

***49th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 17-19 November 2009***

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 49th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 17– 19 November 2009. 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 World Intellectual Property Organization (WIPO), 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 (US FDA) and others.

Dr Hans Hogerzeil, Director Essential Medicines and Pharmaceutical Policies (EMP) opened the meeting and welcomed those present on behalf of the Director General. The Expert Group works as part of the WHO and the preparative work undertaken and the work of the meeting is highly appreciated. He informed the Group of recent advances within the medicines department. The Norms and Standards section has been instrumental in providing formal guidance on issues concerning the world's medicines situation and will help monitor essential medicines policy. Country Support activities have been instrumental in recent years in training WHO field officers to support technical work on medicines programmes and to support governments in this area. Some of these officers are based at WHO HQ but 80% are in or visit the field. Innovative Public Health thinking has developed tools to help governments avoid corruption in the purchase and distribution of medicines. Finally, access to essential medicines is becoming a human right and the WHO is working to help introduce this right in countries' constitutions.

The Chair, Prof Derek Calam, thanked Dr Hogerzeil for his up-to-date review of recent WHO activities and extended the welcome to all members and observers. The Group has been very busy since the last meeting, with 94 new applications to review as well as some previous applications. This is the largest number so far encountered. The Secretariat also has had a heavy work schedule with these applications, including further work on the new online system. The report of the Working Party on Action & Use Statements will be discussed and there will be a meeting with IFPMA representatives. Finally the Chair reminded the Expert Group that they were present in the meeting as individual experts and did not represent any specific body or association.

The Manager of the INN programme, Dr Raffaella Balocco added her thanks to the experts for proving their comments and doing so in a timely manner with the new online database and commentary system.

NOMENCLATURE of INNs

During the Consultation, a total of 128 INNs were discussed, including:

- 99 new INN requests, including 32 for biological substances
- 23 outstanding requests
- 5 previously selected proposed INN, against which a formal objection had been raised
- 1 request for substitution.

As a result of these discussions, 114 new names were selected, which are planned to be published in List 103 of Proposed INNs, while 5 requests were deferred for future discussion. Five requests were rejected by the INN experts, as the substances did not conform to the criteria for INN selection. Two amendments were planned to be published in List 103. Two requests have been withdrawn by their applicants as their development ceased during the selection process.

DISCUSSIONS WITH IFPMA

Monoclonal antibodies

Representatives of the IFPMA¹ met with the INN Expert Group to discuss and provide their views on nomenclature for monoclonal antibodies (mAbs). They expressed concern that post-translational modification of mAbs, specifically glycosylation, is not adequately addressed in the working document (09.251 of 26/06/2009) on General Policies for Monoclonal Antibodies and that no conclusion on this issue had been reached by the INN Expert Group as noted in the Executive Summary of the 48th INN Consultation or in the article published in WHO Drug Information (Vol. 23). The view of the IFPMA is that naming of both stand-alone and biosimilar mAbs should follow the system that has been developed for glycosylated biotherapeutics such as epoetin, i.e. mAbs with the same amino acid sequence but distinct glycoforms should have distinct INNs by the use of a Greek suffix. In the case where a mAb was not glycosylated, a potential follow-on mAb with the same amino acid sequence as a predecessor would be assigned the same INN.

Scientifically, the IFPMA reasoned that glycosylation can affect the biological activity of mAbs and provided examples of this whereby the absence or presence of fucose can have strong effects on the affinity to Fc receptors on immune effector cells and ultimately on its therapeutic effect.

It was also emphasised by the IFPMA that different recombinant mAbs made by the same manufacturer using the same basic cell type will have subtle differences in glycosylation due to small differences in fermentation and purification. When mAbs are produced by different manufacturers, the resulting differences in glycosylation mean that otherwise similar mAbs should have a distinct INN, especially as even subtle differences in glycosylation can have a clinical effect that may be traced back to the manufacturing process. The IFPMA acknowledged that it is not necessarily straightforward to analyse subtle differences in glycoform structure, that these structures are heterogeneous and that the analytical methods used can impact on the extent of glycoform characterisation.

