International Nonproprietary Names (INN) for monoclonal antibodies: an evolving nomenclature system

Sofia S. Guimaraes Koch[a*], Robin Thorpe[b], Nana Kawasaki[c], Marie-Paule Lefranc[d], Sarel Malan[e], Andrew Martin[f], Gilles Mignot[g], Andreas Plückthun[h], Menico Rizzi[i], Stephanie Shubat[j], Karin Weisser[k] and Raffaella Balocco[a]

[a] *INN Unit, WHO, Geneva, CH-1211, Switzerland*

[b] *Welwyn, UK*

[c] *Yokohama City University, Yokohama, Japan*

[d] *Institut Universitaire de France, Université de Montpellier, Laboratoire d'ImmunoGénétique Moléculaire LIGM, Institut de Génétique Humaine IGH, UMR9002 CNRS-UM, Montpellier, France*

[e] *School of Pharmacy, University of the Western Cape, Bellville, South Africa*

[f] *Institute of Structural & Molecular Biology, Division of Biosciences, University College London, London WC1E 6BT, United Kingdom*

[g] *Nice, France*

[h] *Department of Biochemistry, University of Zurich, Zurich CH-8057, Switzerland*

[i] *Department of Pharmaceutical Sciences, University of Piemonte Orientale, Novara, Italy*

[j] *United States Adopted Names (USAN) Program, Chicago, USA*

[k] *Paul-Ehrlich-Institut, Langen, Germany*

[*] *sofiad@who.int*

International Nonproprietary Names (INN) for monoclonal antibodies: an evolving nomenclature system

Abstract : Appropriate nomenclature for all pharmaceutical substances is important for clinical development, licensing, prescribing, pharmacovigilance, and identification of counterfeits. Nonproprietary names that are unique and globally recognized for all pharmaceutical substances are assigned by the International Nonproprietary Names (INN) Programme of the World Health Organization (WHO). In 1991, the INN Programme implemented the first nomenclature scheme for monoclonal antibodies. To accompany biotechnological development, this nomenclature scheme has evolved over the years; however, since the scheme was introduced, all pharmacological substances that contained an immunoglobulin variable domain were identified with the stem -*mab*. To date, there are 879 INN with the stem -*mab*. Owing to this high number of names ending in -*mab*, devising new and distinguishable INN has become a challenge. The WHO INN Expert Group therefore decided to revise the system to ease this situation. The revised system was approved and adopted by the WHO at the 73rd INN Consultation held in October, 2021, and the radical decision was made to discontinue the use of the well-known stem -*mab* in naming new antibody-based drugs and going forward, to replace it with four new stems: -*tug*, -*bart*, -*mig* and -*ment*.

Keywords: International Nonproprietary Name (INN), nomenclature scheme, safety, pharmaceuticals, biologics, biological drugs, antibodies, therapeutic antibodies, antibody based drugs, antibody drug conjugates

List of abbreviations:

ADC	antibody-drug conjugate
CAR	chimeric antigen receptor
CDR	complementarity-determining region
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
Ig	Immunoglobulin
INN	International Nonproprietary Name(s)
mAb	monoclonal antibody
NCL	Nice Classification
rDNA	recombinant DNA
scFv	single-chain fragment variable
U.S. FDA	United States Food and Drug Administration
V_H	variable heavy
V_L	variable light
WHO	Programme of the World Health Organization

Principles of INN classification

In 1953, the World Health Organization (WHO) established the International Nonproprietary Names (INN) Expert Group to assign nonproprietary names that are unique and globally recognized for pharmaceutical substances (chemical or biological). The existence of such an international nomenclature system is important for clear identification, safe prescription, communication and exchange of information for pharmaceutical products among healthcare professionals and scientists worldwide. These unique names, known as INN, have to be distinctive in sound and spelling, be easily-pronounceable and should not be liable to confusion with names classified under class 5 of Nice Classification (NCL) and other common names.[1,2]

INN for pharmacologically and/or structurally-related substances are grouped into classes by sharing the same common "stem". This facilitates the recognition of a similar pharmacological activity and/or structure. Stems are a string of letters that can be used as a prefix, infix or suffix, though most INN stems are suffixes. The suffixes -*ase* for "enzyme" and -*tide* for "peptides and glycopeptides" are examples of biological stems used in INN. A fantasy (meaningless) prefix is added to the stem for identification of individual substances with different structures.[3]

Over the years, the INN nomenclature system has been continuously adapted and revised to encompass scientific developments in drug discovery and clinical practice. The majority of chemical substance classes are identified by a stem only, however there are some stems that also contain infixes, such as -*ast* for "anti-allergic or anti-inflammatory, not acting as anti-histaminics" (e.g. -*lukast*, - *milast* and -*tegrast*), -*tinib* for "tyrosine kinase inhibitors" (e.g. -*brutinib*, -*citinib* and -*metinib*) and *vir* for "antivirals" (e.g. -*asvir*, -*ciclovir* and

-*previr*).[3] With the advent of recombinant DNA biotechnology, many biological substances have been produced which are much larger and have greater complexity and diversity than chemicals. The stem alone was therefore not considered to be sufficiently descriptive for the INN for the majority of biological substances. Thus, the INN nomenclature for most biological substances is based on stems and infix(es) as well as the fantasy prefix.[4]

General INN policies have been formulated for several groups of biological substances. There are some biological groups that do not have an INN, e.g. natural blood products, skin substitutes and traditional vaccines.[5] Conversely, examples of biological groups with clear general policies for assigning an INN are monoclonal antibodies (mAbs), fusion proteins with more than one pharmacologically active component and substances for cell and gene therapy.[4]

Monoclonal antibodies as active pharmaceutical substances

The feasibility and practicality of producing mAbs with predefined specificity was first described by Köhler and Milstein in 1975.[6] The huge clinical potential of these mAbs was clearly apparent. However, problems with efficacy and safety of the early mouse and rat hybridoma-obtained products had to be overcome.

