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62nd Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 12-15 April 2016

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

62nd Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

INTRODUCTIONS

The meeting was opened and participants welcomed by Dr Marie-Paule Kieny, Assistant Director General, Health Systems and Innovation, who took the opportunity to thank INN Experts for their work in the field of medicines nomenclature, discussion of which is led by WHO on behalf of all member states. The strength of INN is worldwide and its use continues to grow. The increasing number of INN applications is a challenge and requires the diligence of all INN experts whilst the integrated data management system developed by the INN Secretariat has been of great value. The challenge of naming novel substances requires the unique knowledge of the Expert Group whilst the initiative of an innovative school of INN has great potential.

The new Chair, Dr Patience Holland, thanked the ADG for her interest and support. Dr Holland has a background in chemistry and has spent many years in the UK scientific civil service. She informed the Expert Group that two vice chairs had been appointed, one for chemical substances and one for biological substances. With the huge number of requests to assess, she called upon the Group to be efficient and effective, to be pragmatic, and to be scientifically accurate.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, INN Programme, in her turn welcomed all participants. She noted the increased number of applications for INN, the evolving nature of naming substances, and acknowledged the extra work put in by experts in various working groups within the Expert Group.

NOMENCLATURE of INNs

During the 62nd Consultation, a total of 183 INN requests were discussed, including:

- 128 new INN requests, including 68 for biological substances
- 50 outstanding requests
- 5 previously selected proposed INN, against which a formal objection had been raised.

As a result of these discussions, 149 names were selected, which are planned to be published in List 116 of Proposed INNs (p.INN), while 29 requests were deferred for future discussion. Two requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One INN application was withdrawn just before the Consultation. One amendment is planned to be published in a forthcoming List of p.INN and one objection could not be retained. Five new stems/substems were selected and 7 suffixes were promoted to the pre-stem list.

The INN selection process

The Secretariat provided Experts with an insight to its behind-the-scenes work on INN selection. Applications are received by the Secretariat and processed for review on a batch basis by the Experts who make use of the online IDMIS system to provide comment. The Experts' pre-meeting comments are summarized by the Secretariat for face-to-face discussion at INN Consultations, highlighting any consensus and individual opinions provided by the Experts. There is a one month period following a Consultation during which decisions can be reviewed by the Experts, and further checks performed on trademark or other conflicts. Outstanding requests also have to be addressed at Consultations and Experts were reminded on how to make use of the IDMIS system to provide comment on these. Following the one month post-meeting review, the Secretariat informs applicants of the outcome of the Consultation. Information pertaining to the substance involved in a newly adopted name has to be validated by INN Experts, the Secretariat and the applicant prior to publication of a name in a proposed list of INN – the p.INN List. There then follows a 4-month period for objections and comments by stakeholders on the names within a p.INN List. Following this, all fully adopted names

for which there are no objections get published in the WHO recommended list of INN – the r.INN List.

SCHOOL of INN

A small group of INN Experts met in Jan 2016 to discuss the idea of setting up a 'School of INN'. Its role would be to educate the pharmaceutical industry on how to design and construct an INN, and to provide information to healthcare professionals on how to interpret an INN. The school would not only be educational but would raise interest in the science of nomenclature and help cultivate a future generation of INN experts. It has been found also that pharmacy students in general do not learn about INN and the value of the stem in referring to the mode of action of the drug. Further, there is a need to differentiate between INN and generic names that are not INN.

Barriers can exist to the use of INN in teaching and practice, for example, industry sponsored courses sometimes prefer not to use INN for commercial reasons. In addition, the extent of use of INN amongst healthcare professionals varies and there is a perception that INN are difficult to use. Consequently, a school to promote the use and understanding of INN on a global basis would be of tremendous value. It will be difficult to establish INN as a key theme in pharmaceutical textbooks but reaching out to the pharmaceutical industry to encourage them to use the INN would be a good start.

In the initial stages, the school would look to publish papers in scientific educational communities whilst (a revised version of) the INN publication *Guidelines on the Use of INN for Pharmaceutical Substances* would be useful in teaching and the promotion of INN. The school needs to be promoted on the web, with e-learning and the use of info-graphics. Its identity needs to be established, with its own logo, so that it can have a proactive presence in pharmaceutical companies and at industry workshops and conferences. Organising inter-professional online workshops would be useful, for example focusing on a particular theme or disease state that uses a range of drugs with different modes of action, whilst the school would proactively interact with professional pharmaceutical associations and the pharmacopoeias.

The school would be a virtual school and a steering committee of INN Experts should oversee its establishment and development. It is foreseen that a technical officer could assist the steering committee. Its website could be hosted on, or at least linked through, the INN website. Funding would be required for publication, advertising and for a full-time technical officer. Seed funding could be provided from the INN Programme but eventually it should be self-funded, for example with registration fees from courses, and interested partners and funding agencies would be approached for sponsorship.

In the course of discussing the idea of a School of INN, it was felt that a survey of the use of INN in practice and education would be useful, to gather information from the ground and to collect suggestions from practitioners and students. Consequently, a short survey comprising ten statements on the familiarity and usage of INN was developed, in which participants would respond to the statements on a five point scale. A small sample of institutions and organisations was selected for the survey, which was conducted over one month shortly before the 62nd Consultation. The statements addressed issues such as the level of knowledge of INN, their use versus brand names by practitioners and by educational establishments, and the use and meaning of stems.

There were slightly over 1000 respondents from 68 countries involving academics, healthcare providers, scientists, industrialists, regulators and students, with pharmacy students forming the highest proportion. Generally participants were aware of and familiar with INN. Comments were also solicited and the large number submitted provided an overview of the usage of INN in practice and education. Most universities' educational programmes use INN in teaching but the industry and healthcare sectors preferred the use of brand names. However, there is a gap in the education of healthcare professionals and even though INN is used in teaching, students were not familiar with the stem system. A greater understanding of the construct of the INN by the students will help them better appreciate the learning of pharmacology and therapeutics.

