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69th Consultation on

International Nonproprietary Names for Pharmaceutical Substances

Geneva, 22-25 October 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

69th Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

ELECTION OF CHAIR, VICE-CHAIRS and RAPPORTEUR

Professor Sarel Malan was proposed as Chair of the meeting, and this was agreed; Dr Akinola Adisa was proposed as the Vice-chair for Biologicals, and this was agreed; Dr Armand Blommaert was proposed as Vice-chair for Chemicals, and this was agreed. The rapporteur was Dr James S Robertson.

INTRODUCTORY REMARKS

The *Chair* welcomed all to the 69th INN Consultation and thanked the Experts for their vote of confidence in electing him as Chair. He expressed his appreciation of the informal nature of the Group and thanked the Experts, including the Rapporteur, and the Secretariat for their work both during and between meetings.

Dr Clive Ondari, acting Director, Essential Medicines and Health Products (EMP), thanked the chair and expressed his appreciation of the great wealth of knowledge and experience of the Expert Committee, which represents one of longest running activities of WHO. He highlighted the three strategic priorities of the 2019-2023 transformation of WHO called for by the Director-General (DG) and approved by the World Health Assembly (WHA). These are universal health coverage for 1 billion more people, health emergencies for 1 billion more people, and health and well-being for 1 billion more people, the so-called 'triple billion'.

To enable this, the EMP Division will be renamed *Access to Medicines and Health Products* (MHP) and have two major departments, a *Health Product Policy and Standards Department* (HPS) and a *Regulation and Prequalification Department* (RPQ). The INN Programme will be prominent within HPS with the title *INN Programme and Classification of Medical Products Unit*, and will include the ATC-DDD. This Unit will be led by Dr Raffaella Balocco. The INN Programme itself is a unique programme with a specific mandate; it needs space to grow and there needs to be flexibility in managing it. Also, within HPS is the *Technical Standards and Specifications Unit* with individual Teams within it covering vaccines and biologicals, blood products, and pharmaceuticals. This will be a key area for work on advanced therapies. There will also be a new division for Science, covering emerging technologies such as gene editing, along with ethical and regulatory issues, and it is anticipated that the INN Programme will be involved with it in the future.

Dr Ondari expressed his appreciation of Dr Balocco's ability in leading and managing the Programme and of the incredible amount of work achieved by the INN Secretariat despite it being such a small team. He is aware of the constraints in operation and the limitations in technology and facilities, and so he is seeking guidance and approval to improve a number of areas to create an improved environment for all concerned.

68th EXECUTIVE SUMMARY

The Executive Summary of the 68th INN Consultation was tabled and adopted, with thanks to the Rapporteur.

NOMENCLATURE of INN

During the 69th INN Consultation, a total of 200 INN requests were discussed, including:

- 165 new INN requests, including 95 for biological substances
- 32 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, 191 names were selected, which are planned to be published in List 123 of proposed INN (p.INN), while 7 requests were deferred for future discussion. One request was 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 of substitution could not be retained as it did not conform to the criteria.

Two new stems/substems were selected, 6 suffixes were promoted to the pre-stem list and it was decided to review the descriptions of 3 stems/pre-stems.

NOMENCLATURE ISSUES

Bi-specific anti-tumour mabs – a new infix?

Many bi-specific monoclonal antibodies are being developed for cancer therapy and the use of a specific infix *-bi-* (creating a *-tabimab* suffix) had been proposed. Bi-specific mAbs may bind two different membrane-bound targets or two different epitopes on the same target, two distinct soluble factors or one membrane-bound and one soluble factor. However, the Experts were informed that there is a myriad of multi-specific antibody-like structures under active development, including many alternative fragmentary structures and fusion proteins, and a strong argument against the introduction of a *-bi-* infix was that many mAbs may have more than two specificities and it would be unrealistic to introduce a new infix for each level of specificity. Even more crucial is that it is likely to be difficult to understand and define the full extent of specificities of many of these new formats, as this could depend on, for example, the Fc component, or IgG1 versus IgG4.

In discussion, it was highlighted that in order to free up more opportunities for distinct mAb names, the 'origin' infix had recently been dropped and the adoption of a new *-bi-* infix would be a retrograde step, increasing the difficulty in creating unique names. It was also felt that the number of available syllables will eventually diminish to the extent that creating acceptable unique names for mAbs will become impossible and creating a totally new stem for novel antibody structures may be required. A new stem would have to be quite distinct from *-mab* and would need a new definition. Problems could still arise through the availability of unique prefixes in front of an alternative stem although similarity in mAb names is also caused by the last 2 or 3 syllables and a new stem would free up some space for new names.

