

***46th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 1-3 April 2008***

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

***Quality Assurance and Safety: Medicines (QSM)
Medicines Policy and Standards (PSM)
World Health Organization, Geneva***

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INTRODUCTION

The 46th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 1-3 April 2008. 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 problems, attended the meeting.

Various intergovernmental organizations and national agencies involved or interested in drug nomenclature were also represented as observers, including the World Intellectual Property Organization (WIPO), the International Union of Pure and Applied Chemistry (IUPAC), the European Medicines Agency (EMA), the Japanese Pharmacopoeia (JAN), the United States Pharmacopoeia Convention (USPC), the United States Food and Drug Administration (US FDA) and others.

Dr Lembit Rõgo, Coordinator QSM, opened the meeting and welcomed participants. The reorganization that is currently taking place, in both strategic and administrative areas, should be complete by the summer (of 2008) and the INN programme will continue to be an important part within the new scheme. The INN programme needs continuity and these changes should not affect the mainstream work. Dr Rõgo especially welcomed representatives from three major regulatory groups from the EU (EMA), USA (FDA) and Japan (PMDA).

The Chair, Prof Derek Calam, also welcomed new members and thanked all for their hard work and contributions submitted between these biannual meetings. The INN Programme Manager, Dr Raffaella Balocco Mattavelli, similarly was very appreciative of the support, help and timely return of data from the experts.

NOMENCLATURE of INNs

During the Consultation, a total of 91 INNs were discussed, including:

- 47 new INN requests, including 17 for biological substances
- 39 outstanding requests
- 2 previously selected proposed INN, against which a formal objection had been raised
- 3 requests for substitution.

As a result of these discussions, 81 new names were selected, which are planned to be published in List 100 of Proposed INNs, while 6 requests were deferred for future discussion. One request was rejected by the INN experts, as the substance does not conform to the criteria for INN selection. One amendment is planned to be published in List 100. The 3 remaining requests discussed were requests of substitution.

MONOCLONAL ANTIBODY NOMENCLATURE

Last year there was a review of monoclonal antibody (mAb) nomenclature. The *-mab* stem along with various sub-stems for the origin of the mAb, the disease class and/or the type of tumour to be targeted, have been used for over 140 mAb INNs and it is becoming linguistically difficult to create adequately short and distinct INNs.

During the Consultation, the Group heard a presentation from Dr Georg-Burkhard Kresse representing the IFPMA Biotech Working Group on the naming of mAbs. Whilst the basic stem *-mab* should be maintained, a major suggestion was to move away from the current sub-stems and replace these with related names for the molecular target and/or the pharmacological class. This is because the origin of the mAb (human, murine, etc.) is no

longer relevant for the prescribing physician whilst many mAbs are increasingly being used to treat different diseases, e.g. anti-tumour and anti-inflammatory conditions. The target is the most basic unique feature for a mAb, it never changes and this should be included in the INN. For example, *cetuximab* and *panitumumab* target the same molecule but this is not apparent from the names. The origin and clinical use can be part of the definition but no longer need be part of the name.

Other suggestions from Dr Kresse were that the Group consider appropriate paths for antibody derivatives such as bi-specific antibodies, antibody-peptide conjugates and pegylated antibodies. A new stem *-fab* should be considered for antibody fragments whilst fusion constructs should be treated as new (fusion) proteins. Post-translational modifications such as glycosylation should be identified somehow, e.g. by the use of a Greek letter suffix, as for all glycoproteins. It was further suggested that since the biological impact of post-translational modifications such as fucosylation can be quite significant, that mAbs even with identical amino acid sequences should be considered different drug substances and therefore should have different INNs; however, it was acknowledged that this would only work if the policy is for those making new mAbs to apply for a distinct INN.

The Chair noted that the INN system cannot demand that a manufacturer applies for an INN. The Group further acknowledged that some existing biological INNs have more than one distinct clinical indication, that this holds true for some chemical drugs also, and that this can be handled within the INN system.

