INN Working Doc. 22.544
June 2022
Distr.: PUBLIC
ENGLISH ONLY

74th Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 5-8 April 2022 (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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EXECUTIVE SUMMARY

WELCOME

Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, welcomed the INN Experts, Advisors and all participants to the 74th INN Consultation, and proceeded directly to the election of the Chair.

ELECTION of CHAIR, VICE-CHAIRS and RAPPORTEUR

Prof Sarel Malan was proposed for the Chair and elected unopposed. Prof. Malan thanked the members for their confidence in him and led the election of vice-chairs and rapporteur. Prof. Menico Rizzi was elected vice-chair for biologicals and Mr Adrian Evans elected vice-chair for chemicals. Dr James Robertson was elected as rapporteur.

OPENING REMARKS

The Chair passed the floor to Dr Clive Ondari, Director, Health Products policy and Standards (HPS) and Director of the INN Programme. On behalf of the ADG, Dr Ondari thanked all participants for their contributions to the INN Programme. The WHO management had decided to restart face-to-face meetings with this hybrid meeting in which a small number were present at WHO HQ and the remainder joining virtually. Subject to the Covid-19 epidemiological situation, a full face-to-face meeting could be held in October. However, Dr Ondari pointed out that virtual attendance will remain available for those unwilling or unable to travel to Geneva.

He noted that the Experts were faced with over 250 requests, 220 of which were new requests with slightly more than half of them for biological substances. Nineteen were related to Covid-19, 18 of which were for monoclonal antibodies (mAbs) and one for a vaccine.

Dr Ondari also highlighted that the biological qualifier (BQ), which has been outstanding for some time but remains very topical, is being re-considered and a BQ concept note had been drafted that will be tabled to senior management to reconsider how to proceed with such a scheme. Feedback from the Expert Group was requested regarding what to take forward, and what additional resources would be needed to get the scheme up and running. Over the past few years WHO has made a deliberate decision to be transparent regarding the adoption of new policies, to reflect especially those of Member States who would potentially use such a scheme.

Dr Ondari was also grateful for the continued work of the School of INN (SoINN) steering committee, the upkeep of the tutorials and the expansion of the SoINN into different languages. He also expressed his thanks to all members of the INN Team. He wished the participants a successful meeting and noted that his de-briefing session with the chair was important and very useful. Dr Ondari ended by thanking the Chair and other elected office bearers for accepting their responsibilities and had full confidence in them steering the consultation to its conclusion.

The Chair thanked Dr Ondari for his leadership and support of the INN Programme without which the Group could not move forward. The Chair remained privileged to be part of this Expert Group and for the small contribution to global health that it makes. He added his thanks to the Experts for keeping up with the work with so much going on, and to the INN

Team who are key to the success of the programme and of the meeting; the manner in which work is presented makes smooth and effective running of the meeting possible.

73rd NOTES of CONSULTATION

The Notes of the 73rd Consultation were adopted without objection and the Chair thanked the Rapporteur for his work.

NOMENCLATURE of INN

During the 74th INN Consultation, a total of 250 INN requests was discussed:

- 212 new INN requests, including 113 for biological substances
- 38 outstanding requests

As a result of these discussions, 240 names were selected, which are planned to be published in Lists 127 (COVID-19-related requests only) and 128 of proposed INN (p.INN). Four requests did not fulfil INN criteria (No INN) and 6 requests were deferred for future discussion.

Six new stems/substems were selected, three suffixes were promoted to the pre-stem list and it was decided to review the descriptions of two pre-stem/substem.

ANTIBODY DEFINITIONS AND ILLUSTRATIONS - the AbML approach

The importance of antibody-based drugs continues to increase with complex multi-specific antibodies (MsAbs) being an up-and-coming class of biologic drugs that differ from natural monoclonal antibodies through their ability to bind to more than one type of antigen. However, as techniques to generate such molecules have diversified, so have their formats and the need for a standardised notation. To this end, the INN Group was informed of a novel text-based antibody markup language (AbML) that had been developed for defining complex Ab structures, as other languages were found to be overly complex and not flexible enough. In this language, Ab descriptions begin with a simple line listing the domains, separated by hyphens, and with vertical bars between each chain. Domain numbers can be added to the descriptor line and interactions can be indicated with colons between domain numbers. Disulphides are indicated within curly brackets and even more complex features can be added using symbols.