Following much research and development, a monoclonal antibody named Orthoclone OKT3 was approved by the United States Food and Drug Administration (U.S. FDA) in 1986, making it the first monoclonal antibody to be approved anywhere for clinical use in humans.[7] Soon after, the mAb was approved by many other regulatory agencies. Following this, several more hybridoma-derived mAbs from a range of species were approved for therapeutic and *in vivo* diagnostic clinical use. The problems of unwanted immunogenicity and low

immunobiological function of non-human mAbs, when used in human recipients, prompted the production of human mAbs, but this proved technically difficult. As an alternative approach, recombinant DNA (rDNA) technology was initially used to prepare chimeric (e.g. Immunoglobulin G (IgG) with mouse variable domains fused to a human constant region) followed by humanized mAbs (e.g. human IgG with grafted mouse complementarity-determining regions (CDRs)). Later, entirely human sequence mAbs were produced using a variety of technologies, ranging from natural or synthetic libraries of human antibodies (e.g. selected by phage display) to animal species carrying a human immunoglobulin locus (e.g. transgenic mice or rats). These antibodies are then typically expressed as recombinant proteins from eukaryotic cell culture. Many such mAbs have been approved for use in humans and animals for a very broad range of clinical indications.[8]

More recently, a great variety of different antibody-based substances have been produced ranging from small antibody fragments (e.g. single-chain fragment variable (scFv)), or antibody domains (e.g. variable domain of the heavy-chain-only camelid antibodies), to large immunoglobulin fusion constructs (e.g. IgG-2scFv). These constructs can be mono-, bi- or multispecific. An immunoglobulin can also be conjugated to a chemical payload to create an antibody-drug conjugate (ADC) or it can be fused to a protein with appropriate effector functions.

The first INN for a mAb

Following the approval of Orthoclone OKT3, the INN Programme received an INN request for this substance in 1987 with the requested INN “muromonab-CD3”; this reflected the facts that the mAb targets the CD3 complex and the name is an abbreviation of ‘murine monoclonal antibody’. At this time the name muromonab-CD3 was already being widely

used ‘unofficially’ in the medical and scientific literature prior to its submission to the INN programme. Owing to this and despite the fact that numbers and hyphenated constructs are to be avoided according to the *INN General principles for guidance in devising INN for pharmaceutical substances*,[9] the INN Expert Group confirmed *muromonab-CD3* as the INN for this substance.[10] However, it was made clear that this decision would not be considered a precedent for naming future mAbs and no further products were named similarly. The reasoning in the *INN General Principles for Guidance in devising INN for pharmaceutical substances* for avoiding numbers, hyphens etc., is that when used in a medical prescription, or when spoken, they can be easily confused with the dose or frequency of use.[9,11]

The first official INN scheme for mAbs

The clear importance of mAbs as medicinal substances and the receipt of several requests for INN for new mAbs indicated that a formal nomenclature system for monoclonal antibodies was urgently required. However, the creation of a comprehensive, appropriate INN system for monoclonal antibodies was challenging. The assignment of an INN is intended for a dual purpose: first to identify a substance in an unequivocal manner and second to convey information to healthcare professionals regarding the activity of the substance. For mAbs, considering their considerable heterogeneity and diverse properties, the latter was particularly difficult. After in-depth discussion, the INN Expert Group agreed that the general stem for monoclonal antibodies would be *-mab*, and that it would refer to a class of substances which are grouped together based on a common biochemical structure, and this stem would not convey any pharmacological-activity information.

Since the information that the one-syllable stem *-mab* can convey is limited, it was considered necessary to add further information as infixes, as had been agreed for other

groups of substances. It was decided to include two such infixes, one describing the disease context or target class, and a second that would refer to the source from which the antibody was derived, as had been the case for the first mAb given an INN. The first eight INN using this new nomenclature scheme, which was approved at the 21st INN Consultation held in Geneva on April 1991, were *biciromab*, *dorlimomab aritox*, *imciromab*, *maslimomab*, *nebacumab*, *sevirumab*, *telimomab aritox* and *tuvirumab*.[12] Many more were to follow over subsequent years. The scheme was expanded and modified slightly over time as presented in Table 1. The most used infixes *-xi-* and *-zu-* for chimeric and humanized mAbs, respectively, were introduced during this time. For ADCs, the INN is made up of two words, the first for the antibody part following the established unconjugated mAb scheme, and the second for the payload. For instance, for mAbs conjugated to a toxin, the suffix *-tox* is used in the second word (e.g. *dorlimomab aritox*), for mAbs conjugated to a maytansinoid derivative, the stem *-tansine* is used in the second word (e.g. *trastuzumab emtansine*), etc. If the mAb is radiolabelled, the radioisotope is listed first in the INN (e.g. *technetium (^{99m}Tc) nofetumomab merpentan*). This scheme was used up to the 48th INN Consultation held in Geneva on March 2009.[13]