A further survey was made of drugs listed in a classical pharmacology text book (Goodman and Gilman's (12th Ed)). About three-quarters of drugs classified according to pharmacological action had useful common stems and classes of drug with no useful stem were typically old drugs.

In surveying the INN Experts present at the Consultation, it became clear that there was a degree of education on INN in their home countries but where this was organised by the pharma industry, there was a tendency for brand names to be used. The Experts also expressed their views that physicians in their home countries tended to use brand names rather than INN. Thus, whilst it would be useful to offer universities educational courses on INN, it was felt that practitioners should also be targeted. It was further highlighted that regulatory personnel tended to have a biological rather than a pharmacy background and these would be good targets for education.

The INN Expert group heartily endorsed the further development of this programme and the Chair congratulated the working group on their efforts on this project.

A draft info-graphics cartoon on the value of INN was shown to, and appreciated by, the Experts.

BIOLOGICAL QUALIFIER

The Expert Group was informed that the original plan to contract out a short study on the application of a BQ had not followed the appropriate WHO procedures and would have to be re-done. With this disruption to the previously agreed plan of action, the situation had been reassessed and it was felt that it would be better to proceed with a provisional implementation of the BQ scheme accompanied by a prospective impact study. This also would have the benefit of not spending a further six months conducting an interim impact study during which time national schemes may get implemented.

To expedite issues it was suggested that the BQ Working Group draw up terms of reference (TOR) for the impact study, which would be used to recruit a suitably qualified body, independent of industry and WHO, to gather data and report back annually to INN. The study would assess countries taking up the scheme, the number of BQs issued and how the database was accessed. Drug funding issues and the quality of the data in the database could be measured using published resources and data from NRAs. In this way, measuring hard rather than virtual data would be a better use of funds. There should be a three-year deadline for the study and if specified parameters were not met, the scheme would be dropped, but if uptake was good with good quality outcomes then it should get fully adopted by WHO. To ensure transparency, it was recommended that the TOR get published so that it would be apparent to all if the scheme is working. The body conducting the study should be announced and annual reports made public.

Consequently, it was proposed to the Expert Group that the BQ be implemented on a provisional basis and that a prospective study gets performed to enable evaluation of the impact of the BQ on access to medicines. Members of the Expert Group expressed support for this plan and agreed to its adoption.

With regard to the impact study, it was felt useful to have countries volunteer to initiate the BQ process and Experts were invited to approach their local regulatory and healthcare authorities in this respect. It would also be useful to gather data from countries not adopting the scheme to better assess the impact in countries that do. It would be important to have a random source of countries in the study so that there would be no perceived bias. Since the FDA has now provided seven biosimilars with random four letter suffixes, essentially the FDA equivalent of the WHO BQ, it would be valuable to include the USA in the impact study. There has been a good degree of communication between INN and FDA personnel on harmonising the BQ and FDA suffix. Assigning identical FDA suffixes and BQ codes would be invaluable.

Technically, a complete BQ system and database would take approximately two months to establish although random BQ codes could be generated within a few days. If needed, codes could be generated in advance and would be available immediately for applicants. Codes would only be assigned when an applicant approached an NRA for drug licensure and so it was likely that very few INN would ultimately be associated with a BQ code as few substances assigned an INN made it through to the licensure process.

NAMING NEUROLEPTICS

In the past, most neuroleptics were derived from phenothiazine or butyrophenone, and their chemical structure was informative regarding antipsychotic activity and side effects. Thus, stems based on chemical structure were appropriate. Currently, there are four stems for neuroleptics: *-peridol* (antipsychotics, haloperidol derivatives), *-peridone* (antipsychotics, risperidone derivatives), *-pride* (sulpiride derivatives) and *-apine* (psychoactive), although the latter two are not specific and many substances with these stems are not antipsychotics. There is no coherence amongst the stems and none of them identify the class as a whole. Also, many neuroleptics on the market have no stem. Whilst none of the stems indicate mode of action, no clinically effective antipsychotic is devoid of dopamine D2 antagonistic activity.

For clozapine and 'atypical antipsychotics' structure-activity is less important whilst emerging data indicate that various neurotransmitters are involved in efficacy and side effects, e.g. 5-HT, glutamate and acetylcholine.

There are many new neuroleptics under development including α-7 nicotinic acetylcholine receptor agonists, 5-HT2A antagonists, and PDE1, PDE9 and PDE10 inhibitors. New neuroleptics could be named on an *ad hoc* basis, creating appropriate stems as and when required, or alternatively a new prospective stem could be defined for DA receptor antagonists, neuroleptics, e.g. *-dant*, *-daleptic* or *-leptic*. The mode of action could be further defined by a substem, for example, *-ser* for action upon serotonin receptors, *-glu* for action upon glutamate receptors and *-col* for action upon cholinergic receptors. However, there would be no need to indicate the subtype of receptor (e.g. 5-HT1, 5-HT2) or the action on receptors (agonist or antagonist).

The INN Experts were requested to consider these comments.

