

***WHO Informal Consultation on International Nonproprietary Names (INN)  
Policy for Biosimilar Products***

*Geneva, 4-5 September 2006*

***Programme on International Nonproprietary Names (INN)  
Quality Assurance and Safety: Medicines (QSM)  
Department of Medicines Policy and Standards (PSM)***

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*The views expressed in documents by named authors are solely the responsibility of those authors.*

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## Opening Remarks

Dr Howard Zucker, Assistant Director General, Health Technology and Pharmaceuticals, welcomed participants to the consultation and emphasized the importance of its recommendations to the future direction of WHO policy on International Nonproprietary Names (INN) for biologicals. New biological medicines need new INNs but the purpose of these names, and how they are assigned, should be very clear and understood by all countries. Dr Lembit Rago, Coordinator, Quality Assurance and Safety of Medicines, reiterated the critical importance of the present consultation which had been convened to exchange views on current issues relating to the nomenclature of biosimilar products in various regulatory settings and to advise the WHO on INN policy for these biologicals. The report and recommendations of the meeting would be discussed further with all interested parties and presented to the WHO INN Expert Group, to the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and to the Expert Committee on Biological Standardization (ECBS). In the present context, the term biosimilar is used to describe a biological product used in medicine that would be similar to and would enter the market subsequent to an approved innovator biological through a specific regulatory pathway which is presently only just evolving globally. The term had been chosen to make a clear distinction between these biological products and purely generic pharmaceuticals. In the USA and Japan, biosimilars are called follow-on protein products, and in Canada subsequent-entry biologics.

Represented at the meeting were the regulatory authorities of Canada, the European Union, Japan, South Korea and the USA. Representatives of the Australian regulatory authority had been unable to attend but had indicated their position in writing. Dr Rago stressed the importance of having National Regulatory Authority involvement in the INN consultative process, especially in developing policy for the naming of biologicals. However, developing policy on the naming of biosimilars should be seen as part of broader WHO discussions on regulatory approaches to these products. The views of both the innovative and generic industry regarding the naming of biosimilar biological medicines and its wider implications were available in writing to the consultation. Dr Rago explained the way the consultation would operate and proposed Dr Derek Calam as the Chairman of the consultation, and Dr Elwyn Griffiths as the Rapporteur. The proposals were agreed.

## Current INN Policy on Biological Products and the Challenges of Naming Biosimilars

Dr Raffaella Balocco-Mattavelli (INN Programme Manager) introduced the WHO INN Programme and explained the process of assigning INNs. She noted that it was a core activity of the normative functions of the WHO and had served the global regulatory community well for over 50 years. In fact WHO has a constitutional mandate to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products". Therefore the WHO collaborates closely with INN

experts and national nomenclature committees to select a single name of worldwide acceptability for each active pharmaceutical substance. To avoid confusion, which could jeopardize the safety of patients, trademarks should neither be derived from INNs nor contain common stems used in INNs.

The INN Programme's purpose is to assign nonproprietary names to medicinal substances so that each would be recognized globally by a unique name. INNs facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. In fact, unlike trade names, INNs do not give proprietary rights and can be freely used since they are in the public domain. The INNs form an essential part of the regulatory process in many countries where a nonproprietary name is required for licensing. The WHO Executive Board, at its meeting in January 2005, had made slight revisions to the INN process. Improvements to the consultative process were also taking place, including the development of internet based tools. She also mentioned the need for countries to protect the INNs from the practice of registering trade names similar to INNs for commercial advantage. The cooperation of National Regulatory Authorities in stopping this practice would be appreciated.

Dr Balocco-Mattavelli explained that INNs are assigned not only to chemical drugs but also to biological and biotechnology derived medicinal products which are more difficult to deal with. The biotechnology field is still expanding, not only in developed countries but also in developing regions of the world, with many new and innovative medicinal products reaching the clinical trials stage of development, including recently, as patents come to an end, the so called biosimilar products.

INNs are intended for use in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. As a result of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the INN.

