

# POLICY POSITION ON NAMING OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

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**IFPMA**  
International Federation of Pharmaceutical  
Manufacturers & Associations



## **POLICY POSITION ON NAMING OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS<sup>1</sup>**

**This is a joint position statement of the innovative biotechnology and pharmaceutical industry associations<sup>2</sup>:  
BIO, EBE, EFPIA, EuropaBio, IFPMA, and PhRMA**

### **Executive Summary**

We recommend that the World Health Organization revise the nomenclature system for International Nonproprietary Names (INNs) to assign distinct INNs to each biotechnology-derived therapeutic protein produced by different manufacturers to accommodate the acknowledged complexity of protein medicinal products and best meet the WHO Objectives for INNs to facilitate safe prescription and dispensing of medicines and preserve patient safety. All therapeutic biotechnology medicines, innovative and biosimilar (also known as follow-on biologics or follow-on protein products), should be assigned distinct INNs to ensure “clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.”<sup>3</sup> Under current WHO policy, there is ambiguity inherent in the INN naming conventions for a biotechnology-derived therapeutic protein, insofar as it specifies only the class of proteins to which the active ingredient belongs and not the specific active ingredient. To fulfill WHO’s objectives, the WHO’s INN policy for biological products should take into account the impact of different manufacturing processes on the active ingredient and the customs and practices with respect to the use of INNs in prescribing and dispensing (rather than the desired role of INNs).

We recommend that the current INN system be updated, so that each biotechnology-derived therapeutic protein produced by a given manufacturer be given a name composed of a common stem with a unique qualifier, to maintain the class identity while indicating the unique nature of the active ingredient. The unique qualifier could be, for example, numeric or alphabetic.

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<sup>1</sup> This position addresses therapeutic proteins and polypeptides, their derivatives, and medicinal products of which they are components, e.g., conjugates. These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

<sup>2</sup> See Appendix for information about our organizations

<sup>3</sup> WHO, Guidance on INN, *available at* <http://www.who.int/medicines/services/inn/innquidance/en/index.html>.

## **Introduction—Why re-examine INNs for Biologics now?**

The current WHO INN system was designed to accommodate small-molecule medicines and their generic copies. The significant advances of the biotechnology industry – which brings with it the development of biotechnology-derived therapeutic protein products of the same class by multiple innovators and the advent of biosimilars – calls for an update to the existing nomenclature system with respect to the nature and function of INNs issued by the WHO for biotechnology-derived therapeutic proteins.

The re-evaluation of an appropriate naming policy for biotechnology-derived therapeutic proteins is timely because of the WHO “Review of International Nonproprietary Names (INN) for Biological and Biotechnological Substances” and the introduction of similar biological medicinal products, “biosimilars”, in the European Union (EU) and elsewhere.

The policy for naming of follow-on biotechnology-derived therapeutic proteins, innovative and biosimilar, is integrally related to physician prescribing and choice of medication, as well as pharmacovigilance, with both public health and individual patient safety implications. It is important to note that aspects of these issues do not uniquely apply to biosimilars, but to all biotechnology-derived therapeutic proteins. The Committee for Medicinal Products for Human Use (CHMP) noted in October 2005, for example, that “there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products,” and that “in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”<sup>4</sup> As more and more innovative biotechnology products reach the market, and as the European Commission (EC) and other jurisdictions begin to approve biosimilar medicinal products, some of which may lack distinguishing brand names, the need for a standardized, global naming policy has become acute.

The innovative pharmaceutical and biotechnology industry supports a policy position of distinct naming, under which each biotechnology-derived therapeutic protein would be distinctly identified by name in prescribing and dispensing, because it furthers patient safety while satisfying WHO objectives for the INN system. A policy of distinct naming would effectively differentiate between proteins with different (or potentially different) clinical profiles. This would enable physicians to prescribe one specific protein within a class, or another, based on the medical needs of the patient and the particular profile of the protein in question. Use of a distinct name would also establish a trigger for the pharmacist to communicate to the physician should a different product be dispensed. In

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<sup>4</sup> Guideline on Similar Biological Medicinal Products (CHMP/437/04) (Oct. 30, 2005).

the event of an adverse reaction with a particular protein, distinct names would enable the physician to tailor his prescribing appropriately. A policy of distinct naming would also ensure that adverse events associated with only one of the complex protein products in a class would be linked to the correct protein and, if needed, enable public health authorities to identify the particular patients to whom that protein (and not any other in the class) was dispensed. In short, distinct INNs for biotechnology-derived therapeutic proteins play an important role in informed and effective medical practice, in effective pharmacovigilance, and in protecting and promoting the public health. Furthermore, implementation of the proposed policy is feasible and would ensure patients and physicians have meaningful access to approved biosimilars.