The second scheme for INN for mAbs

The field of monoclonal antibodies continued to evolve rapidly and the INN Programme was receiving an increasing number of mAb requests (Figure 1 and Figure 2). The stem *-mab*, which had originally been intended for 'conventional' mAbs, such as those produced by hybridoma technology, was now increasingly being used for more recently developed, rDNA-produced immunoglobulins with novel formats, as well as antibody fragments and variants with amino acid changes, often divergent from conventional antibodies. By 2009, it

was clear that the definition of the stem *-mab* needed expanding so that it would include all substances that contained an immunoglobulin variable domain that binds to a defined target, whether it was a complete monoclonal antibody, a fragment or another rDNA construct within this definition.

It was also noticed that some infixes were being used very frequently, like the source infixes *-zu-*, *-o-* and *-u-* for humanized, mouse and human, respectively, and the target infixes *-li(m)-* and *-tu(m)-* for immunomodulator and tumor respectively, creating popular suffixes such as *-lizumab*, *-tumomab*, *-tumumab* and *-tuzumab*. However, other infixes were used infrequently or never, e.g. the source infixes *-a-*, *-e-* and *-i-*, for rat, hamster and primate, respectively, and the target infixes *-go(t)-* for tumor (testis) and *-ma(r)-* for tumor (mammary).

This fact, and the issue of the ever-increasing number of applications for substances using the *-mab* stem was making the selection of “user friendly” (i.e. pronounceable) INN very difficult. It was therefore decided to modify the scheme officially to include the new definition of *-mab* as well as shortening some of the commonly used infixes. This latter modification was intended to help with shortening the INN for mAbs and, where necessary, to allow for longer fantasy prefixes. Examples are *-li(m)-* which became *-l(i)-* and *-fung-*, which was shortened to *-f(u)-*. The ‘source’ infix also needed redefining as ‘the species on which the immunoglobulin sequence of the monoclonal antibody is based’, rather than the source from which the antibody was derived, to take account of evolving changes in mAb technology.

Table 2 shows the revised INN nomenclature scheme for monoclonal antibodies implemented in November 2009 and is reflected in the INN for mAbs published subsequently.

Although most monoclonal antibodies are glycosylated, their INN does not include a terminal Greek letter as for other glycoproteins. It was decided that if an INN application was received

for a monoclonal antibody with the same amino acid sequence as an existing INN, but with differences in the glycosylation pattern, a terminal Greek letter, starting from beta, would be added to the later INN, such as for *adalimumab beta*.[14]

The source infix is discontinued

From 2009 to 2015 the INN nomenclature scheme for monoclonal antibodies remained unchanged, however the definitions of ‘chimeric’ and ‘humanized’ were updated in 2011 and 2014 (Table 3).

During this period, the INN Programme received criticisms regarding the designation of the source infix.[15] While at its inception, the source infixes could be derived from how the antibody was constructed, progress in engineering technologies made this distinction increasingly blurred. Therefore, for a time, sequence identity to human was used to assign the infix. In parallel, the source infix was becoming clinically less relevant with no direct correlation between identity to human and safety profile.[16,17] Nevertheless, differences had emerged in the perception of human (*-u-*) *versus* humanized (*-zu-*) *versus* chimeric (*-xi-*) antibodies, leading some manufacturers to use the source infix as a marketing tool. It was claimed that some manufacturers were designing antibodies in a way that would guarantee the adoption of the perceived ‘better’ *-zu-* or *-u-* infix rather than the ‘undesirable’ *-xi-*, or other infixes despite there being several very successful chimeric mAb products, including some ‘blockbusters’.

As there is no scientific basis for considering any infix *per se* superior to any other, this practice was undesirable and not condoned by the WHO INN Secretariat or INN Expert Group. For the reasons noted above and because it was still proving difficult to select clearly distinguishable INN owing to overcrowding of the *-mab* category, the source-infix was discontinued in 2016, although the “source” would continue to be specified in the definition

paragraph of the INN. It was also recommended that the letters ‘u’, ‘o’ and the syllables ‘xi’ and ‘zu’ should be avoided in direct combination with the stem *-mab*, to avoid inconsistencies and conflicts with the previous nomenclature schemes, although these letters could still be used within the random prefix of the INN. Consequently, it was found necessary to alter certain target infixes; for example, the infix *-t(u)-* was discontinued and replaced by *-ta-*. *Table 4* shows the nomenclature scheme for mAbs that was recommended in 2016, and used until the 72nd INN Consultation in April 2021.

Discontinuing the stem “*-mab*” and its replacement with four new stems.

By 2021, the very large number of applications for mAbs, and thus an overcrowding of the name-space of INN with the stem *-mab* (see previous sections) led to adoption of very long names. Additionally, its continued re-definition over its long period of use led to serious reservations concerning its current and future suitability. The meaning of *-mab* was no longer always clear for all stakeholders as it was now being used for a great variety of different structures. These range from small immunoglobulin fragments to large molecules containing multiple antigen binding sites, but often with little similarity to conventional immunoglobulins. It is acknowledged that the stem *-mab* is very well known, easily recognized, and is ‘popular’. To date there are 879 INN ending in *-mab*, and this limits the number of sufficiently distinct future INN which can be created and names that cannot easily be distinguished increases the risk of medication errors.