Dr Calam (Chairman, WHO INN Expert Group) expanded on the difficulties in developing INNs for biological products due to their complexity. These are, by definition, products used in medicine derived from biological sources and which cannot be fully characterized by physical and chemical means alone. Nevertheless, INNs had been assigned to biological medicines since the early days of the programme, including biotechnology derived products such as monoclonal antibodies and a range of recombinant DNA derived proteins including hormones, haemostatic agents and cytokines. INNs had not been assigned to natural human blood products nor to vaccines. Instead, the Expert Committee on Biological Standardization formally assigns scientific names to these biologicals when developing the appropriate WHO Recommendations and these become the international name.

Dr Calam explained that general policies for assigning INNs to biologicals had been in place for many years but the field was becoming more and more complex. Glycosylated and non-glycosylated proteins posed different problems. Differences in glycosylation

had been handled by adding a Greek letter in full as a second word as, for example, in epoetin alpha, beta or gamma etc. In January 2005, an informal consultation convened by WHO recommended a policy for developing INNs for gene therapy products which took account of both the gene and the vector. In view of the increasing complexity of this whole field, the WHO INN Expert Group had requested the WHO INN Secretariat to prepare a working document intended to summarize and review the past and present INN situation. A current draft of this paper was available to the present consultation. In discussing generic chemical pharmaceuticals, Dr Calam noted these retained the same INN as the innovator product since they are considered to be equivalent, even if synthesized by different routes. In the biologicals field, different sources or production processes have the potential to give rise to different product profiles, which when they occur may raise certain concerns about interchangeability, tracing and pharmacovigilance. However, he considered there would be a need to distinguish between nomenclature matters and regulatory issues.

Dr David Wood (Coordinator, Quality, Safety and Standards) outlined the WHO's constitutional responsibilities in the biologicals field which essentially meant developing, establishing and promoting international standards for biological products used in human medicine. In practice this covered vaccines, blood products biological therapeutics and *in vitro* diagnostics. This responsibility was discharged through an Expert Advisory Panel on Biological Standardization from which the Expert Committee on Biological Standardization was selected annually to develop international norms and standards that provide regulatory support to WHO Member States. The work of the ECBS is supported by specialist scientific advisors together with industry and other relevant stakeholders as observers at Expert Committee meetings. Regulatory guidance is provided by the WHO through global written standards, by physical measurement standards and through support for evidence based standards. Safety is a key element and the potential for various biotherapeutics to induce unwanted immune responses is always kept in mind. At the request of the INN Secretariat, the ECBS provides advice on biological nomenclature and other issues. A pre-meeting on biologicals held at the International Conference of Drug Regulatory Authorities in Seoul in April 2006 had heard that biosimilars were already being produced in several countries but that there was relatively little regulatory guidance presently available. It was recommended that a position from WHO would be extremely helpful. Dr Wood noted that the European Medicines Agency (EMA) already had a guideline on biosimilars. He indicated that WHO was interested in providing comprehensive regulatory guidance to address the risks and benefits of biosimilars.

The challenges of naming biosimilars were introduced by Dr Elwyn Griffiths (Health Canada). He emphasized that these biologicals, based as they were on an innovator product coming to the end of its patent life, could not be considered true generics because biologicals were not identical by definition. For biologicals, the manufacturing process is critical to defining the characteristics of the final product. Nevertheless, some stand alone biologicals had the same INN even if there were slight differences in, for example, glycosylation. In cases where significant differences in glycosylation were known, then a distinctive INN had been assigned using, as already mentioned, a different additional Greek letter designation. It was clear that regulatory policy for dealing with biosimilars

was challenging and still evolving on the global level, although already well developed in the European Union. The regulatory path for biosimilars was expected to differ from that for stand alone biologicals, for example with respect to the amount of clinical data needed to be generated with the new product in support of approval. Considerations regarding the degree of similarity of the biosimilar product with the comparator biological would also be critical; how similar is similar? It was agreed that the concept of a biosimilar product is regulatory in nature, whereas assignment of an INN is a nomenclature process based on scientific characterization of an active pharmaceutical substance. The question of whether the INN for a biosimilar should reflect the regulatory process by which it was approved was central to the discussion on future INN policy.