TWO-LETTER STEMS

It was brought to the attention of the INN Expert Group that two-letter (single syllable) INN stems were often used in general language and as such creating new invented names avoiding such stems was difficult. Often they had been missed by regulators as they were such small entities and not easy to pick up. Six two-letter stems had been identified: '*aj*' and '*io*' as infixes ('*io*' also as a prefix), '*ni*' in nicotinic acid or nicotinoyl alcohol derivatives, '*ox*' as antacids, and '*ur*' and '*ac*' as suffixes. Some of these stems were outdated and some had been misused by the INN system in conflicting longer stems, for example, '*ni*' occurs in the stem *nitro-* whilst longer, more specific, stems such as *-fenac*, *-olac* and *-rac* are used instead of '*ac*'. The use of these stems needed to be reviewed. If the commonly used two-letter stems could be defined they should be retained and protected, whereas some did not need to be kept.

The Chair was grateful for this information which would be addressed by the stem review group.

BIOREVIEW REVISON 2016

Assigning INN to biological substances is an increasingly important part of the work of the INN Expert Group and INN Secretariat. The publication, 'International Nonproprietary Names (INN) for biological and biotechnological substances (a review)', otherwise known as the 'Bioreview', describes the stems, systems and General Policies in place for such substances. The current 2014 version is being updated with the new General Policy for cell therapies, an update of stems, a new section on aptamers and siRNAs, and a revised classification of enzymes. This will be available later in 2016. The outcome of current discussions on vaccine-like substances, monoclonal antibodies and the *–cept* stem (see below) will be published in a future version.

INN WORKING GROUPS

Consideration of new therapies

The INN system was established in 1950 by a WHA resolution to create a global nomenclature system for which there could be free and unrestricted use of the names by all interested parties. To achieve this, the INN Programme had to be based upon intellectual property law (within class 5 of the

Nice Agreement). The global recognition of INN as public domain elements of intellectual property legislation and practice resulted in having to have the two step process of proposed INN (p.INN) and recommended INN (r.INN) in order to help protect the rights of existing trademarks. Over several decades, technology has dragged the INN Programme, a small step at a time, into areas that were not in its original remit, with substances that are not exactly defined being named e.g. biopharmaceuticals, and gene and cell therapies. However, even from the start, many substances which were impure and for which there was only a crude definition, e.g. early antibiotics, received INN. In these cases, the benefit of having INN outweighed the lack of homogeneity. Such an approach stands in good stead for substances developed by current modern technologies. In addition, new groups of therapies need new rules (naming scheme + definition requirements).

INN utilisation is expanding along with an increase in the number of INN and pharmaceutical substances/groups. Indeed, the majority of pharmaceutical substances in use today is designated by an INN. The INN system is regulated by the INN Procedure, most recently revised in 2004 and adopted by the Executive Board in 2005, and further revisions are not undertaken lightly. However, INN General Principles (along with the INN Procedure) do not limit the types of therapies the INN Expert Group should be limited to in its selection of names. General Principles can be revised by the Expert Group and the INN Programme has independence in deciding which groups of substances get names and how defined.

Cell therapies working group

An INN scheme for naming cell therapies has been devised and several cell therapy substances have been assigned INN. However, several hurdles remain. One of these is that the border between cell and other therapies needs to be better defined; for example, autologous cells genetically modified *ex vivo* are considered by INN experts to be a gene therapy procedure whereas the USAN considers this to be cell therapy. Consequently, distinct names are being assigned to the same substance. Each cell therapy application also has to be examined thoroughly to understand how to assign the most appropriate name and often there is a paucity of data by which to fully define the cell substance.

The *-cept* stem working group

Following a debate at the 61st INN Consultation on whether the *–cept* stem (for 'receptor molecules, native or modified') was the appropriate stem for three particular INN applications, a working group reviewed the entire *–cept* class and its definition. Currently there are 22 INN with the *–cept* stem: 2 are soluble receptor fragments, 1 is a receptor fused to a toxin, 1 is a receptor conjugated to PEG, 1 is a receptor linked to a myristoyled peptide, while the remaining 17 are Fc-fusion proteins. These substances generally act by ligand trapping rather than being stimulatory substances. There are also 10 Fc-fusion proteins/peptides with alternative stems: several have the *ef*-prefix to indicate the presence of the Fc moiety, whereas prior to the use of this prefix several had been assigned a variety of stems reflecting their mode-of-action (MOA).

Following extensive discussion, the working group agreed that the essential part of the *–cept* stem is the receptor molecule and not the Fc or other moiety that may be fused to it, and therefore Fc should not become part of the stem definition. A receptor is defined typically as a membrane bound protein that receives a chemical signal from outside the cell. The biological response is usually unidirectional but in the case of cell-cell interaction, it can be difficult to define which is a ligand and which is a receptor. Also, several *–cept* substances bind to a cellular target rather than a free ligand. Thus, it was agreed also that the *–cept* stem could include cell surface molecules involved in cell adhesion and designed to block cell-cell interaction so that the stem is not restricted to classical pharmacological receptors.

One Expert emphasised that *-cept* substances are, like monoclonal antibodies (mAbs), major targeted biologics, and that *-cept* substances and mAbs share a similar binding structure (the two arms of the mAb being 'replaced' by the extracellular region of a receptor, for those with an Fc-fusion format), well defined specificity and similar MOA. As *-cept* substances are used more and more as alternative to mAbs, it was proposed to strengthen the parallel by considering that *–cept* substances could be activatory as well as inhibitory (in the same way as mAbs). This meant that *–cept* could include, for

cell-cell interaction, not only 'receptor' but also 'membrane ligand' acting as an agonist of an activatory receptor or an antagonist of an inhibitory receptor. Furthermore, in order to reinforce the coherence of the *–cept* and *–mab* stems, it was proposed that, in addition to the current substem used to define the protein, a second substem (*-ci-*, *-tu-*, etc.) could be used to define the target class, mimicking the substems used for mAbs.