One area of concern to the Expert Group is when a manufacturer introduces changes to the manufacturing process after an INN has been assigned, that might impact the glycoform profile, e.g. scale up. However, the IFPMA felt this should not be a problem because a single manufacturer can establish that a product is unchanged clinically by use of a bio-comparability trial while this cannot be done readily if two different manufacturers are involved. The IFPMA also held that where a follow-on mAb product was initially shown to be identical to the originator mAb and was assigned the same INN, and manufacturing changes were then made to the originator such that it was now distinguishable from the follow-on product, this was unlikely to occur as it is unlikely that a follow-on manufacturer would ever have an identical mAb. Also, manufacturing changes that would significantly impact on the glycoform profile, such as a cell line change, are unlikely to take place after clinical studies have begun and the INN assigned.

Currently, for the vast majority of mAbs on the market, there is only one manufacturer; however, it is likely that many follow-on mAbs will appear once patents expire. So far there have been no mistakes in naming mAbs and the IFPMA concluded that a system for nomenclature should be established sooner rather than later so that the situation that occurred with EPOs (where several versions were given the same INN) does not arise. IFPMA support the adoption of Greek letters for mAbs and it would be logical to adopt the same procedure as exists for recombinant biotherapeutic proteins. If this approach is taken, it should not be applied retrospectively to current mAbs and a first follow-on mAb should be distinguished from the originator with a 'beta' Greek suffix (and with no need to introduce retrospectively assign an 'alfa' suffix for the originator).

INNs for epoetins

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The IFPMA representatives also provided their views on nomenclature for epoetins. The use of Greek designators to distinguish epoetins with the same amino acid sequence but different glycoform profiles is well established although the level of 'difference' always has and remains open to interpretation. Glycosylation is a highly complex characteristic and assessment of potential differences between comparable products will depend highly on the nature of the analytical methods used. Subtle changes that can impact on biological activity, may not be apparent from physico-chemical analyses and may not be observed until clinical observations are made.

The INN is important for safe use and dispensing. As more and more epoetins appear on the market, it will be a challenge to prescribers to understand clinically relevant differences. One point of concern is that not all epoetin alfas are approved for the same route of administration and this is a potential risk to the patients. Indeed, different safety signals are being observed with alternative epoetin alfa products.

Consequently, the IFPMA propose that a new Greek designator is assigned only when a new epoetin is developed as a stand-alone product; this would remove any emphasis on glycosylation differences, which are difficult to assess anyway. However, where an applicant claims similarity and proposes to use a pre-existing INN, then an additional suffix, e.g. a numeral 1 or 2, should be added beyond the Greek designator to show that not all epoetins are fully identical. It is recognised that WHO do not mandate applications for INNs but it should encourage this and provide appropriate guidance. Regulatory bodies could play a greater role and should comment on the appropriateness of the INN assigned in authorisation applications.

Within the Expert Group, there has been comment that use of Greek designators for these products provides for unique manufacturer's INNs and it was noted that the proposal of an additional suffix could drive it even further in this direction. There is a need for identifying meaningful differences, differences of clinical consequence and the IFPMA felt that such data should be dealt with by the regulatory authorities with better feedback to the INN group. This is a challenge for both sides.

The INN group has tried to evolve in parallel with the complex area of glycoproteins and now insists that compounds have entered clinical trial before submitting for an INN, but it cannot prevent process changes occurring post name assignment even to the extent that a name might have to be altered. This is something the Group will have to reflect upon. There have been problems in the epoetins area and the group has tried to investigate further the definitions with a Greek letter suffix. A problem is the supply of incomplete and varying amount of data on glycosylation. The INN group is trying to find the best way of assigning Greek letters and that a new designator is assigned properly. One approach is to define epoetins by the cell type and the characteristics of the glycoforms. Thus, distinct epoetins are derived from CHO cells with distinguishing glycan characteristics such as the level of LacNAc repeats while other epoetins are derived in BHK cells again with distinguishing glycan characteristics, although in some cases these glycans can be highly similar to structures characteristic of those found in some CHO derived epoetins. Information on these structures has been provided by the applicants; however, some applicants provided no glycan structural details (and were assigned INNs with distinct Greek suffixes).

