

**68th Consultation on
International Nonproprietary Names for Pharmaceutical Substances
Geneva, 2-5 April 2019
*Executive Summary***

Programme on International Nonproprietary Names (INN)

**Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva**

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EXECUTIVE SUMMARY

OPENING of the MEETING

The meeting was declared open by Dr Raffaella Balocco, Group Lead INN.

ELECTION OF CHAIR, VICE-CHAIRS and RAPPORTEUR

Prof. Sarel Malan was nominated and approved as Chair of the meeting. Dr Adrian Evans was nominated and approved as Vice-chair, Chemicals; Dr Karin Weisser was nominated and approved as Vice-chair, Biologicals. Dr James S Robertson was nominated and approved as rapporteur.

INTRODUCTORY REMARKS

The Chair thanked the Expert Group for approving his nomination and welcomed all to the 68th INN Consultation. He was especially grateful to the Secretariat for all the work performed between meetings. He was also aware of the effort required by the Experts in keeping on top of the work required of them prior to the meeting and expressed his thanks for giving up their time for that.

Dr François-Xavier Lery, Coordinator, Technologies Standards and Norms (TSN), added his welcome and provided some background for newcomers to the Consultation. He informed that his role was to support the work done by the Experts and by the INN Secretariat, to ensure that the necessary resources were available for the work and to coordinate with other TSN work-streams, e.g. the Expert Committee on Biological Standardisation (ECBS). The work of TSN is reliant on these Expert Committees, for which there is a core mandate from WHO, and the global guidance provided on INN (by the INN Expert Group) and biosimilars (by the ECBS) is an example of the excellent work accomplished and implemented. It is also important that the work of TSN is linked with other WHO groups such as on pre-qualification and safety of medicines, making use of INN where appropriate in pharmacovigilance and the regulation of medicines.

Dr. Mariângela Batista Galvão Simão, Assistant Director-General (ADG) for Drug Access, Vaccines and Pharmaceuticals, was pleased to attend such a high-level Expert Committee and was grateful for the rare opportunity to listen to some of the discussion. The INN is a WHO entity and has a long and virtuous history that helps shape access to medicines. That INN are widely used and globally accepted is based upon the strength of work of this Committee. The ADG informed the Experts of a major restructuring process taking place within WHO. In 2018, the WHA approved a new 5-year strategy to make WHO more fit for purpose. One important change is that regional directors will be elected by member states within that region, giving regional offices much more autonomy. There is also a need to ensure a strong global agenda for safe medicines and in the new structure there will be a one-stop shop for health products with INN forming an important backbone for this. The ADG was also impressed by the amount of work the Experts had to get through during the Consultation and the changing profile of the substances being named, for example, the increase in biological substances, and had observed this same change in the medicines being assessed by the Essential Medicines List Group, with 50% of them being biological. In closing, the ADG highlighted that INN remains a backbone of access to medicines.

Dr Raffaella Balocco, welcomed all participants to the 68th INN Consultation and, as Secretary of the INN Expert Group, expressed gratitude for the work done by the INN Expert Group between the Autumn and Spring INN Consultations and the invaluable support of the INN Experts to the WHO INN Secretariat.

67th EXECUTIVE SUMMARY

The Executive Summary of the 67th INN Consultation was tabled and adopted, with thanks to the rapporteur.

NOMENCLATURE of INN

During the 68th INN Consultation, a total of 182 INN requests were discussed, including:

- 152 new INN requests, including 81 for biological substances
- 27 outstanding requests
- 3 previously selected proposed/recommended INN, against which a formal objection had been raised.

As a result of these discussions, 163 names were selected, which are planned to be published in List 122 of Proposed INNs (p.INN), while 13 requests were deferred for future discussion. Five requests were rejected by the INN Expert Group, as the substance did not conform to the criteria for INN selection. Two amendments were planned to be published in a forthcoming List of p.INN; one request was withdrawn.

