

***International Nonproprietary Names (INN) Working
Group Meeting on Nomenclature for Monoclonal
Antibodies (mAb)***
Geneva, 6-7 October 2008

Meeting Report

Programme on International Nonproprietary Names (INN)

Quality Assurance and Safety: Medicines (QSM)
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Introduction

The first INN for a mAb, muromonab CD3, was adopted twenty years ago. Following this, the stem *-mab* was proposed and adopted for use for all new INN for mAbs. Between 1991 and 1993 the basis of the INN system for mAbs was devised and developed with the first infixes for source and target of the antibodies being formulated. Since 1998, 173 INN for mAbs have been published and this class of products represents a very high proportion of the total number of INN for biologicals. During this period, there has been a move away from rodent-sequence mAbs to humanized or human mAbs.

The object of this meeting was to review the current situation regarding INN for mAbs and draft recommendations for any necessary modifications to the system.

Requirements for INN for mAbs

INN for mAbs must be unique and unrelated to trade names/trademarks. They must be distinct & transposable into several languages. They need to be convenient for users & it is preferred that they consist of 3 or 4 syllables. INN are intended to provide information concerning the mAbs e.g. to physicians and pharmacists.

Linguistics with INN for mAbs can be very problematical. Many groups of INN are very over-crowded and many look and sound similar. This is made more complex by the need to include systems for pegylated mAbs and for radiolabelled mAbs. mAb conjugates use a second word for the non-mAb part. The length of the words and stems has led to clumsy, long INN when compared to INN for other classes of biologicals and chemicals. The need to adopt INN for an ever increasing number of mAb products is causing INN to become ever longer. At present 52 have 4 syllables, 99 have 5 syllables and 5 have 6 syllables and this trend towards very long names is increasing. The clinical success rate for mAbs is relatively low compared with other products, which results in many adopted INN finally not being needed, at least as names for approved products.

Usage, stems and sub-stems

The stem *-mab* is well accepted and easily recognized as indicating a mAb. However, several antibody products are fragments, such as Fab or F(ab')₂ and a range of other types of fragments (e.g. minibodies) are being developed. It would be possible to adopt new stems for these e.g. *-fab* but this could cause confusion as several Fab fragments have already been given INN with the *-mab* stem. It is also unclear if *-fab* would be used for all fragments or whether further stems would need to be adopted.

Sub-stems (infixes) which indicate species sequence/structure of mAbs are widely understood and used. They may also include some information on how the mAb may have been produced. Four such sub-stems, *-zu-*, *-o-*, *-u-*, *-xi-* (humanized, mouse, human and chimeric mAbs respectively) have been mainly used, but some eg *-e-*

and *-i-* (hamster and primate mAbs) have never been used. However it is possible that this could change in the future, e.g. as there is current interest in some primate antibodies. It has been proposed to discontinue the use of sub-stems & replace them with syllables indicating the specific targets of the mAbs. However, this would cause discontinuity with the existing INN and ignores any need to consider the species origin of the sequence of mAbs.

Sub-stems for disease/target are less well known and useful. The target sub-stems – *li-* (immunomodulatory) & *-tu-* (tumour), have been mostly used, 48 as *-li(m)-* and 50 as *-tu(m)-*, followed by *-vi(r)-*; others have much lower usage. Specific tumour sub-stems (other than *-tu(m)-*) have been used little and some have never been used. In many cases it is possible to select more than one sub-stem for a particular mAb. It may be necessary to introduce new target-related sub-stems for some types of antibodies e.g. bispecific mAbs.

Post-translational modifications: implications for INN

MAbs undergo post-translational modifications which are dependent on the expression system used for production. Most of these do not significantly affect clinical use, but some can influence pharmacokinetics and/or immunobiological functions. In particular, glycosylation can, in some cases, be necessary for optimal clinical activity. Nearly all mAbs are glycosylated, and show expression system and production process related glycan structures. Glycosylation sites are present in the Fc region and sometimes also in the Fab part of the mAb. Differences in glycosylation of MAbs can be introduced deliberately (by glycoengineering) or occur unintentionally because of differences in manufacturing processes. Products are 'mixtures' containing different glycoforms & are not all of one homogeneous glycoprotein structure. Different batches of a product can vary in microheterogeneity and, in addition, modification to production processes can result in changes in glycosylation pattern (and other post-translational modifications). Significant clinical effects of glycosylation may need to be reflected in INN.

