

***51st Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 16-18 November 2010***

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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Executive summary

INTRODUCTION

The 51st Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 16-18 November, 2010. The members of the INN Expert Group, the INN Advisory Group on biologicals, as well as the full INN Secretariat and several specialists, who assisted in specific nomenclature issues, attended the meeting.

Various intergovernmental organizations and national agencies involved or interested in drug nomenclature were also represented as observers, including the International Union of Pure and Applied Chemistry (IUPAC), the Japanese Pharmacopeia (JAN), the United States Adopted Name (USAN) Program, the United States Food and Drug Administration (FDA), the British Approved Names (BAN), the EC Taxation and Customs Union (Taxud) and others.

Dr Lembit Rägo, Coordinator, Quality and Assurance & Safety: Medicines (QSM), as acting director, welcomed participants to the meeting. He informed the Group that in these days of financial uncertainty, the INN programme being financed by fees, is not fully reliant on WHO funding and as such is much more secure than the teams within most medicines departments. There are also two major changes impending; firstly, there will be an election for a new DG soon (or re-election of the current one) and secondly the retirement of Dr Hans Hogerzeil, Director Essential Medicines and Pharmaceutical Policies, will inevitably lead to change. Within the INN Programme itself, the forthcoming introduction of online applications is good and hopefully will be fully functional next year. Greater communication of the INN Programme is desirable and at the forthcoming 14th International Conference of Drug Regulatory Authorities there will be a presentation on INN. More proactive INN seminars are to be encouraged, especially in emerging countries, along with specific training sessions for INN.

The Chair, Prof. D. Calam, also welcomed the INN experts and observers and thanked Dr Rägo for his remarks and the INN Secretariat for their past six months of work; it is helpful to be brought up to date with changes at WHO in order to understand what challenges lie ahead.

Finally, the Manager of the INN Programme, Dr Raffaella Balocco Mattavelli welcomed everyone and was grateful for all the input provided by the experts since the last meeting.

NOMENCLATURE of INNs

During the Consultation, a total of 113 INNs were discussed, including:

- 82 new INN requests, including 28 for biological substances
- 23 outstanding requests
- 8 previously selected proposed INNs, against which a formal objection had been raised

As a result of these discussions, 95 new names were selected, which are planned to be published in List 105 of Proposed INNs, while 5 requests were deferred for future discussion. Four requests were rejected by the INN experts, as the substances did not conform to the criteria for INN selection. Seven amendments are planned to be published in List 105. One objection was not retained and 1 INN request has been withdrawn during the selection process.

MODE of ACTION

Recently a small working group has been assessing and reassigning Action and Use (A&U) Statements published in the p.INN Lists, and reports were presented to the Expert Group on two groups of substances: antineoplastics, and CNS stimulants and psychopharmacologics. In parallel a more comprehensive review project of stem definition has been launched. This will take place over the next few Consultations.

For both groups, preferred expressions for the A&U have been developed and this should provide more clarity in the published A&U statement. On some occasions either no 'Action' or no 'Use' information is provided by the applicant and on these occasions, it is acceptable to have only one of them. For example, for psychopharmacologics, it is mainly the Use that is provided since in many cases little tends to be known about the mechanism of action and a list of expressions that could be used as appropriate was provided (such as Action and/or Use).

Regarding the review of stems definitions, 63 stems and pre-stems definitions have been reviewed and two have been amended.

The Chair noted this very valuable piece of work and thanked the member responsible for it. The stem definition is not always appropriate as such for a publication in the p.INN Lists (e.g. highly chemical, not sufficiently descriptive), whereas these new preferred expressions give more clinical information, which is very valuable for the p.INN Lists publication purposes.

SELECTION of INNs for COMPOSITE and RELATED SUBSTANCES

A document was tabled on Selection of INNs for Composite and Related Substances. The drafting of this had been encouraged by the Secretariat in order to have background information on such specific situations in naming INNs. The document presents information from many years of experience of the INN Programme in this particular area and will be useful when new requests are made for such substances. It will also offer guidance to future INN applicants.

The paper describes approaches that have been used in the INN system to select names for a variety of substances that contain structural elements for which INNs already exist. It categorises various situations of this type and describes ways in which relevant INNs were coined. The paper will be of assistance when new requests of this type are discussed.

