

***50th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 18-20 May 2010***

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

***Quality Assurance and Safety: Medicines (QSM)
Essential Medicines and Pharmaceutical Policies (EMP)
World Health Organization, Geneva***

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INTRODUCTION

The 50th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 18–20 May, 2010. The members of the INN Expert Group, the INN Advisory Group on biologicals, as well as the full INN Secretariat and several specialists who assisted in specific nomenclature issues, attended the meeting.

Various intergovernmental organizations and national agencies involved or interested in drug nomenclature were also represented as observers, including the World Intellectual Property Organization (WIPO), the International Union of Pure and Applied Chemistry (IUPAC), the European Department for the Quality of Medicines (EDQM), the Japanese Pharmacopeia (JAN), the United States Adopted Name (USAN) Program, the United States Food and Drug Administration (US FDA) and others.

Dr Lembit Rägo, Coordinator, Quality and Assurance & Safety: Medicines (QSM) opened the meeting and welcomed those present on behalf of the Director General. The open session with stakeholders had gone well (see Annex to this report) and provided an excellent opportunity for the pharmaceutical industry to express their views to the INN Group. Such openness is to be welcomed and such sessions could be repeated on an bi-annual basis. The increase in INN fees, which had been raised during the open session, had come about due to increased costs and especially to changes in the financing of WHO departments and distribution of core funding. These changes make it necessary for the bulk of costs to be raised by fees, the level of which will need to be assessed each year.

Dr Hans Hogerzeil, Director Essential Medicines and Pharmaceutical Policies (EMP) also welcomed the participants and informed them of an important and difficult issue being discussed at the World Health Assembly, that of counterfeit medicines. There are those who cannot or will not understand the seriousness of the situation and some believe that anti-counterfeit measures are being used to block trade in generics, quoting the recent EU action against so-called generics from India that were stopped in transit through the EU because of counterfeit issues.

The Chair, Prof. Derek Calam thanked Dr Rägo for the explanation regarding the fee increase, which is a difficult issue, and for the introductory remarks from Dr Hogerzeil. This 50th Consultation is a landmark occasion; it will discuss 76 new applications, 30 outstanding and 5 objections, totalling 111 submissions about 35% of which are biological medicines. The Experts have been greatly aided by the new electronic system of reviewing requests and hopefully this has made life easier also for the Secretariat. The Chairman expressed his thanks to all who had contributed to the reviews.

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 INN

During the Consultation, a total of 111 INN were discussed, including:

- 76 new INN requests, including 26 for biological substances
- 30 outstanding requests
- 5 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 93 new names were selected, which are planned to be published in List 104 of Proposed INNs, while 10 requests were deferred for future discussion. One request was rejected by the INN experts, as the substance did not conform to the criteria for INN selection. Three amendments were planned to be published in List 104. Two INN applications have been abandoned during the selection process and two objections could not be retained.

CONJUGATED MABS

Increasing requests are being made for monoclonal antibodies conjugated to a toxin or some other moiety and a consistent approach is needed for naming such conjugates. The use of a one word versus two word name and the consequences when the same mAb gets used in different conjugates were discussed at length by the experts.

This is a complex situation but similar to INN^M's, and perhaps also fusion proteins, where there is an active component plus an additional element. In the case of INN^M's, the substance derived from the base is usually published as the active substance and the ester is named according to INN rules. Thus there may be value in proceeding in a similar way for conjugated mAbs, which is to publish the main component (the mAb) and give additional information about the linkage to a toxin. For fusion proteins where the focus is often on the active component, there is usually a single name INN although in complex cases they may have two names; however, there is a sharp contrast between a fusion protein and conjugates consisting of a chemical moiety.

It was also suggested that the list of toxins in the Radicals book, could be expanded and could include linkers in the description. Such a list would be better than defining a chemical conjugate in the Definition. Alternatively, a stand-alone explanatory document might be useful as different approaches to conjugation will develop with time.

When there is a request for a conjugated mAb where there is no pre-existing INN for the mAb, it was noted that there should be a parallel request for the mAb by itself; this would likely require two separate submissions and two fees: one for the mAb alone and one for the conjugate.