It was therefore decided to discontinue the use of the stem *-mab* and to divide this group of substances into four different groups, with four brand-new stems, to avoid any confusion between the monoclonal antibodies named according to the old nomenclature and those named according to the new nomenclature. The four new stems cover all the prior uses of stem *-mab*.

From a clinical point of view, for healthcare professionals, classification is useful if it can predict therapeutic activity and/or adverse event profiles. Bispecific antibodies can bind to two different cells, e.g. cancer cells and immune cells such as T lymphocytes. The antibody, by bringing these two types of cells together, thus facilitates the elimination of cancer cells by T lymphocytes. *Blinatumomab* was the first antibody in this class and was authorized in November 2015 for the treatment of acute lymphoblastic leukaemia. Bispecific and multispecific antibodies can also bind to different epitopes on the same cell type or to different soluble factors (e.g. *emicizumab* and *faricimab*).

Within the group of monospecific monoclonal antibodies, various engineering techniques have been developed with the aim of increasing efficacy and reducing undesirable effects, such as immunogenicity. Furthermore, antibody fragments are being developed where the Fc part is neither needed nor desired, e.g. to achieve better diffusion and target access. Taken together, these developments have led to monospecific monoclonal antibodies being split into three distinct subgroups. The four new groups (three monospecific and one bi- and multispecific) are thus designed to map potential clinical correlates of these drug substances.

The four new stems (illustrated by examples in Figure 3) are:[18]

***-tug* for "unmodified immunoglobulins"**

The suffix ***-tug*** is used for monospecific full-length immunoglobulins with unmodified constant regions and identical sets of CDRs and that recognize the same epitope. This includes monospecific full-length immunoglobulins of any species and of any class (IgG, IgA, IgM, IgD, IgE), for which the amino acid sequence of the constant region of the heavy and light chains is encoded by a single naturally occurring allele. However, they may have engineered glycans and/or deleted C-terminal lysine codon (introduced for homogeneity since this is generally clipped *in vivo* and often during expression). Basically this group includes all

natural immunoglobulin molecules (which might occur as such in humoral responses of the immune system, including the Camelidae heavy-chain-only antibodies), as well as chimeric and humanized antibodies. It also includes immunoglobulins that can target multiple different epitopes or molecules, but using identical sets of CDRs.

-*bart* for "<u>art</u>ificial immunoglobulins"

The suffix **-*bart*** is used for monospecific full-length immunoglobulins with engineered amino acid changes in the constant regions and identical sets of CDRs and that recognize the same epitope. This includes monospecific full-length immunoglobulins of any species and of any class (IgG, IgA, IgM, IgD, IgE) that contain any amino acid change introduced by engineering for any reason anywhere in the constant regions: hinge (e.g. IGHG4 hinge with Serine>Proline amino acid change), new glycan attachment site, mixed allelic variants which would not occur in nature, altered complement binding, altered neonatal Fc receptor (FcRn) binding, altered fragment crystallizable (Fc)-gamma receptor binding, stabilized IgA, etc. It also includes immunoglobulins with attachments of further variable domains with identical CDRs and that recognize the same epitope.

-*ment* for "immunoglobulin frag<u>ment</u>s"

The suffix **-*ment*** is used for monospecific fragments of any kind that do not fall under stem -*tug* or -*bart*, containing at least one immunoglobulin variable domain that contributes to binding, and feature a complete, partial or absent constant region (e.g. monospecific immunoglobulin-derived constructs without an Fc domain, scFv-Fc constructs, etc.).

-*mig* for "<u>m</u>ulti-specific <u>i</u>mmunoglobulins"

The suffix ***-mig*** is used for bispecific and multispecific immunoglobulins, regardless of the format (conventional or engineered), type (full or fragments) or shape (extensions or not). This group includes immunoglobulins with a bi- or multi-specificity conferred by different variable domains with different sets of CDRs. It does not include mAbs which have multiple specificities through a single set of CDRs (cross-reactivity, e.g. *bimekizumab*).

Further changes to infixes

Following the radical changes made to the stem(s) detailed above, the suitability and need for the current infixes was also evaluated. Should the precedent of discontinuing the source prefix mentioned above be also applied to the disease/target infix; or should more of the latter be introduced for greater clarity and diversity of INN? The conclusion from this discussion was that some infixes are useful, informative and should be retained, such as *-ba-*, *-fung-*, *-toxa-*, *-vet-* and *-vi-*, but others were less useful and poorly defined (e.g. *-li-* for "immunomodulating"). However, it would be confusing to continue using infixes for some INN, but not for others. It was also acknowledged that some infixes provide an indication of therapeutic utilization and side effects associated with particular types of mAbs, and this is clinically useful.

It was subsequently decided to continue using infixes in the mAb nomenclature scheme, but that they should be well defined, informative and useful. The overused and nebulous infix *-li-* for "immunomodulatory" targets was discontinued and replaced by two new infixes that indicate the direction of the immunological action; *-sto-* for immunostimulatory mAbs and *-pru-* for immunosuppressive mAbs. The infix *-ki-*, which originally identified an interleukin as the target for a mAb was expanded to include all cytokines and cytokine receptors (both membrane bound and soluble forms). The infix *-gro-* was slightly modified and its definition was also expanded; previously it was *-gros-* to identify skeletal muscle mass related growth

factors and receptors, while now it is *-gro-* to identify growth factors and growth factors receptors.

