

***53rd Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 18-20 October 2011***

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

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

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INTRODUCTION

The 53rd Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances was held in Geneva on 18-20 October 2011. The members of the INN Expert Group, the INN Advisory Group on biologicals, as well as the full INN Secretariat and several specialists who assisted in specific nomenclature issues attended the meeting.

Various intergovernmental organizations and national agencies involved or interested in drug nomenclature were also represented as observers, including the British Approved Names (BAN), the European Directorate for the Quality of Medicines (EDQM), the International Union of Pure and Applied Chemistry (IUPAC), the Japanese Approved Names (JAN), the United States Approved Names (USAN), the United States Pharmacopoeia (USP), the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the World Intellectual Property Organisation (WIPO).

Dr Lembit Rāgo, Coordinator, Quality Assurance and Safety: Medicines (QSM) opened the meeting on behalf of the WHO and informed the group of the current major challenges facing WHO. There is considerable reorganisation ongoing within the organisation with much of it being driven by the need for cost savings. Income from donors is decreasing and has been exacerbated by the strength of the Swiss currency. This is resulting in a need to reduce staff across the board, including freezing posts and potentially staff cuts; overall the outlook is pessimistic. Alongside this, there is a redistribution of activities, and departments are being reorganised for more efficient output and to reflect the changing needs of the WHO. A new director for the department (of Essential Medicines and Pharmaceutical Policies) remains to be appointed and although the process has begun no-one is likely to be in post until 2012. The DG has requested that activities of the department focus on supporting regulatory authorities and there is to be an internal review of all prequalification programmes and services. Despite the shortage of funds, the INN Programme remains somewhat safe due to it being self-financing and will be relatively unscathed by the financial cutbacks that are occurring elsewhere.

The work of the WHO continues and this week, in parallel to the INN meeting, the Expert Committee on Biological Standardization (ECBS) is meeting, followed next week by an inter-government working group on substandard and counterfeit medicines. This will involve high level political discussion on falsified medicines and providing support to WHO on how to fight these medicines. This activity is connected with the INN Programme as one needs to know the active ingredient in falsified medicines. For the INN, it is important to continue with the stakeholders' meetings and it is recognised that the workload for the plenary meeting is considerable with 93 new INN applications and a trend towards an increasing proportion of submissions for biological substances, in this instance at 46%.

The Chair, Prof. D. Calam, thanked Dr Rāgo for this information as it is extremely important to know about the background; indeed huge changes are taking place, and it is appreciated that funding from applicants is protecting the INN Programme from cuts and this is to be encouraged. The members of the Expert group are also welcomed to the meeting.

The Manager of the INN Programme, Dr Raffaella Balocco-Mattavelli also thanked everyone for their hard work prior to the meeting, especially on the last large batch. The work of the INN staff under great pressure is also greatly appreciated and Dr Balocco-Mattavelli is honoured to work with them and the experts.

NOMENCLATURE of INN

During the Consultation, a total of 124 INN were discussed, including:

- 93 new INN requests, including 43 for biological substances
- 21 outstanding requests
- 10 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 107 new names were selected, which are planned to be published in List 107 of Proposed INN, while 6 requests were deferred for future discussion. Two requests were rejected by the INN experts, as the substances did not conform to the criteria for INN selection. Four amendments are planned to be published in List 107. Six objections have been discussed and rejected by the INN Expert Group. Three INN requests have been withdrawn during the selection process.

Two new stems and one new sub-stem have been selected and three suffixes have been promoted to the pre-stem list. The 2011 version of *"The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances"* has also been presented to the INN Expert Group. The relevant documents can be downloaded from the INN Web pages: <http://www.who.int/medicines/services/inn/stembook/en/index.html>

INTERNATIONAL NONPROPRIETARY NAMES (INN) for BIOLOGICAL and BIOTECHNOLOGICAL SUBSTANCES (a REVIEW)

The version of BioReview 2011 which contains new biological INN published in PL104 and PL105 was tabled. The stem/substem *-motide* has been listed under the section of 'Peptides and glycopeptides' (item 4.22), as well as under the section 'Peptide vaccines/recombinant vaccines' (item 4.23), whilst in the section on 'General policies for glycosylated compounds' (item 3.4) reference to interferons has been removed (as some of these are not glycosylated) and replaced by text related to blood coagulation factors and enzymes. The text for 'interferons' has been correspondingly updated (item 4.17).