In future if a new request is made for the same mAb but different toxin, this would be a new application although the same name for the mAb could be given with a distinct name for the toxin. In the event of a request for an INN for the mAb alone, this also would be a new application. It has been proposed to request two applications: one for the mAb alone and one for the conjugated

It was also felt that fusion proteins are quite a different situation from conjugated mAbs and should remain out of the discussion for the moment. These could be discussed further at the next meeting with a review of nomenclature of fusion proteins and assess the value of using the same situation for fusion proteins mAbs.

CELL THERAPY NAMING SCHEME

The INN Expert Group has previously dismissed the idea of creating INNs for cell therapy medicinal products but is being asked now to reconsider this situation following the adoption of a scheme by the USAN which has named about eight cell therapy products. The scheme appears to have been a useful move and manufacturers understand well how to use it. The Ph.Eur. has published general texts on quality aspects of cell therapy products but there are no specific monographs and the issue of nomenclature is not addressed.

The Group remained dubious about the value of an INN scheme for cell therapy products as they are highly heterogeneous and such INNs would be highly company specific. However, the Group acknowledged that it would be of value to consider this further within a small working group.

EPOETIN INNs and REGULATORY AUTHORITIES

There has previously been an issue with a regulatory authority (European Medicines Agency - EMA) concerning an INN for epoetin and now a new issue on an epoetin INN has cropped up involving the Australian Therapeutic Goods Administration (TGA). A few years ago, Sandoz successfully applied to the EMA for a marketing authorisation for their epoetin via the EMA's biosimilar licensing scheme. Sandoz used *epoetin alfa* as the comparator reference substance and adopted the INN *epoetin alfa* for their product without having applied for an INN. This was accepted by the EMA

despite the glycosylation pattern of the Sandoz product being non-identical to that of the *epoetin alfa* comparator (information provide in the EPAR).

This glycosylation difference has now also been recognised by TGA, which has led them to request a different Australian Biologicals Name (ABN) – *epoetin lambda* – as part of their licence in Australia. Thus, this substance has the INN *epoetin alfa* and a country name based on the INN principal but with a different Greek identifier.

It is the responsibility of a company to apply for an INN and unfortunately, the European regulators accepted Sandoz's own INN assignment of *epoetin alfa* without question. The WHO has expressed their concern about this situation to the EMA. It feels that is the responsibility of regulators to check that a substance is the same as to what it is claiming to be. The appropriate action of a regulator in noting a difference between a biosimilar and the comparator product would be for the regulator to request the company to apply for a new INN. Some companies have also expressed their feelings that where there is a significant difference, a new INN is warranted.

It should be noted that the WHO INN Expert Group is not provided with anywhere near the extent of data regarding a new compound that a licensing authority ultimately receives for licensure purposes. In this particular case, given the data now available, it is likely that were an application received from Sandoz, that a distinct name would be assigned. However, it has to be accepted also that during the development of manufacture, and even from batch to batch, differences in glycosylation may be detected and an INN cannot be assigned every time such a difference is noted.

In summary, the INN Programme offers names for more or less defined substances and it is up to authorities to make use of what is offered; this is as much as the INN Group can do. One of the outcomes of the Australian ABN *epoetin lambda* is if there is a future request for another epoetin, the Greek identifier *lambda*, which has not yet been used for an epoetin INN, should not be used. In this way the entire system could become very confusing. Furthermore, more attention has to be paid to the definition; somewhat vague definitions are often provided and these need to be made more precise and then for regulatory authorities to use these definitions.

DEFINITIONS for EPOETINS

A document was tabled at the meeting on the Definition of Epoetins. When the first epoetin was assigned an INN over 10 years ago (*epoetin alfa*), very little data were submitted regarding glycosylation. Nowadays, considerably more structural data are derived with improved analytical tools and more defined structures are presented in the Definition. The document provided structural data on glycosylation that had been gleaned from the scientific literature and from the Definitions for the various epoetins assigned an INN, which come to nine in total (*epoetins alfa, beta, gamma, delta, epsilon, kappa, omega, theta* and *zeta*), and proposed to define the various epoetins according to the features of the glycoform structures.