The Experts were informed that in p.List 122 (the most recent), the majority of mAb names are for conventional mAbs although there were a significant number of bi-specific mAbs encompassing a variety of formats. Currently, these are being named with a *-mab* stem and without a *-bi-* infix.

A mAb subcommittee has previously met to consider mAb issues and the Experts were advised that this could be re-activated in order for mAb experts to prepare a report for the INN Expert Committee on naming bi-specific antibodies and the possibility of a new stem.

Pegylated substances

Pegylation is performed to alter the pharmacokinetics of a drug substance and can occur at different sites of the molecule, be attached with different chemistry or be cleavable/non-cleavable. For each pegylated substance, the pegylated moiety will inevitably be different and currently there is no systematic way of naming them. Some INN for pegylated substances begin with the prefix *peg-*, some have a *-peg-* infix, and others have the second word *pegol*. INN with the *peg-* prefix are somewhat dominant but result in INN looking similar. The same active substances with alternative pegylation chemistry can be differentiated by using a further fantasy prefix before the *peg-* prefix but can result in overly long names. An alternative option is to use *pegol* as a second word although the disadvantage of this involves concerns about mis-prescribing by the second word being omitted. Overall, where an applicant is claiming a unique or alternative pegylation chemistry, to avoid overly long INN, the most appropriate format is probably a short fantasy prefix on the drug substance INN followed by *pegol* as a second word.

INN for micro-organisms

Assigning INN to naturally occurring micro-organisms that have therapeutic potential needs a dedicated group to consider nomenclature for such substances and a small working group is needed to prepare a concept paper to take this forward. It is unlikely micro-organisms would fall into an existing scheme/group and having a separate naming scheme was proposed. Markers that specify and define them would be required although at these early stages, the mechanism of action may not be understood.

CELL THERAPY SUBSTANCES

Introduction and current issues

An INN-USAN harmonised nomenclature scheme for cell therapy drug substances was approved by the INN Expert Group in 2016. INN for cell therapy substances comprise a one-word name composed of a fantasy prefix, an infix to identify the primary cell type[1], and the suffix *-cel*. A separate scheme using a two-word system is used for genetically engineered (GE) cells. To date approximately 20 INN have been assigned to non-GE cell therapy substances, with about twice as many assigned to allogeneic as to autologous cell preparations. Applicants for cell therapy INN are required to provide code names used for the cells, information on the cell source, phenotypic and secretory profiles, and a description of any manipulation; this Information is used to derive the Description. What has been observed however, is that some descriptions are very scant whilst others are highly similar. For example, haematopoietic stem cell descriptions generally state simply that the cells are derived from cord blood and are CD34 positive. Similarly, mesenchymal stromal cells, often derived for the same source such as bone marrow, display the same phenotypic markers, that is they are CD29, CD73, CD90 and CD105 positive, and CD34 and CD45 negative. This results in a lack of uniqueness amongst the descriptions of several distinct cell therapy INN and there needs to be further consideration of this.

Genetically engineered CAR-T cells

In contrast to non-GE cells, GE cells can be defined uniquely by the sequence of the transgene. More INN have been assigned to GE-autologous cells than to GE-allogenic cells, with there being a preponderance of CAR-T cell requests. The suffixes of the two-word names currently used for genetically engineered therapeutically active T cells are *-cabtagene* and *-leucel*, where

[1] See Bioreview 2019 for the current list of cell type infixes: https://www.who.int/medicines/services/inn/BioReview2019.pdf?ua=1

the *-cabta-* infix stands for cell expressed antibody and T cell activation (note that in this format, the *-ta-* is not an infix for 'tumour'). With most CAR-T cells being autologous in nature, this results in a proliferation of INN of the type ……*cabtagene autoleucel* and care is needed with fantasy prefixes to ensure these names are distinct from each other. Furthermore, with many different formats of the antibody part being developed, including fusion proteins, the Experts were warned against creating new infixes for novel designs of such CAR constructs as every conceivable structure and fusion will be made and if each is given a new stem or infix there would be an overwhelming number of unique infixes.

Mesenchymal stem/stromal cells

Mesenchymal stem/stromal cells (MSCs) are a source of adult cells for regenerative medicine and cell therapy applications, and are distinct from hematopoietic stem cells (HSCs). They can be sourced from bone marrow, adipose tissue or umbilical cord blood. Human trials of MSCs have increased dramatically in recent years encompassing a wide variety of clinical targets. Currently there are almost 1200 'mesenchymal' studies worldwide with the majority in the USA, Europe and China. In the USA, most manufacturing occurs in academic GMP facilities and are regulated by the FDA under 21 CFR 1271.10.