In the 'General policies for gene therapy products' (item 3.3), *-stim-* has been added as an infix for word 1, and *-fo-* (for fowlpox) has been added as an infix for word 2. The title of item 3.5 'General policies for immunoglobulins' has been amended to 'General policies for immunoglobulins fractionated from plasma'. In item 3.6 'General policies for monoclonal antibodies', *-xizu-* is confirmed as a substem for chimeric-humanized mAbs (Table 2) and textual changes were made to the sub-section on 'Second word', in addition, definition for chimeric antibodies and definition for humanized antibodies were modified.

In item 4.22, 'Peptides and glycopeptides', *-glutide* has been added as the new substem for glucagon-like peptide (GLP) analogues. In item 4.26 'Receptor molecules, native or modified', *-ba-* and *-taci-* have been added as preceding infixes for the stem *-cept*.

Some other changes have also been introduced into the bioreview 2011 which are not enumerated here.

INN PHONETICS

Pronunciation of INN is a topic that does not receive much attention. Previously within WHO, there was a software system for translating the INN phonetically, but this is no longer done as the software no longer exists. This is unfortunate and suggestions about how to improve this area are welcome. It is also a very difficult area. Some languages have clear rules whilst others, e.g. in English, the rules are not so strict although this leads to alternative pronunciations.

Some national naming bodies have their own system, for example USAN has a pronunciation guide on their website which is to be used in all Statements of Adoption (post 2006). No diacritical marks such as would appear in dictionaries are used and the pronunciation for a USAN is determined by a person and not by computer. Similarly, in the UK, the BAN book also has a guide, and a major point

the British Pharmacopoeia tries to follow in considering pronunciation is consistency, especially with stems. However, a phonetic dictionary is not followed as this was considered to be too difficult. Interestingly in the UK, there can be a surprising amount of regional difference in pronunciation and indeed, worldwide, there are likely to be variations in English pronunciation of INN and potentially even the USAN and BP guides may not agree. The critical feature is on what syllable there should be emphasis so that in oral prescribing there is no misunderstanding. Furthermore, this is not a matter for English pronunciation only, but for all languages involved.

REVIEW of INN STEMS RELATED to MODIFIED NUCLEOSIDES

A new document was tabled reviewing INN stems related to modified nucleosides. INN stems were created to group together pharmacologically related substances as an aid to prescribers and other health personnel. Currently, there are over 250 stems and these are catalogued in the 'Stems' book¹. When new names are submitted and do not fit easily into an existing stem, the possibility of a new stem (or pre-stem) is considered when several similar substances are named with a common suffix. Not all established INN contain a stem and furthermore, fitting a new name into a particular stem is sometimes difficult because of the diversity of approaches that may exist relating to the part of the molecule that should be the focal part of the INN or in defining the pharmacological activity of the substance. Modified nucleosides are one such group of substances where currently there are ten alternative stems; four of these relate to the heterocyclic base, two stems are based on the sugar moiety, three stems relate to the antiviral action of the substance and one stem is given to adenosine receptor agonists. Altogether >100 substances are classified as modified nucleosides. This current review provides an introduction to stems for modified nucleosides, gives a list of all such INN for each of the ten stems along with their Action & Use, whilst annexes provide the chemical structures of the INN concerned, including several related structures and nucleosides without a stem. The review is intended to aid nomenclature of new modified nucleoside INN and to avoid inconsistencies.

IDMIS SYSTEM

One of the main objectives of the INN Secretariat is to release and disseminate INN data freely in the public domain. However, in the past companies have received INN data from WHO and on occasions they have made this data available to others at a cost; this is difficult to control and to stop on a legal basis. The Secretariat also needs to tackle cases where requests state that INN data will not be sold on, including from government agencies, but ultimately the data are being sold in an indirect manner. Most INN data is for public access and WHO is fully prepared to share this data, but there must be no commercial service involved. Consequently, the Secretariat has developed a Global INN Data Hub to avoid this and over which the WHO will have complete control. There will be free access but for those who will benefit considerably from this access, a fee system will be established.

In this new WHO web service the INN team will have complete control over the right to access of the data. Outside sources can no longer 'see' all data, especially structures, and sell it on. Also names are in images and there are watermarks for anything that gets copied. Access to complete data will have to be requested, and will be provided, but ultimately it is the WHO server that is providing the data. Interestingly it was pointed out that the day after Definitions are published, they appear in *Integrity* (Thomson Reuters IntegritySM); however access to Integrity requires a substantial fee even from WHO. There are many other such situations.

