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65th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 17-20 October 2017

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

65th Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

OPENING REMARKS

Dr Sue Hill, Director, Essential Medicines and Health Products (EMP), welcomed all participants to the meeting. She announced that Dr Mariângela Batista Galvão Simão is the new ADG for the new cluster 'Drug Access, Vaccines and Pharmaceuticals'[1] in which the INN Programme is located. She highlighted that the INN Expert Group (INNEG) is one of four formal expert committees that deliver norms and standards, and for the INNEG it will be a very busy meeting with 150 substances to review. The normative work is continuing to expand and new positive signals within WHO want to strengthen the normative function, and so there is a need to look at how to evolve and keep the work going forward. Dr Hill acknowledged the highly valued contributions of the Committee. Finally, she welcomed the upcoming coordinator of Technical Standards and Norms (TSN), Dr François-Xavier Lery, who will start in November and was present as an adviser, and invited him to say a few words.

Dr François-Xavier Lery commented that he was looking forward to supporting and promoting the work of the Committee.

Prof. Sarel Malan was nominated and re-elected Chair of the meeting; similarly Prof. Wei-Keung Chui was re-elected as Vice-chair for Chemicals, Prof. Armando Genazzani as Vice-chair for Biologicals and Dr James Robertson as Rapporteur.

Prof Malan thanked Dr Hill for her confidence in the Expert Group and welcomed Dr Lery as a future member of WHO staff. New experts to the Committee from Japan, Canada and Australia were also welcomed. He expressed his thanks to the Secretariat for its huge amount of background work that greatly eases the burden on the Expert Group.

He also noted with sadness the recent passing of the previous chair of the INN Committee, Prof Derek Calam, who had been the finest chairperson he had the privilege of working under.

A tribute was paid to Prof Calam. It was highlighted that his knowledge with the INN and the UK regularity council was infinite; he was chair of the Chemistry, Pharmacy and Standards (CPS) Expert Advisory Group (of the Commission on Human Medicines [CHM]), which he chaired highly successfully and for a very long time. He influenced UK medicines assessors greatly and all were very saddened at his passing. His knowledge was such that he could comment on most papers that went to the UK's CHM and CPS. He was not one to take people to task within a meeting but would approach them beforehand and help them, teach them, the best way forward. He was chair of both the British and European Pharmacopoeia Commissions, and brought about looking at pharmaceutical matters on a worldly basis. He was a very gentle man with a passion to serve. When a note was passed around the (UK's) MHRA, there was an outcry at his passing; he was a fountain of knowledge and will be greatly missed.

Dr Raffaella Balocco-Mattavelli, Lead INN Programme and Secretary of the INNEG, shared with INN colleagues that a few days before he died, Prof Calam had sent a final message, wishing her and the INN Experts good luck, and that he had enjoyed working with everyone.

A minute's silence was observed in his memory.

EXECUTIVE SUMMARY

The Executive Summary of the 64th INN Consultation was tabled and approved.

NOMENCLATURE of INNs

[1] Post meeting note: The cluster has been renamed 'Access to Medicines, Vaccines and Pharmaceuticals'

During the 65th INN Consultation, a total of 152 INN requests were discussed, including:

- 110 new INN requests, including 50 for biological substances
- 36 outstanding requests
- 6 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 134 names were selected/reconfirmed, which are planned to be published in List 119 of Proposed INNs (p.INN), while 9 requests were deferred for future discussion. Three applications have been closed since the requested information had not been received. Two requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One amendment was planned to be published in a forthcoming List of p.INN, 2 requests of substitution and 1 objection could not be retained as they did not conform to the criteria. Three new stems/substems were selected, 2 suffixes were promoted to the pre-stem list and it was decided to amend the descriptions of 2 stems.

PUBLICATION ISSUES

Imiglucerase

It had been brought to the attention of the INN Committee by the originator company that *imiglucerase*, an INN provided in 1992 for a CHO derived recombinant enzyme (for enzyme replacement therapy in Gaucher's disease), is being used widely for the same enzyme marketed by a separate company. The originator company's concern was that, given post translational structural differences between its own and the alternative enzyme, and subsequent potential clinical differences, preparations of separate marketed products should be using distinct INN to avoid substitution of one for the other and for accurate pharmacovigilance.

The INN Expert Group found the following. The original INN *imiglucerase* should have been *imiglucerase alfa*, since it is a glycosylated protein, but this was mistakenly omitted. It was noted however that no amino acid sequence was provided in the INN Definition or any information regarding glycosylation. With regard the second company using the INN *imiglucerase* for its active substance, there is nothing the INN can do regarding this; this is a regulatory matter. If the company were to submit for an INN, and the glycosylation differences were deemed to be different from *imiglucerase*, it would likely be given the INN *imiglucerase beta*, but this could only occur if a submission was made to the INN Programme and as a matter of procedure, the INN Programme cannot impose this. A comment will be made in the Bioreview regarding the discrepancy of the original INN *imiglucerase* lacking an *alfa* suffix.

The originator company had further highlighted that two other forms of the enzyme, *alglucerase* and *velaglucerase alfa*, were given distinct fantasy prefixes despite having the same amino acid sequence. The INN Experts noted that this should not have happened and was an error on the part of the INN Committee.