Although most mAbs are glycosylated, INN for them have not been given terminal Greek letters as has been done for some other glycoproteins (e.g. hormones). However, the possibility exists that two or more mAbs could be produced which have the same amino acid sequence, but differ in glycosylation. To introduce terminal Greek letters for all new INN could cause confusion and discontinuity with existing INN. At present all existing INN for mAbs relate to mAbs with different amino acid sequences. If future INN applications are received for mAbs with the same sequence as an existing mAb, but different glycosylation, the INN for the later application could be the existing INN but with a terminal beta added. Subsequent Greek letters could be used for further INN for mAbs with this antibody sequence, as for other glycoproteins. However, concern was raised that the use of Greek letters to denote any difference in glycosylation could lead to product specific INN which would

undermine the non-proprietary nature of the INN. Nevertheless this is consistent with the INN policy for recombinant DNA derived proteins.

Definitions

The INN cannot possibly fully describe all the characteristics of a mAb. The description/definition should be the source of detailed information concerning the mAb. Definitions are very important but some are very complicated & detailed. They should consist of two parts, one general & easy to follow & the other more detailed. The definition is linked to the amino acid sequence.

Applicants will need to be asked to provide the required information for the definition as well as details on glycosylation etc. The details of the type of information needed are available e.g. on the INN application form. The correct amino acid sequence must be included in this. The clone name should also be included, but not in the general definition. If mAbs contain a glycosylation site, then they will normally be glycosylated. If the mAb is glycoengineered, this should be indicated in the definition.

Other matters

Information relating to details of structure (which must be provided by the manufacturers/applicants) is crucial for deciding on an appropriate INN. It is up to manufacturers to approach WHO for INN. Regulators should request companies to apply for an INN. They are also responsible for checking and validating if an INN is correctly used and corresponds to the substance which is the subject of a Marketing Authorization.

Companies should apply for an INN when clinical evaluation begins. INN are needed for a product at this stage, as alternative means of identification e.g. using manufacturer's codes, are very confusing.

Many mAbs reach, but fail at phase 3. This is late in the evaluation process, when they will almost certainly have an INN. This accounts for the many INN which exist for clinically failed mAbs.

Recommendations

The present system needs some modification. It needs some revision & improvement to deal with specific problems. However, it has been used successfully for 20 years and so changes should be carefully considered and implemented only where they are necessary.

The stem *-mab* should be retained. Also *-mab* is to continue to be used for mAb fragments. The description should clearly indicate if the product is a fragment.

The system for conjugates & radiolabelled mAbs need not be changed.

The stem *-mab* is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

The prefix *peg-* can be used for pegylated mAbs, but this should be avoided if it leads to over-long INN. In most cases, it is best to adopt two-word INN for pegylated mAbs, with the first word describing the mAb and the second being *pegol*. This is consistent with INN for other pegylated substances.

The use of sub-stems is valuable, but possibly too complicated. The 'source' sub-stem should be kept, but redefined as 'the species on which the immunoglobulin sequence of the mAb is based'. The 'tumour group' sub-stem should be simplified to *-tu(m)-*, the other tumour sub-stems should be discontinued. But *-tu(m)-* should be truncated to *-t-* or *-tu-*. Similarly *-li(m)-* should be truncated to *-m-* or discontinued & replaced with more precise sub-stems, which relate to the target. Also the other sub-stems for 'disease or target' should be shortened, e.g. *-fung-* to *-f-* etc.

The use of Greek terminal letters to indicate e.g. differences in glycosylation cannot be introduced retrospectively. However, mAbs which have the same amino acid sequence but different glycosylation may need distinct INN, unless significant differences on post-translational modifications are excluded /disproven. Particularly, if the glycosylation has been glycoengineered to produce a different structure, then the glycoengineered mAb should be given a different INN to the parent mAb.

When the antibody is directed against a toxin, the infix *-toxa-* can be used in the name. For monoclonals conjugated to a toxin, the suffix *-tox* can be used in the second word. This will be clarified in the mAB naming rules.