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44th Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 22-24 May 2007

EXECUTIVE SUMMARY

Programme on International Nonproprietary Names (INN)

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

The 44th Consultation on International Nonproprietary Names (INNs) for Pharmaceutical Substances was held at WHO Headquarters in Geneva on 22-24 May 2007 to discuss requests for the selection of new INNs and to review various issues related to the selection of substance names.

The members of the INN Expert Group were present at the meeting as well as the full INN Secretariat and several specialists who assisted in specific nomenclature problems. 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 Pharmacopoeia Commission (EPC), the Japanese Pharmaceutical and Medical Devices Agency (PMDA), the Japanese Pharmacopoeia (JAN) and the United States Pharmacopoeia Convention (USPC).
Professor Derek Calam chaired the meeting.

During the Consultation, a total of 102 INNs were discussed:

- 77 new submissions for INNs, including 22 submissions for biological substances;
- 22 requests previously deferred due to insufficient information provided by the originators were also reviewed;
- as well as three previously selected proposed INNs, against which a formal objection had been raised.

As a result of these discussions, 82 new names were selected, which will be published in List 98 of Proposed INNs, while 16 requests were deferred for future consideration due to insufficient information on the substance. Four requests for selecting INNs were rejected by INN experts, as the products do not conform to the criteria for INN selection.

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

General policies for assigning INNs to biologicals have been in place for many years, but as the field is becoming more and more complex, there is a need for a systematic review. The last review was carried out in 2002. In order to accommodate subsequent developments, the INN Programme convened in April 2007 an *Ad-Hoc Meeting* to review the nomenclature of biological and biotechnological medicinal substances.

The INN Expert Group reviewed the notes and the recommendations of this *Ad-Hoc meeting* (see Annex 1) and was pleased to note that the nomenclature systems in this field are generally working well. The INN Expert Group accepted the recommendations of the *Ad-Hoc Meeting* that no changes should be made to the existing policy for certain groups of substances. In particular, it was confirmed that natural blood products, vaccines, cell and tissue therapy products should remain outside the INN system. However it was agreed that small peptides,

intended for use as 'peptide vaccines', are within the scope of the INN system and should be treated as a sub-group within the peptides.

The INN Expert Group noted that there was a range of opinion but no consensus within the Ad-Hoc Group on possible changes to the policy for naming glyco- and other post-translationally modified proteins. In view of this, the INN Expert Group agreed that the present policy should continue.

After reviewing various issues related to the naming of biological products raised by the Ad-Hoc group, the INN Expert Group recommended that the INN Secretariat should:

- put in hand a comprehensive review of existing definitions of complex biologicals to bring them up to current standards of characterization and to be consistent with the information now being requested at the time of an INN application. This should help to distinguish better between individual substances in view of the debate about how much information should be conveyed in a name and how much in a definition,
- investigate the possibility of developing a discretionary, but not mandatory, coding system for identifying expression systems for recombinant products. These ancillary coding systems are in use in some countries and the availability of a set of codes would promote international harmonization,
- consult a small group of experts on the development of the nomenclature system for monoclonal antibodies. The current system was developed prospectively but experience shows that some elements of the system are redundant and have never been used whilst new scientific and technical developments (e.g. use of antibody fragments, bifunctional antibodies, different antibody types) require names for substances not envisaged originally,
- continue to liaise closely with the WHO Biologicals Unit and the WHO Expert Committee on Biological Standardization (ECBS) on nomenclature issues of common interest.

The INN Expert Group discussed also issues related to the establishment of new INN stems, i.e. the syllables indicating the pharmacological relationship between substances for which INNs are selected. The Group noted a trend observed in recent years, whereby manufacturers applying for new INNs increasingly also request the establishment of a new INN stem to indicate a novel mode of action or a new therapeutic approach. The Group agreed that an excessive number of new stems would limit considerably the ability of creating new distinctive INNs. Furthermore, in view of the resolution WHA 46.19 which discourages the use of trade names derived from established INN stems, a proliferation of new stems may also impact adversely on coining future T/Ms for pharmaceuticals.

The INN Expert Group confirmed therefore its policy of using existing stems whenever possible and encouraged the INN Secretariat to publish a document advising INN applicants that for a new stem to be established, substantial clinical and preclinical data will have to be submitted, documenting that the new substance does not fit into existing nomenclature schemes and that a new stem is thus warranted.

The INN Expert Group reviewed also the existing lists of INN stems and pre-stems and decided to expand them by establishing and defining new ones. Those stems (and sub stems) will be published on the INN Website as Addendum to the document ***"The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances".*** The INN Group also decided to include several new distinctive syllables used in new INNs to the list of pre-stems, for possible future establishment as INN stems.