-Grel inhibitors

The INN Secretariat had received correspondence regarding the incorporation of the stem *-grel* into names with a *-grelide* suffix and subsequent confusion that may arise because the *-grel* stem is defined as antiplatelet agents, which may suggest that they lower platelet numbers, whereas they inhibit platelet aggregation. It is *-grelide* substances that inhibit platelet numbers by inhibiting their synthesis, and the correspondent had recommended a novel suffix for these.

The definition 'antiplatelets' for the stem *-grel* was held to be rather ambiguous. There are two potential modes of antiplatelet activity: inhibition of platelet aggregation and inhibition of platelet synthesis. The various drugs that inhibit platelet aggregation have differing mechanisms of action but all are used for the same indication, so there did not appear to be any need for substems. For drugs that inhibit platelet synthesis, there is no stem. Two such drugs have a common suffix *-grelide*, and they are used for thrombocytopenia. Since there appeared to be no real risk for patient safety and that

this was an academic issue, it was concluded not to change the *-grel* definition or to introduce *-grelide* as a new stem with an appropriate definition distinct from that for *-grel*.

Lutetium (^{177}Lu) oxodotreotide

A stakeholder had raised concern that the chemical commonly known as *Lutetium (Lu177) dotatate*, and assigned this name as a USAN, had been assigned a different name *lutetium (^{177}Lu) oxodotreotide* as the INN, and that this would result in confusion for practitioners and patients. This unfortunate situation came about because the sponsor submitted applications to the USAN and INN Programmes at the same time, with neither programme being aware of the other application. It was noted that the INN cannot be changed for this reason.

The *-glitazar* stem

There had been a request to substitute the INN *saroglitazar* as the originator claimed that the *-glitazar* stem was inappropriate as it was confusing prescribers that it could be used for diabetic control when it is approved only for hyperlipidaemia.

Peroxisome proliferator-activated receptor (PPAR) ligands are therapeutic agents involved in hyperglycaemia, inflammation, and obesity-related disorders. Three subtypes of PPAR have been identified to date:

- PPAR-α is expressed in skeletal muscle and liver, is involved in fatty acid oxidation and PPAR-α activating fibrates lower triglycerides and raise HDL
- PPAR-γ, present in adipocytes, regulates adipogenesis, and agonists are insulin sensitizers
- PPAR-δ is widely expressed, but it is the least-studied PPAR.

The *-glitazar* stem is for drugs that show PPAR-γ activity and not for substances showing predominantly PPAR-α activity, although in practice, *-glitazar* has been used for dual agonists of both PPAR-α and PPAR-γ. *Saroglitazar* is a dual α,γ agonist; unlike other *-glitazars* it appears to predominantly activate α-receptors although it is difficult to extrapolate *in vitro* receptor specificity data to *in vivo* action.

Comparison of published clinical trial data of various *-glitazars* shows them to have similar effects on lipid parameters and blood glucose to those of *saroglitazar*. Also, only 300 patients were treated in trials with *saroglitazar* and so there is insufficient data to determine accurately its profile of adverse effects. The drug is marketed in India only where there is no organised pharmacovigilance, so it is not proven that side effects of *saroglitazar* are different from other *-glitazars*. For these reasons the INN Expert Group concluded that the INN should remain *saroglitazar*.

In further discussion, the Experts agreed that the *-glitazar* definition should be modified from '*PPAR-γ agonist activity*' to '*dual PPAR-α,γ agonist activity*'. The definition for the *-glitazone* stem was satisfactory as '*PPAR-γ agonists that are thiazolidinedione derivatives*' whilst the *-fibrate* stem '*clofibrate derivatives*' should be modified to include '*PPAR-α agonist activity*' to highlight their mechanism of action.

Criteria for Establishment of a New Stem

A small group of Experts reviewed the issues around the establishment of a new stem. Stems are agreed common suffixes that classify substances according to their structure, mode of action or clinical indication. In highlighting drug substances with similar mechanisms of action, the use of similar drugs is minimised or, on the other hand, facilitates seeking an alternative if one is not working. Stem groupings should be neither too narrow nor too broad. If too broad, the effectiveness of the grouping gets lost whilst if a group is too narrow, mechanisms of action are too specific with too few members within a group.

Recently there has been an upsurge in requests for the assignment of new suffixes/stems, reaching the point where there is no grouping and the point of having a common suffix gets lost. There is also a concern of running out of distinct names for stems. Thus, there is a need to limit the number of new stems but avoiding not assigning a new stem where there is a legitimate need. Requests for new stems are usually based upon slight modifications of structures for a new clinical indication, where an

existing stem is to be avoided because of an association with specific adverse events, or where the applicant wishes a new substance to stand out from the crowd.

The subgroup of Experts proposed three points concerning the assignment of a new stem:

- Requests for new stems based solely upon new uses should be discouraged since uses usually change or get added to with time. An exception is when there will clearly be no alternative use, e.g. an anthelminthic.
- A stem should not be assigned when there is no new structure.
- A new prospective stem or suffix should require supportive clinical data, especially at least phase II data. This is because as new clinical data emerge, the indication(s) often changes.

Previously it had been an unwritten rule that a new drug substance should have entered clinical studies before an application for an INN was made. It was agreed that the above points should be set out formally in guidance highlighting that if a new stem/suffix is being requested, then appropriate information on mechanism of action and/or clinical indication will be required.