Included in this category of substances are salts, esters and solvates; for these a rule whereby the active moiety only is allocated an INN was established, the Modified INN scheme (INN^M).

For substances which have one or more chiral centres, this is not specifically indicated in the INN but is described in the definition. Where a substance contains two or more chiral centres, again a one word name is the norm and the specific diastereomeric configuration is described in the definition. When, at a later date, a request has been received for a single diastereomer, individual decisions on a relevant name have been made. A similar approach is used for racemic substances and only occasionally has it been considered necessary to indicate this using a *rac*- prefix. However, where a racemic substance has previously been named and a name for a single enantiomer is requested, it can be important to establish a distinct name for the enantiomer in the event that it shows better therapeutic properties than the racemate.

When a substance contains an inactive element of considerable size, a two-word name is normally used. Typically these elements are incorporated as carriers, often to improve the pharmacokinetic properties of the product. Such carriers are often polymeric in nature e.g. polyethylene glycol (PEG) and PEG moieties are indicated either with a *peg*- prefix, or where there is an overabundance of names with the *peg*- prefix, a two-word name has been created, typically with *pegol* as the second word. Other such substances include carriers consisting of biologically active proteins (e.g. a monoclonal antibody) attached to a toxin.

Substances containing radioactive elements or specific isotopes are highlighted with the element name and the isotope number. Initially, for technetium ^{99m}Tc compounds, only the technetium carrier was named; however, it was later decided that the whole technetium complex should be named.

Finally, where a request is received for a combination product for which the components already have INNs, the INN is usually created by taking the two previously existing INNs together. In most of these cases, the INN of this type are not usually published unless there is a specific need. This situation might also exist where only one moiety of a combined substance has a pre-existing INN in which case the new INN is published and where appropriate would include a form of the pre-existing name.

UPDATES from COLLABORATORS

International Union of Pure and Applied Chemistry (IUPAC)

The 2nd edition of "Principles of Chemical Nomenclature; A Guide to IUPAC Recommendations" will give the basic principles, but not all the details, of organic, inorganic, polymer and biochemical nomenclature. It briefly mentions INNs and is expected to go to the printer by the end of the year.

The revision of the Blue Book "Nomenclature of Organic Chemistry" is nearly complete. This will be a large book giving more complex examples than previously but not giving new nomenclature. What it does give for the first time is the preferred IUPAC name (PIN) for anyone who needs one, such as regulatory authorities. Recent INN lists of organic names have made use of the PIN rules. A similar project has now started to select the PIN for Inorganic names.

Also relevant is the work of IUBMB (International Union of Biochemistry and Molecular Biology) which is documenting enzymes at an increasing rate. A significant number of new entries are added at approximately monthly intervals and are classified by the reaction that they catalyse (and not their structure). The enzyme needs to have been isolated, and the reaction checked with the isolated enzyme, before it will be listed.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

The Division of Standards for Drugs, which prepares Japanese Approved Names (JAN) and the Japanese Pharmacopoeia (JP), is one of two divisions within the newly formed Office of Review Management, previously the Office of Compliance and Standards. The JAN committee considers applications four times per year and has two types of submission, those already assigned an INN and those without. For the latter, the selected JAN name will go forward as an INN proposal; if this is not accepted by INN, the JAN will be changed to reflect the adopted INN. In 2009 there were 34 applications and to date in 2010 there have been 46 applications of which 6 were for both JAN and INN consideration. The JAN follows the same INN rules on stems.

United States Adopted Name (USAN) Program

The 2010 summer USAN Council meeting was held in Chicago at which 32 names were adopted. Five new stems were approved, four stem definitions were revised and one designation for radicals and anions approved. Fifty-six USAN applications were forwarded to the INN programme for INN designation. The USAN archive project has been completed in which all USAN adoption statements from 1961 onwards have been scanned and data fields for USAN file number, drug name, manufacturer, WHO number and CAS number have been logged in a searchable database.

To date, in 2010 USAN has processed, researched and made recommendations on 130 new applications and in the first ten months of 2010, 122 USAN were adopted. In July 2010, the USAN programme was presented at the USP's Drug Nomenclature Workshop by Dr Gail Karet. The winter Council meeting is planned for January 2011 in New Orleans.