The language was stated to be far simpler than anything else and very flexible, and to assist users, a tool, abY draw, had also been developed. This can draw antibody schematics from AbML strings or generate an AbML string from a drawn antibody schematic. An example of a normal IgG structure was shown and how complexities could be added to it. The designer of the language has started using it to define Abs for INN definitions as it provides a flexible way of describing and comparing highly complicated structures. It was also stated that it can be made available publicly and that it would be good if companies adopted it.

PEPTIDE NAME HARMONISATION: -IMUT versus -*motide*

Distinct nomenclature schemes exist between INN and USAN for naming peptides. The INN scheme uses the stem -*motide*, first used in 1999, while USAN uses the stem -IMUT, first used in 2007. An attempt to find common ground was held via a one-hour video conference in March attended by representatives of USAN, CBER, the INN Secretariat and the INN Expert Group. Most of the meeting was taken up by a presentation from CBER, and so little

progress was made. Further discussion will continue at a later date as everyone agreed it would be beneficial to have a harmonised system.

Details of the USAN -IMUT system were provided to the participants of the Consultation. The -IMUT stem is for therapeutic immunomodulators (cancer vaccines) with separate infixes for peptides (-PEPIMUT), proteins (-PROTIMUT) and cell lysates (-LISIMUT). In addition, a qualifier is added at the end of the name via a hyphen: R for recombinant, S for synthetic and T for autologous. Nine PEPIMUT, 4 PROTIMUT and no LISIMUT substances have been named to date. Some PEPIMUT substances have been assigned INN, for example, the substance ADEGRAPEPIMUT-S was assigned the INN *adegramotide*. A significant difference between the two schemes is that mixtures of peptides can be, and are, named with the PEPIMUT stem, whereas INN are not assigned to mixtures. Thus, the USAN OMBIPEPIMUT-S comprises two peptides and these have been assigned individual INN – *adegramotide* and *nelatimotide*. IMUT substances can be even more complex, e.g. MAVERIPEPIMUT-S comprises 6 peptides plus a synthetic polynucleotide adjuvant. CBER stressed that peptide mixtures containing 100's of peptides are being developed and can be assigned a single IMUT USAN but clearly it would be impractical if not impossible to assign individual INN to these. Considerably more discussion will be required to find common ground between the two schemes.

In discussion, there was a comment that philosophically CBER views substances in a different way from the INN Programme; for CBER single substances can be mixtures and the distinction between substance and product is less clear. CBER also considers certain information on the active ingredient proprietary while the INN Programme aims to define each substance fully. Potentially the INN should leave the naming of complex peptide substances such as proteolytic digests of biological substances, tissues or organs to the regulatory authorities.

BIOLOGICAL QUALIFIER

The Biological Qualifier (BQ) is a unique identifier of biological substances comprising a 4-letter code to be used in conjunction with the INN. It was developed by the INN Expert Group (EG) in 2014 and presented to WHO management in 2016, but was never acted upon. At the previous Consultation, the Director, Health Products policy and Standards (HPS), suggested re-opening the BQ issue and preparing a concept note to share with management, but without re-opening any previous discussion. The BQ working group chair (now an ex-member of the EG) kindly agreed to collaborate in drafting this new concept note and to introduce the topic to the current members.

By way of background to the BQ, it was highlighted that biological medicines are very different to chemical drugs in their molecular size, structural complexity and manufacturing complexity, and that by virtue of their cellular biosynthesis they are highly heterogeneous. Since INN are allocated to biologicals based upon their amino acid sequence, the INN alone cannot distinguish the heterogeneity between supposedly similar biologicals, and so in 2014, the BQ was proposed, adopted by the INN EG in 2016, and presented to WHO management.

Since then, various national identifier schemes have been established. The US FDA created a 4-letter suffix, including vowels, that gets attached by a hyphen to the USAN in the product. In Japan, the PMDA distinguishes biosimilars from the reference medicine by the addition of a suffix, such as BS1 and BS2. The European EMA did not establish a separate scheme but placed emphasis on the brand name and a 2D barcode for pharmacovigilance purposes. In Australia, the TGA distinguishes glycosylation in biologicals using a Greek letter (as does the

INN) but unfortunately on one occasion insisted on using a different Greek letter from that assigned by INN.