SCHOOL of INN

The 6th meeting of the School of INN (SoINN) steering committee took place the day before the 65th Consultation. Three new members from the INN Expert Group were welcomed. Within the committee there are three subsections, (i) communications, cooperation and outreach, (ii) training (through collaborating centres and internally), and (iii) publications. With respect to publicity, Dr Balocco-Mattavelli was invited to and gave a presentation at the International Pharmaceutical Federation (FIP) annual meeting, in Seoul, Korea, Sep 2017. Despite there being a small audience in the WHO session there was considerable interest and following from this, the SoINN was invited give a presentation at the Deans Forum in Glasgow, Scotland, preceding the FIP 2018 International Congress in Sep 2018. This gets attended by heads of pharmacy teaching universities and so will be a good move to get SoINN into teaching. SoINN has also been invited to the next annual meeting of the European Association of Faculties of Pharmacy (EAFP) (Parma, May 2018) and to give a presentation on an inter-universities (Grenoble-Geneva-Lausanne) post-graduate course on clinical pharmacy. A SoINN e-platform is being established and a poster and/or brochure are being considered for circulation.

SoINN Publications

A new WHO publication 'Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances' was tabled. Its contents include information on the structure and use of INNs, rules for their selection and a list of common stems. It also introduces the new School of INN and it was suggested that the publication could be used as starting material for a future INN course. There was a proposal from one of the Experts to translate it into Russian, and this was welcomed by the Secretariat.

A report of the survey on INN use, conducted in March 2016[2], has been accepted for publication in the WHO Drug Information journal. A paper about the awareness of INN amongst students and academics is being drafted and will be submitted to Pharmacy Education, an FIP International Journal. Finally, a paper on naming biologicals is nearing completion; potential targets for publication include Biologicals, JAMA or the Journal of Pharmacology.

In developing resources for teaching and learning, the SoINN will also reach out to textbook publishers. This is an urgent piece of work and is anticipated to be finalised by January 2018. Attempts are also being made to engage pilot sites, e.g. universities, and to establish collaborative projects.

The Chair was grateful to the steering committee for their efforts and invited all members of the Expert Committee to contribute ideas. There is a need to achieve worldwide standards in teaching. The next meeting of the steering committee will be held in Gruyere, Switzerland, in January 2018.

[2] see: 62nd INN Consultation Executive Summary
http://www.who.int/medicines/services/inn/62nd_Executive_Summary.pdf?ua=1

e-platform of SoINN

A new web platform is being developed by the INN IT officer and is sited on WHO's MedNet, a WHO collaborative platform for scientific information exchange. It is an open source of information and the platform allows for searching of the INN database for INN names, and for names published on recommended or proposed lists. There is also information concerning existing national names, ATC codes if assigned to INNs and basic chemical information. The INN Status query allows for tracking the status of INNs within the INN process. Information about the SoINN is available and in future the site can be used for online courses. The service has free access: https://mednet-communities.net/inn.

REVIEW of NOMENCLATURE for BIOLOGICAL SUBSTANCES

Nomenclature for mAbs

The 'source' infix (substem b) of mAb INN was discontinued in July 2017 and instead the source will continue to be described in the Definition. Two stakeholders had written to the Secretariat concerning this revision. Both supported the discontinued use of the source infix although one expressed concern regarding the use of particular vowels immediately preceding the *-mab* stem, while the other was concerned about the way in which the source of a mAb would be described within the Definition.

Regarding the use of vowels preceding the *-mab* stem, it had indeed been recognised by the Committee that care would be required to ensure that the target infix, which will now immediately precede the *-mab* stem, does not appear to suggest a 'source'. This can be achieved to a degree by avoiding the use of the vowels, *i*, *o* and *u*, and, for example, replacing the target infix *-tu-* with *-ta-*. As INN get assigned on a case-by-case basis, the Experts felt that confusion can be avoided by being vigilant.

Regarding the description, the Committee needs to consider how best to expand the current single word term with a greater description. The Experts were reminded that during the Open Session for Stakeholders held in conjunction with this Consultation, the IFPMA had made a similar proposal on providing more information for the Definition and not relying on a single term such as 'humanised'. The Committee has not yet made a decision on the description but it acknowledged that terms such as 'humanised' and 'chimeras' should probably be replaced with a more descriptive wording to reflect how mAbs are currently made. It needs careful discussion to find the most appropriate way forward.

It was separately opined that sequence databases remain an important source of information and that the Committee should think carefully about removing this from the description. It is good to know for example which amino acids have been changed; companies now provide all this information and it should remain available in the Definition.

Dr Raffaella Balocco-Mattavelli is to attend the Antibody Society's annual meeting in San Diego where she will introduce the INN Programme and discuss how best to redesign the scheme. Both academia and large and small biotech companies will be present and the INN Programme will be open to collaboration.

Nomenclature for advanced therapies

A summary of the current nomenclature rules for advanced therapies was provided for information.

All genetically modified advanced therapy substances, whether they are plasmids, viruses, bacteria or cells, are given a two word name with the first word defining the gene component and the second word defining the vector. The first word has the stem *-gene*, a preceding infix describing the gene and a fantasy prefix. The second word has a stem that refers to the nature of the vector, thus, *-plasmid* for plasmids, *-vec* for non-replicating viral vectors, *-repvec* for replicating viral vectors, *-bac* for bacterial vectors and *-cel* for cellular vectors. The preceding infix provides more precise information on the vector and there is a fantasy prefix. For cell vectors, there may be an additional infix describing pertinent manipulation of the cells.