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

Scaffold proteins nomenclature

Nomenclature to be used for scaffold proteins (also known as binding proteins from non-antibody proteins or antibody mimetics) was discussed. At the 64th INN Consultation, the INN Expert Group selected the name *eftaltermant alfa* for a human fibronectin tenth type III domain variant fused to an Fc fragment, making use of a new USAN Council suffix *-termant* for ‘antagonists of TGFs’. However, during post-meeting comments phase following the Consultation, the name was changed to *talditercept alfa*, i.e. making use of the *-cept* stem for receptors. This was done in full awareness that the substance is an artificial or engineered decoy receptor and that the definition of the *-cept* stem would have to be modified to include the term ‘synthetic’. USAN agreed to this change and so the new definition for the *-cept* stem became: receptor molecules or membrane ligands, native, modified *or synthetic* (change highlighted in italics) and this was published in the INN Stem Book 2018. However, an objection was raised against *talditercept alfa* on the grounds that this protein fits into so-called scaffold proteins for which the novel suffix *-par* had already been used for *abicipar pegol* (108)(70) and an alternative INN *eftalditerpar alfa* was proposed; this also meant the definition for the *-cept* stem could revert to its original, i.e. removing the term ‘synthetic’.

In discussion of the use and assignment of the suffix *-par* for scaffold proteins, the Expert Group was informed that there are numerous varieties of scaffold proteins on the horizon, most of which have more than one biological function and so to name them based upon mode of action would be somewhat futile. There was general agreement then to use a short defined suffix for them, but since so many scaffold proteins were on the horizon, the *-par* suffix was felt not to be best as it was too close to the INN *seladelpar* (115)(77) and *fonadelpar* (114)(76) and to the pre-existing stems *-parcin*, *-parib*, *-parin* and *-parinux*. The resulting discussion identified the syllable *-bep* as a distinct novel suffix that could be used for “binding engineered or synthetic protein scaffolds, non-immunoglobulin variable domain derived”. In addition, the

infixes that are used in mAb nomenclature, e.g. *-ci-* for cardiovascular and *-li-* for immunomodulating, would also be used in this terminology.

During the 68th INN Consultation, 5 names were created using this new *-bep* suffix.

SURVEY on the USE of INN in MEMBER STATES

Results from a survey conducted by the INN Secretariat on the use of INN in Member States (MS) were reported. These were not the final results as data were still being collected. There were four main types of questions covering the direct use of INN, interchangeability, branding and marketing.

Fifty-one MS completed the questionnaire; although this represented a minority of the MS, the respondents covered a majority of the world population. In addition to the INN, some MS also have a national naming system, e.g. China, USA, Japan and UK; all such national bodies work closely with the INN Programme. From the data gathered so far, there were several significant take-home messages: (i) INN are well implemented in MS, (ii) the use of INN is linked to substitution by the pharmacist, (iii) INN prescribing can facilitate existing pro-generic reimbursement or supply policies, (iv) pro-generic policies correlate with high penetration of non-originator products and reduced prices, (v) in most MS the INN only is not sufficient for prescribing biological therapeutic products, (vi) INN are widely used for reporting adverse events, and (vii) INN labelling is essential to reducing information asymmetry and is well accepted.

In discussion, it was noted that whilst India was one of greatest sources of generics, prescribing focused on brand names. However, in India, the INN itself or a very small modification of it, is often used as the brand name, and the Secretariat is working with Indian authorities to combat this infringement. It was also noted that the payer, e.g. medical insurance, often determines which brand gets purchased.

It was also commented that in the UK, the interchangeability policy sometimes had to be overlooked for some forms of active substances, e.g. if part of a device, or if it were in the interests of the patient. Indeed, the study itself showed that in some cases, interchangeability of certain medical groups, e.g. anticoagulants, was forbidden, and in others where substitution was not allowed it was usually in extreme cases, e.g. potential allergy of an excipient. Indeed, many MS had a mechanism by which a patient could be taken out of a general interchangeability policy.

Tunisia was highlighted as a good example of a MS with good generic penetration and a Tunisian participant of the Expert Group offered to assist the Secretariat in collecting additional data from that region of Africa, which the Secretariat would very much appreciate.

Dr Lery, TSN coordinator, pondered how to make best use of the data, whether to share data across WHO, e.g. with the pharmacovigilance group, and suggested that at some stage the review could be linked with intelligence from other WHO colleagues to assess the impact on access.