In conclusion, substantial changes are being suggested for INNs for mAbs. This is not impossible, but from a practical point of view the legal consequences for all products on the market and the attitude of the whole industry towards such changes would have to be considered. Dr Kresse acknowledged that changing existing names would be too difficult but that for new names and maybe for recently named mAbs that are not yet on the market, changes could occur. **It was agreed that this issue would be dealt with best by the Secretariat organizing a small expert group to consider the current mAb nomenclature system, any need to modify it, and to report back to the next Consultation meeting.**

DEFINITIONS for EPOs

The Japanese Accepted Names (JAN) committee showed that INN named epoetins since 1989, from *epoetin alfa* to *epoetin kappa*; these are all identical in formula, amino acid sequence, disulphide bonds and glycosylation sites. JAN proposes a Definition of epoetins that incorporates the cell substrate of origin, mol. wt., extent of sialylation, and the nature of *N*- or *O*-linked glycans. Both epoetin epsilon, derived from hamster BHK21 cells, and epoetin gamma, derived from murine C127 cells, have three *N*-linked and one *O*-linked oligosaccharide, whose structures are well defined. Epoetin epsilon has a higher NANA content whilst *epoetin gamma* has sulphated oligosaccharides. The carbohydrate moieties of several epoetins have been analysed in detail at the National Institute of Health Sciences (NIHS); in a comparison of alfa and beta by mass spectrometry, alfa has much more acetylation, and even within different epoetin alfa's, differences were observed. It is clear that details of carbohydrate structure can be obtained with state-of-the-art analytical techniques. The data presented by the NIHS show that epoetins differentiated with different Greek letter suffixes can indeed have different oligosaccharide structures.

Inclusion of the production method in the definition of a biotechnological INN was questioned. Such features are not new to biological INNs and even with chemical drugs, different production methods may result in product differences, e.g. a different impurity

profile, so this is not a new concern. An example was provided for human insulin for which there are three sources, two recombinant (*E. coli* and yeast) and one chemically modified (porcine); all require totally different quality control issues but none of this appears in the Definition. Consequently, there would not appear to be much need for this in the Definition for a biological such as EPO.

In conclusion, it was agreed that the INN Secretariat should pursue the Definition for a glycoprotein but this would need to be assessed by the INN Expert Group before publication.

GLYCOSYLATION and INNs

The implications of glycosylation on INNs were discussed more than once during the meeting. It has been discussed before that the INN Expert Group receives very little data in INN submissions concerning the glycoform structure of a glycoprotein, that the extent of the data provided is highly variable and that the Group does not necessarily have the expertise to assess critically the significance of any differences in glycoforms between two biosimilar glycoproteins. In addition, and very importantly, there are no rules as to what constitutes a significant difference.

It also has to be realized that an INN is issued at a snapshot in time, usually during the early stages of product development and characterization. Process changes during drug development might alter glycoform patterns of the drug, or greater detailed information on structure might become available, but whilst regulatory authorities are presented with this information, the INN committee is not, and is unlikely ever to be provided with this. For licensure purposes a manufacturer has to present such data to show comparability of the different batches and demonstrate that they have the same clinical effect. However, these are regulatory matters quite separate from INN nomenclature issues.

Consequently, the Group has taken a conservative view that post-translational modifications such as glycosylation are not going to be identical between any two otherwise similar glycoproteins and have adopted the Greek letter for distinction purposes. It is clear that great advances have been made in analytical technology and glycoforms can be characterised in much more detail, but it is not clear that current technology provides all the necessary information nor that these details need be part of the INN.

ACTION and USE STATEMENTS

A document on Action and Use Statements (A&U statements) was tabled for discussion. The growing complexity of structures of drugs was making it extremely difficult to recognize the expected activity of a drug from its structure and so A&U statements were introduced 20 years ago to minimize any confusion between existing and proposed names. The primary aim of these statements is to indicate early in the INN selection process the therapeutic area in which the new name will be applied. This is useful in assessing if any conflicts might arise with trademarks or other names already in use. However, the introduction of these statements early in the INN selection process results in them being of a provisional nature only as drug use in therapy might change during its development. Consequently, statements published in Proposed Lists are not repeated and a disclaimer is inserted into Proposed Lists that the A&U statement merely provides an indication of the potential of the drug at the time of INN selection. This is in contrast to various national nomenclature bodies e.g. BAN, JAN and USAN whose systems permit updates in subsequent editions.

