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45th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 19-21 November 2007

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

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

INTRODUCTION

The *45th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances* was held in Geneva on 19-21 November 2007. The members of the INN Expert Group, the INN Advisory Group on biologicals as well as the full INN Secretariat and several specialists who assisted in specific nomenclature problems attended the meeting.

Various intergovernmental organizations and national agencies involved or interested in drug nomenclature were also represented as observers, including the World Intellectual Property Organization (WIPO), the International Union of Pure and Applied Chemistry (IUPAC), the European Medicines Agency (EMEA), the European Directorate for the Quality of Medicines (EDQM), the European Pharmacopeia Commission, the Japanese Pharmaceutical and Medical Devices Agency, the Japanese Pharmacopeia (JAN), the United States Pharmacopeia Convention (USPC), the Thai FDA and others.

During the Consultation, a total of 116 INN were discussed, including:

- 72 new INN requests, including 21 for biological substances
- 35 requests previously deferred
- 3 previously selected proposed INN, against which a formal objection had been raised
- 6 requests for substitution and reconsiderations of previous decisions.

As a result of these discussions, 95 new names were selected, which are planned to be published in List 99 of Proposed INNs, while 11 requests were deferred for future discussion. One request was rejected by the INN experts, as the substance does not conform to the criteria for INN selection. One objection was withdrawn, one remains and one amendment is planned to be published in List 99. The remaining requests discussed were reconsideration of previous decisions and requests of substitution.

Other issues discussed during the consultation concerned the nomenclature problems for biological substances, the creation and use of INN stems, the protection of INNs and the "safety" of INN.

WELCOME and OPENING REMARKS.

Dr Lembit Rägo, Coordinator QSM, opened the meeting on behalf of Dr Hans Hogerzeil, Director PSM, and welcomed the INN experts and selected observers to Geneva for the 45th Consultation. Dr Rägo reminded participants that there is a large number of INNs to assign and that there will be several presentations and discussion on biological products as the INN remains intimately concerned with these and regulatory implications. There will also be discussion on fixed-dose combinations and naming issues where the use of INNs is problematic.

Last year a new Director-General was appointed and is assessing the priorities of WHO. Dr Rägo stressed the fact that WHO needs to continue to identify appropriate and promising experts for the Group. Dr Rägo thanked all participants for their input and commitment and handed over to the Chair.

The Chair of the meeting thanked Dr Lembit Rägo for the kind introduction and on behalf of the senior members and secretariat of the Group welcomed the various new members and new observers. For this Consultation there are 72 complete new applications, about 25% of which are biologicals. WHO appreciates that the INN experts are assisting throughout the whole year and not only at meetings, and the Secretariat appreciates receiving comments in a

timely manner. Even more, if names can be adopted by consensus prior to the Consultation, this eases the load of the meeting. WHO is a global organization and it is a pleasure and a privilege to have a wide range of people at this meeting.

Dr Raffaella Balocco Mattavelli, Manager of the INN Programme, commented that on the first page of the new WHO booklet *"Working for health - An introduction to the World Health Organization"*[1], the Director-General stated that some activities are invisible, but affect all, such as the work of the INN; this must be the first time ever that WHO has acknowledged the work of this group on the first page of a WHO introductory general document.

BIOLOGICALS ISSUES

Introduction

Dr Raffaella Balocco Mattavelli, Manager of the INN Programme introduced the subject of INNs for biologicals. The greatest area of debate has been for so-called "biosimilars or follow-on biologics". Discussions on these were held in 2006 amongst biologicals experts, regulatory authorities and industry, culminating in a final review of INN policies for biologicals earlier this year (2007), after which the INN Expert Group at their 44th Consultation concluded that the naming procedure for post-translational modifications of biological therapeutic proteins should remain as is, that is making use of Greek letter identifiers to differentiate different glycoforms. However, there is a lack of consistency between nomenclature groups (INN, BAN, USAN, JAN) on definitions for biologicals and this needs to be reviewed and agreement reached. Consideration needs to be given also to the provision of a code based upon the method of manufacture, although it is unlikely that such a code would be part of an INN.

Definition of Biologicals at JAN

Definitions of biologicals within the Japanese Accepted Name (JAN) was presented. The JAN is updating their 1991 guidance due to the increasing complexity of biologicals and the need to clarify structural differences. The approach of the new guideline is based upon three features of the protein; its origin including the method of manufacture and any substitution or modification of the protein, the nature of the cell from which the protein derives if it is a glycoprotein, and the structure of the protein. The application of these features in defining a protein was illustrated by a series of examples of increasing complexity ranging from a synthetic peptide analogue to complex fusion glycoproteins.