SCHOOL of INN

Since the 67th INN Consultation, the School of INN (SoINN) has met twice, once in Madrid in December 2018, and again in the afternoon before the 68th Consultation. Two main topics had been addressed: (i) finalising the modules for the online teaching programme, and (ii) establishing pilot sites for the teaching modules. In Madrid, the steering committee also visited the nearby Universidad de Alcalá where the members gave short presentations of the SoINN

and its purpose to the staff of the Pharmacy Faculty; the staff were very interested in the project and keen to be involved.

Three levels of collaboration of stakeholders with the SoINN are conceived: (i) Friends of INN, for corresponding stakeholders, (ii) pilot sites, in which the stakeholder would be actively involved in organising training courses using the online modules, and (iii) Collaborating Centres. Collaborating Centres (CCs) are officially approved WHO centres that provide significant and constant contributions in terms of study, proposals and activity, and only get appointed through a long selection procedure, described in a WHO guideline. Only a few CCs for SoINN/INN would be expected to be established.

Pilot sites would be involved in translating SoINN teaching modules and work is already underway to translate them into Spanish and French, at universities in Barcelona and Grenoble, respectively.

For the teaching modules, digital voice-overs of the presentations have been created electronically, with surprisingly high-quality results, and INN Experts were requested to access the courses online and provide feedback. It is planned for the online courses to go live later this year in pilot universities in Cape Town in South Africa, Barcelona in Spain and possibly in Singapore. Ultimately the courses will be in all six UN languages and collaboration with those who can assist in translation is being sought. Regional WHO offices and others may be invited to listen to the presentations. Recently, the WHO Director-General elaborated on a virtual academy for WHO and the SoINN would most likely be part of this. Also, the INN Secretariat will be presenting SoINN at a conference in Monastir in Tunisia and collaborations would be sought for translating the courses into Arabic.

On the publication front, a booklet developed by members of the SoINN on “Learning clinical pharmacology with the use of INNs and their stems” has been published by WHO. The publication has been exceedingly well received in various quarters and the authors were highly congratulated.

Two manuscripts, entitled “The Science of Nomenclature – a global language for drugs” and “The INN Global Nomenclature of Biological Medicines: a continuous challenge” have been submitted for publication and responses are awaited.

GLOBAL SUBSTANCE REGISTRATION SYSTEM (GSRS): SOFTWARE, IMPLEMENTATION and DATA

Regulators and industry stakeholders have struggled to efficiently and accurately exchange information about what substances are in any given regulated product and Dr Frank L Switzer of the US FDA gave a presentation on the Global Substance Registration System (GSRS). US NIH's National Center for Advancing Translational Sciences (NCATS), US FDA's Office of the Chief Scientist and the European Medicines Agency (EMA) have partnered to develop the GSRS to facilitate this process. Instead of relying on names, which vary across regulatory domains, countries and regions, GSRS enables substances to be defined by standardized, scientific descriptions. All ingredient substances can be classified as chemical, protein, nucleic acid, polymer, structurally diverse, or mixture as detailed in ISO 11238 and DTS 19844. GSRS is ISO-compatible open-source software developed to globally extend the SRS system that FDA has used successfully for over a decade in support of electronic listing. GSRS includes ISO 11238 substance and specified substance data structures necessary for regulatory purposes along with robust cheminformatic and bioinformatic toolkits and integration with multiple database platforms.

GSRS generates FDA's Unique Ingredient Identifiers (UNII)s used in electronic listing and other regulatory activities throughout the regulated product life cycle. FDA created SRS and the UNII because no other code system met the agency's regulatory needs. UNII)s can be generated at any time in the regulatory life cycle for any substance from an atom to an organism. Two public UNII datasets currently exist: a flat file and simple search developed for electronic listing submitters hosted by US NIH's National Library of Medicine (<http://fdasis.nlm.nih.gov/srs/>) and a public GSRS instance hosted by NCATS (<https://ginas.ncats.nih.gov/ginas/app/>). Active GSRS instances are also known to exist at the US Pharmacopeia, Health Canada, BfArM in Germany and CBG-MEB in The Netherlands.