An alternative international system, the IDMP (Identification of Medicinal Products) cannot comply with INN naming rules as it is a number, identifies the final product and not the drug substance. Furthermore, it lacks global harmonisation, has not begun tackling biologicals, and identification and definition of the medicinal product is done by industry rather than a centralised National Regulatory Authority or global body.

The INN's BQ proposal is a code of 4 random consonants, omitting vowels to avoid names inadvertently being created, and can contain an optional checksum involving 2 extra digits. It would be quick and simple to obtain a BQ via an automated online system, for which a prototype was established and which should be easy to restart. There would be an initial registration fee and so would be self-funding. The INN Programme would administer the scheme with all data provided by the applicant held in a secure database. The new BQ Concept Paper, essentially outlining the above, was tabled at the Consultation and is ready for submission to WHO management.

In discussion, participants were informed that the original BQ proposal was not concluded in 2016 because there was no consensus among WHO member states for its adoption. There had also been objection from biosimilar groups that did not want a system that would distinguish a biosimilar from the innovator substance. Indeed, during the discussion, one Expert queried what would be solved by progressing the BQ as proliferation of biosimilars was happening without the BQ.

The difference between the FDA 4-letter code and the BQ was further explained. The FDA code followed on after the conception of the BQ and uses all letters and not only consonants. It does not change the USAN but is shown on the product hyphenated against the USAN. The code is applied to all biologicals and not only biosimilars and has been used for every biological approved since its inception. It was also highlighted that the code has not led to a reduction in the use of biosimilars.

The Chair thanked the BQ working group chair for his contribution and the development of the new concept paper, and confirmed that the concept paper will be submitted to WHO management.

NAMING VIRAL VECTOR VACCINES

While traditional vaccines (e.g., live attenuated vaccines, inactivated vaccines, toxoid vaccines) are not assigned INN, it is the policy of the Programme to assign INN to modern well-defined vaccines. To date there is no specific nomenclature scheme for a vaccine, nor a specific infix/suffix highlighting that the substance is a vaccine, and INN are assigned when requested based upon the molecular nature of the vaccine (i.e., protein, mRNA, DNA or viral vector). Thus, a viral vector vaccine would be named according to the gene therapy two-word scheme with no indication within the name that it is a vaccine, although none have yet been assigned. However, there was a growing opinion that it would be expedient to assign a vaccine specific name to prophylactic vaccines. It would be especially useful to assign a one-word name to viral vectored vaccines instead of the long cumbersome two-word names assigned to gene therapy substances which would unlikely be used for a vaccine.

This approach was not favoured by all Experts and a counter argument was that the mode of action of a viral vector vaccine was the same as a viral vector gene therapy substance, that is to transfer a gene, and all that was required was to change the name of the scheme from 'gene

therapy' to 'gene transfer'. Furthermore, creating a specific suffix for vaccines could be problematic as INN are assigned to the active substance only and vaccines are generally considered to be the final formulated product.

It was highlighted though that there were significant differences in the use of a viral vector substance for gene therapy versus as a vaccine, for example, gene therapy vectors are normally administered to a very small number of unhealthy patients and it is crucial that the expressed protein is non-immunogenic, whereas a viral vector vaccine would be administered to a large number of healthy subjects with the intention that the expressed protein is highly immunogenic.

Ultimately, a majority of Experts were in favour of an alternative name for viral vector vaccines with a preference for a memorable one-word name for the vaccine substance.

In creating a one-word INN for viral vector vaccines, further discussion revolved around inclusion of 'va' or 'vac' to indicate that the substance is a vaccine, the use of 'vec' to indicate that the substance is based upon a vector, inclusion of an infix to indicate the nature of the vector, and inclusion of an infix to indicate the target disease (expressed transgene). Another consideration was that the name should be kept short for labelling purposes and that not every detail need be included within the name as full details of the substance would be in the definition.

Ultimately it was agreed that *-vavec* would be the most useful suffix for vectored vaccines, with 'va' for vaccine and 'vec for vector. An infix would also be included to indicate the nature of the expressed transgene/disease target but not the nature of the vector as inclusion of both could be confusing and full details would be in the definition. There is also the potential to use 'va' for other types of vaccine.

