

***52nd Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 12-14 April 2011***

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 52nd Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 12-14 April 2011. 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 Pharmacopoeia (JAN), the United States Pharmacopoeia (USP), the British Approved Names (BAN), the World Intellectual Property Organisation (WIPO), and others.

In welcoming the participants to the meeting, Dr Lembit Rägo, Coordinator, Quality and Assurance & Safety: Medicines (QSM) outlined recent changes brought about by the current financial constraints facing WHO. The Department of Essential Medicines and Pharmaceutical Policies (EMP) will continue and will be joined by the section from the Department of Essential health technologies (EHT) that deals with medical devices. This, he felt, was a good move for EMP as member states are increasingly requesting advice on controlling medical devices especially diagnostics, and with good cooperation with regulators already in place within EMP, the department can build on these pre-existing networks. The QSM team itself is working well, is stable and continues to produce good technical work. It is a struggle throughout WHO to retain current staffing levels and in order to help the INN programme to continue to develop and grow, a strategic plan has been developed and the input of the Group to this is greatly welcomed.

The Manager of the INN Programme, Dr Raffaella Balocco-Mattavelli thanked Dr Rägo for his remarks, and welcomed the experts to the meeting, with thanks for the input already provided.

The Chair, Prof. D. Calam, also welcomed the INN experts and observers, Dr Rägo for his remarks and the INN Secretariat for their past six months of work. The background information provided by Dr Rägo is extremely useful to the Group and to appreciate the conditions under which the Secretariat is working; it appears that the INN group is relatively unaffected, at least for the moment. The Strategic Plan is a key document and will be for the next few years. Prof. Calam also highlighted the need for members to avoid individual contact with applicants and to refer any requests from applicants to the WHO Secretariat to ensure that the procedure for selecting an INN remains a collective process within the WHO.

NOMENCLATURE of INNs

During the Consultation, a total of 82 INNs were discussed, including:

- 60 new INN requests, including 24 for biological substances
- 21 outstanding requests
- 1 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 73 new names were selected, which are planned to be published in List 106 of Proposed INNs, while 6 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 amendment is planned to be published in List 106. One INN request has been withdrawn during the selection process.

Six new stems have been selected and 2 suffixes have been promoted to the pre-stem list.

STRATEGIC PLAN OF THE INN PROGRAMME

A draft 5-year strategic plan of the INN Programme was tabled at the meeting. An internal audit had identified the absence of such a plan and QSM Coordinator Dr Rågo requested one be developed. The DG herself has praised the INN Programme publicly and a strategic plan would further raise the profile of the Programme especially within WHO itself. The document explains the global impact of INN, identifies the stakeholders and outlines the proposed activities of the Programme over the next 5 years including the development of a global data hub.

WHO would be the owner of such a global hub and it would be free for stakeholders such as WIPO to access. Continued and improved collaboration with WIPO and Trademark offices is an important activity along with training to explain the Programme, its value and its use. A first course has been held at WHO for 30-40 participants from pharmaceutical companies and others, and was received very enthusiastically. There is a need for the Programme staff themselves to be promoted and increased to cope with the training function.

Dr Rågo thanked the Secretariat for developing this document. Strategic plans need to provide high level direction and must be a living document to accommodate a changing world. From a pragmatic point of view, few in WHO really understand what this group does and this document provides a short summary to those not familiar with INN; it informs WHO that thought has been given to the future direction of the programme and the importance of the work. Consideration also needs to be given to whether this should be an internal or external document. Initially, it is better for it to be regarded as an internal document and reflect upon it; ultimately it can only be of benefit in making it public.

The Secretariat was also congratulated by the Expert Group which sees the plan as an accurate reflection of what the Group views as the areas for development over the next 5 years. Caution was expressed though in handling biological compounds where advances in technology will affect the work of the INN Programme and which cannot be captured adequately within the Plan. Also the input of WIPO will be important, to help improve the avoidance of conflicts between INN and trademarks. One essential element is that the Plan should stick with the science behind INN and this was agreed. Comments on the document were requested from the Group bearing in mind that it would remain internally in the first instance; it can be modified for external consumption at a later date.

The Group supported and endorsed the document.