UPDATES from COLLABORATORS

British Approved Names (BAN)

The BAN 2012 was published in August (2011) with an effective date of 1st January 2012.

¹ The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

Nomenclature experts within the British Pharmacopoeia Commission Secretariat met with colleagues from the Pharmacovigilance sector. Whilst there were very few instances where a name was the source of a medication error in the UK, UK nomenclature experts are conscious of being more likely to comment on the similarity of a name within an INN application to a published name (nonproprietary as well as proprietary). This is mainly because of generic prescribing in the UK and an intention to ensure there are no patient safety issues due to name similarity. Currently, there are two names which are a cause of concern (*mercaptapurine* and *mercaptamine*).

European Directorate for the Quality of Medicines and HealthCare (EDQM)

A major change at EDQM is that from January 2012, the hard copy of *Pharmeuropa* will no longer be issued and it will be freely available online only; also there will be free online access to the *Pharmeuropa* archives and to *Pharmeuropa Bio & Scientific Notes*.

In the titles of Ph.Eur. monographs published before 2000, there is no indication of the degree of hydration. A lack of consistency in the naming of monographs for hydrated substances has led the EDQM to conduct a survey to gather information on hydration/anhydrous forms of chemicals currently found on the European market. This survey will run until the end of March 2012. Related to this, the EDQM wants to harmonise the way of presenting salts and wants to mimic the INN approach. The EDQM may try to develop a policy but would appreciate the opinion of the Expert Group to stay in line with WHO proposals.

The Chair commented that the water content range has also been discussed in the UK, and it was concluded that it would be best not to specify the exact number of water molecules in order to avoid the situation where differing levels of hydration may exist for the same chemical from alternate sources. It would also be useful for EDQM to feed back to WHO if there are areas of the guidance on modified INNs that are not clear and the group could look to see how to improve advice.

The EDQM is also developing an anti-counterfeiting project for the EU called eTACT. This would involve the mass serialisation of each packet of a medicine, from point of manufacture to the patient. Codes can be checked all along the supply chain and will give patients the option of verifying the authenticity of their medication. The project is currently in a pilot phase.

International Union of Pure and Applied Chemistry (IUPAC)

The Expert Group were informed that the *Principles of Chemical Nomenclature, A Guide to IUPAC Recommendations*, 2011 (ISBN: 978-1-84973-007-5, RSC Publishing, 2011) would be available in the next month or so. Also, a new edition of the *Compendium of Terminology and Nomenclature of Properties in Clinical Laboratory Sciences* (recommendations 1995) (Rigg, Brown, Dybkaer & Osen, Blackwell Scientific 1995) is in preparation and comments or suggestions are welcome.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

The Japanese PMDA was recently restructured and the functions of the Japanese Pharmacopoeia (JP) and Japanese Approved Names (JAN) fall within the new division "Division of Pharmacopoeia and Standards for Drugs". The JAN expert committee has fourteen members and meets four times per year to consider submissions. The JP has been revised periodically with the 16th edition being freely available from April 2011 on their website; an English version is currently being translated and will appear on the website in the near future.

United States Approved Names (USAN)

The 2011 Summer meeting of the USAN Council marked the 50th anniversary of the USAN Program and took place in Chicago in July during which names were recommended for 33 substances. Two new stems and 2 new infixes were also approved and posted on the USAN website whilst four designations for radicals and anions were approved and posted. Forty-nine INN applications for proposed USAN were submitted to the INN Programme for discussion in the 53rd Consultation. Through to the end of September 2011, USAN processed, researched and made recommendations for 121 new USAN applications and forwarded this information to the USAN Council. Also, by

September, 68 USAN and 42 modified USAN were adopted during 2011 with further revenue raised for an additional 9 negotiations. The winter 2012 USAN Council meeting is scheduled for January 19-20 in Florida.

United States Pharmacopeial Convention (USP)

Similar to the European PharmEuropa publication, the USP Pharmacopeial Forum (PF) is now no longer available in print form but is available free online.

With regard to hydrates, according to FDA rules hydration does not provide a change in structure sufficient to warrant usage of the term in the drug name. So the title of a monograph is always for an anhydrous form, and alternative degree of hydration is mentioned only in pertinent tests (loss on drying, or content of water). It is called a "flexible monograph". There is usually appropriate labelling requirement included in such cases. It is recognised that manipulation of hydration is usually a manufacturing issue, often a way of circumventing a patent.