MSCs will grow aggressively on plastic in the presence of serum to produce large quantities of cells. Some cells will self-renew whilst others will become mesenchymal progenitor cells which differentiate further into osteoblasts, adipocytes and chondrocytes, depending on how cells are manipulated during expansion. There should be careful differentiation of stem versus stromal cells. The current definition of a stem cell is the capacity for self-renewal, whilst the term stromal should be reserved for those that differentiate. Mesenchymal stromal cells will be CD105, CD73 and CD90 positive and should be negative for CD45, CD34 (a marker for haematopoietic cells) and other markers. Ideally, MSC's should be named stromal unless there is rigorous evidence of stem-ness, i.e. self-renewal.

Unproven cell therapy

By early 2018, there had been almost 1000 clinical trials of cell therapy products worldwide, mainly in phase 1 or 2, with only 50 approved cell therapies. While many cell-based interventions involve innovative and informed medical care, there are also a significant number of unethical trials. So-called unproven cell therapy (UCT) is a billion-dollar business involving unclear scientific rationale, a lack of understanding on the mechanism of action, inadequate disclosure of information to patients and uncontrolled experimental procedures. Patients can pay upwards of $40,000 per treatment for a variety of conditions, with anti-ageing using stem cells ranking highest. Demand for cell therapy is driven by the need and the expectation of new technologies but results in stem cell 'medical tourism'. UCT makes use of well organised business strategies, such as misrepresentation of risks and benefits, and weak or absent scientific rationale, alongside tokens of scientific legitimacy. One specific treatment recently offered in Italy for leukaemia and neurological disease using developing but unproven technologies was ruled to be illegal and appropriate action ensued. Thus, new models for the use of cell therapy and new laws are required, and are being enacted. Pioneers of cell therapy need to understand how cell therapies work, they need to define the product, have robust manufacturing processes and a robust regulatory framework, and as such are working on the basis of SMAC – *Science* (based nomenclature)/*Manufacturing*/*Accurate* (information for patients)/*Consistency* (in product and delivery). Towards this end, a task force will report to the International Society of Cell & Gene Therapy (ISCT) at its 2020 meeting in Paris next May.

Discussion

There was concern about the low level of information provided by some applicants for cell therapy substances INN and it was suggested that, at these early stages, this could be tackled by a questionnaire as was done for mAb INN applications. Currently, it is difficult to know which biomarkers are useful and which are not, which are process related and which have an effect on the phenotype of the cell. It was noted that since these substances are going through regulatory authorisation, there will be an investigator brochure and more information (than is usually provided) on cell characteristics should be available. Clinicians find themselves in a similar situation of not knowing what surface markers and what cytokine expression are relevant for treatment of a specific disease.

STRUCTURAL BIOLOGY of PROTEINS

The Experts were reminded that the mechanism of action of a protein is based upon its structure and that a single change, even limited to a small structural element, can alter protein function. Thus, structural biology contributes to our understanding of protein function especially when normal folding of the structure goes wrong resulting in the loss or a change of function, e.g. prion proteins whose misfolding can result in serious pathology. Protein folding is heavily dependent on the amino acid sequence but the micro-environment can also affect the folding process. Furthermore, post-translational modifications such as glycosylation can cause slight to severe changes in folding or may affect the stability of a protein. Thus, expression of a protein in different cell types can affect folding, function and stability.

These aspects of protein folding impact on both originator and biosimilar biotherapeutics and there is a lack of data in the literature on the stability of biosimilars stored under different conditions. The WHO guideline on the comparability of biologics and biosimilars lacks adequate guidance on structural and stability studies and on this point, biosimilars may not be comparable. For example, the term ‘degradation’ should be replaced with ‘mis-folding’ and structural studies relying on the use of a single technique (for example X-ray crystallography or NMR) may not pick up local misfolding; thus, different and complementary specific techniques may be required.

In discussion, it was highlighted that studies are indeed required for different climatic conditions, e.g. in high humidity tropical regions studies are required to understand the stability profile of an originator versus biosimilar, including degradation profiles to determine extent of similarity. It was also highlighted that the ECBS (the Committee responsible for the WHO biosimilars guideline) has recently decided to update this guideline including issues of regulatory guidance, interchangeability, and reimbursement.

