

***54th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 1-3 May 2012***

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

***Quality Assurance and Safety: Medicines (QSM)
Essential Medicines and Pharmaceutical Policies (EMP)
World Health Organization, Geneva***

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INTRODUCTION

The *54th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances* was held in Geneva on 1-3 May 2012. The meeting was attended by members of the INN Expert Group, the INN Advisory Group on biologicals, several specialists who assisted in specific nomenclature issues and the full INN Secretariat. The Consultation was preceded by a Stakeholders Meeting at which members of the pharmaceutical industry made representation to the Expert Group.

The intergovernmental organizations and national agencies involved or interested in drug nomenclature that were represented as observers included the British Approved Names (BAN), European Directorate for the Quality of Medicines and Healthcare (EDQM), International Union of Pure and Applied Chemistry (IUPAC), Japanese Approved Names (JAN), United States Approved Names (USAN), United States Pharmacopoeia (USP), United States Food and Drug Administration (FDA) and the World Intellectual Property Organisation (WIPO).

Dr Lembit Rägo, Coordinator, Quality and Assurance & Safety: Medicines (QSM) opened the meeting on behalf of the WHO and updated the group on current issues. In conjunction with the 2012 World Health Assembly (WHA), there will be a high level meeting, sponsored by Brazil, to improve collaboration with and between national regulatory authorities and to further develop regulatory capacity; a previous such meeting had been held in Singapore. Funding remains difficult and much of the forthcoming WHA will address WHO reform being brought about by the realities of limited finances. The Essential Medicines Pharmaceutical Policies (EMP) Department remains under threat although the INN Programme, having its own funding source through fees, is not as badly affected as other programmes where staff numbers are having to be reduced. Also, for staffing, the WHO is thinking ahead to a model where people from national settings are seconded to WHO; this also improves links with national regulatory authorities and currently the division has three staff seconded from regulatory authorities, two from the UK and one from Ghana.

The new director of EMP, Mr Kees de Joncheere, has recently been appointed and will start at EMP on 14th May (2012). He was previously at the WHO European regional office in Copenhagen and is a very experienced WHO staff member. For this the 54th INN consultation, Dr Rägo wished the participants well and was grateful for their continuing support of the programme. Their collective knowledge is a great asset to WHO and a great help to the INN Secretariat.

The Chair of the meeting, Prof. Derek Calam, welcomed the experts to the INN plenary session. There is a full agenda with 83 new applications of which 40% are for biological requests. The Chair was grateful for all the work conducted prior to the meeting by the experts and by the Secretariat alike.

The INN Programme Manager, Dr Raffaella Balocco-Mattavelli similarly welcomed the participants and thanked them and her team for their input between and at meetings.

SELECTION of INNs

During the Consultation, a total of 104 INNs were discussed, including:

- 83 new INN requests, including 33 for biological substances
- 21 outstanding requests

As a result of these discussions, 96 new names were selected, which are planned to be published in List 108 of Proposed INNs, while 4 requests were deferred for future discussion. Three requests were rejected by the INN experts, as the substances did not conform to the criteria for INN selection. One INN request has been withdrawn during the selection process.

Two new stems have been selected and three suffixes have been promoted to the pre-stem list.

ACTION and USE STATEMENTS

A few years ago a small team within the Expert Group began reviewing Action and Use (A&U) Statements published in the p.INN Lists with its objective being to assess and reassign, where necessary, the stem definitions and preferred expression for A&U. At this meeting the team reported on proposals for Hormones and hormone release-stimulating peptides, Anti-infectives, and Immunomodulators and immunostimulants. The proposals were accepted although these will be for internal use only by the INN Secretariat and the Expert group.

REVIEW of NOMENCLATURE for PEGYLATED COMPOUNDS

Pegylation is the attachment of a polyethylene glycol (PEG) chain to a drug and is usually performed to increase the half life of the drug after administration. The PEG chain is derived by polymerisation of ethylene oxide and pure macromolecules with up to six ethylene units are readily available. High molecular weight polymers are mixtures with a range of molecular weights. Pegylated drugs are usually named with a one-word INN starting with the syllable *peg-*, or a two word name with a unique identifier word followed by '*pegol*'.

In a document on pegylated compounds tabled for discussion, all pegylated INN were presented in tabular form along with the available information for the pegylated moiety from the INN definition. In many cases information is missing concerning the details of the pegylation; frequently for the size of the pegol moiety and occasionally for other features such as the nature of the linkage to the active moiety. This may have resulted from limited information being available at the time of the application; however, a subsequent examination of the literature or the web, for example USAN records, can uncover more information on the pegol chain. The precise nature of the pegylation, the attachment sites, the size of the chain(s), whether complete or partial pegylation, will all affect the rate of release and thus the PK and clinical features of the substance; thus this information is important for the definition. Of note, PubMed provides 286 references to *pegol*, all of which mention *certolizumab pegol*, yet significant information on the pegylation of this substance is missing from its INN, including linkage.