With regard to Fc-fusion peptides, there was full agreement that Fc-peptides should not automatically be assigned a *–cept* stem and that they should continue to be named according to their MOA, making use of the *ef-*prefix and that inserting an infix to indicate the peptide class would be appropriate. However, the term CPCA (composite proteins for clinical applications) should be avoided.

In conclusion, it was agreed by all that *–cept* should not be restricted to Fc-receptor fusion proteins in order to allow for its use with future formats of a receptor protein, but that the working group should consider further whether membrane ligand substances should be included in the definition.

Polyethyene glycol (PEG) working group

The main issue currently being debated by the PEG working group concerns the nature and naming of the linker group, the chemical entity that links the PEG moiety to the principle active substance.

Vaccines-like working group

Several recent INN applications have fallen into a grey area of vaccine-like substances and the working group has been tasked with elucidating a way forward. According to the INN Bioreview (2014), traditional vaccines are not assigned INN, vaccine nomenclature being more the remit of the WHO Expert Committee on Biological Standardisation. However, the Bioreview states that recombinant (protein) vaccines may fulfil the requirements of being defined and homogeneous substances and so could be assigned INN, although to date none have. Also, peptide vaccines being defined molecules can be given INN and many have been so with the stem *–motide* being assigned to them. However, the peptides so far named with the *–motide* stem have immunomodulatory activity but are not true vaccines containing microbial-derived antigens that stimulate an immune response. What is not clear is whether entities such as viral/bacterial vectored vaccines (viruses/bacteria that have been genetically modified to express a heterologous antigen) and oncolytic viruses should be assigned INN. It is also not clear whether DNA/RNA vaccines should be assigned INN. There is a precedent for naming such substances in that viruses, bacteria and DNA plasmids used as gene therapies can be and are being assigned INN according to the INN scheme for gene therapy. Consequently, the working group has been tasked to determine to what extent vaccine-like substances should be given INN.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

The British Approved Names (BAN) 2017 will be published in August 2016 with an effective date of 1st January 2017, in line with the publication of the British Pharmacopoeia 2017. The BAN 2017 will contain the BAN 2012 (and Supplements 1-4) along with 31 new names that are being used in the UK market. The BAN 2017 will contain updated 'Action and Use' statements for radiopharmaceuticals and anticancer drugs along with a new appendix for names that are not harmonised across regions. Mr Evans and Dr Holland thanked those members of the Group that participated in the preparation of the new appendix and indicated that it should be a useful addition to the BAN publication.

European Medicines Agency (EMA)

The latest version of the 'Guideline on the acceptability of names for human medicinal products processed through the centralised procedure' came into effect on 1 January 2015. Based upon feedback from the INN Secretariat, it makes clear reference to the WHA resolution on the protection of stems (WHA46.19). The EMA's Name Review Group (NRG) assesses about 500 names per year. Objections to invented names containing INN stems or similar to INNs are frequently endorsed by the NRG in each meeting.

International Union of Pure and Applied Chemistry (IUPAC)

A project to generate a pdf file of the 'Blue Book' (Nomenclature of Organic Chemistry) for free web access has been initiated and is proposed to be completed by 2019 for the centenary of IUPAC. Another part of the project is to prepare an improved index.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs within the PMDA has two main tasks, preparing the draft Japanese Accepted Names (JAN) as the JAN Secretariat and preparing the draft Japanese Pharmacopoeia (JP) as the JP Secretariat. The JAN Expert Committee met on five occasions in 2015; 62 requests were considered and 60 JAN published. The proportion of biological requests over chemical requests has been increasing and reached 40% for 2015.

The 17th Edition of the JP was published in March 2016 and contains 1962 monographs; an English version will be published in September 2016.

The objective of the WHO Good Pharmacopoeial Practices guidance is to harmonise approaches and policies in establishing pharmacopoeial standards and the next International Meeting of world Pharmacopoeias will take place in Tokyo on 13-14 September 2016, co-hosted by PMDA. Following this, on 15 September, the JP will hold its 130th Anniversary Symposium, also in Tokyo.

United States Adopted Names (USAN)

The 2016 winter USAN Council meeting took place on January 7-8, 2016 in Lake Buena Vista, Florida where names for 37 drug substances were reviewed and discussed. Thirteen new stems or infixes with existing stems were approved and added to USAN's stem list. Two stem definition revisions were approved to harmonise with the INN programmes' definitions.

Policy discussions included trademark abandonment requests, biosimilar drug nomenclature, cellular therapy nomenclature harmonisation with the INN, and ISMP medication errors reports. Forty-three INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 62nd INN Consultation in April, 2016.

Through April 1, 2016 USAN staff will have processed, researched and made recommendations for 40 new USAN applications and forwarded this information to the USAN Council for its review and selection. Through March 2016, 23 USAN, 4 modified USAN and 1 revised USAN will have been adopted for 2016. Revenue will be realised for an additional 3 negotiations.

The 2016 summer meeting of the USAN Council is scheduled to take place July 21-22 at the American Pharmacists Association headquarters in Washington D.C.

United States Food and Drug Administration (FDA)

The FDA Office of Safety Evaluation, Division of Medication Errors Prevention and Analysis (DMEPA) examines invented names in relationship to USAN stems. As of this time, there is no provision for the default permission to utilize two-letter stems within the invented names (see above discussion on 'Two-Letter Stems'). The current policy is that all USAN stems are protected and should not be utilized as part of an invented name.

The FDA issued a draft Guidance entitled "Nonproprietary Naming of Biological Products", which addresses the definitions of and nomenclature of related biological products, biosimilar products, and interchangeable biological products. FDA documents designed for use by sponsor and applicants are classified as guidance.

A new Commissioner of the FDA, Dr. Robert M. Califf, has been appointed after approval by the US Congress.