RECEPTORS, AGONISTS, ANTAGONISTS and MODULATORS

The term receptor refers to the cellular macromolecule or macromolecular complex with which endogenous compounds interact to elicit a cellular or systemic response. Agonists are drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signalling compounds. An antagonist binds to receptors but does not activate them; the primary action of antagonists is to reduce the effects of agonists (endogenous or otherwise) that normally activate receptors. The antagonism generally results from competition with an agonist for the same or overlapping site on the receptor. A ‘primary agonist’ is a drug that binds to the same recognition site as the endogenous compound. Binding of antagonists and agonists may also be allosteric, i.e. binding to a site on the receptor distinct from that of the endogenous signaller. The term ‘partial agonist’ refers to drugs that block the natural agonist

but are also capable of a low degree of activation. Antagonistic drugs may also act by neutralisation of the endogenous agonist.

Modulators in contrast are much less well defined and there is no proper definition in clinical pharmacology text books. To modulate is to adjust to keep in proper measure or proportion, and drug modulators can enhance or diminish an action or activity. They can act directly or allosterically, and be selective or non-selective. Indeed, to illustrate the broad usage of the term 'modulate' in pharmacology, the definition of eight INN stems contains the term 'modulator' or 'modulation' e.g. the definition of the suffix/stem *-limab* is 'immunomodulating mAb, whilst that for *-ifene* is 'antioestrogens or oestrogen receptor modulators, *clomifene* and *tamoxifen* derivatives.

LIPOSOMAL FORMULATIONS in the EU

Liposomal formulations are employed to deliver drugs with enhanced properties such as controlled release kinetics, biocompatibility, half-life or targeted delivery. In the past few years, medication errors resulting from confusion between liposomal and non-liposomal formulations of the same active substance have been reported. There had been no agreed approach within the EU to naming these products and the European Medicines Agency (EMA) considered that the risk of confusion was enhanced when using the INN along with the company name or trademark only, although the invented name alone did not seem to address the issue. The EMA consequently wrote to the INN Programme requesting advice and suggesting that the term 'liposomal' could be added in front of the INN as a modified INN.

Concerns regarding naming liposomal formulations had previously been discussed by the INN Experts and those conclusions were sent to the EMA highlighting that INN are assigned to well-defined substances, for the active part only, not for mixtures and would only ever be changed under highly exceptional circumstances. Alternative pharmaceutical preparations altering stability, pharmacokinetics and toxicity already exist for numerous other active ingredients. These are considered to be different formulations and outside the remit of the INN Programme. One approach suggested to the EMA was to highlight the dosage form alongside the INN. Also, the manufacturer could be advised to include the formulation term in the product's dosage form.

The EMA's resolution issued in July 2019 noted that where there was a clear risk of medication error, the name should include the qualifiers 'liposomal' or 'pegylated liposomal' using the format 'invented name + qualifier + strength' or 'INN + qualifier + company name/trademark name + strength'.

It was clear that this was a regulatory issue concerning drug product labelling but the INN Programme is willing to work alongside the EMA on common issues.

SCHOOL of INN (SoINN)

The SoINN Steering Committee met on 21 October, the day before this Consultation. The online SoINN was officially launched on 1 October 2019 and is now fully operational. A colour leaflet, in both English and French, has been produced and two pilot site universities are now using the SoINN for teaching: the University of the Western Cape, South Africa, and the University Piemonte Orientale, Italy. Other pilot sites at Grenoble in France, Barcelona in Spain and one in China, are being established. In the first week of November (2019), two SoINN webinars will be held, one for academia and one for stakeholders. New material is being sought from stakeholders to go onto the platform.

It was also highlighted that work is underway to translate the courses into Spanish, French and Arabic and additional universities in Tunisia (Monastir) and Australia (Monash) have shown an interest in the courses.

It was very good news that the SoINN is now active and proving useful.

WEB STATISTICS

For information, statistics of visits to INN-associated websites were provided.

- IDMIS (for use by the INN Experts) had been accessed by 52 users on 2,328 occasions involving 28,232 clicks since the beginning of the year.
- SoINN (School of INN) platform had been visited 1,650 times by 353 users, and 36,000 pages visited since 1 October.
- Mednet (a WHO collaborative platform for scientific information exchange and sharing) has 20,230 users in 160 countries, with 150 new members every month; it is probably the largest web community of WHO.
- INN Hub (the Global Data Hub provided to organizations that want access to INN names in their website or database) has 11 users, e.g. WIPO, and had 545,000 queries this year so far.
- Of visits to the WHO EMP site, the INN pages are the most visited with about half the hits aimed at the INN pages (49,000 this year to date).

COLLABORATORS' UPDATES

International Union of Pure and Applied Chemistry (IUPAC)

The 'Brief Guide to Organic Nomenclature' has reached the proof stage.