The Institute for Safe Medical Practices (ISMP) continues to signal recurring problems to the USP in the mis-prescribing and misuse of morphine versus hydromorphone in clinics. The background to the origin of these names in the USP and National Formulary (NF) suggests to the USP that they can act legally to resolve the situation but with no clear path to follow. One possibility is to request the owner of Dilaudid, a tradename for hydromorphone, to donate the name to the public domain. This happened in the past for aspirin. Regardless of what transpires, something has to be done due to the continuing errors that occur either through mix-up between the two drugs or with other drugs with similar sounding names (generic or invented) and any help from the members of the INN Expert Group would be welcome. It is not known to what extent such errors are occurring in Europe.

Center for Drug Evaluation and Research, US FDA (CDER)

In the USA, approval of a new chemical drug requires a New Drug Application (NDA) and is undertaken by the FDA under the Food, Drug & Cosmetics Act. In an NDA, the official legal source of the established name is the USAN. Biological medicinal products are sometimes submitted as NDAs or sometimes as Biologics Licence Applications (BLA). BLAs fall within a different legal Act and biologics are not required to have an established name designated by USAN or USP. There are increasing numbers of BLAs and currently there are internal discussions on how to make the naming situation consistent between chemical and biological drugs. Once this is finalised, the INN Expert Group can be informed properly of the outcome.

European Medicines Agency (EMA)

The main item to report from the EMA is the appointment of a new Executive Director, Prof. Guido Rasi from the Italian Medicines Agency, who will take over from Dr Thomas Lönngren on 15 November (2011). This comes after a period of re-structuring at the Agency including the (Invented) Name Review Group.

World Intellectual Property Organisation (WIPO)

WIPO has been developing a publicly accessible and searchable database of brands which was launched in March 2011 – the Global Brand Database. The database includes three collections: international trademark registrations, appellations of origin, and national and IGO emblems. The database will be useful for both new trademark applicants and for the application receiving office. Receiving offices are able to examine and refuse, if local legislation permits, trademark applications that would be in conflict with pre-existing rights or with subject matter that is excluded from trademark registration, e.g. INNs. Currently, the database contains only international registered trademarks (circa 94,000) but WIPO expects this to be expanded to include those registered by national offices. The database can be searched in various ways e.g. alphabetically, by country, by date, and ultimately the over 1 million existing trademarks will ultimately be on the database. Note that although WIPO is the receiving office for international applications, it does not examine these; such applications are examined by the office of the originating country or another designated office.

CLOSE OF MEETING

At the close of the meeting, the Chair proffered his sincere thanks to all present at the meeting. There had been difficult issues to resolve and the Chair was very grateful for the discussions and hard work put in by the experts, the observers and the INN secretariat.

The 54th INN consultation will take place in Geneva on 1-3 May 2012.

Annex to the 53rd Consultation Executive Summary
INN open session meeting with stakeholders, 18th October, 2010

This 4th open INN meeting with stakeholders was opened by the chair, Prof. Derek Calam. The format is that after each presentation there would be the opportunity for comment and discussion. No decisions would be made by the INN Expert Group during the open session but the issues raised would be discussed during the following closed plenary session (53rd INN Consultation) and decisions ultimately fed back to the presenters. All presentations concern compounds under development and so the proceedings here are to be kept confidential by all those present.

Dr Raffaella Balocco-Mattavelli, Manager of the INN Programme, similarly welcomed the three groups of visitors, and also on behalf of Dr Lembit Rägo, the Coordinator of Quality and Assurance & Safety: Medicines.

Bausch & Lomb Pharmaceuticals

Representatives from Bausch & Lomb and Nycox presented their case for a particular two word name for compound BOL-303259, a novel chemical that yields two species, both of which are active against glaucoma and which have distinct mechanisms of action. The nitric oxide (NO) component was stated to reduce intraocular pressure and protect against neural degeneration; the other component is a prostaglandin F₂ α agonist commonly referred to as latanoprost acid and this also will reduce intraocular pressure. Both compounds act together to produce results superior to either working on their own. BOL-303259 is currently in Phase 2b clinical development for glaucoma.

In a 2009 application for an INN, a single word *latanoprostinod* was proposed; however, the INN committee rejected this in favour of a two word name – *lataoprosten bunod*. At this open forum, the company proposed an alternative two word name, *nitroxibutil latanoprotanate*, for the following reasons. Firstly, that it accurately and intuitively describes a molecule that comprises two distinct active moieties and complies with INN rules; secondly, that the compound targets two distinct anatomical compartments that affect aqueous humour flow; and finally, there is the potential for NO mediated sparing of optic nerve damage and retinal cell degeneration, since this occurs under high intraocular pressure. This new name incorporates the acid moiety as the second name in accordance with INN practice; furthermore, by doing so it would avoid mis-prescribing with *lanatoprost*, a single word INN for this particular moiety.