With some residual hesitancy regarding this novel suffix, it was highlighted that the INN Group does not necessarily always achieve the perfect solution but that it should make progress with this area and be prepared to make further adjustments if need be.

SCHOOL of INN

The Chair of the School of INN (SoINN) steering committee reported back from its 17th meeting, held the day before the start of the 74th INN Consultation.

In addition to the original English, the SoINN website now has French, Spanish and Arabic versions; not all courses have been fully translated, but work is in progress.

Two courses are being updated, one on vaccines and one on monoclonal antibodies (mAbs). An introductory course on the Anatomical, Therapeutic and Chemical (ATC) classification system and the Defined Daily Dose (DDD) system will be prepared by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo. The 'Stem in a Pill' series, a learning tool of the SoINN, has been enriched with 5 new sheets since the previous meeting. Also, since the last meeting, two articles concerning SoINN and the activity of the INN Group have appeared in the WHO Drug Information, a WHO medicines newsletter. A future article could concern brand names and INN.

There are currently four pilot university sites that promote the SoINN. They have started publishing their experience of using SoINN courses and have participated in their translation. A web meeting with these centres is being planned for May with the aim of preparing a face-to-face meeting in September, which could also be open to other interested parties.

Overall, the SoINN is very active but is not a private body, and anyone is invited to join and bring fresh ideas; it is very stimulating work. The SoINN Chair thanked fellow members of the Steering Committee and others who had contributed considerably to the working of the SoINN website especially the INN Programme IT manager.

COLLABORATORS' UPDATES

Agência Nacional de Vigilância Sanitária (ANVISA), Brazil

ANVISA is the Brazil National Health Surveillance Agency with a responsibility for the Brazilian Pharmacopoeia. Since the previous INN meeting in October 2021, the DCB (Denominações Comuns Brasileiras) Committee has held three meetings in December 2021, and in February and March 2022. Overall, it approved 49 new names, including 15 excipients, three vaccines and two medicinal plants.

International Union of Pure and Applied Chemistry (IUPAC)

Very recently, the latest version of the Blue Book (on Nomenclature of Organic Chemistry), with all corrections and modifications, became available:
https://iupac.qmul.ac.uk/BlueBook/PDF/

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since last October, the Japanese Accepted Names (JAN) Expert Committee took place virtually two times, and 11 names have been published. The Japanese Pharmacopoeia (JP) 18th edition was implemented last June and its English version was published this March. The English version can be freely downloaded from the website.
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066597.html

Therapeutic Goods Administration (TGA), Australia

In March 2022, the TGA registered a number of new prescription medicines including one COVID treatment EVUSHELP (*tixagevimab*/*cilgavimab*) - approved for the treatment of pre-exposure prophylaxis of COVID-19. Other COVID-19 therapies (excluding vaccines) that have been provisionally registered since the pandemic began include:
-*molnupiravir* (LAGEVRIO)
-*nirmatrelvir* + *ritonavir* (PAXLOVID)
-*regdanvimab* (REGKIRONA)
-*tocilizumab* (ACTEMRA)
-*casirivimab* + *imdevimab* (RONAPREVE)
-*sotrovimab* (XEVUDY)
-*remdesivir* (VEKLURY)
A list of prescription medicines approved or under evaluation by the TGA is available on the TGA website.
https://www.tga.gov.au/prescription-medicines-applications-under-evaluation
https://www.tga.gov.au/prescription-medicines-registration-new-generic-medicines-and-biosimilar-medicines

Consultation on repurposing of medicines closed on 1 April 2022. Repurposing medicines is the process of identifying potential new therapeutic uses (or 'indications') for older medicines through new research and evidence. This includes indications where a public health benefit has been identified, including indications that are:
a) already approved overseas
b) for a less common disease

c) already accepted clinical practice albeit 'off-label' and
d) likely to be less commercially profitable.

The intention of this consultation is to inform the development of options for Government on how to overcome potential barriers and better facilitate repurposing of medicines.
https://www.tga.gov.au/consultation/consultation-repurposing-medicines

Finally, after almost 30 years in its current location (Symonston, ACT), the TGA has commenced relocation to its new purpose-built site in April 2022 at Fairbairn near the airport.

