assigned when the substance is concluded to be new).

EU legislation requires each medicine to have an invented name and acceptability of the proposed invented names is overseen by the Invented Name Review Group (NRG). This Group reviews submitted brand names and raises objections needed; inclusion of INN stems is a common reason for objection. NRG is also occasionally notified by healthcare professionals of cases where there have been near misses or where there is a risk of confusion between two INNs. In the absence of an adverse event, such cases are not included in the Eudravigilance database and EMA will discuss with the INN secretariat how best to bring such cases to the awareness of WHO.

International Union of Pure and Applied Chemistry (IUPAC)

The most significant publication for the INN meeting was the publication of "A brief guide to the nomenclature of organic chemistry. An IUPAC Technical Report". The document is available free in *Pure Appl. Chem.* 2020; **92**, 527-539.[1]

Another IUPAC document that may be of interest to some INN members has appeared as a provisional document which was open for comment until 31 May 2020. It is "End-of-line hyphenation of chemical names".[2]

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since October 2019, the Japanese Approved (Accepted) Names (JAN) expert committee met on two occasions. Forty-two names have been published including one biosimilar. An English version of Supplement 2 to the 17th Edition of the Japanese Pharmacopoeia (JP) has been available since February 2020 on the PMDA website for free.[3]

PMDA is now preparing the 18th version of the JP which will be implemented in 2021.

Therapeutic Goods Administration (TGA), Australia

TGA is drafting a standard for the serialisation of medicines utilising data matrix codes, intended to be released for public consultation in 2020. The standard is a key step towards implementing a future medicine track-and-trace system in Australia.

From 30 April 2020, the TGA will publicly display the formulation details of all medicines and biological products in the Australian Register of Therapeutic Goods (ARTG), on the TGA website. Each ARTG summary will display the names of excipient ingredients present in the formulations of the product to increase transparency of TGA-held regulatory information and improve consumer access to important ingredient information.

In 2016, the TGA updated over 200 active and excipient ingredient names used in Australia to align with names used internationally, including INNs. Medicine sponsors were allowed a four-year transition period to update labels and relevant documentation. This transition period will end on 30 April 2020. From 1 May 2020 all medicines released for supply in Australia will need to reflect the updated ingredient names on labels and in supporting documentation such as Product Information (PI) or Consumer Medicine Information (CMI) leaflets.

The TGA has partnered the Australian Department of Foreign Affairs and Trade, to establish the Indo-Pacific Regulatory Strengthening Program (RSP) until June 2022. The program is

[1] https://doi.org/10.1515/pac-2019-0104 (pdf)
https://www.qmul.ac.uk/sbcs/iupac/BriefGuide/organic.html (html version)
[2] https://iupac.org/recommendation/end-of-line-hyphenation-of-chemical-names/
[3] https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0019.html

being mainly run out of the TGA's base in Canberra however there is a posted position in Singapore to have a regional presence.

The program aims to strengthen the capabilities of National Medicines Regulatory Authorities in the region and improve regional collaboration to improve access to quality registered medicines and medical devices, mitigating diseases threatening public health. The RSP is using the WHO's Global Benchmarking Tool assessments to focus its efforts on areas that have identified gaps and are a priority for the country.

Countries involved in the program include Cambodia, Indonesia, Papua New Guinea, Myanmar, Laos, Vietnam and Thailand.

United States Adopted Names (USAN)

The 2019 Winter USAN Council meeting took place on Dec 5-6, 2019 at the Diplomat Resort in Hollywood, Florida, where names for 44 drug substances were reviewed and discussed. Two new stems and infixes were approved and added to USAN's stem list. Three stem definitions were revised. Forty-two INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 70th INN Consultation. Revisions were approved for 4 USAN Council names previously recommended.

Through March 2020, USAN staff will have processed, researched and made recommendations for 49 USAN applications and forwarded this information to the USAN Council for their review and selection. Also, through April 2020, 50 USAN will have been adopted for 2020 while revenue was realized for an additional 4 negotiations. Currently, there are approximately 175 active USAN negotiations.

