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IFPMA Proposal to the WHO INN Expert Group: Principles for Naming of New Monoclonal Antibodies

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IFPMA Biologicals and Vaccines' Biotech Working Group members have developed the following key principles* on the naming of "new" monoclonal antibodies for the WHO 46th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances which will be held on April 1-3, 2008.

The accompanying presentation is posted at: <http://www.ifpma.org/Issues/Biologicals/>

1. The naming convention for monoclonal antibodies should follow the same policy as established for all glycoproteins. Thus, protein drug substances (including Mabs) with **differences in amino acid sequence** should always have different INNs.
2. IFPMA proposes to continue the use of the **common stem –mab** for monoclonal antibodies. For antibody fragments (such as Fab fragments), the use of –fab instead of –mab might be considered.
3. An **invented part** of the INN is still considered necessary. IFPMA proposes that WHO makes efforts to provide related names for Mabs directed against the same molecular target (although these Mabs nevertheless may differ in amino acid sequence, epitope specificity, immune effector functions, binding constants, etc.).
4. Consistent with the naming conventions for other glycoproteins, it is mandatory that **differences in post-translational modifications** (for example, but not limited to, the glycosylation pattern) are indicated in the INN of Mabs. This might be done using designators (e.g., Greek letters, details to be decided by WHO) as for other glycosylated proteins. This requirement is justified scientifically since it has clearly been shown that differences in glycosylation (e.g., fucosylation, galactosylation, sialylation) influence immune effector functions and thus may have an impact on clinically relevant properties. Consequently, Mabs with identical amino acid sequence but different glycosylation pattern have to be considered different drug substances and therefore should have different INNs.
5. At the time of INN application it may not yet be clear whether modification (e.g., glycosylation) is identical or different, monoclonal antibodies **made independently** (i.e., by different manufacturers using different processes) should generally obtain **distinct INNs**. These distinct INNs should have the same stem but include different designators or identifiers. It should be noted that this policy in practice will only be efficient if WHO and the drug regulatory authorities agree to make it **mandatory** for the second manufacturers to present their substances to WHO and apply for a distinct INN.
6. Generally, the INNs should contain information on the "**pharmacological class**" of the substance. Until now, this has been done for Mabs by including a sub-stem for the "disease or target" class. However, targeted therapies such as monoclonal antibodies often address **biological mechanisms** (and molecular targets) which may be involved in more than one indication or disease. Therefore, it is likely (and already reality in some cases) that Mab drug substances will be used in more than one disease (e.g., cancer and inflammatory diseases). While it is recognized that information on the disease is

* Please note that the order does not reflect importance.

useful for the physician, IFPMA believes that WHO should discuss whether it is appropriate to include information on the disease, or rather on the molecular target (e.g., CD20, HER-2, etc.) in the INN.

7. IFPMA does not believe that more detailed information on the **mechanism of action** (e.g., inhibitory, stimulatory, etc.) has to be part of the INN to avoid too much complexity of the names. This information should rather be part of the substance description. However, this should be left to WHO's discretion.
8. Specific information for which subtype of disease (e.g., **kind of tumour**) an antibody drug substance is used (e.g., colon, testis, ovary, etc.) is not useful because many Mabs in oncology may be used for several tumour types. Naming according to the first indication (which often will turn out not to be the most important) would be misleading. IFPMA proposes to remove this information from the INN.
9. In order to simplify the INNs for Mabs, IFPMA also considers INN differentiation dependent on the "**source of product**" (human, mouse, chimeric, humanized, etc.) no longer necessary. On the one hand, this distinction is scientifically questionable due to the fact that there are emerging approaches to design Mab sequences *in silico*, in order to reduce immunogenicity, for removal of T-cell epitopes; the resulting Mabs can neither be classified "murine" nor "chimerized", "humanized", or "human". The same in principle applies for Mabs generated by e.g. phage display. This type of information should be part of the description of the substance rather than the INN.
10. Distinct names should be assigned to **derivatives of antibodies** including e.g. bi-specific antibodies, antibody-peptide or antibody-toxin conjugates, and radio-labelled antibodies. INNs for conjugates might be composed (e.g. as two separate words) from the names assigned to the individual components. In accordance with the naming policy for other pegylated proteins, pegylated Mabs and Fabs should obtain the prefix "peg-". Differences in conjugation (e.g., site of modification, conjugate chemistry, linker chemistry, chain length of polymer, etc.) would require differentiation as for other types of modification. As far as possible, the naming of antibody conjugates should follow the naming convention applied to non-antibody conjugates.
11. **Fusion constructs** containing parts of an immunoglobulin molecule genetically fused to another sequence have to be treated as a new protein and should obtain individual INNs. WHO should discuss whether it is more appropriate to follow the policy for Mab naming, or for non-antibody proteins in these cases.

About IFPMA:

Established in 1968, International Federation of Pharmaceutical manufactures and Associations (IFPMA) is the global non-profit, non-governmental organization representing research-based pharmaceutical, biotech and vaccine manufacturers as well as more than 60 national/regional pharmaceutical industry associations in the world.

Naming proposal presented here is endorsed by the members of the IFPMA Biotech Working Group, including 20 companies and 2 regional and 3 national associations located in Europe, Japan and USA. For more information, please visit the biologicals issues and insights at <http://www.ifpma.org/Issues/Biologicals/>

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