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48th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 31 March-2 April 2009

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

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

INTRODUCTION

The *48th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances* was held in Geneva on 31 March – 2 April 2009. The members of the INN Expert Group, the INN Advisory Group on biologicals, as well as the full WHO 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 (EMEA), the Japanese Pharmacopeia (JAN), the United States Adopted Names (USAN) Program, the United States Food and Drug Administration (US FDA) and others.

Dr Sabine Kopp gave a warm welcome to all on behalf of the Director of the Department of Essential Medicines and Pharmaceutical Policies (EMP) of the WHO. She emphasized that the INN Programme is widely recognised by medical practitioners and the work of the INN Expert Group is routinely reported to the Expert Committee on Specifications for Pharmaceuticals Preparations. In October 2008, for the first time two major WHO committees, the Expert Committee on Specifications for Pharmaceuticals Preparations and the Expert Committee on Biological Standardisation held a joint meeting with the INN Programme being a component of the agenda. Dr Kopp acknowledged that the members of the group were present on a personal basis for their expertise and wished them a successful meeting.

The Chairman, welcomed both new and older members of the Group and thanked Dr Raffaella Balocco Mattavelli, INN Programme Manager, and her team for the immense amount of work done since the last meeting, and noted the considerable change that had taken place with the new INN Integrated Data Management Information System (IDMIS), a web-based online information and commentary system. There were fewer applications to consider at this meeting compared with the previous, but more time would be spent on Action and Use statements and on biologicals discussions. The Chair also reminded the experts of the confidentiality and commercial sensitivity of the information they would be discussing.

The Manager of the INN Programme, Dr Raffaella Balocco Mattavelli added her thanks to the experts for engaging successfully with the new online database and commentary system.

NOMENCLATURE OF INNs

During the Consultation, a total of 89 INNs were discussed, including:

- 59 new INN requests, including 16 for biological substances
- 27 outstanding requests
- 2 previously selected proposed INN, against which a formal objection had been raised
- 1 request for substitution.

As a result of these discussions, 77 new names were selected or reconfirmed, which are planned to be published in List 102 of Proposed INNs, while 5 requests were deferred for future discussion. Four requests were rejected by the INN experts, as the substances do not conform to the criteria for INN selection. One amendment is planned to be published in List 102 and one request has been abandoned. The remaining request discussed was a request of substitution.

IDENTIFIERS FOR GLYCOSYLATED BIOLOGICAL PRODUCTS

– the Case of Greek letters

INNs have come a long way from the initial naming of single chemical entities, to the need to properly define a medicinal substance and the introduction of a stem system which gives INN users an indication of the group of substances to which a drug belongs. INNs have also evolved from the naming of well defined chemical drugs to less defined products such as insulins and low molecular heparins, and eventually to more complex types of drugs such as enzymes and recombinant glycoprotein drugs.

For most groups of compounds a single word INN has been sought, and as names became broadly used by prescribers and the medical profession in general, certain restrictions were imposed on the use of single letters, numerals and Latin names to avoid confusion with handwritten prescriptions.

In naming more complex compounds, different approaches have been used, e.g. for insulins, initially descriptive names were given e.g. suspension or crystalline, but for recombinant insulin, a two word name involving the insulin stem and a name for alternate structures was conceived. When recombinant glycoprotein drugs first appeared on the market, it was recognised that the same product being produced by different manufacturers would not necessarily be identical due to differences in complex post translational modifications such as glycosylation, and that an additional identifier within the INN name was needed. A possibility for extending a name had always been the use of a supplementary Greek letter spelled out in full and so this was adopted for these compounds. It was first applied to recombinant erythropoietins, and so they were named epoetin alfa, epoeitin beta, etc. Where the amino acid structure was distinct, this was encapsulated by the use of a distinct prefix e.g. darbepoetin. The system has been extended to other recombinant glycoprotein drugs such as blood coagulation factors and interleukins. Some difficulties have ensued e.g. where biochemists had already used a nomenclature system that incorporated Greek letters for alternate groups of complex proteins such as the interferons, where interferon alfa and interferon beta describe distinct amino acid forms of the protein.

The programme has faced challenges over its lifespan with the need to assign names to new groups of products. It has also had to take onboard the inherent heterogeneity of some of these compounds, further complicated by advances in analytical chemistry that can define in increasing detail the nature of a mixed population of molecules.

One particular challenge has been nomenclature for glycoproteins and it was discussed if defining the nature of the cell substrate used to manufacture a particular glycoprotein drug might be of value in defining such substances, in particular epoetin, as the cell substrate is a major factor in determining the nature of post-translational modification. However, whilst a general type of glycoform may be associated with a particular cell substrate, finer differences can exist between alternative lineages of a particular cell type and on the metabolic state of the cell. Furthermore, defining glycoform structures in words would be an exceedingly difficult challenge and in some cases, for example where an INN was assigned many years ago, a detailed structural analysis would not have been available at that time. A further obstacle would occur if a cell line was specifically engineered to alter its glycosylating mechanisms. Any of these changes might occur for a particular substance and if an INN had already been assigned, it would be overly difficult to change.