Food and Drug Administration (FDA), USA

A new regulation at FDA might impact on established names. It will require a review of existing labels by project managers, pharmacists and physicians, and during the process some problems with

nomenclature and structures have been noticed. This has led to requests to USAN to change parts of definitions and this could potentially lead to an objection of an already approved name. There is also debate at the FDA on the proper way of expressing an established name especially if it is a salt or if there are multiple dosage forms, e.g. if a monograph exists then the established name has to be used and these do not include the salt; however, this has now changed and the correct legal established name, e.g. doses with no salt or doses that express the salt, is unclear. If no salt then the name is more harmonised with INN.

United States Pharmacopoeia (USP)

USP has formed an advisory group with members from various organizations, including industry and the regulatory agency, to discuss the implementation of the USP Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations. The policy will be in effect in 2013 and the implementation plan involves communication, education and training for the stakeholders. Monograph titles of USP-NF monographs for drug products are legally recognized established names for the purpose of labelling in the USA.

Regarding the USP's Drug Nomenclature Workshop held in July 2010, the USP representative proffered thanks to members of the INN Group for making presentations and for helping with speaker arrangements.

European Commission, DG Taxation and Customs Union (TAXUD)

Under the umbrella of the World Trade Organization, the 4th revision of the Pharmaceutical sectoral arrangement between several important pharmaceuticals-producing countries has been finalised. The purpose of this international arrangement is to provide duty-free treatment on certain pharmaceutical products bearing an INN and pharmaceutical intermediates. The 4th revision includes INNs from proposed INN lists 94-99 (altogether 380 INNs) and pharmaceutical intermediates (359 products). It is intended that from 1st January 2011 the covered products will benefit from duty-free treatment when traded between the US, EU, Japan, Canada, Switzerland, Norway and Macao (China).

DG TAXUD has also established a European Customs Inventory of Chemical Substances (ECICS) database

(http://ec.europa.eu/taxation_customs/customs/customs_duties/tariff_aspects/ecics/index_en.htm)

which is publicly accessible. Currently entries (e.g. for INNs) are available in 11 languages but with plans to provide translations into the 23 official EU languages.

European Pharmacopoeia, European Directorate for the Quality of Medicines (EDQM)

The INN Group was informed that EDQM have a database that provides official names of pharmaceutical dosage forms, routes etc., and is available in twenty-nine European languages and is now preparing the same list in Chinese and Russian. These names are normally used in drug applications.

British Approved Names (BAN)

The British Pharmacopoeia 2011 edition is now available. Also, the British Pharmacopoeia Commission has recently moved its offices to a new location within London (to Buckingham Palace Road) which has imposed on work progress.

UPDATE of IDMIS (INN Integrated Data Management Information System)

The IDMIS system has been improved for members of the Expert Group with a new facility for the addition of post-meeting comments online and with an improved view of others' comments.

A major new feature is the imminent availability of an online INN application facility. With this, applicants will be able to download forms from the website to be filled in electronically and uploaded back onto the WHO/INN server, in encrypted format. A pdf file must also be saved by the applicant and emailed to the INN secretariat which needs this as it contains an electronically generated key

which allows the encrypted file to be opened. The Chair congratulated and thanked the secretariat staff for this major development.

CLOSE of MEETING

At the end of this 51st INN Consultation, thanks were proffered to the Experts, to the INN Secretariat, and from them to the Chair, for the work performed before and during the meeting.

The 52nd INN Consultation will take place in Geneva on April 12-14, 2011.

Annex to 51st Consultation Executive Summary
INN open session meeting with stakeholders, 16th November, 2010

Prior to the 51st INN Consultation, there was a short open session with stakeholders. The participants were welcomed by Prof. D Calam, chair of the INN Expert Group and Dr R Balocco Mattavelli, INN Programme manager. This is the second occasion in which stakeholders can make direct representation to the INN Expert Group. In these open sessions, the experts do not provide final decisions but will listen to the arguments put forward by stakeholders and anticipate fruitful joint discussion.

Dr Gianella, Clavis Pharma ASA

Clavis Pharma is developing an ester of *gemcitabine* (62)(30). According to the applicant this substance improves the clinical efficacy of *gemcitabine* by rendering cellular uptake independent of nucleoside transporters such as hENT1 and by increasing the retention of the active metabolites into the cancer cells. Antitumor activity has shown to be different from that of *gemcitabine in vitro* studies. The end result is to overcome resistance mechanisms and schedule dependency that limit the efficacy of *gemcitabine*. In the NCI screen antitumor selectivity is tested in a panel of 60 cell lines: results indicates *similar but not identical mechanisms of action*. Dr Gianella expressed a desire for a one-word INN for their modified *gemcitabine* as two-word names are more likely to cause prescription confusion and/or dosage errors, illustrating this with some examples. Clavis intends to submit a one-word name as a proactive approach to reducing risks for patients and proposed two potential one-word names for their compound.