REVIEW OF INN FOR BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES: INTERFERON

Nomenclature for various groups of Biologicals was reviewed in an *ad hoc* meeting held in conjunction with the 51st INN Consultation. The *ad hoc* meeting discussed cell therapy products, issues concerning epoetins, and the current nomenclature for interferons and fusion proteins. The situation for interferons was further discussed. Interferon was first published as an INN in 1962. The name was revised in the 1980's when structurally distinct interferons (interferon *alfa*, *beta* and *gamma*) were identified. The situation with rules for nomenclature for interferons is slightly unusual as the International Society for Interferon and Cytokine Research (ISICR) nomenclature committee had previously established widely recognised names for interferons and it was considered undesirable to have INN which differ from the ISICR nomenclature. However, this has led to some confusion with interferon nomenclature (where *alfa*, *beta* and *gamma* designations refer to different interferon species with differing amino acid sequences) and inconsistency with INN rules for other substances (where *alfa*, *beta* and *gamma* designations refer to differential glycosylation).

At present there are no problems with the terms for *interferon alfa*, *beta* and *gamma*, but the use of further divisions involving Arabic numerals and lower case letters has led to some inaccurate INN. For example *interferons alfa 2a*, *2b* and *2c* would be expected to have the same amino acid sequence

but differ in some other way e.g. in glycosylation, but in fact they differ in amino acid sequence and are not glycosylated.

In combating this situation, it would be very difficult and problematic to change existing INN for interferons. It would be far simpler to revise the rules to introduce consistency although the rules would have to remain interferon-specific as they do at the present. The rules of naming interferons were therefore revised and then presented to the INN Expert Group during this Consultation. The approved revised rules will be addressed in Section 4.18 (Interferons) of the Review of INN for biological and biotechnological substances (the Bioreview), update December 2011.

Section 3.4 (General policies for glycosylated compounds) has also been revised to remove reference to interferons and to expand/clarify for other potentially glycosylated compounds, although it may be useful in this section to refer to Section 4.18 for interferons. A few other sections of the Bioreview may need some revising and this should be done sooner rather than later.

A report on the *ad hoc* meeting on biologicals held after the 51st INN Consultation was also provided. The Chair thanked the Secretariat for this report and Dr Kawasaki for her thorough document related to definition of epoetins.

STEMS REVIEW PROJECT

Following a recent review of Action and Use (A&U) Statements published in the proposed INN Lists, the small working group concerned has also started to review stem definitions. A principle recommendation of the working group is that the stem definition should give the Mechanism of Action (MoA) wherever possible; the A&U Statement should not necessarily give the MoA but should provide the clinical use. This working group has done a huge amount of very complex work and is to be thanked for this and their recommendation is, in principle, accepted by the Expert Committee. Stems will undoubtedly need some adjustment from time to time. As an aside, once a stem is created it is protected by the WHO Assembly Resolution 46.19 which cannot be applied retrospectively and thus it is good not to wait too long before promoting a pre-stem to a stem.

INN FOR COMPOSITE AND RELATED SUBSTANCES

At the request of the INN Programme, the creation of modified INNs (INNM) and INN for composite and related substances is being reviewed and draft guidance on this was tabled. INNs are created for individual pharmaceutical substances solely through the INN Programme; however INNMs which are used for related compounds such as salts or esters can be created by users such as pharmacopoeia commissions, regulatory bodies and pharmaceutical manufacturers, using standard practice for naming chemical compounds. Thus no formal list of INNMs exists as they are not confirmed by the INN Programme (although some INNMs are issued through the Programme).

The INNMs approach was formally accepted in 1975 at the 20th INN Consultation but only described in detail in 2005 (INN doc. 05.167/3). This currently tabled guideline provides advice on how INNMs should be created and gives examples of specific situations including INNMs for salts of basic compounds, for salts of acidic compounds, for hydrates, for esters, and for many other situations. A new feature is the extension of the scheme to substances with an amide bond as prodrugs with an amide linkage are being developed with many already listed, e.g. *gabapentin/gabapentin enacarbil*. Following a request from the European Pharmacopoeia, to aid prescribers a further recommendation is to allow reversal of the usual order of certain two word INNMs so that the active ingredient appears as the first word e.g. *valproate magnesium* instead of *magnesium valproate*.