Most infixes used in the new scheme are unchanged from those adopted for the 2016 modified system (Table 5). It is acknowledged that the mechanisms of action of monoclonal antibodies are complex, that it may be different for different indications and that this might not be completely understood during the development phase. Therefore, the disease/target infix is assigned according to the applicant's proposed known mode of action at the time of the INN request.

Antibody-drug conjugates (ADCs)

The class of ADCs will remain and the definitions used in reforming the *-mab* scheme will be applied, with all new mAb-drug applications being named based on the mAb part, using the four new stems, and with the conjugated drug name as the second word, as before.

mAbs as components of fusion proteins

The INN Programme defines a fusion protein as "*a multifunctional protein derived from a single nucleotide sequence which may contain two or more genes or portions of genes with or without amino acid linker sequences. The genes should originally code for separate proteins, with at least two of them endowed with pharmacological action (e.g. action and targeting)*". Such substances can be made up of a great variety of different component structures and can be used for a large array of clinical indications.

The suffix *-fusp* for fusion protein was adopted in 2017. A detailed description of the INN scheme for fusion proteins is beyond the scope of this paper. For further information, see Robertson *et al*.[19].

mAbs or mAb fragments/related substances often comprise parts of fusion proteins. Initially, these were given an INN using the *-mab* stem, but this was soon considered unsatisfactory and replaced by the *-fusp* stem when it was adopted. In the current scheme, fusion proteins containing a mAb component as the targeting moiety are given an *-a-* infix (e.g. *tebentafusp*, *bintrafusp alfa*). Other infixes are used for other components of the fusion protein. Fusion proteins containing IgG Fc are commonly produced to enhance the half-life of the non-IgG component. These substances are given an INN with the *ef-* prefix to indicate the non-targeting Fc component (e.g. *eftrenonacog alfa*).

mAbs as components of substances for cell-based gene therapy

With the advent of new technologies, mAb components can also be present in substances for cell-based gene therapy, as it is the case of chimeric antigen receptor (CAR) T-cell therapies. The CAR construct used in conventional CAR-T cells is composed of an scFv consisting of an antibody variable heavy (V_H) and variable light (V_L) domains. These substances do not follow the INN mAb nomenclature scheme, instead they follow the INN nomenclature scheme for substances for cell-based gene therapy. A two-word name is given to these substances, in which the first word is identified with the suffix *-gene* and refers to the gene component, and the second word is identified with the suffix *-cel* and refers to the cell component. In the specific case of the CAR T-cell therapies named so far, the first word contains the gene infix *-cabta-* for “cell-expressed antibody and T-cell activation” (e.g. *lisocabtagene maraleucel*). A detailed description of the INN scheme for substances for cell-based gene therapy is beyond the remit of this publication. For further information, see Loizides *et al*.[20] and ref. 4.

Engineered or synthetic scaffold proteins with non-immunoglobulin-variable-domain derived binding domains

Recent advances in technology have allowed the production of engineered or synthetic scaffold proteins with non-immunoglobulin-variable-domain-derived binding domains. These engineered non-immunoglobulin-variable-domain scaffolds are not mAbs, but they share the capacity to bind antigens. Although, they are sometimes described as ‘antibody mimetics’, they share little, if any, structural homology with mAbs and their synthesis does not result from a V-D-J gene rearrangement which is the hallmark of the variable domains of the antigen receptors (immunoglobulins or antibodies and T cell receptors). For these types of proteins, the suffix *-bep* has been adopted by the INN Expert Group.

Monoclonal antibodies: Prescribers and patients

A major use of INN is for prescribing. At present, 114 mAbs with approved INN are actively marketed. This represents 13% of the total number of mAbs with an INN. The clinical indications which are suitable for treatment with mAbs are very varied (). The number of mAbs within each clinical group also varies. Several modifications to the INN mAb scheme have been driven at least in part by prescribing issues e.g. division of *-mab* into four groups and subdivision of *-li.*

Conclusions, afterthoughts and future challenges

INN for mAbs have been assigned for many years with few significant unresolvable problems arising and with a broad acceptance in naming. However, the system has required several modifications and adaptations to take account of scientific and technological progress in mAb production and the ever-increasing numbers of applications for such INN in order to

remain useful and practicable. Although some mAbs are very successful products, a few being “blockbusters”, most mAbs having received an INN fail in clinical trials, especially at the phase III stage. Indeed, only around 10-15% of those named have been approved in Europe or the United States. This implies that many INN given for such mAbs are effectively never used clinically as the products they represent never reach the marketing stage. It would be impossible and dangerous to re-use such names, and so they remain assigned, but in ‘limbo’, still being part of over-crowding of the name space, which increases the difficulties of formulating distinctive new INN for mAbs.

It is hoped that the radical new changes to the mAb INN system implemented recently and detailed above, will address this problem and update and improve the INN procedure, and that the present scheme will remain in use for some time. However, the adaptable and flexible approach adopted by the INN Expert group will allow any future necessary modifications to be made with relative ease.