The INN Expert Group has also been informed during the Consultation about relevant activities of several institutions using INNs through presentations of various national nomenclature bodies such as the British Approved Names (BAN), the Japanese Accepted Names (JAN) and the United States Adopted Names (USAN). WIPO reported about steps taken by them towards the timely dissemination of INN documents and information to national trademark registration bodies. The Expert Group on Safe Medication Practices of the Council of Europe and the International Society of Drug Bulletins also presented their activities related to the use of INNs in prescribing and dispensing of medicines.

The INN Secretariat informed the Expert Group that the INN Cumulative List 12, containing INNs included in lists 1-57 of recommended INNs and lists 1-96 of proposed INNs, has been recently produced and is available on CD Rom. The INN Expert Group congratulated the INN Secretariat for this accomplishment, indicating the high effectiveness of providing this form of interactive information to INN users.

Finally, the INN Expert Group has been presented with recent software improvements initiated by the INN Secretariat, which will significantly ease the INN data management and the ways of working together.

Recommendations from the INN Ad-Hoc Meeting on Biologicals, Geneva, 23-24 April 2007

The objective of this meeting, which brought together representatives from various national nomenclature institutions, from the innovator and generics industry, from the INN Biological Advisers and from the INN Expert Group, was to discuss and review in-depth the INN policies for naming and defining biological medicinal substances, and to submit recommendations to be discussed by the full INN Expert Group during the 44th INN Consultation in May 2007. Following is the outcome of the discussions:

1. INN Policies on post-translational modifications of proteins:

- Existing INN definitions of glycoproteins are inadequate and should be reviewed in terms of current knowledge and consistency of application.
- More information should be requested at the time of application for an INN.
- Arguments were made for and against the present practice of including specific Greek letters to differentiate different glycoforms of a given molecular entity (e.g. epoetin). In view of the lack of consensus, no change in the INN nomenclature policy pertaining to post-translational modifications is recommended at this time. The proposal of eliminating the Greek letter therefore should not be considered, even in a prospective manner.
- Consideration should be given as to how much information should be included in the name and how much in the definition, bearing in mind that there are protein modifications other than glycosylation (e.g. phosphorylation, lipidation).
- Consideration should also be given to drawing up a list of internationally agreed codes to reflect different production processes (such as *E. coli*, yeast, CHO cells etc). The use of such codes would not be part of the INN but discretionary, and used in labelling when regulatory authorities wished to distinguish different production systems.

2. INN Policies for Monoclonal Antibodies

- The nomenclature rules for monoclonal antibodies are complex. Current developments in the use of different antibody types (e.g. IgG 1, 2) with different functions, antibody fragments and "glyco-engineering" is adding to this complexity. Consideration should be given to establishing a small expert group to review these developments and to make specific recommendations on INN policy for monoclonal antibodies.

3. INN Policies on Vaccines and Gene, Cell and Tissue Therapies

Vaccines

- No major changes are foreseen in the policies for naming vaccines, which are a diverse group of biologicals.

- The WHO Expert Committee on Biological Standardization should continue to assign international and proper names to prophylactic vaccines. Consideration should be given to reviewing current inconsistencies in nomenclature and to extending the scheme to all prophylactic vaccines, as well as to developing internationally agreed abbreviations.
- Some small peptides used in the treatment of cancers should be considered as therapeutic immunostimulants rather than vaccines and be given INNs.
- Close liaison between the INN Expert Group and the Expert Committee on Biological Standardization should be established to monitor nomenclature policies in this evolving field and to consider appropriate policy on specialized issues, such as viral vectors for use as cancer vaccines.

Gene, Cell and Tissue Therapy

- No change in the INN policy for gene, cell and tissue therapies is recommended for the time being.
- Cells and tissues, including stem cells, are considered to be outside the remit of the INN system.
- The Expert Committee on Biological Standardization should consider developing guidelines for the quality control and safety evaluation of stem cells and tissue engineered medicinal products.

4. INN Policies on Blood Products

- No changes should be made to existing policies since these were already well established.
- Recombinant DNA-derived substances should therefore continue to be assigned INNs but the complexities already referred to with respect to post translational modification of proteins, as well as intended modifications, need to be taken into account.
- All naturally-derived blood products should still be considered to be outside the remit of the INN system.
- Nomenclature policies in this evolving field should be monitored through close liaison between the INN Expert Group and the Expert Committee on Biological Standardization, who consults with the *International Society on Thrombosis and Haemostasis* as well as the Blood Regulators Network.

5. INN Policies on Transgenic Products and Enzymes

Transgenic Products

- It is recommended that there be no separate policy for products derived from transgenic animals or plants.
- The codes developed to reflect different manufacturing processes mentioned above should include transgenic systems.

Enzymes

- No changes are proposed in the policy for assigning INNs to naturally-derived or biotechnology-derived enzymes. However this position may need review in future.