

***Meeting report of the 47th Consultation on
International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 18-20 November 2008***

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 47th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 18-20 November 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 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 European Medicines Agency (EMA), 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 participants. Recently, under organisational changes at the WHO initiated by the Director General, a new department – EMP – was created by the merger of two previous units, the PSM (Medicines Policy and Standards) and the TCM (Technical Cooperation for Essential Drugs and Traditional Medicines). The EMP, of which Dr Hogerzeil is the new head and under which the INN program is managed, is now fully operational. Dr Hogerzeil expressed his appreciation for the work and time spent by the members of the panel and the expertise that they bring as individuals to the work of the WHO.

The Chair welcomed new members and thanked all for their hard work and contributions submitted between these biannual meetings; it was noted that the experts attend as experts in their own right and not as members of their home organisation. The INN Programme Manager, Dr Raffaella Balocco Mattavelli, similarly was very appreciative of the presence of the experts and for their work performed outside of the INN meeting.

NOMENCLATURE of INNs

During the Consultation, a total of 122 INNs were discussed, including:

- 84 new INN requests, including 28 for biological substances
- 29 outstanding requests
- 6 previously selected proposed INN, against which a formal objection had been raised
- 3 requests for substitution.

As a result of these discussions, 106 new names were selected, which are planned to be published in List 101 of Proposed INNs, while 10 requests were deferred for future discussion. Three requests were 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 101. The remaining requests discussed were requests of substitution.

WORKING GROUP on NOMENCLATURE FOR MABS

The creation of novel distinct INNs for mAbs is becoming more and more difficult due to the large number already issued and the complexity of nomenclature. At the previous INN Consultation, the Expert Group requested that the biologicals experts meet to review names for mAbs and to draft recommendations for future nomenclature. A draft report of the informal discussion was tabled at this 47th Consultation; however, it had only recently been drafted and so not all biologicals experts had had time to comment. Consequently, the report will not be adopted until the next INN meeting in the spring of 2009. Those who were invited to the informal discussion but who could not attend will also be asked for comment.

The report highlighted that a major issue is the number of mAb INNs, currently 173¹ with numbers increasing; some groups are overcrowded, names are becoming similar and increasingly long names

¹ At the time of the informal discussion of the working group

are being created which results in pronunciation issues and clumsy names. The present system has worked well but some revision is needed. The stem *-mab* is well known and has been widely accepted. However, many mAbs nowadays are fragments, e.g. Fab fragments, and it is appealing to adopt *-fab* as a stem, but some Fabs are already named with the stem *-mab*, which could cause confusion if it is changed. Furthermore, not all fragments are Fabs e.g. single-chain Fv's and would not necessarily fit into a *-fab* stem. The working group recommended that the stem *-mab* should be retained and used for all mAbs including Fab and all other fragments. The system for conjugates and radiolabelled mAbs was felt to be adequate and should be kept whilst the *Definition* remains an important feature as the INN name cannot encompass all relevant information concerning a mAb.

Substems have been useful but overall are too complicated. Several substems exist to denote the origin of the mAb but some have never been used and four of them predominate *-zu-*, *-o-*, *-u-*, *-xi-*. Substems defining the source of the mAb should be kept but redefined as the nature of the species that the mAb represents rather than its original origin. The use of substems for disease indication has also been uneven, with some used rarely or not at all. The group recommended that *-tu(m)-* should be kept but with no indication of the precise nature of the targeted tumour because the indication of many *-tu(m)-* mAbs is changing; indeed some mAbs might target tumours and be used for non-tumour indications such as rheumatoid arthritis. A further step that could cut down on long names would be to use *-t-* instead of *-tu(m)-* and applying this approach (purely for trial purposes) to various established names worked well. Similarly, for the *-lim-* class, *-l-* was generally easier to pronounce than *-m-* although one single letter is not terribly exact in defining a target.

For pegylated mAbs, the stem *-peg* can be used but it is probably better to put this into a second name to avoid an overly long INN, e.g. by the use of *pegol*, whilst modifications of *pegol* may be useful to indicate different types of pegylation, even although differential pegylation is common to all pegylated proteins.

All mAbs undergo post-translational modification, which is largely dependent on the production method but which generally does not affect clinical use although glycosylation can affect the pharmacodynamics/kinetics of the drug. Some mAbs might be derived from glyco-engineered cell lines or have been engineered themselves to remove or add a specific glycosylation site.