There was no clear consensus on trying to fill gaps in r.INN definitions. The INN programme cannot readily amend published definitions, even if the additional data could be gleaned from the companies, unless there is a specific reason or request to the INN

programme to do so, for example where a clear error had occurred. However, for future INN applications the tabled document recommended that the definitions of pegylated substances should provide the details of the end group, the chemical structure of the polymer chain, the average number of repeat units in the chain (to two significant figures), the nature of the linker, and where the linker is attached to the active moiety. Where information is lacking for published INN, the tabled document could be supplemented with data from the literature and the web, to whatever extent this can be achieved, and published as a stand-alone document.

Further, with pegylation becoming an increasingly popular and convenient way of modifying a substance for improved PK properties, the Group will run into difficulties in creating distinctive names. Use of *peg-* as a prefix is already heavily used and two word names with *pegol* are close behind. In the future there will be a need for new ways to create names for pegylated compounds that are distinctive.

UPDATES from COLLABORATORS

British Approved Names (BAN)

The publication of supplement No.1 to the BAN 2012 has just been completed. There are two points to highlight, (i) it was noted that there were differences between the information received from the manufacturer and that included in the published INN list for *conestat alfa*, and this is being investigated, (ii) attempts have been made to obtain the sequence of *belimumab* from GSK and a response was awaited. Any information received in the near future will be forwarded to the INN Secretariat. The Secretary and Scientific Director to the BP Commission retired in December 2011 and his replacement is Dr Samantha Atkinson.

International Union of Pure and Applied Chemistry (IUPAC) and International Union of Biochemistry and Molecular Biology (IUBMB)

Work is continuing on the revision of IUPAC 'Blue Book'. This edition will recommend preferred organic names. The revision is a complicated process and will impact on INNs. A sub-committee of Division VIII, the Joint Commission on Biochemical Nomenclature (JCBN), which is joint with IUBMB, is currently working on flavonoids and on small molecules of interest to biochemists.

Enzymes are being increasingly well characterised and the IUBMB published list of enzymes has been growing for some years at about 50-100 per year, but in 2010 there were 167 and in 2011 there were 365 new entries. The Principles of Chemical Nomenclature, A Guide to IUPAC Recommendations, 2011 (ISBN: 978-1-84973-007-5, RSC Publishing, 2011) was published in November, 2011.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

Japanese Approved Names (JAN) and the Japanese Pharmacopoeia (JP) are administered by the Division of Pharmacopoeia and Standards for Drugs within the PMDA. The JAN expert committee has 14 members and considers applications four times per year. The number of names published has been increasing each year and for 2011-2012 there were 53 names published, of which 7 were for biologicals. The JAN database is on the NIHS website and can be searched by JAN name, chemical name or CAS registry number; the chemical structure can also be downloaded (<http://molddb.nihs.go.jp/jan/index.aspx>).

The 16th edition of the JP came into effect in April 2011, with an English version available for free on the PMDA website (<http://www.pmda.go.jp/english/pharmacopoeia/online.html>)

United States Approved Names (USAN)

The 2012 winter USAN Council meeting took place in Florida in January. New names were recommended for 41 substances and a new USAN Council member, Dr Judith K Jones, was welcomed. Four new stems (*-lisib*, *-pertin*, *-rian* & *-sarm*) and one revised stem definition (*-clidine*) were approved and posted on the USAN website. Two new designations for radicals and anions (*Elaidate* & *Napadisylate*) were approved. Thirty-six INN applications for proposed USAN were sent to the INN for discussion at this Consultation. Up to April 2012, 62 new USAN applications were processed, researched, recommendations made, and forwarded to the USAN Council. In the same time period, 36 new USAN and 15 modified USAN were adopted during 2012 and revenue was realized for an additional 3 negotiations.

The 2012 Summer Council meeting is scheduled for July 12-13 in Washington DC.

Food and Drug Administration (FDA), USA

Positive discussions have taken place between INN and FDA about further FDA representation at INN meetings in the area of biologics. Within the FDA, biologics are divided between CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research), with the greater proportion in CDER which handles biotherapeutic proteins including monoclonal antibodies. The particular expertise that the INN Secretariat would appreciate from the FDA needs to be confirmed taking into account that CDER uses INN and USAN, whilst CBER which handles primarily blood products, vaccines and cell therapies, does not.

It is also worth noting that the FDA provides input to USAN ballots and that for monoclonal antibodies, decisions get made based on information reviewed by CDER staff in the human monoclonal antibodies division. The Chair opined that with CBER heavily involved with the WHO ECBS on blood products and such biologicals, in which the INN is not involved, that representation specifically from CDER might be best.