The current public datasets contain over 100,000 UNII)s linked to over 1,000,000 terms and codes including identities associated with the vast majority of published INN, USAN and JAN substances. UNII)s are also included as identifiers in published USAN adoptions. The public GSRS at NCATS also contains concept records where a UNII is not available. FDA's internal GSRS instance also associates substances with FDA applications, clinical trials and adverse event reports. Approximately 1000 new UNII records are added each month by FDA staff and associates, and GSRS is fast becoming the global source for regulated substance identity information.

COLLABORATORS' UPDATES

British Approved Names (BAN)

The most recent BAN publication was BAN 2017 Supplement 3 which contains those materials new to the EU/UK market. There were 35 new entries in the supplement, comprised mainly of INN that were granted a licence for the first time by EMA. This number related to approximately 10% of INN that were assessed in the preceding 12 months and was a good indicator of the number of INN that eventually received a licence for use.

It was also noted that the EMA had now published the Article 57 database for public viewing on their website (a listing of every product available within the EU). This strengthens pharmacovigilance within the EU as it includes the contact details of product owners that would receive any comments on the individual products. This database also contains the brand name and INN for each product and was proving to be invaluable for groups interested in coining new safe names.

European Directorate for the Quality of Medicines (EDQM)

In July this year a conference will be held at the EDQM in order to mark the publication of the 10th Edition of the European Pharmacopoeia. Every 3 years, all of the texts are republished in a single new edition, now in 3 volumes. It's an opportunity to make systematic revisions and harmonisations to many texts at once, so there are always a lot of updated texts in a new Edition. The conference will also mark the 25th anniversary of the establishment of the General European OMCL Network (GEON), which is the network of the Official Medicines Control Laboratories, and the 25th anniversary of the Certification of Suitability to the monographs of the European Pharmacopoeia (CEP).

OMCLs are independent public institutions that support national authorities in a range of tests on medicinal products; they share data, expertise and laboratory resources. The Network is co-ordinated by the EDQM, and includes over 70 OMCLs from over 40 countries. It covers a wide range of activities related to ensuring the quality of medicinal products throughout their lifecycle, from pre-authorisation testing to post-marketing surveillance; they work with customs and law-enforcement agencies to combat falsified and illegal medicines; they help

develop testing methods and establish reference standards. Their work reduces the risk to patients of exposure to defective, falsified and illegal products.

The EDQM's CEP inspection programme is an integral part of the Certification procedure (whereby manufacturers submit dossiers to the EDQM that are assessed for their compliance with the requirements of the European Pharmacopoeia standards) and checks compliance with both Good Manufacturing Practice (GMP) and the Certificate of Suitability (CEP) at the manufacturing and distribution sites covered by the CEP (i.e. they are not limited to Europe). Inspections are normally carried out by teams composed of an official inspector from the competent authorities and an inspector from the EDQM. They typically last 3 days. About 40 on-site inspections and re-inspections are performed every year, and are carried out following risk assessments and EU recommendations.

Finally, 2019 marks the 70th anniversary of the Council of Europe, which is the parent organisation of the EDQM. On 5 May 1949, the Treaty of London was signed by Belgium, Denmark, France, Ireland, Italy, Luxembourg, Netherlands, Norway, Sweden and the United Kingdom, founding the Council of Europe. Europe had experienced centuries of war, and both politicians and citizens were looking for a way to prevent any new descent into conflict. The 10 founding members of the Council of Europe have now expanded to 47 member states and 6 observer states, with the main aim of upholding human rights, democracy and the rule of law. The Council of Europe co-operates with many international organisations, including of course the European Union and, since 1951, has developed close ties with the United Nations. Indeed, the European Convention on Human Rights that was signed in 1950 was based on the United Nations Universal Declaration of Human Rights that had been adopted 2 years earlier. The work of the Council of Europe has increased considerably over the years, covering (among many other subjects) social and cultural rights, monitoring of elections, promoting international youth interaction, combatting cybercrime, even fairness in sport via its anti-doping convention.

Access to good quality medicines and healthcare is considered to be a basic human right, hence the EDQM's place in the Council of Europe. Since the creation of the European Pharmacopoeia on 22 July 1964, the range of healthcare issues has expanded considerably, and there are currently 39 members (38 countries and the EU) and 30 observers, including the WHO.