All mAbs so far have different amino acid sequences but it has to be considered that a request may appear for a mAb with the same sequence as one with a pre-existing INN. This would invoke a consideration of the use of Greek letters. The working group felt that if a mAb appeared with the same amino acid sequence but a significantly different glycosylation pattern, it should have a different INN, although the definition of significant becomes problematic; however, it was felt that in particular a glyco-engineered mAb should be given a different INN from the parent mAb. Moreover there is no reason to take a different approach from that taken for recombinant proteins, i.e. the use of Greek letter suffixes, and so an application for the same amino acid sequence but a deliberately changed glycosylation pattern, e.g. the specific absence of fucose, the INN would differ by a Greek letter and the *Definition* would be crucial in further defining the product. There was no clear consensus on how to handle such mAbs but certainly if a Greek letter system were to be followed, the original INN could not be assigned one retrospectively as too many are already in use (without a Greek letter suffix).

The recommendations of the working group were generally acceptable to the INN Expert Group. However, it was noted that if two substems are retained along with the *-mab* stem, there could still be a requirement for at least three syllables. It would be worthwhile for the Secretariat to test the application of the above points and to draw up a document showing current principles, an indication of the above changes, specific examples of changes and what it would be like for new applications. This would allow a focus on issues where decisions need to be made.

The Chair was grateful for the report but before the INN Expert Group could take on board any recommendations, it would be important to seek out comments from all attendees of the meeting and also those experts who were invited but could not attend the meeting, with the final decisions being taken at the next INN Consultation meeting.

DEFINITIONS for EPOs

It has been discussed previously that the Definitions for EPOs are inadequate because of the difficulty in getting information on glycosylation patterns and micro heterogeneity. At the previous INN meeting, the principal structural properties of nine different EPOs were discussed. The extent of information available on glycosylation for the Definition was highly variable, but the glycosylation pattern or the role of any given glycan was generally not provided when an INN application is made, and may not even be known. Glycosylation is dependent on the cell substrate; however, it was felt that inclusion of this information in the Definition was not useful and that the INN should pursue the obtention of further information on glycosylation from companies.

It has been difficult to extract further information as some companies no longer exist or have been bought over. The IFPMA network is helping out. However, four companies have provided more specific information on glycosylation for their particular EPO whilst other information has been gleaned from the literature. Overall, since the glycosylation sites are constant and mammalian cells do not differ greatly in their glycosylation machinery, differences between EPOs tend to exist in the form of unique but minor glycans, in the extent of terminal glycosylation of antennary structures, or in the relative amounts of the major glycans.

There is now a tendency to expect much more data on glycosylation patterns because of advances in analytical techniques. For example for epoetin lambda, much more information for the Definition was required than had been in the past, and this trend may well continue. However, it remains difficult to conclude on how much information should appear in the Definition. Furthermore, a linguistic description of the structures is highly difficult due to their complexity.

ACTION and USE STATEMENTS

Most INNs show a pharmacological indication via the use of stems, but the assignment of a stem may not be straightforward and is usually based upon an applicant's declaration of presumed action and use. Until 1987, action and use information in INNs was presented solely via the stem but since 1988 it has been published as a distinct entity in the proposed INN (pINN) lists as action and use (A&U) statements, and from PL59 to PL100, there are 2,627 INNs with A&U statements. The information conveyed by stems is for general use by prescribers and pharmacists. In contrast, the A&U statement is not for general use as it is of a temporary nature being information provided at the time of application only and is really aimed at assisting in a review of possible conflicts as assessing the use of a compound from its complex chemical structure cannot easily be achieved.

The problems associated with selection of A&U terms are similar to selecting stems. INNs are created early in the development of a drug and based upon the information provided by the applicant. The information may be provisional and so a specific disclaimer is provided in the pINN lists as the WHO is not in a position to query A&U information or to pass comment on any efficacy claimed. The A&U statements do not get revised as the INN Programme does not follow the fate of the use of a product and its associated INN; consequently, the A&U statement is not repeated in the recommend (rINN) list. This situation is different in national publications such as BAN, JAN and USAN as these may be linked to national regulatory authorities. Also, A&U statements being of a general nature are highly condensed and may quote only a single activity or main intended use. Thus there are links between the INN stem system and the A&U statements.