The 2020 summer meeting of the USAN Council is scheduled to occur on June 12 and will be a virtual meeting.

United States Food and Drug Administration (FDA)

FDA guidance on naming of new biological drug products using a 4-letter suffix appended to the established name of the substance remains in force. However, some names can become quite long such as *ado-trastuzumab emtansine* and *fam-trastuzumab deruxtecan-nxki*. The FDA is trying to expedite review of drugs involved in tackling the Covid-19 pandemic, including drugs for investigational use such as *remdesivir*. Also, importation of appropriate drugs into the USA is being expedited. The FDA will probably remain in lockdown till June.

United States Pharmacopoeia (USP)

Like the FDA, the USP is also in lockdown due to the Covid-19 pandemic with staff working remotely and only very essential personnel allowed to work on site. This has complicated celebration of the 200th anniversary of the USP next month which has been under preparation for some time and there will be a virtual event instead. The USP is reacting to the coronavirus pandemic also by reviewing and revising monographs that impact the virus in any way, e.g. the hydroxychloroquine monograph is being revised and reference standards re-evaluated. In view of a severe shortage of hand sanitisers, the USP reacted quickly by loosening their formulae, for example to use different alcohol grades, while the FDA has adjusted the necessary law. Finally, the USP continues to transition to the Global Substance Registration System (GSRS) as the main source of chemical information and encourages chemists around the world to use this platform. The platform is an open resource that cannot be made proprietary and anyone can download and install it. Indeed, the German Federal Institute for Drugs and Medical Devices (BfArM) has transitioned to the GSRS platform while the Australian TGA is enthusiastic about using it.

World Customs Organization (WCO)

The INN Secretariat meets regularly with WCO to explain INN and their selection. The Secretariats of both the INN Programme and the WHO Model List of Essential Medicines collaborated recently with the WCO in drawing up a priority list of medicines relevant for use during the Covid-19 pandemic, in order to ensure the removal of fees for cross border movement of these medicines. The list has been offered by WHO to WCO and is published on WHO's website. Some medicines may not yet be on the list until appropriate evidence of their value during the pandemic is available; the list is a living document and will be updated if and when necessary.

WHO Collaborating Centre for Drug Statistics Methodology, Norway

Following reorganisation at WHO HQ in Geneva, the Unit Head of the INN programme is now responsible for co-operation with the WHO Collaborating Centre for Drug Statistics Methodology. The Centre has together with the INN Expert Group currently finalized the revision of the classification of the protein kinase inhibitors in L01XE in the Anatomical Therapeutic Chemical (ATC) system. A new subdivision with twelve new pharmacological ATC 4th levels has been decided, in addition to four new pharmacological ATC 4th levels for substances at present classified in L01XX Other antineoplastic agents. All-in-all about 80 different ATC codes have been reclassified and the changes will be valid from January 2021. This should improve users' experience of the classification. A similar reclassification is also planned for the monoclonal antibodies (L01XC) and the immunosuppressants (L04), as there cannot be more than 100 substances within an ATC group, and they will need to be subdivided in order for the system to cope with their increasing numbers.

CLOSE OF MEETING

Dr Balocco apologised that the director, Dr Clive Ondari, could not be present for the close of the meeting but passed on his regards to all participants. This was the first time for a virtual meeting and the Director hoped it was a good experience; he was very grateful for all the work in organising it. Dr Balocco herself thanked all participants for their contributions and especially the Chair and Vice Chairs for their leadership. A special thanks was given to the whole team at WHO, especially the IT officer, for the immense amount of work in organising this meeting. Hopefully the next Consultation will be face-to-face.

The Chair thanked the director for opening the meeting and commented that chairing the WebEx meeting had been easier than he thought. He appreciated the leadership of the INN Secretariat and the work of the whole INN team. He thanked his colleagues for sharing chairing, and the rapporteur, and looked forward to seeing everyone in October for the next Consultation.