The list of corrections for 'Nomenclature of Organic Chemistry. IUPAC Recommendations and Preferred Names 2013' (the Blue Book) is now almost complete. As a follow-on, there is a project to convert the book into an html document on the web with the corrections applied.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since April 2019, the Japanese Approved Names (JAN) expert committee has met 3 times. Thirty-eight names have been published including 6 biosimilars. Supplement 2 to the Japanese Pharmacopeia (JP) 17th edition was implemented in June 2019 and its English version will be published in the near future. The latest face-to-face meeting of the Pharmacopoeial Discussion Group (PDG) was hosted by the JP in Tokyo on 1-2 October 2019. The PDG 30th Anniversary Symposium was also held on 3rd October.[2]

Therapeutic Goods Administration (TGA), Australia

The TGA will be carrying out consultations soon on development of standards for 2D barcode for 'track and trace' of medicines.

As reported previously, the generics medicines reform is ongoing and final positions are still being developed. It is anticipated that this reform will touch on changes to requirements for the use of overseas references; early advice for biowaiver justifications; the use of international templates to support work-sharing, and incentives for generic prescription medicines applications.

[2] PDG F2F meeting (Press Release): https://www.pmda.go.jp/files/000231993.pdf
PDG F2F meeting (Meeting Highlights): https://www.pmda.go.jp/files/000231994.pdf
PDG 30th Anniversary Symposium: https://www.pmda.go.jp/english/symposia/0162.html

The TGA is also consulting on making non-active ingredients of medicines visible on its online register; this is already available on labels.

Following its medicines and medical devices review implementations, the TGA is now engaged in multiple workshare with other regulators including HC, HSA, SWISS MEDIC and FDA. This hopefully will foster global collaborations, regulatory convergence and reduction in regulatory burden.

The TGA also continues to develop interactions and cooperation with SE Asian countries through the Regulatory Strengthening Program.

United States Adopted Names (USAN)

The 2019 summer USAN Council meeting took place on 13-14 June 2019 at the American Pharmacists Association Headquarters in Washington DC, where names for 34 drug substances were reviewed and discussed. Seven new stems and infixes were approved and added to USAN's stem list, 2 stems were revised, 2 radicals and anions, and 3 stem definitions were revised to harmonise with the INN Programme. Forty-three INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 69th INN Consultation. Revisions were approved for 6 USAN Council names previously recommended.

Through October 2019 USAN staff will have processed, researched and made recommendations for 218 USAN applications and forwarded this information to the USAN Council for their review and selection. Also, through October 2019, 163 USAN will have been adopted for 2019. Revenue was realised for 2 additional negotiations. Currently there are 179 active USAN negotiations.

USAN staff were featured in an LA Times syndicated business article in July 2019.

The 2019 winter meeting of the USAN Council is scheduled to occur on 5-6 December 2019 at the Diplomat Resort in Hollywood, Florida.

United States Food and Drug Administration (FDA)

The FDA guidance on the use of a 4-letter suffix in naming biologics was amended earlier in 2019 to exclude already licenced biologics, i.e. retrospective naming will not take place.

A new Guidance for Industry document on Bispecific Antibody Development Programs is a short document addressing regulatory, CMC, nonclinical and clinical considerations of bispecific antibodies. Two broad categories of bispecific antibodies are recognised: those that bridge two target cells, e.g. those designed to bring immune effector cells into close contact with particular tumour-associated antigens for cell killing, and those that do not bridge two target cells, e.g. binding two soluble cytokines. The document however does not discuss names for these types of biologics.

The FDA is working with regulators on an international collaborative study on testing for nitrosamines and the FDA has developed an improved method for its determination; the nature of the old methods actually generated nitrosamines during the test resulting in false high results.

There is a new nominee for the vacant post of FDA Commissioner but the approval process will have to go through a senate committee.

United States Pharmacopoeia (USP)

USP continues to work on harnessing the Global Substance Registration System (GSRS) platform to serve as a consistent source for common chemical data element in future USP publications, including the USP Dictionary.

USP has also formed a dedicated chemical information team to focus on enhancing quality and consistency of the presentation of chemical information in compendial publications.

CLOSE OF MEETING

The Chair summarised discussions that highlighted the need for working groups to address specific issues raised during the meeting: the working group on monoclonal antibodies should be re-established to consider how novel antibody-like structures, including bi-specific mAbs, should be named; a working group should consider if and how to name therapeutic micro-organisms; a working group on cell therapy substances (that should involve CBER) should consider the information requested from applicants and the content of the Definition of such substances, and this should involve CBER also. It was further noted that the INN Group should be involved with the WHO Biosimilars Group. These were agreed.