Terminology for A&U statements was unified with the WHO pharmaco-therapeutic classification in 1992, encompassing preferred terms from synonyms, whilst the spelling and word presentation fell into line with WHO editorial office rules. The published terminology was amended in 1997 and contained 175 preferred terms at that time. A draft revision of the 1997 amendment was tabled at this 47th INN meeting and was based on a review of A&U statements in pINN lists 59-98 in which there are 2,482 INNs with A&U information, 70% of which incorporated a stem or prestem. Also 18% of the A&U made reference to action on receptors or of enzymes (there were 88 receptor names and 60

enzyme names assigned in the past 20 years). In this current draft, the preferred terms of the 1997 update were followed and correlation between A&U terms and stems was generally found to be adequate. Some problems were uncovered including discrepancies in formulations and in designation of receptors and enzymes. In the new draft revision, there are proposed guidelines on formulating A&U statements, a list of preferred statements, and expressions for substances acting on receptors and enzymes (the preferred expressions are listed in annexes).

A&U statements related to action on receptors and of enzymes required special attention as the area has grown considerably since 1992. In two further annexes of the tabled draft, expressions connected to action on receptors and for enzymes (respectively) are provided to unify their nomenclature; this might require the redefinition of stems that have been created many years ago. Major changes should be avoided unless there is sufficient justification. In a final annex, specific topics for discussion are presented including antineoplastics, the *-ster-* stem and the *-plase* substem.

The chair proffered his thanks to an INN Senior Adviser for the huge amount of work involved in drafting this amended A&U document which involved the assessment of over 2,000 INNs and an analysis of all A&U statements.

In discussion, information was sought on the relationship between A&U statements and the Anatomical Therapeutic Chemical (ATC) classification codes. A&U statements are assigned when the application for an INN is made, which is generally during development of a drug, and give a tentative indication only; in contrast ATC's are given only to products on the market and as such much more information is available for the ATC. Thus assignment of an INN and an ATC code is not a parallel operation and inconsistencies can appear, but they should agree in general. After publication in a pINN list, an A&U statement is not reviewed and does not appear in the rINN list.

In further discussion and in appreciation of the fact that changes occur along the way, it was suggested that it might be better to publish information on the mode of action (MOA) rather than an A&U statement in order to classify a drug in a pharmacological class. Also, there would be value in a trial application of the terminology presented in the new draft, especially for mAbs since for them an action might be similar whereas the intended use may vary greatly. Thus, the MOA information may be better information in creating an INN than an A&U statement.

A subgroup was nominated to examine the draft revision in detail and report to the INN Expert Group.

DEVELOPMENTS in DATA MANAGEMENT

An integrated web-based data management system has been developed within WHO to enable members of the INN group to access INN information, application details and ultimately to allow online applications. This system is highly restricted and not available to the public. It is ready to be launched for assessment of applications for the next INN Consultation although information will be distributed in parallel via a separate media as back-up in case of teething problems in using the web-based system. The security level will be high and users will require certification.

UPDATES from COLLABORATORS

European Medicines Agency (EMA)

The INN Expert Group was informed that the Name Review Group (NRG) completed its first year of practical implementation of revision 5 of the 'Guideline on the acceptability of names for human medicinal products processed through the Centralised procedure' (CPMP/328/98 Rev 5), which was published on the EMA website in January 2008. It was also subject to an exchange of viewpoints at the Annual NRG/Interested parties meeting held on 3 November 2008, which included the participation of the EFPIA, AESGP, EGA and EAEPC industry associations.

From an NRG perspective, the introduction of flexibility and removal of *a priori* restrictions from the Guideline has resulted already in a slight increase in the acceptance rate of proposed invented names in the centralised procedure, but will need to be monitored in the future.

From a more detailed analysis of the type of objections raised it can however be deduced that the majority (>80%) of objections raised pertain to potential confusion in print, speech and handwriting with other names authorised within the European Union. The remaining objections involved unacceptable qualifiers, promotional and misleading connotations and similarity with own or different INNs and/or the inclusion of the INN stem.

The NRG is currently discussing with industry a way to clear the NRG database of any unused acceptable names so as to avoid unnecessary blockage of any future proposed similar invented names. This could include the introduction of a validity period to the acceptability of a proposed invented name proportional to the time in which it is reasonable to expect a marketing authorisation to be filed and granted. (Note: in contrast, once an INN is assigned, there is no provision for the deletion of any [unused] names).

On a point of information, in the EPAR for Micera, replacement of the INN with the common name was overlooked and is being corrected; this was an error during entry into the EPAR.