United States Pharmacopoeia (USP)

In the USA a law has recently been passed governing follow-on biologics and which concerns the price of medicines more than their science. The law has consequences for the USP and its policies. The USP is of the opinion that two such follow-on biologics are the same until shown otherwise, and the burden of proof is on the manufacturer; so if there is a desire to have a new monograph in the USP, the manufacturer must have a test to show that their product is different (from an already marketed product). For example, for *epoetin alfa* and *beta*, these cannot be distinguished in current tests submitted to USP, and this leads to the conclusion that there will be only one monograph for *epoetin*, applicable to both *alfa* and *beta* (and probably without reference to *alfa* and *beta* forms). The details remain to be established.

A new edition of the USP dictionary of nonproprietary names has been published and again publishing the pronunciation of drug names is important to USP. The pronunciation has also been included in the new edition of the USP-NF. There are plans to record the sound files with these names and provide a “talking dictionary” as an online product or maybe mobile phone application.

USP Nomenclature committee approved the policy for naming drug products containing salts, which will take effect next year, on May 1 2013. Together with an Advisory Group with participation of the industry and all major pharmaceutical professional associations, USP is working on the communication and education plan to provide information to the practitioners. The policy recommends that the names of drug products containing salts shall be based on the active moiety. Names based on the salt are still acceptable if it is clinically relevant.

World Intellectual Property Organisation (WIPO)

Whilst the WIPO representative had no new update for the Group, the INN Secretariat informed the Group that the INN programme continues to collaborate closely with WIPO and that INN manager Dr Balocco-Mattavelli had been invited to attend the twenty-seventh session of the WIPO Standing Committee on the Law of Trademarks, Designs and Geographical Indications (SCT), to be held in Geneva from September 18-21, 2012, in order to brief the SCT on the functionalities of the recently launched WHO Global Data Hub on INNs. WIPO continues to distribute INN material and together with the INN Secretariat wishes to create a way of including, under the control of WHO, INN data in WIPO databases.

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

The MEDICRIME Convention was established by the Council of Europe to establish counterfeiting offences and a framework for national and international cooperation in combating counterfeit medicines. eTACT is EDQM's anti-counterfeiting traceability service for medicines. It involves generating a unique medicine identifier (UMI) at the manufacturing stage that can be traced and verified by the different stakeholders in the legal supply chain through to the pharmacy, including online pharmacies, and the patient.

The European Pharmacopoeia (EP) bases the titles of its monographs on WHO INNs. Where the subject of the monograph is a salt or ester of an INN, INNMs are used, as appropriate. In order to achieve a harmonised approach to the use of INNMs for creating names within the European Pharmacopoeia, it has been proposed that a guideline be drawn up and that it is based upon the WHO INN Working Document 05.167/3, on International Nonproprietary Names Modified.

During a review of 05.167/3, a number of questions arose regarding the rules and examples contained therein. The rules appeared to be possibly more complicated than is necessary and consequently the EDQM prepared a commentary for presentation at this Consultation. The document commented on various examples for naming salts, esters and the ratio of salt moieties, and proposed what were felt to be more simplified rules for creating INNMs. The document is seen as a first step in the development of a guide for the creation of such names for EP monographs and to clarify the intent of the rules of 05.167/3. Comments on the commentary document were requested.

In the ensuing discussion it was clear that there were several opinions on precise mechanisms for naming salts and esters and that other pharmacopoeia had looked into this. Overall, however, it was felt by the Experts that there was no driving need to modify the current WHO guidance for naming INNMs at this moment in time. It was agreed that the Experts should provide comments on the EDQM proposals by the end of May.

The Group was also informed that there were two new observers to the European Pharmacopoeia, Singapore and the Republic of Guinea.

IDMIS and INN e-paper

Members of the Expert Group were informed that in order to reduce the level of paperwork and folders, that beginning with the next meeting, all documents would be provided electronically on tablet computers. Members of the Group will be provided with tablets for the meeting, on which everyone would be able to view all papers and add comments

electronically. Data can be saved into a personal folder. The Chair suggested that at the start of the next meeting a short tutorial is held on instructing the Group on the use of these tablets.

CLOSE of MEETING

The Chair thanked the members and the Secretariat for the work they had done both prior to and during the meeting. There had been difficult issues to discuss and lively discussion, but in the end consensus had been reached. In return the group thanked the Chair for his work and efficiency.

The 55th Consultation will take place on October 16-18, 2012 in Geneva and will be preceded on October 15 by a one day special meeting on biological substances.

OPEN SESSION to STAKEHOLDERS

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Open sessions to INN stakeholders are held twice per year in conjunction with INN Consultations and give companies the opportunity to present concerns about INN applications or other associated issues. Whilst members of the INN Expert Group may ask questions and be involved in discussion, no decisions will be made during this session. Following the session, there will be a closed meeting of the INN Experts for 3 days. The Chair of the meeting, Prof. Derek Calam, welcomed stakeholder participants to the meeting and indicated those present from the INN Expert Group, representatives from various international organisations, and the INN Secretariat. Two stakeholder groups attended this meeting to make representation – a team from Celltrion-Paraxel and one from IFPMA.