A&U statements involve two alternate approaches, one based upon the pharmacological activity of the drug (e.g. potassium channel blocker) and the other on the specific therapeutic use (e.g. antibiotic). In practice it is impractical to use both and in most cases only one aspect is addressed. Furthermore, the 'action' or 'use' designation is provided in condensed format to avoid any future misinterpretation of a more detailed description. Such condensed formats are often represented by a single word and results in a need for unification of terminology. The early lists of terms used by the INN programme were based upon WHO pharmacotherapeutic classification. A review of the use of A&U statements indicates that in the past 20 years, 2482 INNs were published for which 70% contained formal stems or prestems. This subset was examined for equivalence of stem/prestem usage and the type of A&U statement. For the majority of cases, good coherence existed between the stem and A&U statement.

A number of issues were presented to the Group for consideration:

- (i) that the A&U statement should remain a provisional element during the proposal stage only and that they should not be modified later,
- (ii) that the disclaimers presented in Proposed Lists are retained unchanged,
- (iii) that the current form of the A&U statement is retained,
- (iv) that the preferred terms to be used are included at present in document WHO/PHARM/97.594 but as the list contains very few terms related to receptors and enzymes an expanded and revised version should be produced, to be linked to INN stems and listing also preferred forms of receptor and enzyme names,
- (v) that A&U statements for INNs with common stems should be identical.

The group agreed unanimously with the above five points.

FUSION and CONJUGATED PROTEINS NOMENCLATURE

Fusion proteins comprise a single protein in which all or a portion of the coding region of a gene is fused to all or a portion of a distinct gene and the entire coding sequence is expressed as a single protein. A single INN name is usually adopted for such entities. The current rules for naming a fusion protein of this sort is that if a stem exists for one or both entities comprising the fusion protein then these should be incorporated somehow as infixes into the name. However, applying this has not been straightforward and if no stem exists at all, there is the dilemma of trying to invent a suitable name that might comprise a novel stem, or might not. Also, if a partner in the fusion protein is a short polypeptide derived from a protein which has been assigned a stem, that stem might be inappropriate for the short polypeptide involved. Furthermore, the use of *-tide* to designate a peptide would also be inappropriate as the peptide in question is now part of a larger polypeptide due to the fusion event. For conjugated proteins, for example where a peptide is fused post-translationally to another protein, a similar complex situation exists. In one case, a two-word name has been proposed based upon a precedent for such a situation. Again the naming and use or non-use of stems remains problematic.

These scenarios are going to occur with increasing frequency and probably increasing complexity in the future and considerable thought needs to be given as to how to react to them and to plan for future fusion and conjugate types of protein drugs.

UPDATES from COLLABORATING INSTITUTIONS

World Intellectual Property Organization (WIPO)

Within WIPO, the *Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications (SCT)* is a forum to discuss issues, facilitate coordination and provide guidance concerning the progressive international development of the law of trademarks. The majority of membership is represented by official Intellectual Property (IP) offices and national trademark departments and a presentation by the INN Secretariat at their next meeting on how resolutions on INNs are applied by industrial property offices would be very useful. It is important for trademark offices to spot conflicts between INNs and trademarks, and the SCT would hope to identify areas of convergence when examining trademarks against INNs; there is wide disparity between IP offices in this area. The INN Secretariat was very positive about this; reactions of trademark offices vary across the world and it would be useful to have more harmonization in the area of cross-checking trademarks against INNs and the acceptability/non-acceptability of them is highly important.

United States Pharmacopeia (USP)

The USP has just finalized an important monograph policy for naming drug substances that are salts. The issue of how to express the name and dosage of salt drugs is not new. There are alternate ways of achieving this, by naming the active moiety, or the salt, or as the acid or the base. The choice, as stipulated within this new monograph, is to go for the active moiety. This has been necessary to rule out misinterpretation of prescribing quantity that could result in a doubling or halving of the dose e.g. the molecular weight can double between the salt and the acid. The USP website describes the implementation process but essentially it is being spread out over the next five years and after 2013, application of the 'salt naming policy' will be mandatory. The policy does not cover esters.