By best satisfying the principles above, a policy of distinct naming also best satisfies the objectives of the INN system: clear identification of products, safe prescription and dispensing of medicines to patients, and effective communication and exchange of information among health professionals.

### **Rationale for an updated INN policy for Biotech-Derived Therapeutic Proteins**

#### **The INN for a complex protein is inherently ambiguous, unlike the INN for a small molecule drug.**

The INN for a small molecule drug effectively states the exact molecule that is the drug's active ingredient. But complex proteins can exhibit inherent microheterogeneity, due to differences in starting materials (especially, different cell lines), manufacturing processes, and other factors, which cannot be fully described by current analytical technology. Due to differences in manufacturing processes and in analytical methods and equipment, each biotechnology-derived therapeutic protein product must have its own unique specifications<sup>5</sup>. Additionally, regulators have recognized that "direct comparison of the active substance in the similar biological medicinal product to a publicly available standard as a reference (i.e., Ph.Eur., WHO, etc) is not appropriate to demonstrate comparability of the active substance, since this material may not have known and defined safety and efficacy profiles." Thus, compendial standardization of biotechnology-derived therapeutic proteins is not possible as for chemical entities<sup>6</sup>. As a result, the INN for a biotechnology-derived therapeutic protein can describe only the class of proteins to which the active ingredient belongs and not the exact active ingredient. Thus, under the current INN framework, an INN cannot precisely identify a complex protein in the same

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<sup>5</sup> ICH Q6B, Section 3.0

<sup>6</sup> EMEA CHMP 49348/2005, section 5.1

way that it can a small molecule drug. The WHO should therefore amend and update its INN policy for biotechnology-derived therapeutic proteins so that a product's INN identifies its protein class *and* differentiates it from other products in the class made by different manufacturers. This amendment to the INN policy would make the system unambiguous for biologic products, in the same way that it is currently unambiguous for small molecule drugs.

**The WHO's INN policy should take into account the customs and practices with respect to INNs, rather than the desired (or original) role of INNs.**

It has been suggested that INNs were originally conceived as a system for identifying and cataloging pharmaceutical substances and their active ingredients. While this may have been the goal of INNs in 1953, the WHO itself now recognizes their pivotal role in drug prescribing and dispensing. In 2001 comments to WIPO, for example, the WHO claimed the INN system was established in large part to provide health professionals with a clear identification mechanism for the safe prescription and dispensing of medicines to patients.<sup>7</sup> The WHO 1997 "Guidelines on the Use of International Nonproprietary Names (INNs) For Pharmaceutical Substances" similarly explains that the INN is "important for the clear identification, safe prescription, and dispensing of medicines to patients."<sup>8</sup> The WHO has even encouraged the use of INNs to facilitate generic drug use. For example, in a 1993 resolution, the 46th World Health Assembly "acknowledging with satisfaction the increasing contribution of generic products to national drug markets" specifically requested that Member States "enact rules or regulations" to ensure that INNs are used in labeling and advertising and that they "encourage" manufacturers to use INNs when promoting and marketing "multisource products introduced after patent expiration."<sup>9</sup>

Although INNs may not have been intended in the 1950s as a means of communicating interchangeability, INNs have been adopted into the medicine approval and pharmacy laws and practices of many countries participating in the WHO. Although determinations about product interchangeability should be based on scientific data and evaluated by regulators, not the INN Expert Committee, as a result of the current use of INNs, the INN has become the basis for interchangeability decisions in many advanced and less advanced regulatory systems. To ensure that interchangeability determinations instead rest exclusively and unambiguously with regulatory authorities, products that may not contain the identical drug substance (*i.e.*, biotechnology-derived therapeutic proteins) should be assigned different INNs. Moreover, pharmacovigilance structures in the many WHO member states permit reporting by INN. To ensure

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<sup>7</sup> See <http://www.wipo.int/amc/en/processes/process2/rfc/rfc3/comments/msg00058.html>.

<sup>8</sup> See [http://whqlibdoc.who.int/hq/1997/WHO\\_PHARM\\_S\\_NOM\\_1570.pdf](http://whqlibdoc.who.int/hq/1997/WHO_PHARM_S_NOM_1570.pdf).