Modifications to INN schemes are not implemented retrospectively. To do so would be confusing and dangerous to drug (or medication) safety and existing INN will remain as they are.

Funding

No funding was received.

Acknowledgments and disclosures

We thank Dr Marjorie Shapiro, US FDA, Center for Drug Evaluation and Research, Dr David Lewis, US FDA, Center for Drug Evaluation and Research, Dr Gail Karet, USAN Program, and Dr Ursula Loizides, INN Unit, WHO, for their helpful comments and contribution to the

discussions. Antibody representations in Figure 3 were generated using abYdraw (Sweet-Jones and Martin, submitted).

The authors report that there are no competing interests to declare.

Table legends:

Table 1: INN mAb nomenclature scheme used up to 48th INN Consultation held in Geneva during March 2009.

Table 2: INN mAb nomenclature scheme adopted at the 49th INN Consultation held in Geneva during November 2009, which includes names published from Proposed INN List 103 up to 117.

Table 3: Definitions of chimeric and humanized antibody.

Table 4: INN mAb nomenclature scheme adopted at the 64th INN Consultation held in Geneva on 4-7 April 2017, which includes names published from Proposed INN List 118 up to 126.

Table 5 INN mAb nomenclature scheme adopted at the 73rd INN Consultation held in Geneva during October 2021.

Figure legends:

Figure 1 Caption: 'The number of published INN through the years: totals, biologicals and monoclonal antibodies..

Figure 1 Alt Text: A clustered column graph plotting the number of total INN, INN for biological substances and INN for monoclonal antibodies published from 1988 until 2021. An increase in the INN for monoclonal antibodies is observed along the years, especially since 2015.

Figure 2 Caption: Percentage of published INN for biological requests and monoclonal antibodies through the years.

Figure 2 Alt Text: A line graph plotting the percentage of published INN for biological substances and for monoclonal antibodies from 1988 until 2021. An increase is observed along the years. In 1988, 7% of published INN were for biological substances and 0.7% were for monoclonal antibodies; in 2021, 52% of published INN were for biological substances and 25% were for monoclonal antibodies.

Figure 3 Caption: Schematic figures of some possible formats that *-tug*, *-bart*, *-ment* and *-mig* stems can have. VH, Variable Heavy; CH1, Constant Heavy 1; CH2, Constant Heavy 2; CH3, Constant Heavy 3; VL, Variable Light; CL, Constant Light; VHH, camelid heavy chain-only; “red dot” and *, modification.

Figure 3Alt Text: Schematic figures of some possible formats that *-tug*, *-bart*, *-ment* and *-mig* stems can have and that are described in the main text.

Figure 34 Caption: Marketed INN for mAbs by target infix.

Figure 4 Alt Text: A pie chart showing the current percentage of marketed INN for monoclonal antibodies by target infix. The immunonodulator class has the highest number of marketed mAbs (39%), followed by the tumour class (29%), cardiovascular class (9%), interleukin class (8%), neural class (4%), bone class (3%), toxin class (2%), viral class (1%) and bacterial class (1%). The remaining 4% are of all other current classes.

References

1. World Intellectual Property Organization. About the Nice Classification. [accessed 2022 Mar 14]. https://www.wipo.int/classifications/nice/en/preface.html.

2. World Intellectual Property Organization. Class 5 of Nice Classification. [accessed 2022 Mar 14]. https://www.wipo.int/classifications/nice/nclpub/en/fr/?class_number=5

3. The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances, WHO/EMP/RHT/TSN/2018.1; Geneva, Switzerland: World Health Organization; 2018. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/stembook-2018.pdf.

4. International Nonproprietary Names (INN) for biological and biotechnological substances (a review), Geneva, Switzerland: World Health Organization; 2019. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/bioreview2019.pdf.

5. Robertson J.S, Loizides U, Adisa A, López de la Rica Manjavacas A, Rodilla V, Strnadova C, Weisser K, Balocco R, International Nonproprietary Names (INN) for novel vaccine substances: A matter of safety. Vaccine. 2022; 40(1): 21-27. doi: 10.1016/j.vaccine.2021.11.054. PMID: 34844820

6. Köhler G, Milstein C, Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975; 256(5517): 495-497. doi: https://doi.org/10.1038/256495a0

7. Ecker DM, Jones SD, Levine HL, The therapeutic monoclonal antibody market. MAbs. 2015; 7(1): 9-14. doi: 10.4161/19420862.2015.989042. PMID: 25529996

8. The Antibody Society. Therapeutic monoclonal antibodies approved or in review in the EU or US. [accessed 2022 Mar 14]. https://www.antibodysociety.org/resources/approved-antibodies/.

9. International Nonproprietary Names: revised procedure; Geneva, Switzerland: World Health Organization; 2004. [accessed 2022 Mar 14] https://apps.who.int/gb/archive/pdf_files/EB115/B115_11-en.pdf.

10. WHO Drug Information. Vol. 2 (2), List 59 of Proposed International Nonproprietary Names (INN) for Pharmaceutical Substances; Geneva, Switzerland: World Health Organization; 1988. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl59.pdf.

11. Guidance on the use of international nonproprietary names (INNs) for pharmaceutical substances. 2017, Geneva, Switzerland: World Health Organization. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/who-pharm-s-nom-1570.pdf.