## Drug Regulatory Authority Views on the Nomenclature for Biosimilar Products

The Australian Therapeutic Goods Administration position on the naming of biosimilar products (available to the Consultation in writing): The WHO should not take a different approach to naming these products from that used in assigning INNs to innovator biological products. Nevertheless, there is room for improvement in the currently used non-proprietary naming scheme for glycosylated proteins. Glycosylation is known to be species specific and consideration should be given to distinguishing these differences in the INN according to host cells, viz murine, baby hamster kidney, Chinese hamster ovary and so on. The Australian Biological Names convention currently adds a restricted subset of the British Approved Names suffixes already in use to nonproprietary names in order to indicate the host cell employed in the production of biologicals. The Therapeutic Goods Administration also proposes that the WHO INN Expert Group consider publishing the full amino acid sequence of a product together with any other modification in order to unambiguously define the product named.

Representative from Health Canada: Health Canada possesses a comprehensive regulatory framework for drugs, biologics, medical devices, natural health products and generic drugs. At present there can be no true generic biological and is in the process of developing a regulatory framework for dealing with what in Canada are called subsequent-entry biologics. The package will address scientific, regulatory and legal issues related to these products. A fact sheet on subsequent entry biologics is available on the Health Canada web site ([http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi\\_seb-pbu\\_07-2006\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006_e.html)). As an interim measure, subsequent entry biologics are subject to all of the regulatory requirements for innovative biologicals, except that the extent of clinical data required may be less than that required for a stand alone innovator product. The extent of such data would be determined on a case by case basis but would need to be sufficient, along with data from the comparator biological, to provide assurance of safety and efficacy. Several issues are under consideration, including the nature of a Canadian reference of comparator, impact of intellectual property issues on regulatory policy, and guidance on long term pharmacovigilance planning for biosimilars.

Canada uses the INNs when they exist, but Health Canada had not been too involved in the past in their development. Following policy analysis, it is now seeking to take a more active role.

Representatives from the European Union / the European Medicines Agency: The European Union (EU) policy in dealing with biosimilars is already well developed. Like other biotechnology products, it would be mandatory for biotechnology derived biosimilars to take the centralized EU licensing procedure but for these products there would be a simplified dossier requirement. The expectation is for a full dossier on quality issues, and detailed comparability data to a given licensed EU reference product as far as quality, non-clinical and clinical criteria are concerned. Two applications, both for somatropin biosimilars, have already been given market approval in the EU using this approach and more submissions for biosimilars are expected soon. Although the EMEA / Commission is responsible for decisions on market authorization in the EU, prescribing policy is strictly a national responsibility. Regarding the INN policy, the EU view is that the INN is a classification system based on molecular structure and mechanism of action. The assignment of INNs to biological drug substances should be based on scientific criteria. It is recognised that 'biosimilar' is a regulatory and legal term and is distinct from the INN assignment process for biological drug substances. There should be no specific process applied for the naming of biosimilar substances, rather the policy for the assignment of INNs should be applicable to biologicals in general. The EU recognizes the complexity of biologicals and that variability may exist between innovator biological products with the same INN or even within the same manufacturer. Posttranslational effects in the field of biologicals contribute to that complexity and variability.

Representatives from the National Institute of Health Sciences of Japan: Although Japan is developing a regulatory policy on generic drugs, there could be no real biogenics, and prefers the name follow-on biologics or biosimilars to make this distinction clear. For the regulatory oversight of biosimilars, Japan would be following the same principles used in the comparability evaluation of biologics subject to major changes in their manufacturing processes, although it recognizes that the relationship between specific quality attributes and safety and efficacy has not been fully established. For this reason, a pharmacovigilance plan would need to be established to confirm safety. Japan has considered that follow-on biologicals could be given the same INN as the innovator product in the case of simple protein products. On the other hand, since the sugar chains in the glycoproteins produced by the different company should be different, because of heterogeneity of glycosylation, follow-on protein products modified post-translationally should be better discriminated from the innovative product in the INN. However, concerning these products, Japan recognizes that the present naming system should be reconsidered because it is complex and has a number of anomalies. Since follow-on biologicals are considered to be similar to but not identical with the innovator product there would be safety and efficacy concerns due to product related aspects and impurity profiles. Pharmacovigilance and traceability are important and Japan considers that follow-on biologicals should somehow be distinguished from the innovator product during prescribing. A system could be devised to identify biologicals with the same INN but which additionally indicated the cell substrate used in production. Aparting from the Pharmacovigilance and traceability problem, Japan has been also looking to a future

when glycoprotein drugs whose sugar chains are artificially changed for special pharmacological effects would come into the market, and there would be a need to discriminate this and unmodified product in the non proprietary name.