International Union of Pure and Applied Chemistry (IUPAC)

IUPAC's publication Nomenclature of Organic Chemistry, commonly referred to as the Blue Book, has an extensive list of corrections and by July (2019), when the project team next meets, the list of corrections should be complete except for those that the working party will consider at its meeting.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

This January, the Division of Pharmacopoeia and Standards for Drugs was transferred from the Office of Standards and Guidelines Development to the Office of Review Management within PMDA. The Division continues to be responsible for preparing the Japanese Accepted Name (JAN) and the Japanese Pharmacopoeia (JP).

Since October last year, the JAN Expert Committee has met 3 times. Twenty-five names have been published including 2 biosimilars; the second biosimilar of *etanercept* and the first biosimilar of *bevasizumab*. Recently, MHLW/PMDA received the first application for an antibody without a "source infix". However, as most applicants of JAN submit applications after receiving an INN, MHLW/PMDA continue to receive applications with a "source infix" and publishing the names according to their INN.

In two months' time, Supplement 2 to the 17th Edition of JP will be published.

Therapeutic Goods Administration (TGA), Australia

The TGA approved its first CAR T-cell product (Kymriah, Novartis) in December 2018. Consistent with the trend of INN requests over the last few years, it expects this to be the beginning of a cell/gene products wave.

Following on from this development, the Australian government launched a \$105 million Centre of Excellence at the Peter MacCallum Centre in Melbourne with an ambition of making it a global hub in cellular immunotherapy. The expectation is that more patients will have access to clinical trials (and treatment) with this and similar advanced immunotherapies.

The TGA also approved six more biosimilars in 2018 (which is a record for a year) and has approved two more since January. This now takes the number of biosimilars at the TGA to over 30 (including additional trade names).

Implementation of the Medicines and Medical Devices Review recommendations is now largely complete. For prescription medicines, the TGA now has pathways for priority and provisional approval, use of comparable overseas regulators reports and, in limited cases, workshare with overseas regulators.

Finally, since 2018, in reporting adverse events and in the absence of an international BQ suffix, the brand name must be quoted, and any new biologic coming to the TGA must have a brand name

United States Adopted Names (USAN)

The 2019 winter USAN Council meeting took place on January 17-18 at Palm Beach Gardens, Florida where names for 31 drug substances were reviewed and discussed. Nine new stems and infixes were approved and added to USAN's stem list, four stems were revised and one stem definition was revised to harmonise with the INN Programme. Policy discussions included infixes to use with the '*-rsen*' stem and the ISMP Medication Safety Alert of November 29, 2018.

Seven INN applications for proposed USAN were prepared and forwarded to the INN programme to be discussed at the 68th INN Consultation.

Through March 2019 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 March 2019, 57 USAN will have been adopted for 2019 and revenue was realized for two additional negotiations. Currently, there are 143 active USAN negotiations.

The USAN Program and staff were featured in AMAToday Spotlight Feature in February.

The 2019 summer meeting of the USAN Council is scheduled to occur on June 13-14 at the American Pharmacists Association headquarters in Washington DC.

United States Food and Drug Administration (FDA)

In the previous month, the FDA published new draft guidance on the naming of biological substances; this is not final but is published for comment. It states that the FDA will continue to assign four-letter suffixes to originator biologics under a BLA as well as to biosimilars, interchangeables, and similar biologics (under a BLA). However, the FDA will not assign suffixes to already approved biologic drug substances, nor to transition products, i.e. substances considered biologics but approved under the Food, Drug and Cosmetic Act, e.g. hormones and insulins.

There have been 173 approved biologic drug products including 86 monoclonal antibodies, 12 of which are biosimilars. Twelve biologics have so far been named using the FDA four-letter suffix. Applicants have the opportunity to submit 10 four-letter options, with no underlying meaning, and one will be appended by hyphen to the USAN, but only in the name of the product. Vaccines, cell therapy products and coagulation factors are not included in the suffix system so products authorised by CBER are unlikely to be given a suffix.

Finally, the FDA Commissioner resigned recently and currently there is a stand-in.

United States Pharmacopoeia (USP)

The USP Dictionary of USAN and International Drug Names was published in January, and this is the second online-only edition of the publication.