Additional points that will be addressed in the new guideline will be the requirement for gene sequence data, a definition of synthetic peptides and a requirement for glycan structural data. A significant feature in the development of this guidance is the diverse background expertise of the committee members. Clearly, the JAN has a well developed system that is very advanced and the INN Expert group agreed to review INN definitions in the light of what was presented.

Definition and Structure of Epoetin

An INN biologicals expert adviser from the Swiss Institute of Bioinformatics provided a summary on the situation with erythropoietins (INN name – epoetin + Greek letter identifier spelt in full for the different glycoforms). Produced in the kidneys, erythropoietin is a normal protein of all mammals and fish, but curiously not of birds, and is well conserved across these species. Synthesized as a precursor molecule for secretion, structurally it belongs to the four-

[1] http://www.who.int/about/brochure_en.pdf (ISBN 92 4 1563135)

helical cytokine family and has post-translational modifications including disulfide linkages and both *N*- and *O*-linked glycosylation. Its function is to stimulate the production of red blood cells which it does by binding to a specific receptor that triggers the JAK2/STAT5 signalling cascade.

Recombinant proteins are used as a therapeutic agent to treat anaemia associated with chronic kidney disease and there are five (INN) forms commercially available – *Epoetin alfa, beta, omega, delta* and *darbepoetin alfa*, this latter form having five amino acid substitutions compared with the native form. Differences between these forms involve glycosylation and especially the extent of sialylation which strongly affects the half-life in the circulation. *Epoetin delta* is derived from a human cell line and so most closely related to the native form. Pegylated epoetin, which can extend the half-life, is also in the pipeline.

Regulatory guidelines on biosimilars –Department of Quality Safety and Standards, (QSS) WHO

A WHO meeting was held in April 2007 discussing regulatory issues for so-called biosimilar biotherapeutics (biosimilars), and was attended by regulators from developed and developing countries, by both the 'innovative' and 'generic' industries, and by academics. The objective was to assess the current directions and challenges in the regulation of biosimilars and how WHO should respond to worldwide needs in this area. Biosimilars claim to be similar to an innovative product and generally can be licensed via a reduced data package. Both a pre-meeting questionnaire and the participants of the meeting itself gave WHO a positive mandate to proceed with the development of guidance for the establishment of a regulatory pathway for biosimilars. Key areas to be addressed were identified including the scope, the reference product and nonclinical and clinical studies; this latter point is likely to be the most difficult. WHO noted that the term 'biosimilars' is currently being used as a temporary measure only.

EU marketing authorization of biological medicinal products including biosimilars

The INN Consultation was also updated by the European Medicines Agency (EMEA) on how the European Union (EU) is approaching marketing authorization of biosimilars. The EMEA makes use of an EU-wide network of competent authorities and experts to evaluate licence applications via a centralized procedure that results in applicants receiving a licence valid in all EU member states, if successful.

The EU has produced an extensive list of guidelines to help manufacturers of biologicals and in recent years, has developed guidance for similar biological medicinal products (biosimilars) extending from an overarching guideline, to guidelines for quality, nonclinical and clinical issues and now guidance for specific products is being developed. For a biosimilar, a full Module 3 for Quality is required, but a reduced Module 4 and 5 for nonclinical and clinical aspects are anticipated and there would be an integrated comparability exercise from the modules 3 to 5. For biosimilars, two somatropins were the first biosimilars to be authorized (in 2006) and two epoetins were authorized recently in 2007.

Antibody-mediated pure red cell aplasia in Thailand

The Thai FDA reported that thirteen erythropoiesis stimulating agents (ESAs) had been approved for those with kidney disease or in chemo-induced anaemia in cancer, including two innovative epoetins, ten epoetin biosimilars and one modified epoetin, darbepoetin. New biosimilar epoetins are expected.

In 1998, there was an increase in the number of EPO-associated cases of antibody-mediated pure red cell aplasia (PRCA) in those treated with recombinant epoetins administered sub-

cutaneously (s.c.). So far 56 cases have been identified; higher than other areas of the world. A prospective immunogenicity surveillance study is being established by a Thai ESA working group to identify the possible root cause of the PRCA. This will incorporate a multicentre, immunogenicity surveillance registry employing a prospective cohort design for patients using epoetin and who will be observed for the development of immunogenicity and PRCA over a three year period. Most cases of PRCA occurred 1-2 years after initiation of use of EPO and besides the s.c. administration, no specific risk factor has been identified.