World Intellectual Property Organisation (WIPO)

Both WIPO and the INN are improving mutual cooperation. The issue of trademarks and INNs has been discussed in several sessions of the WIPO Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications (SCT) and accessibility to lists of INNs and the information they contain has been improved in the past year by distribution of a CD-ROM to the industrial property offices of WIPO member States worldwide. In 2008 also, at the invitation of the SCT, a representative of the WHO INN Programme attended their July meeting. INN representation was extremely useful for the SCT and WIPO members, and there was a request from examiners of trademark applications for contact details at WHO for day-to-day queries in their work. WIPO has also agreed to increase their distribution of INN information to SCT members, electronic subscribers and non-governmental organisations by email alert. WIPO met recently with WHO to review collaboration including database access and details of the INN Programme. WIPO looks forward to continued cooperation with the INN Programme, further enhancement of accessibility to INN lists and a future presentation on the INN database at the June 2009 SCT meeting.

In the context of trade names, an advert was shown by the INN Secretariat to the INN members in which it was clear that the trade name Ratiograstim has made direct use of the –*grastim* stem. It is a difficult area and the INN Programme needs assurance that such issues will be picked up in the future and that stems do not get used inappropriately. It was noted that a similar case had indeed arisen and the trade name rejected. However, the Representative from WIPO pointed out that trademark registration comes under the legislation of individual jurisdictions and that WIPO cannot intervene on whether a sign may or not be registered as a mark by a given Office. Some SCT delegates have commented that they would most likely refuse a trade name that was not sufficiently distinct from an INN. But the answer is less straightforward for names that took part of a stem and it would be up to the examiner to assess if there was sufficient distinction on a case-by-case basis; it is for such cases that examiners would appreciate useful contact details within the INN Programme.

United States Adopted Name (USAN) Program

The 2008 summer USAN Council meeting took place in July in Chicago where names were recommended for 48 substances; 10 new stems were also approved and posted on the website. Since the July 2008 meeting, the USAN has also researched, reviewed and forwarded to the Council an additional 57 applications for naming decisions and as of the end of October 2008, 118 USANs were adopted. Revenue was also realised for an additional 23 negotiations. The next (winter) USAN meeting will take place on 29-30 January, 2009 in San Diego.

The USAN also reported success in having a U.S. trademark abandoned for the USAN/INN *tasimelteon* and has approached the owner of the *Biolimus* trademark to abandon this also.

The USAN Director made a presentation on USAN and INN to the American Medical Association's Council on Scientific Affairs and Public health in June 2008 whilst USAN staff completed an evaluation of USAN nomenclature practices based upon USP's MEDMARX data.

British Approved Names (BAN)

The British Pharmacopoeia 2009 is now available in addition to the British Approved Names 2007 and British Approved Names 2007: *Supplement No. 2* - a dictionary of drug names for regulatory use in the UK.

US Federal Drug Administration (FDA)

The FDA is receiving more and more applications concerning fusion proteins and other biologics, and seems to have a heightened interest in choosing names for biologics. Consequently, it would appear useful for the INN group to have FDA participation and help can be provided in identifying a suitable representative.

Also, as noted before, the USP in future monographs will list substances as the active moiety and not the salt. The FDA will retain labels with both the moiety and the salt in the descriptive section, this being more in line with INN and USAN requesting dual names, one for the salt and one for the ester.

International Union of Pure and Applied Chemistry (IUPAC)

IUPAC is well under way in harmonising lists with the INN Secretariat and is to revise IUPAC's 'Blue Book' nomenclature of organic chemistry. Entire chapters of the Blue Book have virtually been revised and these will form the basis for a new edition which will hopefully be well under way by spring 2009. IUPAC nomenclature division 8 has also recently published a document on rotaxanes.

Taxud/EC

The outcome of INN meetings is very important for the work of the Taxation and Customs Union Directorate-General (TAXUD) of the European Commission. INNs are used in EU legislation and subject to international trade agreements. Negotiations for a fourth revision of the Pharma-GATT trade agreement are about to start and INNs represent one pillar of the database European Customs Inventory of Chemical Substances (ECICS). WHO/INN representation at WCO meetings would be welcomed.

CLOSING REMARKS

In closing the meeting, both the Chair and Dr Lembit Rägo, Coordinator, Quality Assurance & Safety: Medicines, noted that very few of the new applications were deferred and along with a large block of outstanding applications, >100 new names were adopted, which must be close to a record. This was a huge amount of work and congratulations are due to the experts and the Secretariat.