The USP has also been working in the GSRS platform to enhance the development and maintenance of accurate, up-to-date chemical information.

Finally, the USP has created a team to focus on enhancement of the presentation of chemical information in compendial publications.

World Customs Organisation (WCO)

The WCO has close cooperation with WHO as INN classification is used to distinguish pharmaceutical from chemical products, with many countries having a zero customs rate for pharmaceuticals compared to chemicals with a higher rate.

The Harmonised System (HS) is a multipurpose nomenclature for trade, and is one of the most successful instruments developed by the WCO. The Harmonisation Committee recently finalised its 5-year review for 2022, planning ahead to let government customs agencies have time to review the updated classification system. Within the 21 sections and 97 chapters of the HS, many countries develop their own multi-digit numbers for classification and require considerable time for translation, legal approval and setting new tariffs and trade levies.

The WCO is very grateful for the support received by the WHO INN Programme and the presence of a member of the INN Secretariat at annual WCO Scientific Committee meetings to help classify pharmaceuticals.

On May 2-3, 2019, there will be a WCO Conference on the future direction of the Harmonized System at WCO headquarters in Brussels for all stakeholders including customs officers, traders, statisticians, academics and policy makers, to express their views on what is needed for a 21st century Harmonized System.

WHO Collaborating Centre for Drug Statistics Methodology, Norway

In a recent re-organisation, the Collaborating Centre (CC) moved within the Norwegian Institute of Public Health from the Division of Mental and Physical Health to Drug Statistics in the Division of Health Data and Digitalisation. The CC has 8 staff, some full time, some part-time, but with retirement of experienced staff, effort is going into training new comers.

In the past year approx. 70 new Anatomical Therapeutic Chemical (ATC) codes, including 20 for combinations, were created along with more than 50 Defined Daily Doses (DDD) with about 10 for combinations. Twelve new DDDs for antimicrobials were established, as the CC is now collating data on antimicrobial resistance (AMR), collaborating with WHO Europe in assessing CAESAR project data from E Europe and Asia, and also with ECDC on European data. The Centre is also involved in AMC work in connection with the WHO global action plan on antimicrobial resistance.

Some ATC groups are reaching capacity (there is a maximum limit of 90 ATC 5th levels for human medicines per group) and so further sub-divisions are required, for example, protein kinase inhibitors need to be subdivided. Monoclonal antibodies may need to be subdivided also in the future. There are not too many gene and cell therapy products but it is a great advantage with INN for these products since the “generic names” for these types of substances are long and not user friendly for the ATC system; codes will not however be assigned to these until they are marketed.

World Intellectual Property Organisation (WIPO)

At end of 2018, WIPO and WHO concluded an agreement to share information on INN via their websites. It took some time to negotiate and settle the final legal points of the agreement but now TradeMark (TM) offices and WIPO have direct access to WHO INN and this enables them to better monitor newly applied for TM's. This is a unique partnership and shows how important it is that UN organisations work together and facilitate sharing information for members. The agreement will continue to be improved and webinars will be used to show how information can be searched. It will also be useful to the INN Committee as a way to search TM's.

IDMIS UPDATE

A new improved cloud-based sharing system within IDMIS, the INN Programme's online work tool for the Experts and the Secretariat, was demonstrated. The Experts were also reminded that when providing comments on applications, both pre- and post-meeting, it was mandatory to do so via IDMIS.

CLOSE OF MEETING

The Chair thanked all present for their input and wished them all safe travel home. In return, the Chair was thanked for his conscientious chairing of the Consultation.

Next meeting

The 69th INN Consultation will take place in Geneva at WHO HQ on 22-25 Oct 2019.

SESSION for INN STAKEHOLDERS

68th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 2nd April 2019

OPENING REMARKS

Participants of the Open Session adjoining the 68th INN Consultation were welcomed by the Chair, Prof. Sarel Malan. He indicated that this was an opportunity for stakeholders to present on a topic of their choice but stressed it would be science that will influence the Experts and not emotion. The Group looked forward to learning from the stakeholders and help them make decisions.