International manufacturing codes

The WHO INN Secretariat provided an update on the use of a three-letter code to indicate the system of manufacture (expression system). BAN, the British nomenclature group, has established such a system although it is discretionary and only a few BANs incorporate the code. At the INN *ad-hoc* meeting on biologicals in April 2007, the use of an internationally agreed code was promoted and the INN Expert Group agreed to investigate the use of a non-mandatory system for identifying the method of production. It was also noted that the proposed JAN system under development incorporated the nature of the host cell within their definition of nomenclature.

Discussion on biological issues

The INN Programme is one of the oldest WHO Programmes, is voluntary and its policies are driven by science. WHO itself can only make recommendations and it is up to individual nations to do what they want; it is not a regulatory body and there is a clear distinction between the activities of a nomenclature group and that of a regulatory body.

The general approach for INNs is that groups of substances get linked with 'stems', e.g. all monoclonal antibodies have names ending with *–mab*; also for glycosylated proteins, in addition to the appropriate stem, if the source material differs there may be a different glycoform profile and so a Greek letter identifier is used to distinguish them. In contrast, if a generic drug is made by a different synthetic route, the same INN is applied. It is appreciated that even within a specific manufacturing process, a change in the process such as scale-up or removal of calf serum, can result in a difference in glycoform profile approaching the same level as might be found with different cell substrates. At the 44th INN Consultation, the application of the Greek letter identifier was re-reviewed and a decision made to retain the system and not to review further in the future.

The information provided by an applicant for the Definition has often been insufficient and guidance notes have been established for complex glycoproteins. Despite such guidance, many applicants continue to provide scant information. It is recognized that the current INN system for biologicals is inadequate and needs to be reviewed. Similarly with CAS, the definition is that of the applicant and not a CAS definition *per se*.

For many earlier biological INNs, the information being requested today was not available. Modern analytical technology can provide detailed information on for example glycoforms; but the problem remains of extracting this information from the sponsor. In the future, technological advances may permit analyses that provide information on proteins that one would not expect to be supplied today. In the meantime though, in assessing an INN for a glycoprotein, it should be assumed that, in the absence of any data, the glycoform profile differs from a similar product. One such application, for epoetin zeta, was a case in point.

The Chair proposed to endorse a recommendation that the Secretariat undertake a review of Definitions of biological products and this was confirmed by the Expert Group. An update on this project should be provided at the next Consultation in April 2008. It was further

recommended that since only a minority of complex proteins with an INN are on the market, experts concentrate on these and on those about to come off patent.

It was also felt that the Secretariat should continue to explore manufacturing codes but that these would not be part of the Definition; such codes would have to be carefully designed and less specific than the BAN manufacturing codes.

COLLABORATIONS

World Intellectual Property Organisation

The Group heard that WIPO, the World Intellectual Property Organisation, has been a UN specialized agency since 1974 and promotes the protection of intellectual property (IP) amongst its 184 members worldwide. It helps ensure INNs are not misappropriated as trademarks by transmitting WHO INN information to its member states' intellectual property offices and WHO assists in this by supplying updated lists on CD for distribution to the IP offices in WIPO member states.

In examining trademarks, the practices of IP offices tend to fall into two groups, those that refuse a trademark if there is a conflict with an INN, in full or in part, or those that refuse a trademark if it includes an INN or even a similar word to an INN, e.g. with a stem, such that trademark might be associated with an INN. The standing committee of WIPO is to invite the WHO INN Secretariat to make a presentation concerning WHO recommended INNs at their meeting in June 2008.

In discussion, it was highlighted that good cooperation with WIPO is important in promoting INNs, and to have an impact on local trademark offices where different language barriers can be overcome.

Potential Standardized Identifiers for Fixed-Dose Combinations

Representatives from HIV and Pre-qualification Programmes in WHO joined the Group to discuss issues concerning fixed-dose combinations (FDCs) and abbreviations for FDCs. FDCs are important aspects of many therapies such as for malaria, TB and HIV, and sometimes can be taken for life. They might be co-formulations or co-packaged drugs and many policy and global guidelines implicitly refer to them. With increasing production of generic combination products, there are increasingly chaotic labelling situations and issues with terminology.

The main rule has always been to use INNs with no abbreviations plus a means of distinguishing multiple components. However, stringing together several INNs leads to an unwieldy length of name and errors are creeping in due to the use of non-standardized shorthand abbreviations in healthcare settings, in paperwork and in tables. Many FDCs have their own abbreviations, but this can vary amongst different agencies; for example, *zidovudine* is generally abbreviated to AZT although in USA it is usually ZDV. If abbreviations are to get used for combination products, standardization is required including under what circumstances an abbreviated name gets used.