The Group needs to be clear in its minds as to what it is trying to achieve. INNs are produced for unique chemical substances and the ideal situation is where there is a clear structural indicator that defines the product. However, as structural analyses of glycoforms are provided in increasing detail, what impact should small but defined differences have on the provision of a unique INN, as even within a single manufacturing process, changes might occur through modification of cell culture conditions? It is recognised that there may even be variability from batch to batch but this would never evoke the need for a different name. The Group needs to consider these discussions and to move forward; some INNs were assigned up to twenty years ago in the absence of any

glycoform structural data, and detailed structural information as would be provided today is unlikely ever to be available to the INN experts.

Assignment of INNs to complex mixtures is not new and such challenges have had to be faced in the past. The Expert Group can only take into account the information that is provided by the applicant and that is state-of-the-art at any particular time. These discussions on the use of Greek letters and on cell types were initiated for clarification and information, and the Chair was grateful to those responsible for providing background material for promoting the discussion. Further editing and publication of the background paper to the use of Greek letters is recommended.

WORKING GROUP ON NOMENCLATURE FOR MABS

A small *ad hoc* group of biological experts met on 6-7 October 2008 to discuss the nomenclature for monoclonal antibodies (mAbs). An oral report was made at the 47th INN Consultation alongside preliminary recommendations of the experts. The objective of the meeting was to investigate alternative naming strategies for monoclonal antibodies as names were becoming complex with long prefixes. The final report of this expert group was adopted at this 48th Consultation and the recommendations discussed. It was suggested that it could be published to help explain the background to the new nomenclature system and also what is not changing.

The report recommended that the stem *–mab* is retained for all mAbs and fragments thereof, but that the use of infixes that denote the animal species of origin of the immunoglobulin sequence and the disease or target class should be revised, adopting single vowels or letters where appropriate. In many cases this could reduce by one the number of syllables required to produce a unique INN.

The immune-modulator and tumour groups especially are overcrowded and sometimes overlap, and a means of expanding the list of infixes for disease or target is required, e.g. there are over 60 – *li(m)*- names under lymphocytes and immunmodulators, i.e. there are two uses of *–li(m)-*. In contrast there are currently only four names assigned to the *le(s)*- (inflammatory lesions) group and this could be discarded as an infix. This was agreed by the Group. Also, it was agreed that the tumour group should be simplified to *–t-* or *–tu-* and all other tumour related substems discontinued as these are assigned based on the predicted indication of the medicine but which might change during development and use of the mAb.

There was no consensus on a policy for mAbs regarding glycosylation. Similarly, for biosimilar mAbs, different views were expressed on the need to distinguish mAbs with the same amino acid sequence but differential post translational modification such as glycosylation. Thus the only conclusion was that they would have to be distinguished.

A further attempt to ease the difficulties in developing unique INNs for mAbs could be to identify products with previously assigned names which are no longer being developed; this would provide an option of assigning a new name close to a previously assigned but now redundant INN. However, there could be difficulties in doing this due to the occasional long timelines in developing a mAb.

The FDA provided written comments on the *ad hoc* meeting report and expressed broad agreement.

ACTION AND USE STATEMENTS

At the 47th Consultation, a revised draft Action and Use Statement was tabled for discussion. Consequently, suggestions were proposed regarding classification of stems. Firstly, it was noted that Group A products (CNS depressants) includes two types of product, actual CNS depressants and anti-pyretic agents, and there could be value in moving the analgesic-antipyretic agents, comprising ten stems, into a new Group AA. There was also a proposal to dis-establish group D (peripheral nervous system drugs), moving the two existing stems into Group E. Other proposals

were that a new Group ZZ is created for gene therapy products and a new Group YY for drugs with multiple activities, and this might incorporate 19 such stems.

It was clear that this recent assessment and revision was a huge amount of work but that the revision and suggested proposals need further consideration. Stems develop with scientific knowledge and some stems are no longer being used and indeed should not be, whilst new stems are continually being created for new classes of drugs. For example, a new group for anti-pyretics could encompass anti-inflammatory agents in general.

Overall it was agreed that the current stem classification needs to be revised and it was concluded that a small working party should meet to consider the revision and proposals. It should also consider future guidance that would be valuable to applicants. The revising group needs to address any need to subdivide broad groups or introduce new categories. It was also agreed that a new revision or review of Action and Use statements should be made public with an introductory statement for guidance and clarification as to what stems are available and their context. However, it was also felt that a group should not be dis-established or removed but rather applicants should be discouraged from using any stems that are no longer of value and perhaps mark them as dormant rather than complete removal from the document.

UPDATES FROM COLLABORATORS

United States Adopted Names (USAN) Program

At the 2009 winter USAN Council meeting in San Diego, names were recommended for 36 substances. Nine new stems were approved and have been posted on the USAN website, along with 4 designations for radicals and anions. Policy for the use of 'restricted letters' for naming contact lens materials was approved and USAN C requested that the FDA add two drug names, DACTINomycin and DAPTOmycin to the FDA-Approved List of Established Drug Names with Tall Man Letters. A redesign of the USAN website was presented to the Council and a USAN update was prepared for the AMA Board of Trustees. The 2009 summer meeting is scheduled for July in Chicago and already by March 31, 38 USAN had been adopted during 2009.