Representative from the Korea Food and Drug Administration of Republic of Korea: Like some other jurisdictions, the Korea Food and Drug Administration (KFDA) is in the process of refining its regulatory pathway to take account of biosimilars, although it does not have an exact definition nor criteria for such biologicals. These products would follow the same pathway as stand alone rDNA products but could have a simplified package of clinical study data which would be considered as confirmatory. Extensive comparative data between the biosimilar and innovator product would be expected. Recently, Korea introduced the INN in regulations and the non proprietary names of biosimilars will follow the INN of the innovator product. However, there are inconsistencies in the current naming schemes. Monoclonal antibodies are glycoproteins but the use of a Greek letter designation to distinguish glycosylation patterns is not used in the INN designation for these biologicals. Korea believes the INN scheme should be clarified and the descriptions for biologicals standardized. Interchangeability and traceability of biological medicines is thought to be less of a problem in Korea since physicians prescribe according to the brand names.

Representatives from the United States Food and Drug Administration (US FDA): The US Food and Drug Administration continues to support the original purposes and uses of the INN and believes the system has contributed much to global public health, especially in the exchange of scientific data on various products with the same active ingredient(s). The US FDA acknowledges that, to date, INNs have been granted on considerations of molecular characteristics and pharmacological class. However, the US FDA is concerned about proposals to change this policy for biosimilars supposedly to allow for adequate pharmacovigilance and to prevent inappropriate substitution of these complex proteins. The US FDA is of the opinion that INNs for biologicals should not be used to imply product interchangeability in the absence of credible scientific evidence. Likewise, however, INNs should not be used to differentiate biological products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist. Examples of stand alone innovator proteins exist which share the same INN. In the opinion of the US FDA, interchangeability and traceability do not fall under the remit of the INN Committee, but rather are issues for the regulatory authority, industry and other pertinent health authorities within the country. Regulatory mechanisms should be in place to prevent inappropriate and potentially dangerous substitutions of biological medicines. In the context of global pharmacovigilance, the INN is a useful tool but should not be the sole means of product identification for drug products including biologicals. All available tools should be employed, such as lot number and national drug code. The US FDA believes that INNs should continue to be granted only on considerations of molecular characteristics and pharmacological class of the active ingredient. The US FDA encourages the WHO to investigate the prevalence of use of INNs as a determinant of interchangeability.

## General Discussion

Although not the main topic of the meeting, the approaches of the various regulatory authorities to biosimilars showed regulatory policy for dealing with these products to be challenging and still evolving worldwide. However, it was apparent that there is shared thought among the regulatory authorities concerning the regulatory path for biosimilars. Specifically, it should not be the same as for generic chemical pharmaceuticals, but would nevertheless be simpler than for 'stand alone' biologicals, especially with respect to the amount of clinical data needed to be generated with the new biosimilar product itself. However, the extent of differences in requirements for biosimilars and stand alone biologicals was likely to be decided on a case by case basis. Some regions e.g. EU have developed a legal framework and guidance for marketing authorisation applications for biosimilars. WHO indicated that they are considering developing regulatory guidance on biosimilars.

The main focus of the consultation, that of the nomenclature of biosimilar biological products, generated considerable discussion. However, there was complete agreement amongst the national regulatory authorities present that the INN policy for biosimilars should be based on scientific considerations and that the INN system should not be altered to reflect regulatory processes. The assignment of INNs should be independent of the regulatory process or of considerations of prescribing interchangeability or the use of INNs in pharmacovigilance. It was agreed that the term "biological" is scientific in nature whereas the term "biosimilar" is a regulatory and legal route for licensing, and the two should be clearly differentiated. Thus, it was recommended that no distinctive designation to indicate the regulatory term biosimilar be built into the INN for these products. Instead, it was proposed that INN policy for naming biosimilars be the same as that for stand alone biologicals. However, there was a need to explain clearly to stakeholders the scientific basis for assigning INNs and their purpose, as well as the limitations of this nomenclature for biologicals.