Dr Clive Ondari, (acting) Director EMP, expressed his willingness, upon receipt of a request from the INN Secretariat, to assist in establishing these working groups. Dr Ondari also expressed his appreciation to the Expert Committee for their hard work during, and in preparation for, the Consultation. This work is of great value and forms the main remit of the INN Programme. The Chair was thanked for his capable leadership of the Expert Group, and the INN Secretariat for their valuable work. He expressed his intention to explore how to assist the Secretariat in supporting the Experts.

The Chair, was grateful for his remarks and thanked the Secretariat and the Experts for their contributions to the meeting. The Chair in turn was thanked by the Secretariat for his support of the INN Consultation.

Next meeting

The 70th INN Consultation will take place in Geneva at WHO HQ on 21-24 April 2020.

SESSION for INN STAKEHOLDERS

69th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 22 October 2019

OPENING REMARKS

Stakeholders attending this Open Session were welcomed by the Chair, Professor. Sarel Malan who assured them that the INN Experts would be listening intently to the presentations and take this into account when items were discussed during the plenary session of the 69th INN Consultation. He reminded the guests that all information presented and discussed during the session are to be kept confidential until the official report of the meeting is published. The Chair welcomed the Experts and the Secretariat to the meeting and invited Dr Clive Ondari, acting Director, Essential Medicines and Health Products (EMP), to address the meeting.

Dr Ondari thanked the Chair and gave a warm welcome to the stakeholders on behalf of Dr Mariângela Simão, Assistant Director-General, MHP. He extended a special thanks to the work of the INN team. With several consultations running in parallel at this time, Dr Ondari apologised that he would not be able to participate fully in the deliberations. He also highlighted that a major WHO re-organisation, requested by the DG within the new global strategy programme, was taking place and would run until 2023. He reiterated the Chair's remarks that the Committee would be listening closely to stakeholders' issues and take them onboard during the INN Consultation.

Dr Raffaella Balocco, Group Lead, INN, added her welcome to the stakeholders and the INN Experts and encouraged the INN Experts to question and discuss openly the issues raised by the stakeholders.

Alliance for Safe Biologic Medicines (ASBM)

This was the 13th appearance of the ASBM before the INN Committee to urge WHO to assume global leadership on naming biologics. ASBM was of the opinion that the delay in implementing the biologic qualifier (BQ) was a result of opposition to it and reasoned that arguments for delay were baseless and nullified. It also contended that during this delay period, WHO was pressurising smaller regulators and proponents to drop support for the BQ despite the ASBM having addressed the main objections raised by opponents. A great majority of US physicians already support the FDA 4-letter suffix with most of them also supporting the decision not to apply the suffix retrospectively. The ASBM also reported that at the DIA annual meeting in June 2019, an FDA representative identified enhancement of pharmacovigilance and safe use as major factors in implementing their suffix, alongside the inconsistent use of other identifiers such as the National Drug Code (NDC) number. According to the FDA, there should be adequate mechanisms in place to differentiate adverse events arising from reference or biosimilar products. In a Canadian survey of 2017, only 20% of physicians recorded the non-proprietary name in patient records and only 1% of those identified the medicine using the Drug Identification Number.

The ASBM also queried whether the INN Expert Group's recommendation to WHO had changed, highlighting that neither the WHO Constitution nor Bylaws require unanimous consent of all stakeholders. It felt strongly that if WHO had moved to introduce the BQ many member states would have adopted it by now. Even in the EU, adverse event reporting data shows that a need remains for a specific non-proprietary biologics identifier, such as the BQ,

despite reporting by brand name being required by law. The ASBM felt that broad support for the BQ remains amongst regulators and prescribers and urged the WHO to act now and adopt the BQ.

In discussion, the ASBM was informed by the Secretariat that the INN Group's recommendation remained valid and that to enhance good communication, the INN Programme had established a School of INN to help communicate and better understand pharmacovigilance. It is up to WHO management, taking onboard other global considerations, whether or not to implement. It is not uncommon for recommendations from Expert Groups not to be implemented where there is good reason. In this case it was understood to be a lack of a consensus, and others who oppose.