British Approved Names (BAN)

Supplement No. 3 to the BAN 2007 book is being prepared. The names listed are those for products on the UK market for which licences have been issued plus all rINNs and Ph.Eur. monograph titles that are not BP approved names (or rINNs). Supplement 3 will also include the relevant parts of the preliminaries included in the BAN 2007 book.

On the pharmacopoeial front, monographs for traditional herbal medicines (traditional Chinese medicines and Ayurvedic medicines) are being developed. Approximately thirteen of these appear in the BP 2009.

Directorate-General Taxation and Customs Union (DG TAXAUD), European Commission

Multilateral negotiations regarding the 4th revision of the international Pharma-GATT Agreement (or "zero-for-zero" agreement) have started. Ultimately customs duties will be relieved for a significant number of new products used in e.g. the pharmaceutical sectors of the EU, USA, Japan and Switzerland. Products included in proposed INN lists 94-99, as well as pharmaceutical intermediates, will be subject to the ongoing negotiations.

It was noted that INNs are not only used within the pharmaceutical sector but also in the area of trade and customs.

European Medicines Agency (EMEA)

The INN Committee was updated on the fact that the Name Review Group (NRG) performed an analysis of the information provided within the initial proposed name and justification process, with the aim of providing additional recommendations to industry for future submissions.

International Union of Pure and Applied Chemistry (IUPAC)

The most significant recent development is the publication of a revision of the Purple Book, the Compendium of Polymer Terminology and Nomenclature. Nomenclature for rotaxanes (molecules in which a ring encloses another rod-like molecule having end-groups too large to pass through the ring) has also been published. Other IUPAC publications are gradually being published in additional languages, for example the Red Book is now available in Spanish.

US Food and Drug Administration (FDA)

The recently established new US administration has got nominees for a new FDA Commissioner and Deputy, , and also a nominee for the Secretary of Health in Human Services. The FDA is also now hiring new review personnel in all disciplines. With respect to INNs, at least in biologicals and therapeutic proteins, the Office of Biologics is taking a more active role in nomenclature for complex biologicals.

World Intellectual Property Organization (WIPO)

The last Standing Committee meeting was held in December 2008, and trademarks and INNs were included in the discussions. There continues to be improved access in WIPO member states to INN lists and they propose that INN could help further, for example by the supply of approved and proposed lists of names on CD-ROM to WIPO to distribute to trademark offices. Informing trademark offices when new lists and stems are available would also be valuable. WIPO will continue to circulate INN lists by paper and by email letter to all offices of its members and looks forward to continued cooperation with INN, especially improved accessibility to INN lists.

On a separate issue, ICANN, the organisation responsible for assigning and policing internet domain names, is considering expansion of the number of top level domains from the current number of about 20 to a greatly expanded list, and WIPO warned the INN Group about any list of such domains being created that encompass or compromise individual INNs. WIPO itself has expressed its concerns to ICANN regarding trademarks, which are owned by a company or person, and second and lower-level domain names which are provided on a first-come, first-served basis and which are then owned by the person registering the name. WIPO is also working with ICANN in an attempt to safeguard trademark protection in (top-level) domains. The INN Group should similarly be concerned about the possibility of abuse of INNs by the creation of new domains or domain names from them. Currently there is no specific protection for an INN but the situation should be monitored, WIPO warned. Registering an INN as a domain name would be straightforward as the INN is not ‘owned’ by anyone whilst a domain name would be owned by the person registering it; obtaining the rights to a new top-level domain will obviously be more difficult and subject to procedures. ICANN is open to receiving comments concerning such procedure in the context of the expansion of top level domains although time is running out for submitting comments.

There was general concern within the Group that INNs could be abused in this way and that if something could be done to provide them with protection against their use as domains and domain names, then this should be done. Continued collaboration with WIPO in this area would be useful; however it appeared to be fundamental to get ICANN to ban the use of INNs as domains and domain names. It is likely that ICANN is not aware of them and the need to protect them.

DEVELOPMENTS IN DATA MANAGEMENT

The IDMIS online system is an important new device for providing comments, and it is good that experts are now using it. As yet there is no facility for adding post-meeting comments but it should become available later in the year. Access to an archive of comments and decisions would also be useful although access should be available to two year old requests at least. The system continues to evolve and improve and the originators were congratulated on the system.

CLOSE OF MEETING

There being no other business, the Chair closed the meeting noting that it had been highly successful with a large majority of applications having a name assigned and very few deferred, and most outstanding applications dealt with. This allowed time to discuss some broader issues affecting the work of the Group and the Chair and Secretariat gave a special thanks to those involved in preparing Action & Use and Use of Greek Letters papers and presentations. The Chair was also appreciative of the work carried out by experts outside of the meeting, to all those present at the meeting and especially to the Secretariat for their immense amount of work on the applications and on the new online system.

The 49th INN consultation will take place in Geneva from 17-19 November 2009.