Dr François-Xavier Lery, Coordinator, Technologies Standards and Norms (TSN), joined in welcoming participants to the WHO and expressed his appreciation of this interaction between stakeholders and the INN Expert Group. A major transformation of WHO had recently been declared by the Director-General and it was good that structures that work well will continue including retaining INN as a core activity of WHO, and strengthened if need be. The transformation will address how WHO interacts with partners and address sustainable funding in order to make WHO more efficient. The work of the INN Group on consistent naming of world medicines is very much appreciated and he wished all a good session.

Dr Raffaella Balocco, Group Lead INN, similarly welcomed the visitors and was pleased to meet those with whom she had corresponded over several months. She stressed that whilst the meeting is open to stakeholders, all matters discussed must remain confidential until the report in the Executive Summary is published.

KaNdy Therapeutics

KaNdy Therapeutics, UK, is developing a breakthrough non-hormonal treatment for multiple symptoms of the menopause including hot flashes and night-time awakening. Their small molecule drug, NT-814 is specifically designed to be a balanced antagonist of both neurokinin(NK)-1 and neurokinin(NK)-3 receptors. After a successful proof-of-concept trial, NT-814 is currently being studied in a Phase 2b multinational dose-ranging study in post-menopausal women suffering hot flashes called SWITCH-1.

The company name reflects the action of NT-814 on the KNDy neurons, located in the hypothalamus, which play a pivotal role in the hypothalamic-pituitary-gonadotrophin (HPG) axis that controls reproductive function and health, and which can also influence the regulation of body temperature. Hyperactivity of the KNDy neural network in menopausal women due to loss of estrogen production is hypothesised to cause the hot flashes and night-time awakening; these symptoms can be ameliorated by antagonising both NK-1 and NK-3 receptors with NT-814.

Based upon a multitude of experimental and clinical studies, including studies in guinea-pig brain slices, the gerbil 'foot-tapping' behavioural response, the guinea-pig 'wet dog shaking' behaviour, positron emission tomography clinical studies, and reduced levels of circulating levels of testosterone in human male volunteers, the company was able to demonstrate that NT-814 is an antagonist of both NK-1 and NK-3 receptors. The pKi of NT-814 for both receptors is very similar, in the nanomolar range, with no dominance of the effect on one receptor over

the other, indicating a balanced activity. Clinically, by targeting both receptors and dual blockade, it is hypothesised additional benefits (e.g. improved sleep) may be observed clinically compared to the effect of hitting just one receptor. This hypothesis is being tested in SWITCH-1.

Hence, the company is requesting a novel suffix *-neptant* for the INN for NT-814, that combines the *-ne-* of the NK-3 infix *-netant* and the ‘p’ from the *-pi-* of the NK-1 infix *-pitant*. With a suggested prefix of *elinza-*, the company respectfully requested the INN *elinzaneptant*. Such a unique suffix would reflect the dual activity of the drug.

Alliance for Safe Biologic Medicines (ASBM)

With an increasing number of biologics and biosimilars, the Alliance for Safe Biologic Medicines (ASBM) has met regulators from the US FDA and Health Canada (HC) on three occasions over the past year to discuss the need to improve confidence in the use of biosimilars. Key observations at these meetings were that biosimilars are critical to increasing patient access to biologic therapies and to controlling health costs and that unique and harmonised nomenclature is necessary to increase confidence in the safe use of biosimilars by promoting better pharmacovigilance globally.

At these meetings it was also agreed that leadership from WHO was essential to avoid proliferation of different naming systems. Following the publication by ASBM of a white paper on this topic, the UAE Health Ministry offered its support for the WHO BQ and for ASBM harmonising this effort, in the absence of which some regulators have moved away from the WHO scheme. However, in February 2019, HC announced that it would not follow a distinct non-proprietary naming policy and instead shared INN would cover multiple products alongside a reliance on the Drug Information Number (DIN) used primarily by pharmacists. This decision stems from an HC stakeholder consultation along with the lack of an internationally adopted naming scheme. The ASBM however was critical of the Canadian consultation in that the opinion of patients and physicians was underrepresented while an ASBM survey showed strong support among Canadian physicians for distinct naming.