Whilst there were many similarities in glycoform structures, it was suggested that greater emphasis could be made on the differences and that these be highlighted in the Definition. Also it would be useful to assign the percentage of major glycoforms, and type of methods used for the analysis. It was further suggested that it might be more appropriate to describe this paper as a 'Description' of Epoetins rather than a 'Definition' and refer to typical structures derived from a particular cell type.

Changes in glycoform structure brought about by manufacturing changes remains a difficult issue. However, it is important to remember that epoetins are heterologous mixtures, much based on the extent of sialylation and the proportion of different structures, which make a defined Definition very difficult. The Chair requested the Group to reflect on this paper and provide feedback.

PUBLICATION ISSUES

At the 49th Consultation, there was a short discussion on how the information contained within the Definition for biological requests should be presented. One issue that remained to be resolved was the use of the term 'human' when referring to the amino acid sequence of a protein in case this implied a human origin of the substance, or whether it would be more appropriate to use the term 'human sequence'. The Group, after a short discussion, decided that remaining with the term 'human' was adequate and there was no need to change this.

ANTI-VENOM ANTIBODIES

There had been a request from BioClone of Mexico, made during the open session with stakeholders, that anti-venom antibody preparations be included within the INN Programme. However, such preparations are mixtures whose exact composition and sequence are unknown, including the Fab2 preparations. Consequently, there was unanimous agreement that these are not suitable for INNs.

TRANSLATION of GREEK LETTERS into SPANISH

In translating certain Greek letters into Spanish, problems have arisen with the Greek *theta* and *zeta* because *theta* in Spanish is *zeta* which gets confused with *zeta* (*dseta* in Spanish). This has led pharmacovigilance experts to view them as two different compounds with same name. This is an issue for *epoetin theta* and *epoetin zeta*. However, it is a warning to the Group that if such a situation occurs in the future for other compounds, the use of *theta* and *zeta* should be avoided. Interestingly, Russian has similar problems with *zeta*. In addition, it has been pointed out that in Annex 3 of the Radical book, an official transliteration of Greek letters into the three Latin languages has been published.

IDMIS SYSTEM

The new electronic data management system, IDMIS, is now available for online applications. The main format is .pdf files and has open fields for applicant to fill out their details. There are areas for uploading other files, such as proof of payment and CAS numbers. The online submission takes no more than two minutes to upload and in doing so is encrypted for data protection that is enhanced by the use of two separate security codes.

NOMENCLATURE for PEGYLATED COMPOUNDS

Pegylation is an increasingly popular approach to enhance the activity of a biological compound by increasing its *in vivo* half-life. In 1998, the INN Expert Group first discussed nomenclature for pegylated compounds and considered two alternative approaches. One is by the use of the prefix *peg-*, the other is by adding a 2nd word, with *pegol* being chosen for this. Both approaches have now been used.

This area has been highly subscribed and the initial approach of using a *peg-* prefix is running into linguistics difficulties especially for compounds already with multi-syllable INNs. However, a problem has become apparent with the use of *pegol* as a second word. *Peg-* used as a prefix stem does not define a specific structure for the pegylation moiety and can be used irrespective of the nature of the pegylation. Comments were made recently, that according to IUPAC rules, *pegol* used as an extra word should indicate a precise chemical modification and be used only for this

modification. For the few names already containing *pegol*, and in some recent requests, there is no evidence of similarity in the pegylation moieties and different linkers have been used

Modification of the Definition should be considered to reflect that the '*pegol*' moieties are not identical. An "ad-hoc" paragraph for *pegol* will be inserted in the next version of the Radical Book.

UPDATES from COLLABORATORS

World Intellectual Property Organisation (WIPO)

The WIPO Committee has previously requested a liaison with WHO to improve access to INN databases and this has resulted in the Manager of the INN Programme, Dr Balocco Mattavelli, interacting closely with WIPO to explain the functioning of the INN Programme and by providing an electronic warning when WHO publishes new lists of recommended INNs. This appears to be working well although for some of the 180 trademark offices, there remains concern that it is still not possible to make a quick search of databases for conflict between trademark applications and INNs. Access to MEDNET has been achieved by some offices but WIPO would appreciate data to be more accessible in electronic format and are eager to continue working with the INN programme on this. Indeed MEDNET provides for searches but one has to be proficient in this and for those in trademark offices attempting this occasionally, it is likely to be technically demanding.