The United States Approved Names Program (USAN) noted that it was taking this on board and the Group agreed with the need for this policy. The INN should similarly stick with active moieties as much as possible.

United States Approved Names Program (USAN)

During 2007, 128 USAN were adopted and 37 so far for 2008; 14 new stems were approved. USAN has reviewed the applications procedures and policies and developed a policy statement on the scope and types of products that warrant a USAN. There is also a new policy for additional rounds of balloting for ongoing negotiations and, since the rules for naming esters have not been addressed for 10 years, these have been clarified. The USAN cell therapy scheme has been reviewed by the Center for Biologics Evaluation and Research/FDA and a recommendation was forwarded to the FDA requesting that "tall-man" lettering be used with hydromorphone to distinguish it from morphine. A request from USP to change the USAN/INN *poliglusam* was rejected. The next meeting of USAN will be in July in Chicago.

United States Food and Drug Administration (USFDA)

The USFDA has had a peripheral role so far in this area but it would seem that more direct communication between USFDA and the INN Programme would be beneficial. The FDA is moving more towards the use of INNs for future applications and is using the active moiety rather than salt, mimicking the USAN policy.

British Approved Names (BAN)

The BAN 2007 Supplement 2 and the BAN Pharmacopoeia are both due to be published in August 2008. The BAN made a plea to the INN Committee to keep names as short as possible; when a name is too long, some pharmacists have been inventing their own codes and this has contributed to prescribing errors. It is important that the INN in its entirety can fit onto dispensing labels in order to maintain patient safety.

European Medicines Agency (EMA)

The INN Committee was informed that the 'Guideline on the acceptability of names for human medicinal products processed through the Centralised Procedure' has been adopted and is published on the EMA website.

The addition of product specific guidance on non-prescription medicines to take account of the extension of the EMA Centralised Procedure to cover such types of applications was highlighted. The use of qualifiers/abbreviations within the proposed invented name should aid selection/identification/differentiation of the product by the patient and should minimise the risk of inappropriate use. In addition, in view of the specific legal context of these medicines in relation to promotion and advertisement, the Name Review Group (NRG) will have to determine whether a name is to be considered misleading, promotional or instead carries an acceptable positive connotation.

Another aspect specific to non-prescription medicines is that it is up to the applicant to decide whether to keep part or all of the name of the prescription version of the drug or to propose a different name when switching legal status from prescription to non-prescription medicines. Based on the above, the NRG is faced with names that have been previously accepted through national authorization procedures but which according to the above-mentioned Guideline potentially raise INN concerns both in terms of similarity with their own or different INNs, or inclusion of INN stems.

The INN Committee was also informed that EMA is currently discussing how to proceed with active moieties that are unpublished INN, for identification of salts for generic/hybrid applications in the Centralised procedure.

Japanese Pharmaceutical and Medical Devices Agency (PMDA)

The responsibility for Japanese Approved Names (JAN) lies with the Standards Division of the PMDA. In assigning a JAN, the committee follows two approaches, if an INN already exists (as is the majority of cases), the JAN is a translation of the INN, where no INN exists, the JAN is created according to INN rules. About a quarter of submissions are for biological drugs and these have been increasing in number since the establishment of the JAN in 2006. A current project of the JAN is to establish model definitions for each type of biological.

International Union of Pure and Applied Chemistry (IUPAC)

There are some recent significant IUPAC publications including *Nomenclature of Inorganic Chemistry*, and *Graphic Representation of Stereochemical Configuration* and *Graphical Representation Standards for Chemical Structure Diagrams*, the latter two of which are available as pdf-files. The International Chemical Identifier (InChITM) which was issued in September 2007 and allows the regeneration of structures is being used extensively and will have over 36 million structures. The revision of the *Blue Book*, the IUPAC nomenclature for organic compounds, is scheduled for completion by July 2008 with publication in 2009; it includes the provision of preferred IUPAC names, which are often needed for regulatory purposes.