Cell therapy substances that are not genetically modified are given a one word INN. The structure of this one word is identical to the second word for genetically modified cell substances, *viz.* it has a *-cel*

stem, a preceding infix describing the type of cell, a further infix to describe manipulation and a fantasy prefix.

In discussion, the Expert Group debated whether or not a separate INN should be required for the vector component of cell-based gene therapy (to date these are all viral vectors); this would need further consideration. It was also mooted that the second word of genetically modified autologous cells is not given a fantasy prefix or a common prefix is used to highlight the cells as autologous. The INN advanced therapies working group would reflect on this also.

Virus-based therapies

To date, virus-based therapeutic substances that have been given INN fall into the class of viruses termed oncolytic viruses, i.e. their intended mechanism of action is to destroy tumour cells. The current nomenclature scheme comprises the stem *-rev* for therapeutic virus, a preceding infix *-tu-* for tumouricidal, a further infix denoting the virus type and a fantasy prefix. The infixes used to define virus types are identical to the infixes for virus types in the scheme for virus based gene therapy.

In discussion, concern was expressed that some virus type infixes are three syllables long and attempts should be made to shorten them; this will be given further consideration.

Fusion proteins

In the past year a specific scheme for fusion proteins had been proposed. The scheme would apply to fusion proteins where the final substance has two [or more] major biological effects such that it is difficult to determine the most appropriate stem. Such fusion proteins would be assigned the stem *-fusp*, while a preceding infix would allude to the activity of the substance and the word would begin with a fantasy prefix. Three INN had been proposed under this new scheme and all but one was accepted by the applicant (where one applicant did not approve of the proposed name it was for a separate reason and not the *-fusp* stem). After discussion within the 64th INN Consultation, the new scheme had been circulated to members of the Expert Group for comment and no objections had been raised. During the 65th INN Consultation, three more substances were assigned to the *-fusp* group.

BIOLOGICAL QUALIFIER (BQ)

Report back from the WHO *Expert consultation on improving access to and use of similar biotherapeutic products,* Geneva, May 2017

The INN Expert Group's proposed Biological Qualifier (BQ) was discussed in the above consultation and a small number of INN Experts were invited to attend. A significant outcome presented in the report of the consultation was that no consensus had been reached on whether WHO should continue with the BQ and that WHO will not be proceeding with it. This did not reflect the discussion and was a misrepresentation as no consensus had been sought on the BQ within the meeting, since comments from various participants concerning the BQ have been largely positive. The attending Experts also felt that overall the report of the consultation was poor and noted that it had not been circulated to participants prior to publication.

It was proposed that the Group inform the DG in writing that the report of the May 2017 consultation was not a full reflection of the meeting and that the decision not to make a recommendation on the BQ was not robust enough. Indeed, it would have been preferable for WHO to have made a decision not to adopt the BQ rather than leave it in a perceived undecided state.

In discussion, the INN Expert Group expressed its concerns about the robustness of the decision-making process for the finalisation and release of the May 2017 report and for the final WHO decision of not proceeding with the BQ at present. A draft response to the May 2017 report was discussed and the INN Expert Group gave tentative approval for it being sent to the WHO DG pending final edits post-Consultation[3].

Beyond the BQ, one objective of the May 2017 consultation had been to inform stakeholders about an upcoming pilot prequalification (PQ) of two anti-cancer biotherapeutics and biosimilars, *trastuzumab* and

[3] The final letter was circulated and approved by email on 02 November 2017.

rituximab. Some experts felt that insulins would have a bigger impact on world health than these two cancer biotherapeutics and would have been a more valuable initial target for pre-qualification.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

The British Pharmacopoeia 2018 was published in August 2017 and is available from our publisher. New for the 2018 BP are:

- 35 new BP monographs, 39 new Ph. Eur. monographs
- 185 amended BP monographs
- 6 new monographs for veterinary medicines
- All European Pharmacopoeia monographs integrated (9th Edition as amended by Supplements 9.1 to 9.2)
- Three in-year website and offline download updates to harmonise with the European Pharmacopoeia Supplements 9.3, 9.4 and 9.5

The MHRA, through the BP, is responsible for the naming of medicines in the UK. This is done through the British Approved Names (BANs) system. As the BP works with INN through WHO for all new entities, it only publishes BANs for those entities that are granted licences for use in the UK.

The BAN 2017 Supplement 1 was published in August 2017 and contained 26 new names that were licenced through the EMA. These comprised of 16 chemicals and 10 biological materials. The BAN 2017 Supplement 2 is currently being worked on and currently comprises 22 new names, 7 biological and 15 chemical. These are for new licenced products up to August this year.

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

The EDQM is a Directorate of the Council of Europe and is responsible for the publication of the European Pharmacopoeia (Ph. Eur.).

The majority of the monographs in the Ph. Eur. are for active ingredients and their titles are almost always based upon INN where available. There are now also several monographs for finished products and these generally focus on requirements for the dissolution tests for tablets (for batch-to-batch consistency) and tests for degradation impurities that may appear during manufacture or the shelf life of the product. There is an updated version of the General Principles describing the purpose of finished product monographs, which now includes a section explaining that the title is based upon the INN (or in its absence a modified or national name such as BAN, or another generally accepted name); so far all the finished product monographs are based upon individual substance monographs that use the INN.