The HIV department representative stressed that they were not advocating a change in labelling, but in some documents it was difficult to use continually the full multiple name repeatedly, and it is only in certain situations where it does not compromise patient safety that abbreviations are being considered. One solution might be a second-layer identifier system but this has not been developed and it is not clear what the best way forward is.

Schemes for abbreviated names have been tried in the past but abandoned; for example in the UK a scheme was developed for combination products for prescribers, but very quickly problems arose linking the code name with specific proportions and doses. WHO also has

experience in abbreviated names in some contexts, e.g. for antibiotic discs used to assess susceptibility of an organism to a particular antibiotic. The codes were discretionary, some manufactures followed them, some did not, and ultimately it was abandoned many years ago.

WHO has also considered abbreviations for vaccines with a three letter code for each component but it gets cumbersome with 5- and 6-valent vaccines and was dropped (but is likely to re-surface).

If the use of codes is progressed, the INN Expert Group might be able to advise, but unless there is a mechanism for promoting the code to the end user and it is clear to them, it is likely only to get more complicated. The Expert Group was sympathetic to these problems and agreed that abbreviations are probably the way forward.

FDA/USP Substance Registry Project

The old FDA Ingredient Dictionary suffered from having examples of several names referring to the same chemical ingredient in a drug product, or the same name can often refer to two different chemical entities. Also, names can be misspelled or have foreign spellings whilst brand names were often used in place of generic names.

Thus a Substance Registration System (SRS) was developed, in a joint USP/FDA project, in which all substances are assigned a Unique Ingredient Identifier (UNII) consisting of a 10 character alphanumeric code, the first 9 of which are randomly generated providing trillions of combinations (the tenth character being a 'check' digit). Each chemical structure gets represented on a two-dimensional plane using a chemical drawing program and receives its own permanently assigned UNII. In the absence of a defined chemical structure, an identifying description is used in lieu of the 10 character identifier. In this way, a UNII can be associated with more than one entry in the old Ingredient Dictionary, e.g. water has a unique UNII but several other entries e.g. pure water, water for injection, etc. The UNII is designed to be free, non-semantic, timely, unambiguous, comprehensive, coordinated and current. There are specific rules for entering chemical structures and guidance is available at: http://www.fda.gov/oc/datacouncil/1_11_2007SRS_Users_Guide_5B.pdf

In discussion it was commented that there is a proliferation of such systems due primarily to computerization. For example, IUPAC also has an identifier system (InChI; see below) which has the advantage of providing the structure from the identifier and is used extensively by many different people and organizations. However, it is likely that the FDA prefers their own system for control; bar codes may be introduced, perhaps even for impurities, and can be used to avoid dispensing the same ingredient. The INN Programme will have to think about how to link with these types of systems.

USAN

For USAN 2007 was a busy year with 150 applications of which 125 had been adopted by year's end. The 2008 annual meeting will take place in January in Phoenix, AZ at which new negotiations and outstanding items will be tabled, and policy items such as what products should receive a USAN, e.g. botanical products, and the basis for a manufacturer to require an additional round of negotiation, will be discussed.
More information can be found on the USAN website: http://www.ama-assn.org/go/usan

La Revue Prescrire
The Group heard how La Revue Prescrire, a French independent publication, is highly concerned with INNs and each month has an article about stems. There is both a French and an International edition.

INNs in the Russian Federation
The Director of the Russian centre PHARMEDINFO described the use of INNs in the Russian Federation. Before 1990, INNs were used primarily in scientific and reference literature, but since then have been used in the healthcare system, forming the base of the Russian Drug List. During the 90's, Russia started to harmonize their processes to international regulations and in 1998 brought out the first Russian Drug Law that made INNs obligatory. INNs are now widely used throughout the healthcare system although with ~15000 trade names registered, less than 1000 INNs are used commonly, primarily since the Russian drug market is highly generic with very few innovative products, and many drugs are registered by domestic companies who have not applied for an INN.

The Drug Synonyms Handbook, first developed in 1990, is the first Russian compendium for drug information using the INN approach. This year the 10th edition was published and is widely used by all healthcare professionals. It contains more than 1200 monographs which include names of active substances in Russian, English and Latin. Other features include an ID number, ATC code, trade names in Russian and English, and country of origin. The book has a user friendly interface, is available in CD and paper, and gets distributed to all regions of Russia.

However, there remains a lack of familiarity in Russia with the INN system and educational courses are being provided by the Sechenov Moscow Medical academy, the oldest medical academy in Russia. Also, introducing the INN system has had to overcome linguistic issues, and an *ad hoc* committee within the Russian health authorities sets trade names in Russian and English and helps to provide a link between this committee and WHO. The Committee has also been instrumental in translating the INN publication on the use of stems into Russian.