Where a new substance is related to an existing INN but the use of a novel prefix or creating an INNMs is not appropriate, the draft guideline also provides advice on several other approaches that can be used e.g. for racemic substances, for single enantiomers, for substances with two chiral centres, or for substances that contain carrier molecules or radioactive elements. Racemic substances often use the prefix *race-* whilst specific enantiomers might use *dextro-* or *levo-*. Substances linked to carriers or

toxins often use a two word approach such as in *exotecan alideximer*, *enlimomab pegol* or *denileukin diftotox* although one word names that make use of a specific prefix to denote the carrier are common also e.g. *pegfilgrastim*.

It is highly useful to have such guidance as bodies outside of the INN Programme are allowed to create INN. Occasionally individual scientists may create additional names for derivatives of a pre-existing INN by attaching various chemical prefixes. Such names are sometimes referred to as 'composite' INNs and are considered as inappropriate by the INN Programme. They may create uncertainty as to the exact chemical structure, may hinder the regular INN selection process and may create difficulties in the area of INN protection under intellectual property laws.

The draft guidance provides many examples of how difficulties have been overcome in the past; in the future there might be situations that are beyond the current system and which require specific approaches yet to be created. The current document is for internal use but eventually it will be highly useful to all stakeholders and a future version for outside use would be valuable.

ARABIC INN TRANSLITERATION

INN are published in six languages and there is a need for transliteration of the English versions into Arabic, Russian and Chinese. The collaborating Centre for Drug Registration and Pharmaceutical Registration located in the Tunisian Ministry of Health is responsible for transliteration of INN into Arabic. The Arabic alphabet is the second most widely used in the world. Arabic script is written from right to left and includes 28 basic letters each of which usually stands for a consonant. Arabic transliteration is based upon pronunciation except where the names begin with *tri-* (three-); for these names, the correct translation in Arabic is used.

UPDATES from COLLABORATORS

World Intellectual Property Organisation (WIPO)

A representative from the World Intellectual Property Organisation (WIPO) reported on several measures to improve accessibility of trademark offices to INN databases, including sending circulars to trademark offices when new lists of INN are published, publishing a link on their website to WHO, and developing a nonexclusive publicly searchable database. The INN Secretariat is very pleased with this important collaboration with WIPO and is eager for it to continue. The INN Programme has a mandate to promote and protect INN, and WIPO can reach many stakeholders more readily than the INN Programme and this helps protect INN. INN data are currently accessible through the WHO INN Extranet, MedNet and a special project to improve INN data accessibility named *INN Global Data Hub*, is under development at the test phase level.

Currently and formally, the WHO DG informs Ministers of Health when new names have been selected, and these ministries should then convey this information to national trademark offices. This is a cumbersome task amongst 180 countries and many fail to undertake this. WIPO, being highly supportive and in direct contact with these offices, provides them with the necessary information to avoid conflicts with trademarks. The WIPO gold database now incorporates all trademarks and each office has its own national database, so when a proposed INN arrives, searches for conflicts with new trademark applications for similarity to INN can be done with national laws providing for refusal.

WIPO recently launched this 'gold' database incorporating all trademark names, information on applications on industrial design patents and all IP objects; and would like to incorporate INN data to help avoiding conflicts. It is open to all and can be searched for specific criteria, e.g. part of a name, and will identify all trademarks with that part. The *INN Global Data Hub* would indeed facilitate this data exchange in a safe and transparent manner.

Overall, the system is generally working well and trademark offices routinely refuse applications where a conflict with INN exists; but it is reliant on good access to updates of proposed and recommended INN and any improvements to this are welcome. In converse, it would also be useful

for the Experts and the INN Programme to have improved tools to search for conflicts between requested INN and existing trademarks.

British Approved Names (BAN)

A major item for the BAN committee meeting of February 2011 was the finalisation of the BAN Book 2012, due to be published in Aug/Sep 2011. In the BP 2012 publication, a new supplementary chapter titled Similar Biological Medicinal Products is devoted to how the BP approach drafting monographs for biosimilars. We are also working with other nomenclature bodies, e.g. EDQM, to make sure that, where practicable, the work of the BP Commission with regards to nomenclature is harmonised.