Another area of work of the EDQM is the development, maintenance and publication of the Standard Terms Database, which can be accessed free of charge, and which was initially set up in response to a request from the European Commission. It covers pharmaceutical dose forms (also known as dosage forms), routes and/or methods of administration, units of presentation, and containers, closures and delivery devices, for both human and veterinary medicines, in 34 languages, with the aim of ensuring people use the same words, and mean the same thing. Thus, it is similar to what INN does for active substances. Standard Terms is being used in Europe for the implementation of IDMP, an important global project to make sure everyone identifies medicinal product concepts in the same way. Standard Terms have also now been adopted for use in adverse event reporting by ICH (initially founded by Europe, USA and Japan, but also covering Canada, Switzerland, and more recently Brazil, China, Singapore and the Republic of Korea), thereby contributing to global efforts to improve pharmacovigilance and reduce incidences of adverse events significantly.

The EDQM also provides guides on blood donation, organ donation and transplantation, and the use of tissues and cells for human applications, as well as running programmes to support blood establishments in their implementation of the necessary quality requirements. Of note, among other

subjects that are further developed in the latest editions of the guides, are the many ethical considerations and principles that surround such procedures.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs, Office of Standards and Guidelines Development, within the PMDA is responsible for preparing the Japanese Accepted Name (JAN) and the Japanese Pharmacopoeia (JP). The JAN Expert Committee met 3 times in the past half year and 25 names were published including 3 biosimilars (Infliximab (Genetical Recombination) [Infliximab Biosimilar 2], Etanercept (Genetical Recombination) [Etanercept Biosimilar 1] and Rituximab (Genetical Recombination) [Rituximab Biosimilar 1].

This April, the draft of Supplement 1 to the JP 17th Edition was reviewed and approved by the JP Committee under the Pharmaceutical Affairs and Food Sanitation Council. Supplement 1 to JP 17th is now being prepared for publication and will be implemented as soon as possible. Recently, PMDA has been translating the draft for the public inquiry of new monographs and new general chapters into English and this has been posted on the PMDA website (https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/pub-comments/jp/0001.html). PMDA invites public comments from the outside of Japan, not only in Japanese but also in English, as a trial. The purpose of posting the English version of JP drafts is to provide information to stakeholders outside Japan who are not familiar with the Japanese language.

United States Food and Drug Administration (FDA)

Final guidance for industry for non-proprietary naming of biological products was issued by the FDA in March of this year; however, the FDA has not finalised the rule itself. The guidance requires the use of suffixes for improved pharmacovigilance and to avoid inaccuracies. The rule, when issued, will address the format of any suffixes and requires their application to previously licensed products. Currently, under the guidance, there is only prospective application of the suffixes but after the rule is established it will apply to retroactive applications. The FDA is also working with the USP on how this new guidance fits with USP monographs which provide the official name for drug products.

FDA has now approved seven biosimilars[4], a *filgrastim*, a *bevacizumab*, an *etanercept*, two *infliximabs* and two *adalimumabs*. It has also approved two cell therapies: Kymriah™ (*tisagenlecleucel*) and Yescarta™ (*axicabtagene ciloleucel*) both of which are chimeric antigen receptor (CAR) T cell immunotherapies. Finally, an advisory panel has just voted to approve *voretigene neparvovec*, a gene therapy for a genetic disease.

United States Pharmacopoeia (USP)

USP recently underwent a rebranding initiative and has launched a new logo and a redesigned website, optimized to promote easier navigation.

USP standards are recognized in U.S. law and USP plays a role in creating established (non-proprietary) names for drug products. See http://www.usp.org/about/legal-recognition/standard-categories#biologics.

As mentioned by the FDA representative, USP is working with FDA and other stakeholders on addressing the use of suffixes designated by FDA for biologics licensed under the Public Health Service Act and hopes to clarify USP's intended compendial naming approach in the near future. USP supports a consistent naming approach that resolves discrepancy between names and intends to align with FDA's current naming convention.

[4] The seven approved biosimilars are:
Zarxio® (*filgrastim-sndz*), biosimilar to Neupogen®
Mvasi® (*bevacizumab-awwb*), biosimilar to Avastin®
Erelzi® (*etanercept-szzs*), biosimilar to Enbrel®
Inflectra® (*infliximab-dyyb*), biosimilar to Remicade®
Renflexis® (*infliximab-abda*), biosimilar to Remicade®
Amjevita® (*adalimumab-atto*), biosimilar to Humira®
Cyletezo® (*adalimumab-adbm*), biosimilar to Humira®

Finally, the next edition of the USP Dictionary of United States Adopted Names (USAN) and International Drug Names will be available online only, and production of the print publication will be discontinued.

WIPO

Although the WIPO representative did not provide an update, Dr Balocco-Mattavelli highlighted that it had been an honour to have been invited to the WIPO Standing Committee to present the *global data hub* which WIPO would like offered to all trademark offices. Currently, WIPO distributes all INN to trademark offices but would prefer to work with the global hub only; however, members want all data and the hub, accessed directly from INN.

CLOSE OF MEETING

In closing the meeting, the Chair thanked the participants and the Secretariat for their time and efforts contributed both before and during the Consultation; there had been good discussion with a substantial number of new names created. In return, the Chair was thanked for his leadership of the meeting.

Next Meeting

The 66th INN Consultation will take place in Geneva on 1-4 May, 2018.