United States Adopted Names (USAN)

The 2021 winter USAN Council meeting took place virtually on December 3, 2021. Names for 41 drug substances were reviewed and discussed. Eleven new stems and infixes were approved and added to USAN's stem list. Twenty-three new INN applications and 2 revised INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 74th INN Consultation.

Through March 2022, USAN staff will have processed, researched, and made recommendations for 80 USAN applications and forwarded this information to the USAN Council for their review and selection. During the same time frame in 2021, 75 applications were processed. Also through March 2022, 61 USAN will have been adopted. Revenue was realized for an additional 6 negotiations. Currently, there are approximately 150 active USAN negotiations.

The 2022 summer meeting of the USAN Council is scheduled for the first full week of June 2022 and will be a virtual meeting.

United States Food and Drug Administration (FDA)

There was no new specific FDA news on nomenclature and guidance. Non-critical missions are not yet being approved but hopefully by October, for the next Consultation, that will change. Two persons who will ultimately replace the current FDA representative at the INN Consultations have been identified and will shadow the incumbent over the next couple of years.

United States Pharmacopoeia (USP)

The USP Dictionary of USAN and International Drug Names has been released online with exciting new features and a new user interface. It is based upon the Global Substance Registration System (G-SRS) and can be searched by stems, non-proprietary adopted names, UNII codes along with many other features.

World Customs Organisation (WCO)

Part of the continued cooperation between the INN Programme and the WCO is the WCO presence at these Consultations. The WCO representative reported that since the last INN Consultation in October, the Scientific Sub-Committee (SSC) discussed at its 37th session in January this year, the classification of 154 products listed in the proposed INN List 124, and the classification of 226 products from the WHO proposed INN List 125 and 125 Covid-19 (special edition). The Harmonized System Committee approved during its 69th Session in March 2022, the classifications proposed by the SSC involving approximately 380 substances from INN Lists 124, 125 and 125 Special Edition. Proposed List 126 was received in February from WHO for classification. The WCO Secretariat will start compiling the classification opinions from its members to discuss the classifications of these substances and substances from INN List 127 that should be available in September 2022. The classification

of these substances will be discussed by the SSC in January 2023. The INN Secretariat will be invited to participate in these discussions. The WCO expressed its gratitude for the dedication of the INN Experts and associated colleagues in this work.

The Chair similarly acknowledged the work of the WCO and appreciated the collaboration between it and the INN Programme.

CLOSE of MEETING

Dr Clive Ondari thanked the INN Secretariat for the preparatory work, the participants of the meeting for their input, and the Chair for steering the meeting through so many requests and the discussion of policy matters, adding that the ADG is keen to receive feedback on the meeting. He was also grateful for the initiation of the concept note on the BQ, which is of great interest to other colleagues.

The Chair acknowledged the BQ discussion and that the concept note had been approved by the Group. A significant number of both biological and chemical requests, which are getting more and more complicated, had indeed been dealt with, and a new scheme for naming specific vaccines had been approved that had the potential to be applied to other vaccine substances.

The Chair commended everyone for their contributions and looked forward to seeing everyone around the table at the next Consultation; this would be much better than online although for anyone not able to travel, virtual attendance would still be available.

Dr Balocco thanked the Chair, Vice-chairs and rapporteur, and all those participants who had to attend late at night or very early in the morning. She expressed her gratitude to her team who do a great job and to the IT manager for running the virtual meeting.

Next Meeting

The 75th INN Consultation will be held in Geneva (all going well) on 18-21 October 2022.

OPEN SESSION for INN STAKEHOLDERS

74th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

(a hybrid meeting with some participating virtually and some present at WHO HQ, Geneva)

Geneva, 5 April 2022

Participants to the Open Session for INN Stakeholders being held as part of the 74th INN Consultation were welcomed by Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products Raffaella, on behalf of the ADG and Dr Clive Ondari, Director, Health Products policy and Standards. This was a hybrid meeting with the Chair, Vice-chairs and Rapporteur of the Expert Group, the Chair of the School of INN, and some members of the Secretariat present at WHO HQ in Geneva, and with all other participants including the Stakeholders attending virtually. For those present in WHO certain Covid restrictions such as mask wearing remained in place but Dr Balocco hoped that WHO will relax these measures later in the year prior to the next Consultation. It was noted that with only three presentations, there should be plenty of time for questions and discussion. This was an Open Session for stakeholders, but was not open to the outside world and the discussion and data presented by stakeholders should remain confidential until the agreed proceedings of the meeting get published on the WHO website.