Celltrion-Paraxel

The presentation from Celltrion-Paraxel concerned their INN application for CT-P13. CT-P13 (approved EU tradename Remsima®) has been submitted for licensure to the Korean FDA and the EU's EMA. From a regulatory viewpoint, CT-P13 is a biosimilar monoclonal antibody (mAb), with Remicade® (*infliximab*) as the reference product. CT-P13 and Remicade® were stated to have the same amino acid sequence, similar glycosylation profiles and comparable clinical activity (human PK and immunogenicity). The secondary and higher order structures of the two substances have been compared using methods including peptide mapping, Tandem Mass Spectrometry (MS/MS) analysis, and Fourier Transformed InfraRed (FTIR) and Circular Dichroism (CD) spectroscopy, and were comparable within the limits of the methodology. A strong focus was on the glycosylation and glycan analyses which showed that glycan mass, glycan distribution, sialic acid content and glycosylation profile appeared similar for both compounds.

Analytical data for other biotherapeutic glycoproteins following manufacturing process changes were presented and demonstrable changes in glycosylation profile were observed, with the point being that in those circumstances, regulatory authorities had not requested that new INN be sought. The contention of Celltrion-Paraxel was that CT-P13 is highly similar to Remicade® (*infliximab*) and it would be appropriate to assign *infliximab* to CT-P13 also.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

The IFPMA was represented by two members from the biotherapeutics pharmaceutical industry and a member of its Secretariat. The focus of their presentation was on biotherapeutic medicines and how decisions being taken at the INN meetings are implemented worldwide.

The IFPMA wholeheartedly agrees with the importance of the INN scheme, but would like to discuss how INNs are being used in pharmacovigilance, especially for biotherapeutics and biosimilars¹. In the EU, following from new pharmacovigilance legislation (due to come into

¹ Also termed 'supplementary biological products', or 'follow-on products'.

operation July 2012), and its translation into national recommendations, there will be heightened monitoring of biotherapeutics, and the role of the INN needs to be examined.

The IFPMA has conducted a survey of pharmacovigilance practices in countries around the world. They received only 14 responses from 11 countries and so it is difficult to draw firm conclusions. However, it was highlighted that there are diversified practices and no common system is developing around the world. Many countries have a system under review and it is clear that the INN plays an important role in pharmacovigilance. A point of concern to the IFPMA is how to ensure that when an INN is used in pharmacovigilance, that there is adequate information to identify individual products that have the same INN.

For example, in the EU, there are several biosimilar biotherapeutics on the market, e.g. *epoetin* and *filgrastim*. After the introduction onto the market of biosimilar *filgrastims*, there was a reduction in usage of the innovative product but an increase in adverse event reporting (implying that the biosimilars have contributed more to adverse events than the innovative product).

The new EU legislation on pharmacovigilance recommends that for biotherapeutic products, both the brand name and the INN are reported with adverse events. In Japan, a unique identifier is added onto the INN, whilst a naming policy remains under discussion in Australia, USA, Canada and Brazil.

Prescribing recommendations for biosimilars vary. In most EU member states, prescribing is by brand name whilst in the UK the use of the INN is also encouraged and in Greece prescribing by INN is required. Interchangeability in clinical practice is also variable, for example in Germany, some *filgrastims* are deemed to be interchangeable and some are not, whilst in the USA no states have provision for automatic substitution. For pharmacovigilance, the INN is the most consistent feature reported, brand names are sometimes used and lot numbers inconsistently. Lot numbers tend to be available only when the syringe or vial is to hand, i.e. in acute situations. Thus there are different schemes in different countries and there appears to be a lack of understanding as to how INN should be used in medical practice.

In conclusion, the IFPMA would like to see the WHO, through its INN and Pharmacovigilance Committees, develop recommendations for effective mechanisms for tracking biotherapeutics. If WHO should state more clearly how the INN should be used, there would be a clearer role for it in pharmacovigilance.

The INN Experts agreed that pharmacovigilance for biotherapeutics cannot rely only on the INN but that the INN should remain an important element with the main point being that maximum information should be reported involving the INN, brand name and lot number. The reality is though that the INN gets selected by a small committee and it is left to the outside world – physicians, regulators, companies – as to how they get used.

The Expert Group was grateful for this presentation and the suggestions. The Group remains forward looking and has a mandate not just to create names but that they are user friendly.

In closing the Stakeholders Session, the Chair was thankful to both teams and for the information presented on how INN get used, especially when the system gives rise to problems and INNs are not appropriately employed.