Open Session to Stakeholders

65th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 17th October 2017

OPENING REMARKS

The Chair, Prof. Sarel Malan, welcomed all participants to the meeting including the stakeholders, members of the INN Expert Group, the INN Secretariat and Ms Emer Cooke, Head of Regulation of Medicines and other Health Technologies (RHT). He informed participants that no decisions would be taken at this Open Session but the information provided by stakeholders would be taken on-board during discussion in the plenary session of the 65th INN Consultation.

Ms Emer Cooke thanked the Chair and welcomed all on behalf of WHO and the new Director General (DG), Dr Tedros Adhanom Ghebreyesus. Ms Cooke was appointed Head of RHT earlier in the year and is also acting coordinator of Technical Standards and Norms (TSN) until November when the new coordinator, Dr François-Xavier Lery, will start. Ms Cooke highlighted that the vision of the new DG was for WHO contributing to everyone having a healthy productive life no matter who or where they are. His vision will take a science-led approach, maximising partnership, and this Open Session with stakeholders fits this stance. The cluster in which INN resides has been renamed 'Drug Access, Vaccines and Pharmaceuticals'[5], with a new ADG, Dr Mariângela Batista Galvão Simão. Ms Cooke was also pleased to inform the meeting that WHO's Evaluation Office will be analysing WHO's normative function, with two of them, the INN Programme and the Essential Medicines List, having been selected for that evaluation, which illustrates the importance of this Committee. In concluding her remarks, Ms Cooke formally opened the meeting and thanked all stakeholders, Experts and the INN Secretariat for their contributions.

Dr Raffaella Balocco-Mattavelli, Group Lead INN and Secretary INN Expert Group, thanked Ms Cooke and Prof Malan for their remarks and joined them in welcoming all to the Open Session including those attending via WebEx.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologic Medicines (ASBM)

The ASBM has been and remains a supporter of the Biological Qualifier (BQ) scheme. Representatives of the Alliance have been visiting regulators and healthcare professionals around the world about the clinical use of biologics and biosimilars and the value of distinguishable names. Several regulators have been found to be receptive to and interested in distinguishable names and the BQ system, but are frustrated and confused at the lack of progress and why the BQ has not been implemented. They recognise the benefits of distinct naming for clear prescribing and dispensing, for improved pharmacovigilance and for increased manufacturer accountability. As we move beyond the small number of biosimilars, providers rely increasingly on nomenclature, especially INN, to communicate effectively with each other and for medical records as well as pharmacovigilance.

The Alliance has recently visited regulators, health officials and prescriber bodies in Canada to discuss biosimilar issues and international harmonisation of biologic naming. Similar discussions have been held in Australia with the Therapeutic Goods Administration (TGA) and a number of pharmacy patient groups. The TGA had recently solicited comments on naming, putting forth several options, including distinct naming. The Alliance responded to this to emphasise the need for the WHO's BQ but that any type of universal scheme is far superior to local individual schemes and anything would be better than no distinctive naming. Indeed, the Alliance has noted high support around the world for distinctive naming.

The ASBM has also, very recently, written to the new Director-General of WHO enquiring as to why the INN recommendation for a BQ has not been implemented given the support from different

[5] Post meeting note: the cluster has been renamed 'Access to Medicines, Vaccines and Pharmaceuticals'

countries for distinctive naming. The letter noted that the BQ was developed several years ago and that several countries are looking to WHO for support in distinctive naming. It further noted that WHO is revered for global guidance; confidence in WHO is there and ASBM congratulates the INN Committee on development of the BQ which it fully supports. Regulators around the world are somewhat frustrated on the absence of implementation of the BQ.

In discussion, a member of the Expert Group added that it would be better for WHO to say no to the BQ rather than put off decisions *ad infinitum*. This hesitation by WHO leaves regulators in a state of uncertainty, which is not good, and will lead to a proliferation of schemes around the world; WHO is the organisation to address this.

International Generic and Biosimilar Medicines Association (IGBA)

The International Generic and Biosimilar Medicines Association (IGBA) was given this name in 2015, previously having been the International Generic Pharmaceutical Alliance. Since 2016, it has been an assembly member of ICH and maintains a dialogue with WHO and other international agencies. It is committed to promoting generic and biosimilar medicines worldwide, and consists of a number of generic and biosimilar medicines associations from a variety of countries worldwide.

IGBA welcomed the opportunity to present a regional update on naming of biotherapeutics, highlighting that tracking and tracing can be ensured using product name and batch number for identification. It welcomed the recent WHO decision to keep the BQ on hold as the introduction of any suffix would not improve pharmacovigilance. The EU has the greatest experience with biosimilars and the EMA has adopted a guideline to enhance pharmacovigilance, which requires the use of product name and batch number in adverse event reporting. Indeed, EudraVigilance data suggests continuous robust levels of biological product identification in European clinical practice and at a recent conference the EMA's Biosimilars Working Party chairperson claimed >95% identification of biosimilars and biologicals sharing the same INN.

In Australia, the TGA recently launched a consultation on biological medicine naming, to which the IGBA has submitted comments promoting the use of product name and batch number for proper identification. Such an alignment with the EU would be consistent with TGA practice.

In the USA, the FDA has issued final guidance on non-proprietary naming of biologicals involving a random 4 letter suffix. However, there is an imbalance in its usage with 7 biosimilars having been approved with the 4 letter suffix but with 11 originator biologics approved in 2017 not being assigned a suffix.

In Canada, Health Canada continues to use the INN appropriate for a biosimilar and reference product; however, a consultation on naming of biological medicines is planned with maintaining the status quo, i.e. INN naming, being one option.