IFPMA acknowledged the effort put into these assessments but felt that most glycosylation differences were not so much to be found in precise structural features but reflect more the quantitative differences of particular glycan forms.

The Chair thanked the IFPMA representatives for presenting their views and for their discussion of the above issues.

PUBLICATION OF ADDITIONAL DATA ON DEFINITIONS OF EPOETINS

Much of the data on glycan structures was received after publication of definitions of epoetins in the proposed list. The Group considered making formal changes to the published definitions concerned with updated data but there was no consensus agreement on this and a less formal way was preferred. The Group also needs to consider the advantages to users, manufacturers and regulators whether

glycan structural information should be made public. It would be important to have comments from companies and also other groups developing products on any publication. Companies will have specifications lodged with regulatory authorities and it is important that the definition is consistent with what is approved. However, applicants could be informed that the Group is minded to publish expanded definitions with the further data submitted but not to change the published one. Further, the INN has been provided with structural data only and not quantitative data, and manufacturers could be asked for this along with the analytical methods employed.

It was agreed that the Secretariat should consider how to take this forward and report at the next meeting.

NEW NOMENCLATURE FOR MONOCLONAL ANTIBODIES

The INN Group considered the new nomenclature scheme for monoclonal antibodies (mAbs). This was developed by a Working Group, adopted by the Expert Group and published on the WHO website for three months public consultation. No comments were received and the IFPMA view expressed at the meeting was supportive of the changes. The Chair proposed formal adoption of the paper and this was agreed. Usage of the new mAb nomenclature could proceed immediately for new applications.

NON-PROPRIETARY NOMENCLATURE SCHEMES for PEPTIDE and PROTEIN THERAPEUTIC VACCINES

The Chair welcomed a representative from the Center for Biologics Evaluation and Research (CBER) USA who attended the meeting to provide FDA views on non-proprietary nomenclature schemes for peptide and protein therapeutic vaccines.

So-called therapeutic vaccines are being handled at CBER by the Office of Cellular, Tissue and Gene Therapies. There are approximately 100 clinical trials of peptide therapeutic vaccines and about 12 using protein vaccines, mainly for cancer treatment. The current INN/USAN system of nomenclature is adequate for protein biotherapeutics; however CBER felt that a new scheme would be needed for therapeutic vaccines based upon proteins and peptides. CBER has concerns that a *-tide* scheme already exists within the INN system and has been used already for four vaccine products. It is also concerned that the USAN has a cell therapy scheme for immunotherapy products that captures some of these therapeutic vaccine products; the scheme involves a prefix plus two infixes plus a stem-qualifier.

CBER would prefer a single scheme for all peptide and protein therapeutic vaccines. This would involve a prefix (fantasy element), one infix (*'prot'* or *'pep'*), a stem (e.g. *'imut'*) and a qualifier for the manufacturing method (R for recombinant, S for synthetic). To avoid complicated names, all additional components, including an antigen element, should be avoided. Ultimately though, CBER remains committed to working with the INN and defers the final decision to the Expert Group.

There was some concern from the Group that a protein for therapeutic use with an INN might go into a vaccine and require a new name; however, this would unlikely be a problem as most will be tumour antigens not in use for any other therapeutic purpose. Also, while the need to differentiate between recombinant and synthetic was questionable, this was to signal the different types of impurities that might be present in these vaccines.

It was also noted that the use of the term 'therapeutic vaccine' for such products was being avoided in the EU where they are referred to as immunotherapeutic products and further that some will be mixtures of defined proteins or a more complex mix of relatively less well defined proteins and for this latter group, it would be difficult to have a proper definition for a single INN name. The USAN however already has names in place for complex lysates from autologous cells and CBER is not trying to change the USAN scheme; instead it wants to bring in recombinant and synthetic proteins and peptides.