WHO also now prepares CD-ROMs with a searchable database of names and Cumulative List No. 12 has been sent to WIPO, whilst No. 13 has just been published and will be distributed soon to WIPO and all INN experts. Improved access to the INN database is an ongoing project but at the same time misuse of the non-proprietary data must be prevented and WHO legal is involved in this aspect. For WHO to retain responsibility, the basic data must remain with WHO but it can appear in different databases and will be made available to all public authorities. In external databases, the source of INN data will need to be quoted and perhaps WHO copyright mentioned. The Group also commented that it would be useful for INN experts to be able to search in reverse, i.e. to check new INNs against existing trademarks.

On a separate issue, WIPO has previously reported to INN colleagues about potential misuse of INNs in internet first level domain names. It is unclear at this moment if ICAN (the international non-governmental body for the provision of domain names) will introduce any protection for INNs. The INN Programme manager has written a formal letter via the Director General to the ICAN director, and despite a follow-up letter has not yet received a reply. Dr Balocco has not received any formal complaints from pharmaceutical companies on this issue but is aware that companies often pay to obtain a (second level) domain name with the INN to prevent misuse by others.

European Department for the Quality of Medicines (EDQM)

The European Department for the Quality of Medicines (EDQM) was created to oversee the expanding work of the European Pharmacopoeia (Ph.Eur.), both under the auspices of the Council of Europe (CE). The CE has 36 European country members and many non-European observers of which the WHO was the first. The 7th edition of the Ph.Eur. was issued in July 2010 with each new edition being a compilation of all entries along with relevant changes that are continuously being made to various aspects of the texts. Herbal monographs are now in a separate section and include a number of Chinese medicines. The Ph.Eur. has been available in electronic format for 16 years and is now supplied on a memory stick due to the increased size of the database. In the next edition, all titles will be reviewed and brought into line with INN rules as well as improving consistency.

EDQM recently took over the distribution of WHO International Chemical Reference Substances (ICRS) and in recent years has become responsible for blood transfusion and organ transplantation activities. It is responsible for the OMCL network and a procedure for the certification of suitability to the monographs, which is peculiar to Europe.

The EDQM is also involved in two major International Standards Organisation (ISO) projects, the Individual Case Safety Report (ICSR) International Standard and the Identification of Medicinal Product (IDMP) Standards. For ICSR, ISO is working together with ICH and essentially provides for standards regarding adverse event safety reporting. Potentially it will be finalised before the end of 2010. The IDMP project is less advanced and covers five new standards which again will be implemented by ICH. The draft International Standard is expected to be released by September 2010 with the final standard towards the end of 2011. The scope of the five standards is human and not veterinary medicines and covers pharmaceutical substances, dose forms and routes of administration, units of measurement, pharmaceutical products identifiers (PhPID) and medicinal products identifiers (MPID). The different standards have to accommodate requirements from diverse stakeholders and pre-existing standards. These projects are not available for public comment; comment can only be made via national standards organisations.

The FDA's Substance Registration System (SRS) is a precursor of the IDMP, but the IDMP will be larger and far more complex. Ideally, the database will be provided free by ISO but it is probably naive to think that there will not be a financial aspect for access to the entire database. This is an issue that has caused concern at WHO; if INN data are incorporated in the database, it has to remain free to the user and no commercial use should be made of it.

British Approved Names (BAN)

Supplement No. 4 to the British Approved Names book 2007 will be published in August 2010 and is available for distribution. The British Pharmacopoeia continues to work with licensing colleagues to ensure that INN stems are not being used in deriving proprietary names and, more importantly, keeping them informed of ongoing developments on biological and chemical nomenclature within the WHO INN programme.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

The PMDA organises the Japanese Approved Names (JAN) Committee which meets four times per year. In 2009, 36 JANs including 6 biologicals were approved; this compares with a total of 19 for 2008. INN applicants also consult with PMDA on candidate INNs and 11 such consultations were held in 2009. The PMDA felt it would be useful to interact with the INN Group on these consultations.