In conclusion, IGBA strongly supports the use of the same INN for biosimilars and reference products and that additional suffixes will only cause confusion. Data from the EU has demonstrated that specific product identification can be ensured and the key point is the importance of education of stakeholders in proper adverse event reporting. The IGBA representative ended by commenting that WHO putting the BQ on hold was a good move and suggested that now would be a good time for WHA Resolution 46.19 to be modified to use the batch number alongside the INN and corporate name.

In discussion, the INN Secretariat highlighted that Resolution 46.19 requests the use of the corporate name and INN but not the brand name to promote and market products; in contrast the EU uses the INN, the brand name and batch number for pharmacovigilance.

The FDA representative clarified that whilst Guidance for biological naming had been published, the (legal) Rule has not been finalised and is currently out for comment. Seven biosimilars have suffixes agreed for product labelling and once the Rule has been finalised the discrimination between biosimilars and reference products should be clear. Timelines for this were not known.

A member of the Expert Group commented that for IGBA to argue that the situation in the EU can be applied worldwide was disingenuous. The EU approach involves the use of 2D barcoding which is costing billions of euros and will not be applied worldwide in the short term. The Expert, a member of Australia's TGA, also noted that whilst the EU approach is an option for Australia, it is unlikely to happen due to cost. In addition, biosimilars have been approved in Australia for over 10 years following EU and TGA guidelines. Where there is a difference in naming (the first biosimilar was given a unique Greek letter name), the biosimilar has taken 50% of the market with 90% compliance with pharmacovigilance. Thus, having a difference in the name is not stopping uptake. But with three filgrastim biosimilars, 40% of pharmacovigilance reports are un-attributable, since they are all named simply filgrastim. In his opinion, current naming was not working and data from Australia was not supporting IGBA's statements.

The ASBM representative noted that the data IGBA presented did not show numbers. While experience in the EU is important, it is important also that 60% of physicians in Latin America use only INN and only 40% for pharmacovigilance reporting. This underlines that WHO needs to think globally. The IGBA representative repeated her statement that the INN, batch number, and company name or brand name would be the correct identification that would work to track and trace all medicines.

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The IFPMA presented data on improvements that can be seen with distinguishable names. In its introduction, it highlighted that pharmacovigilance requires accurate and shared monitoring of signals, between and across manufacturers, and that the BQ is a unique tool that could facilitate pharmacovigilance and accurate prescribing. While there is a variety of reporting requirements globally, only the EU has legislation that specifically addresses pharmacovigilance requirements. The BQ could provide a unique global link enhancing patient safety.

An analysis of a chemical medicine following the introduction of several generic products shows a dramatic drop in the market share of the reference product accompanied by a rise in the incidence of adverse event reporting all of which were assigned to the reference product. This type of situation is not acceptable. In a case study of *enoxaparins*, which share the same INN, whilst there was an equal share of the market between the originator and various generic products, considerably more than half of adverse events were attributed to the originator product and only 5% to a specific generic with the remainder being un-attributable. Unique naming would have improved adverse event reporting to the correct medicine.

In the USA, payment claims for biotherapeutics can differ according to whether the medicine is self-administered or given by medical staff. Pharmacies supplying a medicine to the patient claim for payments based upon the unique US national drug code and so are correctly assigned; however institutional and medical claims do not use consistent coding, simply the shared INN, and thus there is no company benefit. Data were also presented to show that with no proper assignment, a company's own database can be contaminated with others' adverse event reports making it difficult for a company to conduct a proper risk benefit analysis.

European data from Vigibase (2012-2016) for *infliximab* show a spike in AE reporting following the introduction of biosimilars in late 2013 with improved brand-level reporting, but by 2016 AE reports using the INN only were running at 18% and thus not manufacturer specific.

Finally, data from Australia show that where biologics have a shared INN (*filgrastims*) the level of ambiguous reporting is high at 36% whereas with biologics with distinguishable INN (*epoetins*) the level of ambiguous reporting is very low at only 3%.

Based upon the evidence presented, IFPMA continues to support the BQ, to support pilot programmes, and believes that all drug regulators should use the BQ for relevant biological products, both proactively and retrospectively.

PRESENTATIONS on INN ASSIGNMENTS

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

Historically, substem B of monoclonal antibody (mAb) INN was indicative of the source or classification of the antibody. Infixes *-o-, -xi-, -zu-* and *-u-* were used respectively for antibodies of mouse, chimeric, humanised or human origin. Recently, a decision was made by the INN Committee to remove this infix from the name but to retain the source classification within the description. However, the IFPMA was calling into question the use of only a single word to describe the source, given that the source is really more complex than the v-domain final sequence homology to the nearest human germline sequence and may not be accurately described by a single word descriptor.

Thus the IFPMA proposed that the source description be a sentence fragment or phrase, rather than a single word, initially with five categories:

- human antibody derived from human B cells
- human antibody derived from transgenic animal
- human antibody derived from synthetic *in vitro* libraries
- engineered antibody derived from a non-human parent
- chimeric antibody with non-human variable domains

Such more specific nomenclature provides more scientifically sound descriptions of antibody origins with flexibility to accommodate future technologies such as bispecific and multi-specific antibodies. It remains relevant to continue to define the percent homology to the nearest human germline sequence but this would not be used to modify source description but for information only. This seems a more scientific approach to the origin of an antibody sequence and does not rely on a one word source descriptor.