Dr Boyce, Hammersmith Medicines Research

Hammersmith Medicines Research has developed a highly selective gastrin antagonist with an affinity for CCK2 receptors considerably greater than that for CCK1 receptors. An INN had been requested and after some discussion between applicant and the INN committee on the appropriate stem and acceptable name, the INN *sograzepide* was adopted and appeared in the proposed INN list. However, the applicant was not in favour of the final proposal and made representation at this open session for an alternative name. It transpired that there had been a fault in communication and the applicant's non-acceptance of the selected INN had not been received. In the light of these problems, the applicant was informed that the Expert Group could view this representation as an official objection to the proposed name and reconsider, especially since the name had not yet reached the recommended INN list.

Dr Benny Bang-Anderson, H. Lundbeck A/S

The company has developed two related candidate antidepressant compounds and the USAN has requested an INN for each. The company initially had suggested the stem *-zodone* for both, USAN suggested *-tiotine*, whilst the INN Committee opted for *-oxetine*. The company however feel *-oxetine* is inappropriate and at this open session, they argued from structural and mechanistic viewpoints that the original request for a *-zodone* stem remains pertinent. Firstly, there is no oxygen ether linkage in their compounds as is present in the *-oxetine* series; instead their compounds have a sulphur linkage and are loosely related to the *-zodone* series. Mechanistically, their compounds have been designated as multimodal neurotransmitter enhancers which again places them more like the *-zodone* compounds rather than the *-oxetine* series. Consequently, the company requested reconsideration of the suffix, with *-zodone* being the most appropriate stem, or as an alternative, a

novel *-tixetine* stem. This is due to be discussed within the plenary session of the current INN Consultation although no new information has been received from the applicant, USAN.

Dr Heaton, Parnell Technologies Pty Ltd, Australia

The INN have considered the company's osteoarthritis *glucuronoxylan sulfate* (GXS) drug to have a *pentosan polysulfate* (PPS)-like structure and have named it accordingly; however the company argued against this, claiming several key structural differences including full sulfation and low polydispersity of their GXS and with a reducing terminus differentiated from PPS. Furthermore, the biological activity of GXS is distinguishable from PPS and displays a different safety profile with respect to propensity to bleed. Consequently, it was requested that GXS should receive a distinguishing INN from PPS.

In discussion it was agreed that biological molecules such as these are indeed a challenge to the INN programme. The company currently appears to be trapped between the INN definition which indicates the substance to be PPS, and regulators who claim it not to be PPS.

Mrs Friedli, Trademark and Design Law Division, WIPO

As reported previously to the INN Expert Group, WIPO recalled that the WIPO Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications (SCT) at its nineteenth session asked the WIPO Secretariat to explore together with the WHO Secretariat possibilities of developing a publicly searchable database for INNs. Trademark (TM) authorities have expressed concerns that lists of INNs, proposed and recommended, are not sufficiently available online to TM offices, for the purposes of search and examination of new applications for trademarks, particularly in the pharmaceutical field. The WIPO Secretariat understands that the INN database has more information than that required by TM offices and, following the mandate received from the SCT, is willing to explore the possibilities of making the information on INNs more readily accessible to all TM offices.

The INN Secretariat replied that it is the mandate of WHO to promote and disseminate INNs; everyone has access to the INNs including WIPO, and CD-ROMs with simple lists of INNs are being distributed to some TM offices. INNs are also on an WHO extranet searchable database. However, a simple global data-hub with the INN as the common identifier and a link to other databases is also being developed. There have been requests from WIPO to populate a WIPO database, but there is a legal impediment here in that INNs have to remain in a public freely accessible arena. A simple global data-hub would have no such legal obstacles but is unlikely to be available until the end of 2011.

These open sessions are very useful to stakeholders and Experts alike. The INN Group is usually, but not always, aware of problems and so open discussion is important. The problems encountered can be complex and there is benefit for the INN Experts to hear about them first-hand.