It was acknowledged that although INNs served as a useful tool in worldwide pharmacovigilance, for biologicals they should not be relied upon as the only means of product identification, nor as the sole indicator of product interchangeability. In the past, some member states had found it useful to add biological product identifiers in labeling which indicated, for example, the nature of the host cell used in production. There was full agreement that, for biologicals in general and biosimilars in particular, decisions on interchangeability should be the responsibility of a national regulatory authority and based on appropriate scientific and clinical data, not simply on the basis of INNs. Likewise, for pharmacovigilance purposes, biological product identification should include in addition to the INN and additional indicators such as manufacturer's name and lot number.

The present practice of applying for an INN relatively early in product development was considered a limitation in granting INNs for biologicals. Not all of the detailed data on product characterization or pharmacological activity might be available at that time to enable the WHO INN Expert Group to make an informed judgment. It was agreed that

the timing of INN application submissions for biologicals and the amount of data needed for these applications was worthy of further consideration by the WHO INN Expert Group.

Discussion of possible approaches to INN policy for biosimilars, led to a discussion of the challenges of naming biologicals in general. It was acknowledged that there were anomalies in the present system which was established many years ago, and the consultation recommended that the whole INN policy for biologicals be revisited to ensure consistency of approach. It was appreciated that the different classes of biologicals, such as non-glycosylated and glycosylated proteins, may need product specific approaches. However, because of difficulties in defining differences in post translational modifications such as glycosylation or phosphorylation, and the fact of batch to batch variation, meeting participants acknowledged the limitations of INNs for biologicals for regulatory purposes. It considered the level of detail required to fully describe a biological product was not easily, if ever, achievable. Whilst there was interest in an alternative simplified nomenclature scheme, whereby an INN for a protein product would be based simply on a combination of the amino acid sequence and other major structural features affecting activity, such as presence or absence of glycosylation, no agreement was reached other than that this proposal should be considered by the WHO INN Expert Group along with other possibilities. Because these discussions extended beyond biosimilars to biologicals in general, it was agreed that general discussion on INN policy for biologicals was needed. The present consultation was not the place to discuss the details of any new scheme for dealing with INNs for biologicals. However, it was recommended that a new policy should not be applied retrospectively to those classes of biological products for which the present approach had been used but again it was agreed that this issue should be discussed at the WHO INN Expert Group.

## Recommendations

### To the WHO INN Expert Group

- 1) INNs should be based, as now, on considerations of molecular characteristics and pharmacological class. No specific process should be introduced for naming biosimilars. INNs for these products should be assigned according to the standard process for naming biologicals. There should be no change in policy and no distinctive INN designation introduced to indicate a biosimilar product.
- 2) An in depth review of the current policy for naming and defining biologicals should be undertaken to further ensure consistency of approach and identify anomalies. Any new policy should not be applied retrospectively.
- 3) Consideration should be given to new approaches to developing nomenclature for biologicals so as to better deal with future products. The simplified nomenclature system discussed for dealing with proteins and their post translational modifications should be one new proposal for consideration. Other proposals included the publication of the full

amino acid sequence of a product together with any modifications in order to define unambiguously the product.

4) Consideration should be given to the timing of application submissions for new INNs for biologicals, and to the amount of information needed to make an informed decision on the issue.

5) The WHO INN Expert Group should develop a clear message explaining the process of assigning an INN and the intended purpose of this nomenclature, as well as its limitations for biologicals.

#### To the Expert Committee on Biological Standardization

6) When developing regulatory guidance for biosimilars, mention should be made of INN policy for biologicals and biosimilars. However, it should be explained that INN policy relates solely to nomenclature and that no distinctive INN designation is introduced to indicate a biosimilar product.