12. WHO Drug Information. Vol. 5 (4), List 66 of Proposed International Nonproprietary Names (INN) for Pharmaceutical Substances; Geneva, Switzerland: World Health Organization; 1991. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl66.pdf.

13. WHO Drug Information. Vol. 23 (4), List 102 of Proposed International Nonproprietary Names (INN) for Pharmaceutical Substances; Geneva, Switzerland: World Health Organization; 2009. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl102.pdf.

14. WHO Drug Information. Vol. 31 (4), List 118 of Proposed International Nonproprietary Names (INN) for Pharmaceutical Substances; Geneva, Switzerland: World Health Organization; 2017. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl118.pdf.

15. Jones TD, Carter PJ, Plückthun A, Vásquez M, Holgate RGE, Hötzel I, Popplewell AG, Parren PWHI, Enzelberger M, Rademaker HJ, et al., The INNs and outs of antibody nonproprietary names. MAbs. 2016; 8(1): 1-9. doi: 10.1080/19420862.2015.1114320. PMID: 26716992

16. Baker MP, Reynolds HM, Lumicisi B, Bryson CJ, Immunogenicity of protein therapeutics: The key causes, consequences and challenges. Self Nonself. 2010; 1(4): 314-322. doi: 10.4161/self.1.4.13904. PMID: 21487506

17. Schellekens, H., The immunogenicity of therapeutic proteins. Discov Med. 2010; 9(49): 560-564. PMID: 20587346.

18. New INN monoclonal antibody (mAb) nomenclature scheme. INN Working Document 21.531; Geneva, Switzerland: World Health Organization; 2021. [accessed 2022 Mar 14] https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/new_mab_-nomenclature-_2021.pdf.

19. Robertson JS, Chui WK, Genazzani AA, Malan SF, López de la Rica Manjavacas A, Mignot G, Thorpe R, Balocco R, Rizzi M, The INN global nomenclature of biological medicines: A continuous challenge. Biologicals. 2019; 60: 15-23. doi: DOI: 10.1016/j.biologicals.2019.05.006. PMID: 31130314

20. Loizides U, Dominici M, Manderson T, Rizzi M, Robertson JS, de Sousa Guimarães Koch S, Timón M, Balocco R, The harmonization of World Health Organization International Nonproprietary Names definitions for cell and cell-based gene therapy substances: when a name is not enough. Cytotherapy, 2021. 23(5): 357-366. doi: DOI: 10.1016/j.jcyt.2021.02.114. PMID: 33820700

Table 1: INN mAb nomenclature scheme used up to 48th INN Consultation held in Geneva during March 2009.

Prefix	**Infix for source**		**Infix for disease or target class**		**Suffix**
Random	*-a-*	rat	*-ba(c)-*	bacterial	*-mab*
	-axo-	rat-murine hybrid	*-ci(r)-*	cardiovascular	
	-e-	hamster	*-fung-*	fungal	
	-i-	primate	*-ki(n)-*	interleukin	
	-o-	mouse	*-le(s)-*	inflammatory lesions	
	-u-	human	*-li(m)-*	immunomodulator	
	-xi-	chimeric	*-os-*	bone	
	-zu-	humanized	*-vi(r)-*	viral	
			-co(l)-	colon tumour	
			-go(t)-	testis tumour	
			-go(v)-	ovary tumour (gonadal)	
			-ma(r)-	breast tumour	
			-me(l)-	melanoma	
			-pr(o)-	prostate tumour	
			-tu(m)-	miscellaneous tumours	

Table 2: INN mAb nomenclature scheme adopted at the 49th INN Consultation held in Geneva during November 2009, which includes names published from Proposed INN List 103 up to 117.

Prefix	**Infix for the species**		**Infix for target class**		**Suffix**
Random	*-a-*	rat	*-am(i)-*	serum amyloid protein (SAP) / amyloidosis	*-mab*
	-axo-	rat-murine hybrid	*-b(a)-*	bacterial	
	-e-	hamster	*-c(i)-*	cardiovascular	
	-i-	primate	*-f(u)-*	fungal	
	-o-	mouse	*-gr(o)-*	skeletal muscle mass related growth factors and receptors	
	-u-	human	*-k(i)-*	interleukin	
	-vet-	veterinary use	*-l(i)-*	immunomodulator	
	-xi-	chimeric	*-n(e)-*	neural	
	-xizu-	chimeric-humanized	*-s(o)-*	bone	
	-zu-	humanized	*-t(u)-*	tumour	
			-tox(a)-	toxin	
			-v(i)-	viral	

Table 3: Definitions of chimeric and humanized antibody.