Prof. Sarel Malan, Chair of the INN Expert Group, also welcomed the stakeholders and fellow members of the Group. It was a privilege for him to be in Geneva and hoped that the entire Group would be here for the next Consultation. These Open Sessions are enjoyed by the Group; the data presented is taken to heart and whilst stakeholders may not get the result they desire, the Group does consider very much what is presented.

Northwest Biotherapeutics

Northwest Biotherapeutics is developing a cancer treatment, DCVax-L, based upon autologous dendritic cells (DCs) pulsed with autologous tumour lysate from a patient's tumour. The company requested an INN for the cells at the 73rd INN Consultation; however, the request was deferred for more information to be provided by the company regarding the preparation of the cell lysates and the tumour types being investigated. The company presented further data at this Open Session to clarify their process and product development.

The tumour lysate is derived by controlled freeze-thaw of surgically removed tumour tissue regardless of the nature or origin of the tumour. The lysate contains proteins of cytosolic, nuclear and membrane origin; most of them will be shared between different patients and different tumour types but will also contain tumour specific antigens. The lysate is loaded onto autologous dendritic cells (DCs) derived by leukaphoresis with minimal use of supplementary agents and no genetic modification. The immature DCs endocytose proteins from the lysate and process them to peptides which DCs select for presentation to T cells. Thus, the DCVax-L final formulation is a suspension of autologous, antigen-loaded monocyte-derived dendritic cells for induction of relevant anti-tumour immune responses.

The most advanced study, at Phase 3, is for brain cancer with other studies in progress for ovarian, breast, thyroid and oesophageal cancers, and Merkel cell carcinoma. The dendritic cells in DCVax-L present the tumour-associated antigen peptides (originating from the lysate) to T cells in the patient after administration. The T cells become reactive to these peptides, proliferate, circulate and attack and lyse both primary tumours and metastases. This mechanism of action is independent of tumour type and for induction of relevant anti-tumour immune responses, heterogeneity between patients is as important as heterogeneity between tumour types.

The company noted that the INN Expert Group had used the infix/suffix combination *–dencel* for other dendritic cell therapies that have not been genetically modified, such as *audencel* (115/77) and *ilixadencel* (116/78) and requested the INN Group to assign a similar *-dencel* name, chosen from the candidate names submitted by the company.

In response to questions, the company clarified that the cells do not comprise a cell line and with regard to the presence of non-protein antigens, the company did not have any relevant data. With regard to the level of heterogeneity between patients and if this was more similar if from the same type of tumour, the company had not yet undertaken such studies but planned to do so.

Janssen

At the 73rd INN Consultation, a request from Janssen for an INN for their Adenovirus based Covid-19 vaccine was considered. The company had submitted names with the suffix *-virvec*/*-viravec* to indicate the viral vector nature of the vaccine substance. However, the INN Expert Group proposed a two-word name *ibacovtogene lomadenovec* based upon the INN gene therapy nomenclature scheme. The company disagreed with this and made representation at this Open Session to explain and re-request a distinct one-word name.

The company highlighted that viral vector vaccines share their mode of action with Covid-19 mRNA vaccines in that a gene encoding the SARS-CoV-2 spike protein is introduced into cells leading to an immune response, but that mRNA vaccines are not designated as gene therapy. Furthermore, the name *Ibacovtogene lomadenovec* was felt to be too long and too complicated for implementation and easy use by prescribers for a vaccine used world-wide. Other adenovirus-based vaccines would end up with similar INN posing a risk of error in prescribing and a short additional syllable for variant Covid-19 vaccines would only add to their complexity. There were also practical issues of getting a long name onto labels on the small vials used for vaccines.

However, the main concern of the company was the designation of the vaccine as a gene therapy medicine. The EU has designated gene therapy to involve the administration of a nucleic acid for "regulating, repairing, replacing, adding or deleting a genetic sequence" and specifically exclude "vaccines against infectious diseases". Adenovirus-based vaccines aim to stimulate an immune response, are transient and do not integrate into the host genome. Taking all the above into consideration, especially that their vaccine is not a gene therapy medicine, the company requested the Expert Group to reconsider the previously submitted names, or not implementing an INN at all.