<sup>9</sup> WHA 46.19 Nonproprietary names for pharmaceutical substances.

that emerging safety data are ascribed to the correct product, products that may not contain the identical drug substance (*i.e.*, biotechnology-derived therapeutic proteins) should be assigned different INNs. Assignment of a common stem to similar proteins allows class-related pharmacovigilance data to be collected, while the distinct identifier permits effects from a single product to be collected and correctly ascribed to that product and not the others in that class.

Currently, all biotechnology-derived therapeutic proteins marketed in the United States and in the European Union can be distinctly identified by their brand name. But biosimilars have already been approved in the EU and other jurisdictions and more are soon likely to be approved. These biosimilars may not carry a brand name and could be identifiable only by their INN, which under the current naming policy will be the same for all products within that class of complex proteins.

The ambiguities, and potential health and safety consequences, of the current INN system for biotechnology-derived therapeutic proteins may be magnified in countries with less developed regulatory systems, which rely to an even greater extent on the INN for making prescribing and dispensing policies and for pharmacovigilance.

We strongly urge the WHO to act now and not to wait for further investigation on this issue or for a public health crisis stemming from inappropriate substitutions or additional pharmacovigilance failures. Instead the WHO should take the proactive and public-health-protective approach of ensuring that every biotechnology-derived therapeutic protein bears an INN that specifies its product class and differentiates itself from other proteins in the same class.

## **Summary**

Each biotechnology-derived therapeutic protein produced by a given manufacturer should be given a name composed of a common stem with a unique qualifier to maintain the class identity while indicating the unique nature of the active ingredient. The unique qualifier could be, for example, numeric or alphabetic.

## Appendix—About Our Organizations

### **BIO**

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. For more information, please visit our website at: [www.bio.org](http://www.bio.org)

### **EBE**

European Biopharmaceutical Enterprises (EBE) represents research-based biopharmaceutical companies of all sizes operating in Europe. EBE promotes a favourable scientific, business and regulatory environment that allows biopharmaceutical companies operating in Europe to successfully research, develop and market new healthcare solutions derived from biotechnology for the benefits of patients and society. EBE has 65 member companies including large pharmaceutical corporations, biotech companies and SMEs, and it operates as a specialised group of EFPIA. For more information, please visit our website at: [www.ebe-biopharma.org](http://www.ebe-biopharma.org)

### **EFPIA**

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represent the pharmaceutical industry operating in Europe. Through its direct membership of 30 national associations and 46 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 2,100 companies committed to researching, developing and bringing to patients new medicines that improve health and the quality of life around the world. The EFPIA overall objective is to improve the competitiveness of the pharmaceutical industry in Europe by setting up a regulatory and political environment, which above all stimulates R&D and rewards innovation. For more information, please visit our website at: [www.efpia.org](http://www.efpia.org)

### **EuropaBIO**

EuropaBio, the European association for Bioindustries, is the voice of biotechnology industry in Europe. EuropaBio has 70 corporate members operating worldwide, 12 associate member organisations, 2 bioregions and 24 national biotechnology associations representing some 1800 SMEs involved in research and development, testing, manufacturing and distribution of biotechnology products. For more information, please visit our website at: <http://www.europabio.org>

**IFPMA**

The International Federation of Pharmaceutical Manufacturers & Associations is the global non-profit NGO directly representing twenty-six research-based pharmaceutical, biotech and vaccine companies and sixty national industry associations in developed and developing countries. The industry's R&D pipeline contains hundreds of new medicines and vaccines being developed to address global disease threats, including cancer, heart disease, HIV/AIDS and malaria. The IFPMA Clinical Trials Portal ([www.ifpma.org/clinicaltrials](http://www.ifpma.org/clinicaltrials)) and the IFPMA Health Partnerships Survey help make the industry's activities more transparent. The IFPMA strengthens patient safety by improving risk assessment of medicines and combating their counterfeiting. It also provides the secretariat for the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and functions as the industry interface with WHO. For more information, please visit our website at: [www.ifpma.org](http://www.ifpma.org)

**PhRMA**

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the United States' leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated \$39.4 billion in 2005 in discovering and developing new medicines. Industry wide research and investment reached a record \$51.3 billion in 2005. For more information, please visit our website at: [www.phrma.org](http://www.phrma.org)