United States Pharmacopoeia (USP)

The schedule for publication of the 'USP Dictionary of USAN and International Drug Names' has changed to coincide with the calendar year, and so the 2016 version is now available.

Dr Raffaella Balocco-Mattavelli, Group Lead of the INN Programme, was invited to the USP's Nomenclature and Labeling Expert Committee meeting of March 2016, to give a short introduction to the proposed WHO Biological Qualifier, which was well received.

The USP continued its Global Health Programs (GHP) to help improve quality of medicines by activities such as education, outreach, standards resources, consulting. A notable example is the Center for Pharmaceutical Advancement and Training (CePAT) in Ghana, a laboratory and education facility that was recently expanded.

World Customs Organisation (WCO)

The WCO provides leadership, guidance and support to Customs administrations to secure and facilitate legitimate trade, realise revenues, protect society and build capacity. Many members of the World Trade Organisation have undertaken to eliminate customs duties on medicaments and pharmaceutical active substances described in INN Lists. In order to ensure such duty free treatment, it is important to decide the WCO's Harmonised System Customs Tariff Classification (HS Classification) of INN substances, the HS being the International Convention for customs classification. Consequently, when new INN Lists are published, the WCO examines the List and decides upon the HS Classification of new INN substances. So far during 2016, the HS Classification for approx. 200 substances described in INN Lists 112 and 113 has been made and overall more than 4,500 INN substances have been subjected to HS Classification. In order to decide the HS Classification of INN substances, detailed information on chemical structure and pharmaceutical activity is often required. If additional information is needed, this is obtained directly from WHO. Moreover, a representative of the INN Secretariat is usually invited to attend WCO meetings on HS Classification of new INN substances. The WCO greatly appreciates the support offered by WHO in this way and hopes to continue the close cooperation between the INN and WCO.

EU Openmedicine Project

The goal of the EU funded 'openMedicine' project is to enhance the safety and continuity of cross-border (and national level) healthcare through interoperable 'ePrescriptions' and to propose concrete solutions to the delivery problem. It plans to achieve this by univocal identification of a medicinal product dispensed in another country, and if and where substitution is permitted or required, dispensation of an equivalent or similar product in line with national regulations. Overcoming the challenges will involve development of a common data model, common nomenclature, harmonisation of therapeutic and economic substitution, and coordination of the practical solutions and policy recommendations of the openMedicine project with the policy recommendations of the EU/US roadmap process for eHealth cooperation.

CLOSE OF MEETING

The Chair was grateful for the support of the INN Secretariat and Experts in this her first role as Chairperson of the INN Expert Group. She also thanked everyone for their diligence both before and during the Consultation.

Next Meeting

The 63rd INN Consultation will take place in Geneva on 18-21 October, 2016.

Open Session for INN Stakeholders

62nd INN Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 12 April, 2016

Dr Patience Holland, Chair of the INN Expert Group, welcomed stakeholders and INN colleagues to the Open Session for Stakeholders Meeting adjoining the 62nd INN Consultation. Stakeholders provide valuable information that assists INN Experts in assigning INN whilst the progressiveness of the WHO in inviting presentations on policy issues from stakeholders was acknowledged. All participants were requested to respect the confidentiality of the information shared during the meeting until the meeting report is in the public domain.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team welcomed participants on behalf of WHO and thanked Dr Holland for taking on the position of chair of the INN Expert Group.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, INN Programme, similarly welcomed all to the meeting and expressed her pleasure in meeting stakeholders face-to-face.

PRESENTATIONS on INN ASSIGNMENTS

Jazz Pharmaceuticals

Jazz Pharmaceuticals continued to object to the INN *dexamfetanol carbamate* assigned to their product JZP-110 on the grounds that the *–bamate* stem was inconsistent with its known pharmacology. Since stems should define pharmacologically related groups, it would be more appropriate to use the *–faxine* stem with *solrifaxine* the proposed INN. JZP-110 is a selective inhibitor of norepinephrine and dopamine uptake and the *–faxine* stem includes such inhibitors, amongst other activities. In contrast, the *–bamate* stem does not include such substances. New information from a phase II clinical trial on narcolepsy treatment also showed therapeutic effects directly opposite from the *–bamate* class, whilst further new data showed a low potential for abuse in a human study (previously the low abuse potential had only been demonstrated in rats).

A second argument against the assigned INN was that *dexamfetanol* lacked distinctive sound and spelling. In a Phonetic and Orthographic Computer Analysis (POCA), *dexamfetanol* scored >70% against *dexamfetamine* which suggests a high risk of medication errors; *solrifaxine* would be much more distinct.

A third concern was that the similarity between *dexamfetanol carbamate* and *dexamfetamine* would lead to confusion and misunderstanding amongst patients and health professionals resulting in an inappropriate perception of abuse potential and thus reduced access to JZP-110. In contrast, *solrifaxine* would provide for clear identification, safe prescribing and dispensing.

A consultant pharmacologist to Jazz Pharmaceuticals reinforced the arguments presented by the company, that the INN *dexamfetanol carbamate* would create an erroneous impression that JZP-110 was an amphetamine and as a consequence would limit appropriate patient access to JZP-110.

erytech

erytech is a small late stage biotech oncology company, focusing on its 'erycaps' technology platform which involves entrapment of therapeutic compounds inside donor-derived red blood cells (RBCs) using controlled hypotonic swelling followed by hypertonic stress. Its product eryaspase comprises a homologous dispersion of erythrocytes encapsulating asparaginase and was described as a circulating bioreactor manufactured from recombinant *E coli* derived asparaginase and erythrocytes from blood transfusion centres. Eryaspase is not simply asparaginase combined with RBCs, but combines the capacity of erythrocytes to actively pump asparagine from plasma followed by its cleavage into aspartic acid and ammonia by the entrapped enzyme, leading to plasma asparagine depletion.