Dr Clive Ondari, EMP, clarified that recommendations by advisory groups are directed to senior WHO management and indeed there are precedents where recommendations have not been taken forward because of consideration of other issues. With respect to delays, there are no timelines and senior management will feed back to the INN Committee in due course. He affirmed that recommendations do not become invalid; they lie more in state of suspended animation until senior management decides.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

The IFPMA noted that the INN, in keeping pace with advances in mAb technology, had dropped the species infix. It also highlighted the evolving complexity of biologic molecules, especially new antibody modalities, and the difficulty in incorporating scientifically relevant information in a single name. The IFPMA proposed that the simplest approach was the incorporation of the number of targets being engaged within the name, with information on the complexity of the molecule in the description. The immediate need is a solution for bi-specific antibodies although tri- and quad- valency antibodies are also under active development. The IFPMA proposition was that antibodies targeting two ligands would have a -bi- infix, those targeting three would have -tri- and those targeting more than three would have -plexa-. Additional and more detailed information would be included in the description. The IFPMA added that access to a database that collects and manages all INN data would be useful, to allow easy retrieval of details about molecules. The IFPMA acknowledged that it takes a lot of work to develop a nomenclature system that accommodates more and more complex modalities.

In discussion it was mooted that with so many mAb variations, it was not clear that a new infix addressing valency would be helpful and may introduce further confusion. The IFPMA responded that it was important for physicians to understand that these more complex modalities would have more than one target and in addition to a valence infix, there may be value in having a new stem altogether (as novel modalities become less like monoclonal antibodies). There was general agreement that the solution had to be clear, helpful and not confusing but with a new stem or system it had to be correct, with details in the description making use of standard terms.

Amgen

Amgen recently disagreed with the INN assigned to four of their antibody constructs that engage two targets as they did not include the -bi- infix, as originally requested. The company highlighted that two bispecific antibodies were already marketed and over 85 were in clinical development. Also, for the many different structural formats being developed, additional infixes would be needed to characterise them. This is recognised by the FDA in a recent Guidance for Industry document on Bispecific Antibody Development Programs which notes that a nomenclature system recognising valency may be helpful and add substantial value.

Amgen's own four antibodies have dual targets and a unique mode of action and re-requested names with a -bi- infix to indicate this feature.

In discussion, the Experts noted that most but not all current bispecific antibodies had a cancer indication for which a -ta- infix is appropriate, as in Amgen's four antibodies. However, it was suggested that with the increasing complexity of antibody-like molecules, the -ta- infix may become redundant. Amgen agreed that a new infix and perhaps a whole new suffix, regardless of indication, may be called for. It was also highlighted that a new naming system should provide as much detail as possible to the prescriber but that specialists would in any case refer to the summary of product characteristics. A complication of an additional valency infix resulting in a three syllable -tabimab suffix (for cancer indications) would be the difficulty in creating hundreds of unique and distinct INN for the many new molecules being developed and a totally new system may be required, with this intent being well taken by Amgen.

Celgene Corporation

The INN *eragidomide* had been assigned to Celgene's drug CC-90009, currently in clinical trials for myeloid leukaemia and myelodysplastic syndromes. However, the company disagreed with the *-domide* stem and presented additional data to support an alternative suffix, with *-gispideg* being the preferred choice.

Cereblon (CRBN) is a protein receptor on the E3 ligase complex involved in the transfer of ubiquitin to targeted proteins for degradation by the proteasome. Drugs with the *-domide* stem such as *lenalidomide* enhance the protein binding properties of CRBN thus promoting the interaction of the E3 complex with proteins that would not otherwise be candidates for degradation. Targets of *-domide* agents include protein substrates Ikaros (IKZF1) and Aiolos (IKZF3) whose degradation is the basis for their anti-myeloma activity. In contrast, CC-90009 is a novel agent promoting the binding and ultimate degradation of GSPT1, whose degradation perturbs pathways unrelated to *-domide* agents leading to a different sensitivity profile across tumour types. In addition, this difference in pharmacology leads to non-overlapping safety observations between *-domide* agents and CC-90009. The company gave examples of where drugs that have similar structure and action but distinct pharmacology are given alternative stems. For example, oestrogen receptor modulating drugs may have the stem *-ifene* or *-estrant*, depending on their function. Consequently, Celgene respectfully requested the assignment of the novel stem *-gispideg* in which *-gisp-* denotes the specific GSPT1 target and *-ideg* the mechanism of induced degradation. This novel suffix would communicate CC-90009's unique target and prevent confusion and medication errors that could arise from grouping drugs with unrelated clinical and safety profiles.

DiscGenics

DiscGenics is developing a cell therapy treatment for lower back pain based upon cells derived from adult nucleus pulposus tissue derived from the central region of invertebrate disc. The treatment has been tested in different animal models and is now in clinical studies in both the USA and Japan. The manufacturing process involves expansion of human disc tissue, selection and expansion of the nucleus pulposus cells followed by fill/finish. Each lot of disc tissue can generate thousands of doses.