It was important for the INN Expert Group to have heard this presentation and the CBER proposals. The current INN scheme does not provide for names for (prophylactic) vaccines, nor for mixtures, which many of these therapeutic vaccines would be. It is a complex proposal and various points of the CBER scheme need to be taken away and considered. The Group should return to this issue at the next meeting.

ACTION AND USE STATEMENTS

At the 48th Consultation, it was agreed that a small working group should revise the stem classification of A&U statements. A&U statements are provided for proposed INNs only and are intended to provide an indication only of their potential activity and clinical use. The reappraisal was needed due to changes in biochemistry and pharmacology over the years and had been discussed in depth at the previous two INN Consultations.

The revised Action and Use (A&U) Statements were tabled at the meeting. In addition to updating many preferred expressions, some new classes have been created such as YY for multiple activities and Z for gene therapy. This new document will guide the Secretariat about which expression is to be used when a given stem is selected.

During revision of the A&U Statements, the working group unearthed some new issues. Firstly, the INN programme has about 300 stems which were classified about 25 years ago; due to scientific progress, these also need updating. Secondly, assessing ~8000 INNs by hand would be extremely difficult and would be more efficiently tackled by computer. A further point that emerged was that when trying to assign A&U Statements to stems, it was realised that a few 'sink' stems required more detailed consideration.

The Chair was grateful to the working group for preparing this new document. There was no suggestion that any changes would be applied retrospectively and with no further comments from the Expert Group, it was agreed by the Group that the Secretariat should implement the new Statements from now onwards and report on progress at the next Consultation. Further thought needs to be given to 'sink' stems. It needs to be borne in mind that at the early stage of clinical development when an INN and A&U Statement are assigned, provision of a precise mode of action is not advisable as this could change during further clinical development.

UPDATES from COLLABORATORS

United States Adopted Name (USAN) Program

The 2009 summer USAN Council meeting took place at AMA headquarters, Chicago, in July, at which names were recommended for 37 substances. Seven new stems were approved and posted on the USAN website. Four designations for radicals and anions were also approved and posted. Fifty-seven INN applications were prepared by USAN and forwarded to the INN programme for discussion at the 49th Consultation; this is the largest number to date but is partly due to the uneven timing of the two annual meetings. The winter 2010 Council meeting is scheduled for January in Miami.

By the end of November, 115 USAN had been adopted during 2009. Revenue was also realised for an additional 22 negotiations. The USAN program instituted a revised fee structure effective Sept 1, 2009 with a 20% rise across the board.

British Approved Names (BAN)

The BAN is working with relatively new assessors to watch out for incorporation of INNs in their entirety or in part in proposed brand names, to avoid misuse of the INN. It was intended to include on the UK licensing website a note about WHO's Mednet site and how to get access to this and links to the INN website to the INN(M) document; this is to help customers avoid misuse of an INN.

The BP secretariat published supplement No. 3 to the BAN 2007 book.

United States Pharmacopeia (USP)

The USP representative brought to the attention of the Group, the enormous contribution of Dr Bill Heller to the USP. He was a founding member of the USAN Council and had been instrumental in putting together the USP Dictionary of Drug names, including a pronunciation guide which was formally balloted by the USP Nomenclature Committee. The USP will include the pronunciation guide in the USP-NF book. In discussion, it was noted that the BAN list also includes a pronunciation guide but that pronunciation in UK bears no resemblance to what is in the BAN book. In contrast, the USP finds that names are being pronounced as in the dictionary.

International Union of Pure and Applied Chemistry (IUPAC)

It was noted that the 2nd edition of the book on Principles of Chemical Nomenclature should be ready for final checking March 2010, and available later in 2010.

US Federal Drug Administration (FDA)

The FDA representative sees the *-grel* stem (platelet aggregation inhibitors) being used as a ‘sink’ stem. Many such substances have widely varying pharmacological and clinical effects and should not be assigned a *-grel* stem; *-grel* should probably be reserved for the clopidogrel family (agents that act at purinergic receptors on the platelet surface).