In the area of biosimilars, MHLW approved two such products in 2009 whose JANs are somatropin and epoetin kappa. The PMDA also believes that pharmaceutical products should have a JAN prior to a new drug application (NDA) and, where a new drug substance is a glycoprotein, the PMDA requests an applicant to apply for an INN and JAN during the consultation for the clinical trial.

END OF CONSULTATION

Note: For the afternoon of the last day of the Consultation, in the absence of Prof. Calam, the meeting was chaired by Prof. Witold Wieniawski.

The 51st INN Consultation will take place at WHO Headquarters, Geneva, on November 16-18, 2010.

Annex to 50th Consultation Executive Summary
INN open session meeting with stakeholders

Prior to the 50th INN Consultation, there was a short open session with stakeholders from the pharmaceutical industry. The industry participants were welcomed by Dr R Balocco, INN Programme manager, and Prof. D Calam, chair of the INN Expert Group, with thanks to the IFPMA for facilitating this session. This is the first time for such a session; it provides a good opportunity for stakeholders to present their thoughts directly to the INN Experts, which in turn will help in developing INN policy. The INN continues to grow and evolve and with this 50th meeting, there have been more than 9,400 applications in total for an INN. In introducing the members of the INN Expert group, the Chair noted the wide spectrum of expertise present from around the world.

Dr Jürgen Römhild (Boehringer Ingelheim)

In the first presentation from a stakeholder, Dr Römhild passed comment on four items. First, in his experience, a rejection rate of INN applications of >50% seemed overly high despite trying to meet all criteria in guidance documents and perhaps the INN Group was applying overly strict standards. Training for industry might help achieve a better acceptance rate. Also, as a trademark lawyer, he has found several instances of similar sounding INNs and provided some examples. Second, the time to registration of a successful application can be 12 to 18 months or even longer if objections are raised. The trademark procedure in comparison is much shorter and he proposed a three month period for rejection as companies are well prepared to check names in a much shorter period. Third, there is a need to avoid competition between INN and trademark names. The INN is named for the active ingredient but there appears to be an increasing tendency by WHO to create INNs too similar to trademarks, which increases the objections to proposed INNs and ultimately the time needed to establish new INNs. Finally, the recent increase in the INN registration fee came as a surprise and compared with the fees for other similar procedures appears excessive.

Commenting on the presentation the Chair indicated that the final point was not further discussed as it was outside the remit of the Expert Group (but note the brief explanation made by Dr Lembit Rägo at the Introduction of the 50th Consultation). However it was disclosed that there are plans for training to be in place by mid 2011, which will be open to everyone, and this should help allay some of the points raised. With regard to competition with trademarks, deriving unique INNs is becoming more complicated, especially for biological medicines, but the Secretariat will look into this further. For some time, there has been a four month period for comment from when names are published in print although nowadays they appear faster on the internet. This period allows both governments and other companies to view proposed names.

Dr Dave Kallend (F Hoffman-La Roche)

Dr Kallend focussed his discussion on the mode of action of cholesteryl ester transfer protein (CETP) inhibitors. CETP plays a major role in the differentiation of HDL and LDL/VLDL. Inhibitors of CETP activity can do so via different mechanisms resulting in different physiological effects and these should be reflected in the Definition for these drugs. Thus, antagonists or blockers (such as *torcetrapib*, *anacetrapib*) non-selectively inhibit transfer of neutral lipid between all lipoproteins and

prevents HDL remodelling, whilst modulators (such as *dalcetrapib*) selectively inhibit transfer of neutral lipids between HDL and LDL/VLDL, do not inhibit HDL remodelling and in contrast to antagonists can induce reverse cholesterol transport.

Commenting on the presentation the Chair indicated that the Expert Group was sympathetic to this situation and whilst there may be room for taking this onboard for future CETP inhibitors, it is difficult to alter already assigned INNs.