The BAN team is also responsible for the assessment of invented names for UK Marketing Authorisation Applications through the MHRA and sit on the EMA Names Review Group (NRG). Approximately 600 names are assessed per year through the NRG. There has been an increase in the number of generic names (using INNs) applied for through the Centralised Procedure since generic medicines could be licensed through the EMA. There are less details that are required to assess these names and the names are generally only rejected because of conflict with an existing name, misleading/promotional connotations or the name contains an INN stem (this is a risk based approach and takes into account pharmaceutical form, legal status and medical setting). Although the NRG guidelines indicate if a stem is for a product in a different medical setting it can be used, it has been argued that it is misleading to healthcare professionals and names containing INN stems are now routinely being rejected.

WHO Collaborating Centre for Drug Statistics Methodology, Norway

The WHO Collaborating Centre for Drug Statistics Methodology in Norway is located in the Norwegian Institute of Public Health in the Department of Pharmacoepidemiology. It has five scientific personnel and in addition to their WHO work they are involved in research on the National Prescription Database located in the department. This database has been available for external users since 2009 at a separate website www.norpd.no. The Anatomical Therapeutic Chemical (ATC) classification system of drugs and the Defined Daily Dose (DDD) were developed and are maintained by the Centre and are used worldwide. The Centre's website www.whocc.no has been available for many years, but in 2009 a more user-friendly version was released. Both the ATC Index and the Guidelines for ATC classification and DDD are freely available on this site. The website is being used increasingly and is working well for the users. Last year the Centre ran a course in the ATC/DDD methodology in Oslo with 37 participants from 21 countries; it went well and was good experience for the Centre.

The Centre is also collaborating with the International Classification of Diseases (ICD) and is discussing the difficult task of mapping ATC and ICD codes. A new project was started last year with the EMA on surveillance of antibacterial medicines in veterinary medicine; all member states are involved and the Centre will contribute data from Norway and assist in the classification of the medicines according to the ATC system. The Centre is also a member of an Advisory Group on Integrated Surveillance of Antimicrobials, having taken this lead from WHO and will host the Group at their annual meeting in June 2011.

United States Pharmacopeia (USP)

Governance of the USP operates in 5 year cycles with a new cycle starting in 2010 at the same time as a workshop on nomenclature. At a USP Committee meeting since the previous INN meeting, discussion was initiated on naming of multi-valent compounds such as salts. This was sparked by the approval by USAN of a name that includes hydrochloride; the USP feels that the use of certain prefixes and other terms such as this can be misleading and is in discussion with USAN on this.

IDMIS ELECTRONIC ASSESSMENT and APPLICATION SYSTEM

The INN Programme has been developing an online application system and global data hub. A successful training course for manufacturers and public authorities has been held and more than fifteen applications have now been submitted online. Feedback from the training session also led to the improvement of online applications and data management. With the success of this programme, online submission is now mandatory.

INN data is distributed by the Programme to various authorities in different formats. To combat difficulties in ensuring the latest data is available, to avoid loss of data and to prevent commercial abuse of INN data, a global hub of INN data is under development, with the INN Programme responsible for it and updating it. Software will be developed for external access. All INN data would stay within the database and open access can, if need be, be restricted; the INN database would be linked to other databases but with INN staying in control of the INN data. Ultimately a network of national authority databases is envisaged and potentially a software company could provide support for this, for external access.

Provision of access to archived INN data and to the comments of the experts on applications is being explored; this is also needed to preserve data for legal reasons.

CLOSE of MEETING

The Chair thanked all those involved in various working parties and to all experts for their contributions both within and prior to the meeting.

The 53rd INN Consultation will be held in Geneva on 18-20 October 2011.

Annex to 52nd Consultation Executive Summary
INN open session meeting with stakeholders, 12th April, 2010

The Chair for this 3rd INN open meeting with stakeholders Prof. Derek Calam introduced himself and the INN Programme manager, Dr Raffaella Balocco-Mattavelli. The format is that after each of the two presentations there would be the opportunity for comment and discussion. No decisions would be made by the Expert Group during the open session but further discussion and decisions would take place during the closed plenary meeting of the INN.

Dr Raffaella Balocco-Mattavelli welcomed the two stakeholders, Clavis Pharma ASA and Vifor Pharma Ltd. For information, Dr Balocco-Mattavelli told the stakeholders that prior to the INN Consultation, much of the work of the INN Group had already been accomplished through virtual consultation, including the involvement of experts unable to attend this open session. However the face-to-face meetings are also an important part of the INN selection process.