Similarly, the stem *-tinib* is becoming a ‘sink’ stem, being used for compounds that inhibited a wide variety of tyrosine kinase inhibitors. It was also noted that several compounds which have been named using either *-tinib* or *-anib* could conceivably be named using either stem; other stems might be more informative than *-tinib*.

Also, the Division of Adverse Events is starting to notice conflicts amongst established names and has approached the FDA for advice on INNs.

Japanese Pharmaceuticals and Medical Devices agency (PMDA)

The PMDA is responsible for most of the scientific and technological evaluations, and reviews on pharmaceuticals and medical devices. The Standards Division within the PMDA is responsible for preparing drafts of Japanese Accepted Names (JAN) and has responsibility for drafting the Japanese Pharmacopoeia (JP). It is also required to prepare standards for Medical Devices.

The JAN system was established under law by the Ministry of Health, Labor and Welfare (MHLW). Where a substance has an INN, the name is translated directly into the JAN. Where no INN pre-exists, a JAN is given according to INN rules. In the past 18 months ~50 submissions have been received, most of which had already been given an INN. JANs are posted on the National Institute of Health Sciences in both Japanese and English.

World Intellectual Property Organisation (WIPO)

Representatives from the World Intellectual Property Organisation (WIPO) joined the meeting to discuss potential abuse of INNs by using them as internet domain names. The health sector is a major target of those engaged in abusive online cases, e.g. online pharmacies selling counterfeit drugs, and 10% of complaints are filed by the pharma industry.

The domain name system is actively monitored for such abuse, for the appearance of ‘drug.com’ or even INN.com. When an INN is abused in this way, where an INN is linked to a TM, e.g. diazepam, the TM owner can take action; but if only an INN is involved, complaints cannot be taken forward as there is no procedure to address that particular abuse.

In 2009, 20 new top level domains and about 250 country top level domains are to be created, including the use of non-Roman scripts such as Chinese or Arabic, and together this might increase the level of abuse. In the future, the number of top level domains may expand even further and there is the possibility of the creation of, for example, *.health* or *.pharma* domains, or even *.INN*. However, abuse at this level may be unlikely due to the high cost of initiating and running such sites. It is understood that ICAN is being alerted to these possibilities to ensure adequate protection of top and second level domains.

The WHO has a mandate to promote and protect INNs and there is a duty to prevent registration of INNs as domain names. A letter is being drafted by WHO to alert ICAN of the need to protect INNs and this should be delivered before the end of 2009 as many domain name changes are anticipated from January 2010. One possible solution may be to make top level domains available to international agencies e.g. *.UN* or *.WHO*, maybe even *.INN* at a reduced cost. WIPO understands that there are proposals for different categories and different fee levels but it appears that ICAN may not be considering this too seriously.

DEVELOPMENTS in DATA MANAGEMENT

The web-based IDMIS system is now well established and should be used for the reporting of all comments. It now contains a search tool which will allow searching, for example, for strings of letters or a particular formula. There is also a facility for checking which submitted names have been assessed by the individual experts. The Chair was very grateful for the huge amount of work gone into the creation of the system.

In addition there is the WHO's MedNet site which contains the INN Extranet site, with more than 9000 users. It is planned to facilitate the communication between the two IT tools, namely the INN MedNet and INN IDMIS.

CLOSE OF MEETING

Prior to closing the meeting, the Chair noted that some experts would continue after the meeting to discuss issues surrounding the publication of definitions for high molecular weight proteins. These discussions would be distributed to others and re-discussed at the next Consultation.

The Chair formally closed the 49th Consultation and thanked the entire Secretariat on behalf of the Expert Group for providing such a smooth meeting. Advisers and observers are also important, but most importantly everyone contributed one way or another to the work being carried out; almost 100 new applications were assessed and only two were deferred, which is remarkable achievement. The IDMIS system is progressing well and needs full use by the users. Dr Hogerzeil has also noted that it would be good to publicise more about the INN programme and the participation of members of the Secretariat and Expert Group in a PDA meeting in June 2010 in Washington will be highly useful to enhance this visibility.

The 50th Consultation will take place at WHO headquarters on May 18-20, 2010.