WHO DRUG INFORMATION

INN lists of names are published formally in the *WHO Drug Information* bulletin in accordance with the "Procedure for the selection of recommended international nonproprietary names for pharmaceutical substances" (INN revised procedure – text adopted by the WHO Executive Board (EB115/11), December 2004); however, it is not clear if this publication will continue. The opinion of the Group was that it is crucial for the INNs to be published formally and as rapidly as possible, and that they should argue for this publication to continue. The INN Expert Group emphasized the need for a regular budget commitment of WHO towards this publication, which is fundamental for the INN process and promotion, as well as the INN Programme in general. This is also in line with a letter written by the experts to the higher management of WHO requesting that the ownership of the INN Programme should be seen to lie with WHO, and that the commitment of WHO to the programme should be reflected in an element of core funding. Indeed, the *WHO Drug Information* and the core funding element were considered fundamental to ensure that the INN Programme has a strong and viable future.

DATABASES

Swiss Institute of Bioinformatics: In collaboration between SIB and INN, there has been a change in the format of names for proteins to increase visibility of the INN name. Also, SIB will link the SwissPROT database to the INN database and is producing a database of protein INNs which SIB would maintain on behalf of WHO.

IMGT®, the international ImMunoGeneTics information system®: It was noted that a database for antibodies and fusion proteins with immunoglobulin fragments with INN name, is also being put together by IMGT in Montpellier, which is along the same lines as the Swiss-Prot database; it is not identical but complements it. This database will be publically available and it would be very useful to have INN reference numbers in this database; this was supported by the INN Expert Group.

INN: The nascent INN database has been built with a very high level of security and this has held up progress and access by the INN Group.

WHO MedNet: this was built 10 years ago as a tool for medicines and health technology information exchange and is useful also for access to INN data. It has restricted access but if the Group considers it beneficial to open up the INN part to the public without registration, then this can be done; this would also remove obstacles for other collaborations such as with Swiss-Prot and IMGT. It was agreed that this would be desirable and the Group should reflect on type of information that should be available and report to the Secretariat.

VARIOUS

Pre-stems: when a number of novel INNs that fall into a group are given names containing common suffixes, the suffix might get adopted as a pre-stem for internal purposes within the Group only. Upon further use of a pre-stem, it is possible to promote the pre-stem to an official stem. Stems are made known publically and can be used by, and are helpful to, companies in suggesting names for their compounds. At present, the list of pre-stems is made available on the WHO website for information and potential guidance to applicants.

Timing of submissions: currently the Group is discussing the timing of INN submissions. It would be preferable for requests to be submitted when substances have entered phase 2 trials.

By naming drugs that are at an earlier stage of development, there is an excessive number of submissions, and through the failure of many drugs at these early stages, too many INN names are getting wasted and lost for future use.

Post-naming process: applicants are informed by the INN Secretariat of the names selected by the INN Expert Group. These names will not formally enter the Proposed List until agreed by the applicant and providing that all information is validated by the INN Publication Experts. In some cases, the applicant may disagree with the selected name and it is therefore re-discussed during the following INN Consultation. Those that are acceptable get officially adopted after a waiting period and reach the status of Recommended INN; this can give them a specific status in many countries. The INN Expert Group agreed that the INN Secretariat should inform officially also National Nomenclature bodies when they play the applicant role.

Naming of esters: as a general rule, since 1975 INNs are selected for the active moiety of pharmaceutical substances. In the case of INNs of salts and esters it is left to the user to devise their names from the INN in conformity with normal chemical practice. Separate names for salts and esters derived from this procedure are not published. The same approach should be followed in the case of combination products. In all those situations, names are referred to as International Nonproprietary Name Modified (INNM).

Some of the radicals and groups involved are, however, of such complexity that shorter nonproprietary names are selected for these inactive moieties, and published in proposed lists under the title "names for radicals and groups". If a "radical and group name" is used in conjunction with an INN, it is also referred to as an INNM. In some cases, a name of an INN Radical describes more than one substituent, e.g. (names in Latin) *acefuras*, *aceponas*, *enbutas*, *stinopras*.

For further details on the INNM, please refer to the INN Working Document 05.167/3 "*International Nonproprietary Names Modified*" which can be downloaded from the INN Programme website: <http://www.who.int/medicines/services/inn/publication/en/index.html>.

Further information on the selection procedure and general principles in devising INNs may be found in the "*Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*" (WHO/PHARM S/NOM 1570).