Assignment of an INN to eryaspase would distinguish it from other available preparations of marketed free asparaginase and aid prescribing and dispensing.

Further, eryaspase does not deplete glutamine as does the free enzyme and so has an improved toxicity profile, as demonstrated in a phase 2/3 clinical trial. The company is investigating two further enzymes – methionine-γ-lyase and arginine deiminase – for RBC entrapment as additional tumour starvation candidates, and an INN for eryaspase would be useful when developing further products using the erycaps technology platform.

In discussion, an INN Expert opined that the company was seeking an INN for a process and that perhaps the more appropriate route would be to consider this as a cell therapy and name accordingly.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologic Medicines (ASBM)

The ASBM congratulated the INN Group on its leadership on the issue of biologics naming. Its message at this critical moment was to proceed expeditiously with a pilot study. Its data indicate strong physician support for clear, distinguishable naming. Patient groups in multiple countries have expressed interest in the BQ programme and distinguishable naming is essential to promote widespread biosimilar adoption and confidence in their use. The ASBM has conducted surveys amongst physicians on distinguishable naming and has presented its data to national regulators, often at their invitation. Its most recent survey amongst US physicians shows overwhelming support for distinguishable naming although a good fraction of physicians bearing 'no opinion', suggests a lack of familiarity with biologics and that education on biosimilars remains a clear need.

Pharmacists typically use three names, tradename, non-proprietary name and the (US) NDC code. Interestingly, whilst US pharmacist organisations have opposed distinguishable names, individual pharmacists attending continuing education programmes on the complexity of biologics compared to simple chemical molecules, showed clear support for distinguishable naming. So despite past objections, ASBM continues to work with pharmacists' organisations to emphasise the importance of distinguishable naming. It will continue to pursue its educational programme on this and to respond to concerns that exist. In conclusion, the ASBM urged the INN Group to proceed with BQ implementation.

Generic Pharmaceutical Association (GPhA)

GPhA represents the manufacturers and distributors of a variety pharmaceutical products, including finished generic products. Many members have developed and manufactured biosimilars for some time and the GPhA Council works to ensure a positive regulatory, reimbursement, political and policy environment for them.

The 2015 WHO proposal for a 'biologics qualifier' composed of a non-meaningful 4-letter code with an optional 2-digit checksum, would be voluntary, would not be part of the INN, would be assigned by WHO and be applied to all biosimilars. The GPhA felt that a BQ will increase naming complexity and the risk of confusion regarding prescribing, dispensing and substitution. It would be unclear whether or not the increased complexity would provide the desired benefit of enhanced pharmacovigilance or create more reporting confusion. Due to these risks, the GPhA stated that the proposed system must be independently tested to ensure it improves identification and reduces risks. Indeed, the BQ scheme should not be implemented until a consensus has been reached and is supported by an impartial and thorough impact assessment.

The GPhA felt that the historic naming system of tradename plus INN works well. Indeed other identifiers are also present such as the company name, lot number and (in USA) the national drug code, which are used successfully for identification and tracking. Thus, whilst GPhA applauds the WHO's interest in developing a global identification system for biologics, it expressed concern that a random 4-letter BQ code will be meaningless and difficult to remember and transcribe. In addition, uncertainty around retrospective application of the BQ may lead to a discriminatory and anticompetitive situation between existing reference and future biosimilar medicines. Finally,

extremely short timelines for a WHO final BQ report will hamper a comprehensive and meaningful impact assessment and there has been a lack of transparency regarding the few national drug authorities that have requested the development of such a system.

Safety is enhanced by the global use of non-proprietary names and the GPhA expressed support for the WHO proposal to keep the INN the same for reference products and biosimilars. The US is an emerging market for biosimilars with the first one approved by FDA in March 2015. The GPhA is concerned also about the FDA proposal to attach a 4-letter suffix to the INN and advocated that biologic products with the same drug substance should contain the same INN.

The WHO BQ needs to be voluntary and should not be implemented in countries with measures that already assure unambiguous identification of biological products. If used it must be applied to all biologics and be applied both retrospectively and prospectively. It should not be required for prescribing and should not include a manufacturing site designation.

In conclusion, the GPhA requested WHO to make fully transparent the positions of all stakeholders during the consultation process, especially the DRAs that requested this action by the WHO. A thorough impact assessment study needs to be conducted and the WHO must be prepared to abandon the BQ concept if the impartial assessment highlights problems with the proposal.

In discussion, the Chair clarified that the BQ would be for all biologics and not just biosimilars. Furthermore, the proposal advocates retrospective application although it is recognised that local legislation may not allow this to occur. The INN Experts also acknowledged that whilst a thorough assessment study is needed, there was a need to move ahead as already some national authorities were activating their own biosimilar identification scheme. All agreed that time was of the essence.

International federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The IFPMA expressed strong support for the BQ. It would enhance patient safety by linking all global systems in use today around the world. The IFPMA recommended that the BQ should now be used in conjunction with the INN, as a tool for pharmacovigilance, should form part of the official record of authorisation of a biological medicine, and should be given to all biologic drug substances awarded an INN. The IFPMA also recommended that all drug regulatory authorities (DRAs) should implement the BQ as soon as possible, and that DRAs using the system passively can choose to permit marketing authorisation holders to include the BQ in product information and labelling. The WHO should also develop practical advice for DRAs for their implementation of the scheme to reduce their administrative burden.

The IFPMA further recommended that subsequent to implementation, DRAs should provide regular feedback to WHO on the operation of the BQ, that surveys of patients and health professionals should be undertaken to assess awareness and impact, and finally that WHO should coordinate educational workshops for all stakeholders.