Next meeting

The 71st INN Consultation will take place on 20-23 October 2020.

SESSION for INN STAKEHOLDERS

70th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 21 April 2020

OPENING REMARKS

The Open Session of the 70th INN Consultation was held via WebEx due to the ongoing Covid-19 pandemic. Approximately 60 participants were present online including the INN Secretariat, INN Experts, INN advisors and the stakeholders. Stakeholders were reminded that although the meeting is open to all stakeholders, what is discussed during the meeting should remain confidential until the report is finalised.

The Chair, Prof Sarel Malan, thanked the Secretariat for organising the meeting, and welcomed all participants to the meeting. He particularly appreciated the support of Dr Clive Ondari, acting Director, Essential Medicines and Health Products (EMP) for his backing of the INN Programme, the help provided by the Secretariat, the support of the stakeholders and the information they bring to the meeting.

Dr Ondari similarly welcomed the three INN stakeholders to the Open Session, and expressed his recognition of the INN family of experts who have worked hard to prepare for this meeting. He also recognised the extraordinary effort of the INN team to set up this WebEx meeting, especially the IT officer responsible. He passed on greetings from the ADG, Dr Mariângela Simão, whose administrative arrangements made it possible to have some of the Secretariat present at WHO HQ to facilitate this meeting. He emphasised to the stakeholders that their feedback was extremely important to the programme and wished them a successful meeting. On thanking the Chair for his leadership, he handed the meeting back to him.

Ascendis Pharma

Previously Ascendis Pharma had requested an INN for their pegylated form of teriparatide, TransCon PTH, in which teriparatide is transiently conjugated to a pegylated moiety via a proprietary linker and released under physiological conditions after administration. The submitted name *lanapegteriparatide*, with a random prefix to distinguish their specific pegylation technology from others, was not accepted by the INN Committee which assigned *pegteriparatide*. This was turned down by Ascendis and submitted names with alternative prefixes that were also rejected by the INN Committee, which then assigned *pateriparatide pegol* instead. This was also not accepted by Ascendis and *teriparatide sonapegol* was proposed in order to highlight again that the *pegol* moiety is uniquely released from the *teriparatide* moiety after administration.

It was highlighted by the company that TransCon PTH acts as a prodrug with the released teriparatide conferring the pharmacological activity of the substance whereas with conventional pegylation, the pharmacological activity is derived from the pegylated construct itself. In clinical trials, pharmacokinetic assessment is of the released unmodified teriparatide at different dose levels. The release of the pharmacologically active teriparatide from the pegylated prodrug is the rational for proposing a name that is distinct from substances with

permanent pegylation. Their proprietary pegylation confers a longer half-life to the prodrug but the pharmacological activity is of the teriparatide itself. The proposed *teriparatide sonapegol* combines the already approved INN for *teriparatide* with a modified pegol moiety that is released from the prodrug.

The Chair asked if the company had a preference for a name with pegol as a second word or with peg in the first word. The company expressed a desire for the latter option.

AVROBIO

Avrobio had previously requested an INN for its *ex vivo* gene therapy for which the name *voxeralgagene autotemcel* was assigned and accepted. For the purpose of publication, the company was asked to provide the full sequence of the vector along with a table of features. However, the company has declined to provide this proprietary information on the basis that sequences outside of the promoter and transgene are part of manufacture and only the promoter and transgene sequences are appropriate for publication.

The drug substance, *voxeralgagene autotemcel*, is a genetically modified cell producing a lysosomal enzyme *in vivo* to overcome a lysosomal storage disease. An analogy was drawn between this process and the manufacture of a recombinant enzyme in a bioreactor. In both cases it is the enzyme that is crucial for characterisation and even when changes are made to any part of the vector, for example for safety reasons, robust demonstration of comparability fulfils regulatory requirements.