The Chair expressed the appreciation of the Group to the Director of PHARMEDINFO for the efforts in establishing INNs in Russia.

BAN, UK
The BAN 2007 became effective as of January 2007; products no longer marketed in the UK have been moved to an Annex, so that greater attention can be put on regularly used products.

A BAN is published once the rINN is available as a licensed medicine in the UK or is the subject of a BP or Ph.Eur. monograph. BAN 2007 Suppl. 1 is now available and Suppl. 2 is being worked on; any comments regarding the BAN 2007 publications should be sent to the British Pharmacopoeia (BP) and would be incorporated in the next consolidated edition of the BAN publication. The BP's Expert Advisory Group on Nomenclature will next meet in Feb 2008 and feedback will be provided to the INN Secretariat.

The British Pharmacopoeia 2008 is now published, containing 50 new texts, with an effective date of Jan 2008. One new issue concerns unlicensed medicines, those medicines prescribed to an individual patient where a licensed medicine is not available. Having recognised some of these medicines the BP has published specific monographs to control some previously uncontrolled medicines.

IUPAC
IUPAC has developed InChI, an international chemical identifier, similar to the CAS registry number, but unlike the registry number the InChI can be converted back to the structure. It is generated by a computer programme that can be downloaded, see www.iupac.org/inchi. It will uniquely number the atoms irrespective of how the structure is drawn and unlike SMILES always gives the same InChI. It has been adopted by a number of journals to be embedded in the electronic version. It is also used by 16 databases so far. For use in search engines, such as Google, a shorter fixed length InChIKey has been produced. This is usually unique but cannot be converted back to a structure.

IUPAC has also now published recommendations for drawing stereochemistry of structures (Pure Appl. Chem. 78 (2006) 1897-1970). A report on the stereochemistry of coordination above six has been published (Pure Appl. Chem. 79 (2007) 1779-1799). Firm recommendations are difficult as it is not easy to decide on the preferred geometry.

This year was a General Assembly year during which it was reported the latest update on atomic weights, for example the atomic weight of zinc was changed.

EMEA
At an EMEA meeting with both the innovative and generic industry, concern was expressed about the high rate of rejection rate of chosen names. External comments on the guideline of trade names have been reviewed and should be finalized in December and appearing on the EMEA web in January.

The EMEA also held an insulin workshop aimed at discussing naming and labelling for insulins. It was attended by representatives from regulatory authorities, patient safety groups and industry. The second highest number of medication errors is linked to insulins, to wrong insulin, wrong doses and devices. Patients and healthcare personnel see the name written differently from regulators, and the end user should also be asked what they think about brand names.

KFDA,
The Korean Adopted name (KAN) was established in 2003 by the KFDA and guidelines issued on the basis of the WHO INNs. It provides nomenclature for new drugs, terminology to harmonize pharmaceutical names in the Korean Pharmacopoeia (KP) and is used for drug approval and labelling. The KFDA has recommended usage of the KAN since 2005 and in order to maintain harmonization with other pharmacopoeia, it is regularly updated.

EC/DG TAXUD-B3 (Taxation and Customs)
There has been a long standing cooperation between WHO/INN and DG TAXUD. The INN Secretariat greatly assists the World Customs Organisation (WCO), the WTO Pharma-GATT trade agreement and the EU Customs Inventory of Chemicals Substances.

Customs tariffs and Customs nomenclature is established by EU legislation and classification of drugs for customs and tariffs is determined in cooperation with the World Customs Organisation (WCO).

DG TAXUD-B3 was the leader in the preparation of the 3rd revision of the WTO Pharma-GATT trade agreement. Relief of customs duty is now provided for virtually all pharmaceutical products covered by INNs and CAS, plus all salts and esters and many intermediate products. However, the new agreement has resulted in a huge revenue loss. A problem remains with non-pharmaceutical INNs – e.g. cosmetics, carrier gas, and common

polymers; these remain troublesome for the WCO and need to be sorted out. The WCO also would like to see the Names for radicals and groups further enhanced.

Finally the EU Customs Inventory of Chemicals Substances was created in 1970 to ease customs clearance and control, and to prepare legislation and trade agreement; it lists more than 30000 chemicals and makes us of various international names classification.

Customs and taxation personnel highly appreciate the WHO INN Programme and the presence of INN personnel at their WCO meetings.

CLOSE OF MEETING

At the close of the meeting, Dr Hans Hogerzeil, Director of PSM, thanked the experts for their work, emphasising that they were indeed part of the WHO and not simply visiting WHO.

The 46th Consultation will be on 1-3 April 2008.