In discussion, a member of the Exert Group explained that the Gene Therapy Working Party of the EMA had coined the phrase 'gene transfer' in place of 'gene therapy', and defined the

characteristics of such substances, in order to capture the broad use potentially being made of recombinant DNA medicines. However, due to the considerable differences in use and safety assessment of gene therapies versus vaccines it was ultimately decided that vaccines against infectious disease should be excluded from gene therapy, as indeed had been highlighted by the company.

Noting that application for an INN was voluntary, the Company was also interested to know that if they were not in agreement with the name, the request could be withdrawn. It was explained that a proposed INN would indeed not be published if the applicant was not in agreement. However, if a similar request is made to an alternative naming body such as USAN, and USAN applies for an INN, any previous decision would stand. The company requested the Experts to think carefully about why vaccines should not be linked to gene therapies and the consequences of long complex names for patients and the prescribing of thousands of doses, especially in the event that a specific non-proprietary name for vaccines became mandatory in the future. The Chair acknowledged that all these points would be taken into consideration in the deliberation of the EG.

Alliance of Safe Biologic Medicines (ASBM)

The INN Experts were reminded of a 2021 ASBM poster 'A Review of Problems with Global Pharmacovigilance' that highlighted the lack of brand names in adverse event (AE) reports in many countries. The poster had generated considerable interest and the ASBM has since been invited to various forums to share their data. This has included the World Drug Safety Congress Americas in in Boston (2021), the World Biosimilar Congress Europe in Basel (2021), and the Festival of Biologics USA in San Diego (2021). The value of real-world evidence and international pharmacovigilance (PV) data has been a continuing theme at these conferences.

The Experts were reminded that many biosimilars and originator products share a common INN but are not fully identical. As an example, 11 *infliximab* substances were highlighted each with a unique brand name which varies from country to country and which can result in misattribution of AE's, inappropriate substitution, inaccurate patient records and inability to do targeted recalls. It was highlighted that the WHO itself has acknowledged that biologics PV along with a lack of a consistent nomenclature standard remain a concern, and it is the WHO itself that is uniquely situated to take the lead in creating a voluntary global nomenclature standard.

The Experts were further informed that this month (April 2022) Health Canada had issued a consultation document entitled 'Handbook for healthcare professionals on biosimilar biologic drugs' which highlights the importance of PV programmes and the need to distinguish AE's for biosimilars from other licensed products. The document acknowledges that there is wide variation in brand name recording in AE reports and emphasises the need for clear identification by recording the brand name and lot number, the non-proprietary name, and any other identifier such as the Drug Identification Number (DIN). But with no distinguishable non-proprietary name and with the brand name and DIN not always quoted (the DIN rarely), there remains a problem. The ASBM is currently undertaking a new survey of Canadian physicians regarding identifiers used in prescribing and AE reporting, and attitudes toward distinct nomenclature and international and regional harmonization, and will report the findings in due course.

In summary, the ASBM noted that it was a decade ago that the WHO recognised the need to improve biological PV and that a WHO survey in 2020 found that the lack of an international standard remains an issue of concern that can lead to PV problems. Several early supporters of universal distinct naming have gone their own way due to lack of WHO action, but have expressed willingness to harmonize should the WHO act. ASBM will continue to work with regulators worldwide to move a global nomenclature policy forward

In discussion, the ASBM was asked if they had looked at how the US FDA 4-letter suffix system for biologics is being used and how easy it is to remember a random code. The ASBM felt that it was too early to say, but that a naming scheme such as the WHO's Biological Qualifier with a 4-letter code is a relatively simple thing and greater use of non-proprietary names and batch numbers would enhance PV systems for biologics and biosimilars and also speed up adoption of these drugs.

The Chair added that the Expert Group is looking at how to progress naming for these biologics and that the concept that was developed previously, viz., the biological qualifier (BQ), will be taken forward and discussed at WHO management level. Thus, the continued presence of ASBM at these sessions has not been in vain.

Close of meeting

In closing the meeting, the Chair thanked the visitors for their presentations and the experts for their contributions, adding that the Expert Group will take onboard all that has been presented.