In conclusion, the IFPMA repeated its strong support for the BQ scheme, that it would achieve its intended outcomes and that it should be implemented as soon as possible.

Medicines for Europe

Medicines for Europe (formerly European Generic and biosimilar medicines Association – EGA) and its Biosimilar Medicines Group continued to appreciate the INN Expert Group's efforts to counteract the proliferation of divergent global schemes for naming biologic medicines. However, it could not support the current final INN proposal for a Biological Qualifier (BQ) as concerns remained regarding its added value over other existing and validated systems. There was also a lack of transparency regarding which WHO member states supported the BQ scheme and with retrospective application only being recommended and not mandated, there was the possibility of creating an undue differentiation among biologic medicines. In contrast, regulatory science supported that 'comparable' and 'highly similar' biologics share the same INN and the scientific principle of comparability should be applied to all biologics including biosimilars.

Introducing a BQ has far reaching consequences and could only be feasible if the need for it was clear and documented, and the proposal was shown to be effectively and safely addressing this need. The INN approach to assessing impact was appreciated and had been a long standing request from the Biosimilar Medicines Group. The reference to the WHA resolution on access to biotherapeutic medicines was welcomed.

The scope of the BQ impact study should cover all intended areas of use of the BQ and ideally should focus on gathering input from all concerned stakeholders on an international basis. Medicines for Europe was concerned that the timelines of the study were overly ambitious and had questions regarding when the study methodology and outcome would be made public, how WHO member states would be consulted, and what the next steps would be.

Different approaches to biologics remain a fact. Developments are underway in the USA and the Japanese system is working well. Consequently, the organisation wished to know which WHO member states supported the BQ, why use was not being made of validated international tools such as ISO IDMP, what would happen if the impact study did not confirm the supposed benefits of the scheme, and finally what was the status of discussions with the FDA and the proposed FDA naming scheme.

The Biosimilar Medicines Group's recommendations were that the basic science-based approach of INN plus brand-name is by far the best approach, that the BQ must be evidence based approach, that there must be transparency on WHO member states official position and that in the long run any system must be robust and fair.

In discussion, the Chair reminded the meeting that divergent schemes were already in place, which was why the WHO INN was developing the BQ scheme, that the BQ would apply to all biological substances and that it had been made clear from the start that the BQ would not be part of the INN. Stakeholders were also informed that the timeline of an assessment study was still being discussed internally and that dialogue especially with the US FDA was ongoing, with comments forwarded to the FDA being publicly posted (by FDA).

The FDA observer at INN, who also liaises with the USAN council, confirmed that the FDA is working with INN to harmonise as much as possible, as having different identifiers would be detrimental. To date, the FDA and INN proposals appear similar. The differences are that the FDA system has no checksum and has a hyphen linking the code to the USAN; however, the FDA system did not intend to change the USAN, the suffix being added to label the product.

The Medicines for Europe's contention that the sole use of INN plus brand name as in the EU was adequate, was challenged. The EU system works relatively well but where similar practices have been adopted in other jurisdictions, there have been problems where biosimilars have the same INN. For example, Australia has registered three *filgrastims* and almost 40% of adverse events are listed simply as *filgrastim* with no way of knowing which one. Similar data has derived from The Netherlands. The idea behind the BQ was to add a bit of extra checking; it would not be perfect but it would add value.

DISCUSSION on MONOCLONAL ANTIBODY NOMENCLATURE

The Antibody Society is a non-profit trade association founded in 2007 representing a number of companies, large and small, involved in the research and development of antibody therapeutics. The Society had been charged by its members to challenge the 2014 changes to mAb INN assignment and so had been invited to attend the open session to discuss naming issues face-to-face with INN Experts. The issues had been documented in a paper by Jones et al, 2016[1], whilst the Society involvement was further backed by a petition signed by 290 individuals from 98 commercial and academic institutions from 23 countries.

The INN designation of the source of an antibody by use of a specific substem (*-omab* for murine, *-ximab* for chimeric, *-zumab* for humanised and *–umab* for human) had been straightforward. But with

[1] Jones et al, MAbs 8:1-9, 2016.

the field growing explosively with highly varied and sophisticated approaches to generate mAbs, an expanding repertoire of Ab engineering options and an increasing number of antibody-based therapeutic platforms, the Society considered that the naming scheme had become outdated and a system identifying source was no longer relevant. Furthermore, in the current (2014) version, source substems are now defined, not by their origin, but by amino acid sequence comparison of the end product to sequences in IMGT, the ImMunoGeneTics international information system. On the other hand, the USAN system requires a >85% sequence identity with human sequences to determine humanisation. This leads to strong inconsistences. Of the 19 marketed humanised mAbs (those with a *-zumab* stem), none would be classified as humanised under the new rules.

The Society felt that the new rules are scientifically flawed as the amino acid sequence does not define human-ness, are inconsistent with previously assigned INN, and do not consider advances in technology. A further criticism was that the designated IMGT database and search tool were not freely available, with payment required for commercial entities. The Society foresaw a risk that companies were already designing mAb therapeutics simply to obtain the humanised (*-zumab*) stem and so alternative approaches are needed. They suggested that the source substem should be dropped and a system developed for near future developments that concentrates more on functional properties should be considered. In conclusion, the Society requested the INN Programme to work with key stakeholders in finding an optimal solution to these issues.

Following this presentation, it was highlighted for information that IMGT is freely available for academics; however, it was correct that there is a cost for companies to cover copyright.

There followed a presentation by the members of the INN mAb Working Group.