The company explained that with *ex vivo* gene therapy, the vector transduces stem cells removed from the patient and it is the genetically modified stem cells that are administered to the patient, and not the vector itself, as it is in *in vivo* gene therapy. Following modification of the vector sequence involving codon optimisation and changes to transcription controlling elements, the stem cells secrete the same functional enzyme, which is the critical component for efficacy, and comparability of the before and after drug product was confirmed to the satisfaction of regulators (including FDA) using a battery of different analytical assays, including assays that focus on the enzyme and not the sequence. Modifying the vector is a common activity during development and only the promoter/transgene sequence need be provided, since efficacy is determined solely by the functional enzyme produced by the cells.

In discussion, it was highlighted by INN experts that an analogy to recombinant proteins was not exactly the same and that the INN policy is to name the substance, i.e. the genetically modified cells that contain the vector, and not the protein enzyme itself. Also, transplantation of the stem cells can be related to transduction efficiency which may vary with changes to the vector. The combination of the cells and vector and the name assigned reflect the complexity of the situation, and distinguish the cells from a future competitor.

Alliance for Safe Biologic Medicines (ASBM)

The Covid-19 pandemic highlights the leadership that WHO has in global health, and ASBM believes that this leadership is critical also for the naming of biosimilars, as it has repeatedly stated, especially as the number of biosimilars is increasing each year. It is also important to recognise that the biological qualifier (BQ) is still valid and that broad support for the BQ remains. The US FDA is supportive of unique identifiers for biologics and has instigated its own random 4-letter suffix. Health Canada (HC) has been a past supporter and is willing to harmonise, similarly the Australian TGA. The ASBM noted that many other countries including Denmark, Japan and Jordan also support the BQ, while physicians are also supportive. However, despite this support, countries have developed their own system but would have used a WHO system if WHO had moved ahead with the BQ.

The most common objection to a distinct suffix is that it implies biosimilars are inferior products and the US Federal Trade Commission (FTC) has raised the possibility that the current FDA naming system deters prescribers from using biosimilars, and impedes competition and price reduction. Some state pharmacists also feel that way. This false impression of inferiority has prompted two recent high-level meetings in Washington DC. The first was a joint FDA/FTC workshop, to address accusations that there had been disinformation to undermine physicians' confidence in biosimilars, to address a perceived need for education on biosimilar safety, and a need to address patent regulation that has held back the use of biosimilars in the USA. However, market share data suggest little, if any, lack of confidence in biosimilar use; for example, the market share of biosimilar ZARXIO (filgrastim-sndz) surpasses that of the reference product NEUPOGEN (filgrastim) in both the EU and the USA. So, the argument that the suffix creates a lack of confidence is false. However, in the USA price is an obstacle with greater discounts being offered in the EU versus the USA.

Physicians do not have low confidence in biosimilars and surveys show that physicians worldwide have consistently supported distinct naming. Distinct naming is not a barrier, rather it builds confidence, and with biologicals now being assessed for treatment of Covid-19, it will be critical to know precisely which drug a patient had received.

Regulators and the ASBM have long called for WHO leadership in naming. As the use of biosimilars increases countries will look to the WHO. The lack of unanimous agreement on distinct naming should not preclude the WHO from assuming leadership here. Following a suggestion by HC, the ASBM proposed that it drafts a petition or letter, to be approved by the INN Expert Committee, to gauge support amongst regulators worldwide for WHO action on distinct naming. The ASBM recognised that an answer would not be forthcoming from this Consultation but perhaps there would be a response in October. There is a desperate need for global leadership, and for example, HC would reverse its decision not to use a unique suffix if WHO provided a standard for global naming.

CLOSE of MEETING

The Chair concluded the meeting and thanked the stakeholders for sharing their data and opinions. Issues raised will be discussed by the INN Expert Group during the 70th Consultation and noted that if anyone is not satisfied with the conclusions, there can be further discussion.