Cadila Healthcare Ltd

Cadila Healthcare Ltd requested the INN Expert Group to reconsider substitution of the INN *saroglitazar* as per Article 9 of Annex 1 of the INN Stem Book, as the drug's development programme did not match that of a diabetes targeted drug and there is a high risk of errors in medication and prescription. There has been a definite misunderstanding amongst clinicians about the use of *saroglitazar* as it was not approved for type 2 diabetes but for dyslipidaemia, a quite different indication. *Saroglitazar* is given for controlling lipids, while anti-diabetic drugs are given to reduce HbA1c, fasting glucose and/or post prandial glucose sugars. *Saroglitazar* works by reducing liver lipids and is being further developed for treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC) due to its effects on lipid management. *Saroglitazar* has mostly non-significant and clinically irrelevant effect on glycaemic improvement and its improper use in diabetic patients may not lead to significant clinical improvement and may possibly worsen the condition. Furthermore, to increase the dose beyond that recommended for dyslipidaemia might precipitate serious AEs. Despite strong efforts to educate physicians in India, where the drug is approved for dyslipidaemia, it remains misconceived in India. The *-glitazar* stem associates it with other *-glitazar* drugs developed for type 2 diabetes, which are all failed drugs, and so a new stem for lipid management unlinked to the infix *-gli-* used for most diabetic drugs is required. The company strongly believes that this is an extraordinary circumstance that justifies substitution of a recommended INN.

In discussion, the value of the *-fibrate* stem versus *-glitazar* was raised; however, the company felt that chemically *saroglitazar* did not belong to the *-fibrate* family, with *-fibrates* being PPAR-α inhibitors while *saroglitazar* is not, although it shows some PPAR-γ inhibitory activity. It specifically works in the liver to reduce hepatocyte ballooning and is not proven to reduce glycaemic parameters including HbA1c.

Verona Pharma plc

The lead project for Verona Pharma, a small UK biotech company, is a dual phosphodiesterase 3/phosphodiesterase 4 (PDE3/PDE4) inhibitor for the treatment of respiratory indications such as COPD, cystic fibrosis and asthma. Verona had previously submitted for an INN for this inhibitor, codename RPL554, requesting a name with a *-fentrine* stem, defined by the WHO stem book as

'inhibitors of phosphodiesterases'. However, the INN Committee provided the INN *ovefemilast*, with the *-milast* stem for PDE4 inhibitors. Verona disagreed with this and participated in the Open Session to explain why.

PDE3 inhibition results in bronchodilation whilst PDE4 inhibition is anti-inflammatory. RPL554 shows both smooth muscle relaxation and the inhibition of release of pro-inflammatory mediators in *in vitro* studies, whilst in phase II clinical studies it gives a rapid and durable bronchodilation in COPD and asthma patients, and a reduction of inflammatory response markers following LPS challenge. Thus RPL554 demonstrates a dual PDE3/PDE4 inhibitory mode of action.

Previously, three other dual PDE3/PDE4 substances have been given INN with the *-fentrine* stem and with structural similarities between these three and RPL554, all being tricyclic dialkoxyisoquinoline derivatives, and also with the PDE3 and PDE4 inhibitory activities being essentially balanced, the company repeated its request for an INN with the *-fentrine* stem. In contrast, none of the substances with a *-milast* stem exhibit PDE3 inhibition, nor do they exhibit bronchodilatory effects.

To conclude, the *-milast* stem was inappropriate as it does not reflect the PDE3 bronchodilatory activity or the dual action of RPL554 and so the company respectfully requested an INN from one of the six names originally submitted.

Mapi Fleury, clinical pharmacist, Lausanne University Hospital

Ms Fleury recounted an incident of misuse of a drug through nomenclature issues and wanted to urge the INN Committee to take action.

Three years ago, a young boy with leukaemia was treated successfully with a bone marrow transplant at Geneva University Hospital. His post-treatment medication involved prednisolone and mycophenolate to prevent graft-versus-host disease, and amphotericin B at 100 mg twice a week intravenously to prevent fungal infections. To enhance his recuperation, he was allowed home with a community nurse administering the anti-fungal. However, after the first administration of amphotericin B at home, the boy reacted badly and after the second he was re-hospitalised with acute kidney failure. With significant intervention, renal function returned, amphotericin B was successfully re-administered and the boy was returned home. Unfortunately the same cycle of events occurred and he was re-hospitalised. Examination of the amphotericin B pouches from his home revealed that the amphotericin B preparation supplied by the community pharmacy (Fungizone®, prepared with deoxycholate) should not have been administered at the levels of 10 mg/kg/day (which is what the boy had been receiving); the hospital preparation had been Ambisome®, a liposomal preparation that is considerably less nephrotoxic. Searching databases for amphotericin B reveals six different preparations but despite each having the same INN, the same active substance, the side effects can vary. Ms Fleury brought this to the INN Committee as a warning and to request that the amphotericin B INN be modified.

In discussion, members of the Committee recognised that an active substance can be formulated differently but that it was for drug manufacturers to conduct a risk management plan for their preparations and that regulatory authorities should compel manufacturers to improve the drug name. Unfortunately this was not an INN matter as a single drug substance can only have one INN; it is an issue with formulation.

CLOSE OF MEETING

The Chair thanked all guests and experts for their comments, reminding participants that items discussed within the meeting must stay confidential until the final report is issued; with that the meeting was closed.