The Expert Group has discussed ester issues many times under the INN system, and the format has always been to follow normal chemical usage for the sequence of two words with the active component of an ester being given more prominence in the name than the additional chemical element. In this case, the situation would appear to be reversed plus both components are claimed to be pharmacologically active; this needs to be discussed in detail by the Group in the plenary session.

Grünenthal GmbH

Grünenthal GmbH has requested an INN for GRT6005, a highly potent centrally acting analgesic with a unique mode of action comprising a balanced NOP (nociceptin/orphanin FQ peptide) receptor and MOR (μ opiod receptor) agonist. It is currently in Phase 2a studies for moderate to severe pain due to osteoarthritis and pain due to diabetic polyneuropathy. The company is lobbying the Expert Group for a new stem for this compound.

GRT6005 is the lead representative of a structurally novel group of compounds. It is the first compound to have a balanced NOP receptor and MOR agonist activity not found by any other known compound. Studies show significantly greater potency than MOR agonists alone in chronic neuropathic conditions. Consequently, it is felt that a new stem is justified. An INN based upon a pre-existing stem may inadvertently lead to misinterpretation of the indication or side effect profile of GRT6005 and preclude its use in patient populations not traditionally treated with classical opiods due

to efficacy limitations or side effect concerns. This creation of new stems is not undertaken lightly and this will be discussed further in the plenary session.

Sandoz Pharmaceuticals

Dr Martin Schiestl of Sandoz Biopharmaceuticals updated the Group on changes that occur to the glycosylation profiles of marketed biopharmaceuticals. These data have been published (*Schiestl et al., Nature Biotechnology, Volume 29, Number 4, April 2011*) and relate to the INN policy of naming glycoproteins with specific reference to the extent to which a difference in glycosylation triggers the need for a new INN.

Data from the characterisation of three commercial products were presented, Aranesp® (*darbepoetin alfa*), MabThera®/Rituxan® (*rituximab*) and Enbrel® (*etanercept*). The objective was to study variation in the quality attributes of these complex biotherapeutics to understand more about acceptable changes that may or may not impact on their safety and clinical efficacy. Analysis of the glycoforms was a major focus and for each product, a single significant change in glycoform profile was identified that correlated in a time dependent manner with the expiry date of the product. It was suggested that these pronounced changes reflected the introduction of process changes in the manufacture of the product. It was also noted that each product remained on the market with unaltered labels indicating that these quality changes were deemed not to impact on their clinical profile.

The point of the presentation was to highlight the impact of advances in analytical technology on the INN policy for naming glycoprotein biotherapeutics. The policy for differential glycosylation does not define how different glycosylation has to be and originates from a time when analytical methods were limited. With increasing application of Quality by Design in the manufacture of biotherapeutics, the INN policy needs to give greater consideration to critical versus non-critical quality attributes. Dr Schiestl recommends that the Greek letter classification for differences in glycosylation is discontinued as data show that many of the glycosylation changes are non-critical attributes. Instead, the INN should be based upon higher level attributes, e.g. amino acid sequence and certain high level attributes e.g. major glycoforms (c.f. pegylation which is similarly highly heterogeneous).

The data from these glycosylation studies are interesting; the INN Group has to make decisions based on data presented in INN submissions and does not receive comprehensive dossiers. Changes in analytical techniques and manufacturing do have an impact, but the Group is constrained in not knowing the clinical impact of these changes. These current studies give the INN Group fruit for thought in assessing applications, and hopefully this will result in better definitions for biological substances. At the 53rd Consultation, 46% of submissions are for biological substances and with a prediction for 2012 that biological submissions will exceed those for chemical entities, the INN Group has a challenging future.

Overall, the issues raised during this open session concern not only specific compounds, but important policy issues, viz., two word names, the sequence of words, the creation of new stems, and the policy for glycoproteins. Issues concerning new stems and INN policy are constantly being considered with the driving force being the need to avoid confusion and convey a clear message to prescribers. The Expert Group may not have immediate answers, even in the following plenary session, but this type of exchange is important.

The Chair closed the open session and thanked the participating stakeholders for their presentations.