Clavis Pharma ASA (Drs Athos Gianella-Borradori and Patrick Mahaffy)

Gemcitabine is widely used for the treatment of pancreatic cancer; the drug is available in generic form and sales of it are high. Most patients diagnosed with pancreatic cancer will receive *gemcitabine* at some point and it is the only proven drug for this disease. There is now data though that only some will benefit. The drug is a nucleoside analog and needs a transporter such as hENT1 for cell entry. hENT1 levels appear to correlate with drug benefit and Clavis has developed a drug CP-4126 that overcomes an apparent resistance to *gemcitabine* in patients with low tumour expression of hENT1. At the 51st INN Consultation, the name *gemcitabine elaidate* was proposed for CP-4126. Based upon a survey of physicians and pharmacists with experience of prescribing *gemcitabine*, Clavis contends that the two word name will lead to prescribing and dispensing errors as many prescribers will simply use the first word or even simply ‘gem’. Clavis’ studies also indicate that patients with low hENT1 do not benefit from *gemcitabine* but are likely to respond well to CP-4126. Consequently, they request a one word INN that is distinct from *gemcitabine* and proposed *elaflurabine*.

Currently, oncologists are not overly familiar with the need for high expression of hENT1 for efficacious use of *gemcitabine*. Clavis is trying to educate the medical community in this respect but will require testing patients for hENT1 levels. Towards this, Roche has developed a hENT1 test which is approved in the EU but not in the USA. A trial has been planned to assess the efficacy of *gemcitabine* versus CP-4126 in low expressers of hENT1. The active moiety of CP-4126 remains *gemcitabine* and the modified version simply enhances uptake into cells (expressing low levels of hENT1). Potentially CP-4126 will not be superior to *gemcitabine* in high hENT1 expressers; the current study is to show advantage in low hENT1 expressers.

The Chair indicated that open sessions give INN experts an opportunity to explain the derivation of an INN and the constraints imposed upon the system. In this case, an explanation of the tools available to the Experts is useful. For example, the modified INN (INNM) approach was created to cope with situations where a new INN was sought for a drug highly similar to a drug already assigned an INN. Thus INNM have been used for salts and esters of pre-existing INN and other groups of modified compounds, and it was following this approach that led to the two word name proposed previously for CP-4126. This case will be discussed further by the Experts during the closed session of the INN Consultation.

Vifor Pharma Ltd (Drs Peter Geisser and Aziza Johnson)

Following the non-assignment of an INN to their compound at the previous Consultation, Vifor Pharma Ltd felt their application had been misinterpreted and so have taken the opportunity of appearing at this open session to discuss the structure in more detail.

The active moiety, ferric-oxyhydroxide (β -FeOOH), is a distinct chemical moiety that already exists in marketed products with an assigned INN. It is a pure crystalline compound with a complicated 3-

dimensional structure which can be broken down to a simple molecular formula. The value of 'n' in the formula cannot be defined and so a precise molecular weight cannot be given; however, it can be defined by x-ray structure and infrared spectroscopy. It is a pure compound and not a mixture, and can be reproducibly manufactured. PA21 is β -FeOOH stabilised non-specifically with sucrose; it is a phosphate binding agent and is not intended for use in iron deficiency anaemia (as are other iron hydroxides). The names proposed by the company had been for the β -FeOOH moiety only and not for the formulation with sucrose stabiliser.

The company requested an INN to help distinguish their product in the market; this is necessary for accurate pharmacovigilance as there is known hypersensitivity to such iron preparations and that different products present a different risk. Current chemical nomenclature is inadequate and there are documented inconsistencies in terminology in use today. Products similar to PA21 are being developed by many pharmaceutical companies and assignment of an INN would be the ideal route to establishing an acceptable global term for polynuclear iron-oxyhydroxide compounds.

The company is also minded to approach USAN as potentially the EU or Japan would accept a USAN name (in addition to within the USA) as the objective is to establish a unique global name for their product to assist in pharmacovigilance.

The Chair gave thanks to both stakeholders; the discussions held at this open session will help the deliberations of the INN experts on these cases. Eventually, applicants are informed of decisions but such decisions must be ratified by the applicant and proposed names will not go forward without such acceptance.