INN for mAbs were introduced in 1991. The naming process had to accommodate an enormous number of mAb substances, which form the largest class of biological medicines. INN are given to mAbs well in advance of regulatory licensure and with many not making it to the approval stage, many names are not used. MAb INN need to provide information on the target, the sequence and need to be able to accommodate advances in technology. The Experts acknowledged that recent modifications to the naming process had been criticised in the paper by Jones *et al*., 2016 and by the Antibody Society, which was the reason for the current discussion.

The criticisms levelled by Jones *et al*., 2016 were that the revised system is critically flawed, ambiguous and contradicts scientific literature. Also that classification was inconsistent and that omission of the sequences encoded by the J-region genes was a major flaw. The paper further stated that the 85% sequence threshold was arbitrary, did not correlate with improved therapeutic outcomes such as reduced immunogenicity, and that there was no specific definition of what constitutes a human antibody and what differentiates it from a humanised antibody. A yet further criticism was that the new rules had been applied retrospectively with no notice period. An initial rebuttal from the INN Experts was that threshold percentages to define INN infixes had not been published by the INN Expert Group.

The basics of mAb nomenclature, as described in the BioReview, were summarised. INN for mAbs are composed of a fantasy prefix, two substems and a common stem *–mab*, as the suffix. The *–mab* suffix is used for all substances with an immunoglobulin variable domain. The substem (or infix) adjacent to the *–mab* stem denotes the species upon which the immunoglobulin sequence is based with the substem preceding that in the INN indicating the target class.

In a chimeric antibody, the chains contain a foreign variable domain (originating from one species other than human, or synthetic, or engineered from any species including human) linked to a human constant region; the variable domain has V region amino acid sequence which when analysed as a whole is closer to non-human species than to human. A humanised mAb has CDRs that are foreign (originating from one species other than human, or synthetic) but with the remainder of the antibody being human; the variable domain has a V region amino acid sequence which when analysed as a whole is closer to human than to other species. Humanisation assessment is based on the resulting amino acid sequence and not on the methodology *per se*, which allows protocols other than grafting to be used.

In addressing the four major issues highlighted by the Jones *et al*., 2016 paper, the INN Experts explained firstly that inclusion of the J region in the assessment would be unrealistic and that for sequence comparison the most relevant part of the molecule is the V region. Secondly, the criticism that the inclusion of macaque variable regions in the IMGT database can skew the comparison away from human was considered unfounded and that these are valuable with respect to having the maximum amount of available information. In response to the Society's comment that choosing an 85% cut-off for 'human' is purely arbitrary, the INN Experts reiterated that the INN system does not in fact prescribe any percentage thresholds for distinguishing human/humanised/chimeric mAbs[2]. Finally, the criticism that even human antibodies may fail the 85% threshold was unfounded again because the INN system does not prescribe a percentage cut-off. The decision of the INN Expert Group is based on the results of V region amino acid sequence alignment as a whole (IMGT/DomainGapAlign) and information on the source of the mAb provided by the applicant.

Keeping in mind the main goal in assigning mAb INN, sequence alignment should remain a major tool; however, other data such as 3D conformation could be a useful adjunct for example by analysis of superimposed structures. In general 3D structures are becoming more routine, including for mAbs, and indeed the recently published Annex document for INN requests that a Protein Data Bank (PDB) file be provided, if available.

In conclusion, INN experts are responsible for selecting INN and the mAb Working Group had noted the concerns raised in the Jones *et al*., 2016 paper. The Bioreview 2014 provides the current reference for mAb INN but percent thresholds are not official INN policy. The INN Experts welcomed dialogue with stakeholders, now and in the future.

General Discussion

The Antibody Society acknowledged that whilst the reason to move from murine to more human-like antibodies was to improve the immunogenicity profile, the source substems do not implicitly imply immunogenicity, although undoubtedly the substem does have an impact on the product. Ultimately this was why the discussion was being held. The INN Experts now look at the amino acid sequence to categorise mAbs but it was not clear that this was the best way as the sequence says nothing? about immunogenicity. In addition, the impending addition of monkey sequences to the IMGT database was likely to impact adversely the outcome of sequence comparison analyses. The Society expressed concern about creating an artificial boundary between humanised and chimeric mAbs since there is a continuum between various animal sources and human.

Nonetheless, the INN Experts felt that there was no alternative to the use of sequence data in classifying mAbs. It had value, as a humanised mAb was expected to have sequences closer to human than non-human and anything not closer to human was chimeric. But the ultimate aim had to be to obtain antibodies that were highly effective in patients even if that meant having a sequence further from human; other aspects are more important for the Ab than the sequence, such as specificity. The INN does not predict whether an antibody will be good or bad medicine. What is important is what should be reflected in the name, or not.

The FDA representative pointed out that the 85% homology threshold between chimeric and humanised mAbs is applied by USAN but not used by the INN. Since at least half the mAbs have both a USAN and an INN, this needed to be clarified. The INN confirmed that its approach is based on an assessment of the totality of evidence presented and not simply on a percent cut-off. Too much was being read into the INN, which says nothing about clinical efficacy, and the limitations of the INN have to be appreciated.

In bringing the discussion to a close, the Chair noted that there was no right or wrong, but inferences were being drawn by stakeholders so the Experts need to improve clarity and explain what has been done.

In conclusion, the Society had enjoyed the discussion. It was all about having a biological medicine that works in patients and not about sequences. All participants need to engage in constructive

[2] An 85% cut-off is used by the USAN naming system, but not the INN

discussion to work towards how best to catch that in a name without negative connotations. The connotations in old names and differences in defining boundaries within a gradient argue for a fresh start with names that have no previous connotation.

Close of Open Session meeting

The Chair had found the discussions enlightening. In closing the meeting, she thanked all participants for their presentations and discussion.