The ASBM described the ‘Swiss Cheese Model’ for designing high reliability safety systems in which several layers provide protection against hazardous conditions becoming an accident, as used in air traffic control and nuclear power plants. Such a model can be used in naming medicines whereby each name contributes to prevention of errors happening. In an ASBM survey of Canadian prescribers, 20% used only the INN in patients’ records and only 1% used the DIN. In addition, only 23% consistently included the batch number and 20% never included it in adverse event reports. Overall, the data showed that cumulatively no approach was 100% effective and in the absence of distinct naming in about 20% of cases the specific medicine would not be identified. The ASBM also added that EU adverse event reporting data showing that 25% of reports for *infliximab* in 2018 did not specify the brand name despite this being required by law since 2012.

At the most recent meeting between ASBM and regulators, regardless of recent HC decisions, HC again emphasized the need for WHO leadership, a feeling echoed by the US FDA. The US FDA has also very recently announced that it will no longer require retrospective application of its four-letter suffix for biologics but that all new innovator and biosimilar biologics will continue to require the suffix.

The ASBM has concluded that in the absence WHO leadership, yet another regulator has developed its own system, that individual country-specific systems are not a substitute for a global pharmacovigilance system for biologics, and that regulators still want WHO to develop a global solution.

In discussion, Dr Lery stressed the importance of pharmacovigilance which is an aspect that goes beyond the INN Group, and highlighted the ISO IDMP (Identification of Medicinal Products) standards in pharmacovigilance reporting. ASBM however re-stressed the better value of a generic-type model plus a BQ to identify products as different organisations use different number coding systems, e.g. the DIN in Canada, which is good for billing but not for prescribing.

Dr Balocco highlighted the 2D barcode being developed within the EU in which a BQ code could be incorporated but added that some regulators had dismissed this approach because of the expense of, for example, having readers in all pharmacies.

Health-Bio-Pharm (HBP)

Health-Bio-Pharma (HBP) was founded in 2012 with an interest in the development of tissue, cell and gene (TCG) products. It participated in the Open Session to comment upon standards these types of substances. The use of TCG products in cellular immunotherapies, either autologous or allogeneic, with haematopoietic stem cells and mesenchymal stromal cells being most commonly used, was highlighted. TCGs can also be modified for personalised medicine, can be embedded in biomatrices or include co-factors. In regenerative medicine, current Good Tissue Practices (cGTP), cGMP and FACT-JACIE, a framework for quality managed programmes, allows for some traceability. Definitions for TCG products are variable and for simplicity HBP follows the US FDA guideline.

The fundamental traits of stem cells are self-renewal and differentiation, e.g. many millions of blood cells are renewed every day, all from stem cells that undergo differentiation. To avoid the ethical issues associated with embryonic stem cells, HBP activities in Switzerland are focused on adult stem cells. These activities make use of so-called bio-waste sources such as placenta, umbilical cord tissue and umbilical cord blood. The greatest use of TCGs has been in oncology although there is a growing use of mesenchymal cells in constructive medicine. A US database of cell therapy trials lists 157 ongoing trials ranging from cancers, to skin diseases, to reconstructive medicine, and 44 separate products are registered, although generally the trials take place in only a few countries such as USA, South Korea and the EU.

HBP is interested in there being a common language and having it disseminated. HBP finds the INN nomenclature for cell therapy substances to be very good, with specific cell designations. HBP would additionally like to see nomenclature that can be broken down into components, for example, allo- versus auto-, paediatric versus adult, the gene targeted, the viral vector and any cofactors, and if there is any manipulation. HBP did not know how feasible or complicated this may be, but was simply trying to apply logic in naming GT and CT products.

In discussion, the INN Secretariat outlined the evolution of the cell and gene therapy nomenclature schemes, which had been developed in collaboration with CBER and USAN, with the most recent adjustment being the use of *auto-* as a prefix for the second word of cell-based gene therapy substances. In addition, it was further highlighted that a continuing problematic issue is that of the definition of cell therapy substances to which HBP advised approaching international organisations involved in cell therapy to contribute to a common language in creating acceptable attributes.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

While IFPMA was represented at the Open Session, there was no specific presentation but IFPMA expressed its appreciation of, and support for, the work done by the WHO INN Programme in uniquely identifying medical substances.

CLOSE of MEETING

The Chair expressed his thanks to the stakeholders who are always welcome at these sessions and provide valuable information to the INN Expert Group.