In requesting an INN for the cells, the company highlighted that none of the current infixes for cell therapy substances are appropriate as their 'discogenic' cells are not MSCs, chondrocytes, fibroblasts, stem cells or differentiated stem cells. Embryonically, the nucleus pulposus cells are derived from the notochord, are phenotypically distinct, and have a unique CD24 surface marker. The manufacturing process excludes cells expressing CD271 and Stro1, surface

markers of MSC cells. The discogenic cells are highly potent at generating extracellular matrix and are also anti-inflammatory.

In requesting a unique infix the company highlighted that cell therapy for back pain is a rapidly growing field that includes both MSC and chondrocyte treatments which are quite distinct from their nucleus pulposus tissue-derived discogenic cells, and respectfully requested the infix -disctem- for their cells.

Following the presentation, it was pointed out to the company that the infix -disctem- could not be assigned as the INN Programme could not assign a stem or infix that reflects the company name. In response the company noted that any suitable alternative name would be acceptable, reflecting for example, nucleus pulposus, invertebrate or spine.

Evelo Biosciences

Evelo Biosciences is developing therapeutic EDP1066 based upon a monoclonal strain of Lactococcus lactis subsp. Cremoris. Having been informed that non-genetically engineered microbes would not be eligible for an INN, the company made representation to the Expert Committee to explain why an INN should be assigned.

Monoclonal microbials are orally delivered and have defined pharmacological properties that are dose-dependent. They remain within the gastro-intestinal tract producing systemic effects via engagement with APC's in mesenteric lymph nodes, with the beneficial effects being manifest by modified effector T cells. EDP1066 is currently being investigated for treatment of psoriasis and atopic dermatitis. Its pharmacological effect is distinct from any effect that may arise from probiotics, is dependent on the monoclonal nature of the specific strain combined with a specific manufacturing process and formulation. Monoclonal microbes are eligible for patenting and are recognised by regulatory authorities as pharmaceutical substances, thus are subject to the same regulatory rigour as any other medicine. EDP1066 is more efficacious that multiple species comparators including a strain that is genetically 99.10% comparable.

Several other pharmacologically active microbial products are under clinical investigation and the company argued that the risk of prescribing error is high if such substances are not assigned INN. This would lead to lack of efficacy and potential harm to patients.

In discussion, in responding to a question on how EDP1066 is defined, the company highlighted the precise strain, the manufacturing process and formulation, all of which are covered by a patent. Unique cell surface markers could be a way forward but these are not yet available. Manufacture involves a master cell bank (MCB) and working cell bank (WCB), and genome sequencing is performed but does not constitute a release assay. The company also added that an almost, but not quite, identical strain with respect to its genome sequence, subjected to the same manufacturing protocol and formulation would not have the efficacious properties of EDP1066, which underlines the need for an INN for this specific monoclonal microbiol.

Kowa

Kowa created K-877 as an agent that significantly lowers triglycerides but does not harm kidney or liver function. In 2014, Kowa accepted the INN *pemafibrate* in order to have the drug launched. However, an accumulation of scientific data shows that K-877 has selective PPARα modulating (SPPARMα) activity which has been recognised by the International Atherosclerosis Society and the Residual Risk Reduction Initiative Foundation as a first-in-

class drug. Because of this data, Kowa would like the INN Committee to now consider a non-fibrate INN for K-877.

K-877 was initially screened out of 1,300 compounds for high selectivity and high potency compared to PPARγ and PPARδ fibrates. It has different structural features that provide a better molecular fit within the PPARα ligand binding site. This highly selective PPARα feature enhances expression of genes with desirable effects on lipids and inflammation and blocks the expression of genes with adverse renal and hepatic function. This is reflected in improved clinical data on triglycerides and HDL-C, on remnant lipoproteins, improvement of liver function and a decrease in inflammatory biomarkers. Thus, in contrast to fibrates, K-877 can also be co-administered with statins. Consequently, for improved care of patients and to avoid mis-prescribing, Kowa requested a change of INN to a non-fibrate name.

In discussion, Kowa was made aware that requesting an INN substitution falls under Article 9 of INN rules. This requires certain conditions to be fulfilled before the INN Committee could propose substitution and then the INN Secretariat would have to write to all 194 UN member states for approval. INN substitution has only ever been done a few times, for serious reasons and prior to marketing approval.

CLOSE of MEETING

The Chair thanked everyone for their contributions and ensured stakeholders that their presentations would be discussed fully by the INN Experts during the INN Consultation.