Dr Fernando Paniagua (Instituto Bioclon)

According to Dr Paniagua, there is a worldwide need for anti-venoms and Instituto Bioclon, based in Mexico, is developing anti-venoms from various species; in Mexico scorpions are a particular problem with 250,000 incidents per annum. The anti-venoms manufactured by Bioclon consist generally of purified equine immunoglobulin with the most recent products being purified Fab fragments. Anti-venoms are listed by the WHO as essential medicines and WHO guidelines for their production and control have recently been published. The WHO's Expert Committee on Biological Standardization has anti-venoms on its agenda, and on the web there is now a user friendly list of where to find and how to obtain anti-venoms. The question Dr Paniagua had for the Expert Group was, can INNs be assigned to these anti-venoms? The creation of a new group of biological substances could overcome the inconsistency in anti-venom nomenclature and help local authorities identify specific products.

Commenting on the presentation the Chair indicated that there was agreement within the Expert Group that indeed there was a need for good nomenclature but also that as a heterogeneous mixture of molecules, anti-venom immunoglobulins did not comply with INN rules for nomenclature.

Novartis Pharma AG

A team from Novartis made representation in support of an on-going INN submission that concerns a novel oral phosphate binder for use in patients with chronic kidney disease and hyperphosphatemia. It comprises a polymeric chemical entity consisting of an iron-oxide-hydroxide covalently bonded with sucrose and carbonate, all of which is bound to starch. Mössbauer spectroscopy, the accepted analytical method for iron oxides, reveals it to have a unique structure. The team emphasised that all components were part of the active ingredient, that it is not a mixture and that an INN designation would assist in avoiding confusion in treatment of hyperphosphatemia.

Commenting on the presentation the Chair indicated that the Expert Group found this to be an example of a borderline product and it would be discussed further during the 50th Consultation.

Dr Martin Schiestl (Sandoz)

In the final presentation to the Expert Group in this session with stakeholders, Dr Schiestl raised two pertinent points regarding the use of Greek letter qualifiers to identify glycosylated proteins with different glycosylation patterns. Sandoz has been monitoring marketed originator biotherapeutic compounds with qualified glycoform analytical methods. In two instances where companies have obtained a Variation (on the EU market) for manufacturing changes, there have been clear changes to the glycosylation patterns which, since the changes were approved by regulatory authorities under the same licence, presumably means they do not impact significantly on the safety or efficacy of these compounds; however, the original INN was retained. Dr Schiestl suggested two alternative courses of

action for the INN Group to avoid such inconsistencies with INN policy: (i) to revise such INNs and change the Greek letter qualifier according to current practice or (ii) revise WHO guidance and discontinue the classification based upon differences in glycosylation. The first option suffers from the difficulty in defining at what magnitude of difference a Greek letter designator should be added or changed. Option (ii) was preferred by Dr Schiestl and added that in this option, the presence/absence of glycosylation or of a conjugate such as pegylation should be indicated in the INN but no further.

The second point raised by Dr Schiestl concerned a biosimilar erythropoietin marketed in the EU and Switzerland by Sandoz with the INN *epoetin alfa*. In 2010 it gained approval in Australia but was given the Australian Biological Name (ABN) epoetin lambda (which is not an INN). The Australian Therapeutic Goods Administration had considered that the glycosylation pattern of Sandoz's epoetin was sufficiently distinct from *epoetin alfa* already marketed in Australia that it should not be given the same ABN despite Sandoz arguing that the differences were minor and smaller than that observed between *epoetin alfa* products marketed by the innovator in different countries. This case highlights the difficulties in the application of Greek letter designators for glycosylated proteins and especially in the criteria for a different glycosylation pattern.

Commenting on the first point in the presentation the Chair indicated that it was already suggested that companies should provide a more precise Definition, defining the glycosylation pattern and where there is significant change apply for a new INN; alternatively the Definition could be left quite broad. However, the Definition is made early in product development and subsequent changes in production might be made that affect glycosylation, or finer analytical methods might be used to define further the glycoforms. Science is developing all the time and can have direct impact on selection and use of an INN, which is to designate a unique name for a unique chemical substance, but is becoming very difficult for biologicals.

In respect of the second point, the Chair indicated that this is a difficult and unfortunate situation which the INN group did not have the opportunity to comment upon and was undertaken solely by the Australian regulatory authorities. This type of issue has been discussed before and will be discussed during the 50th Consultation (see page 3 & 4 of the Executive Summary)