	Year	Definition
Chimeric	2009	A chimeric antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable domain of both heavy and light chains linked to heavy and light constant regions of human origin.
	2011	A chimeric antibody is one of which both chain types are chimeric as a result of antibody engineering. A chimeric chain is a chain that contains a foreign variable domain (V-D-J-REGION) (originating from one species other than human, or synthetic) linked to a constant region (C-REGION) of human origin.
	2014	A chimeric antibody is one for which both chain types are chimeric as a result of antibody engineering. A chimeric chain is a chain that contains a foreign variable domain (originating from one species other than human, or synthetic or engineered from any species including human) linked to a constant region of human origin. The variable domain of a chimeric chain has a V region amino acid sequence which, analysed as a whole, is closer to non-human species than to human.
Humanized	2009	A humanized antibody has segments of foreign-derived amino acids interspersed among variable domain segments of human-derived amino acid residues and the humanized variable heavy and variable light domains are linked to heavy and light constant regions of human origin.
	2011	A humanized antibody is one of which both chain types are humanized as a result of antibody engineering. A humanized chain is a chain in which the complementarity determining regions (CDR) of the variable domains are foreign (originating from one species other than human, or synthetic) whereas the remaining chain is of human origin. By extension an antibody is described as humanized if more recent protocols were used for the humanization.
	2014	A humanized antibody is one for which both chain types are humanized as a result of antibody engineering. A humanized chain is typically a chain in which the complementarity determining regions (CDR) of the variable domains are foreign (originating from one species other than human, or synthetic) whereas the remainder of the chain is of human origin. Humanization assessment is based on the resulting amino acid sequence, and not on the methodology per se, which allows protocols other than grafting to be used. The variable domain of a humanized chain has a V region amino acid sequence which, analyzed as a whole, is closer to human than to other species.

Table 4: INN mAb nomenclature scheme adopted at the 64th INN Consultation held in Geneva on 4-7 April 2017, which includes names published from Proposed INN List 118 up to 126.

Prefix	**Infix for target class**		**Suffix**
Random	*-ami-*	serum amyloid protein (SAP) / amyloidosis	*-mab*
	-ba-	bacterial	
	-ci-	cardiovascular	
	-de-	metabolic or endocrine pathways	
	-fung-	fungal	
	-gros-	skeletal muscle mass related growth factors and receptors	
	-ki-	interleukin	
	-li-	immunomodulator	
	-ne-	neural	
	-os-	bone	
	-ta-	tumour	
	-toxa-	toxin	
	-vet-	veterinary use	
	-vi-	viral	

Table 5: INN mAb nomenclature scheme adopted at the 73rd INN Consultation held in Geneva during October 2021.

Prefix	**Infix for target class**		**Suffix**
Random	*-ami-*	serum amyloid protein (SAP)/amyloidosis	*-tug*
	-ba-	bacterial	*-bart*
	-ci-	cardiovascular	*-mig*
	-de-	metabolic or endocrine pathways	*-ment*
	-eni-	enzyme inhibition	
	-fung-	fungal	
	-gro-	growth factors and growth factors receptors	
	-ki-	cytokine and cytokine receptors	
	-ler-	allergen	
	-sto-	immunostimulatory	
	-pru-	immunosuppressive	
	-ne-	neural	
	-os-	bone	
	-ta-	tumour	
	-toxa-	toxin	
	-vet-	veterinary use	
	-vi-	viral	

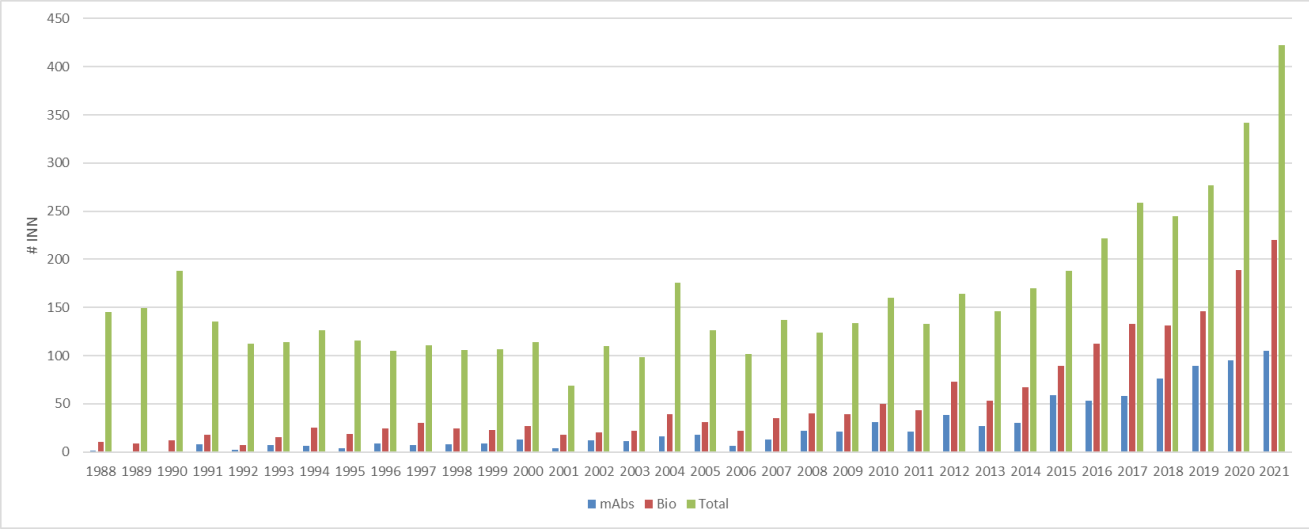

Figure 1: The number of published INN through the years: totals, biologicals and monoclonal antibodies..

Figure 1 Alt Text: A clustered column graph plotting the number of total INN, INN for biological substances and INN for monoclonal antibodies published from 1988 until 2021. An increase in the INN for monoclonal antibodies is observed along the years, especially since 2015.

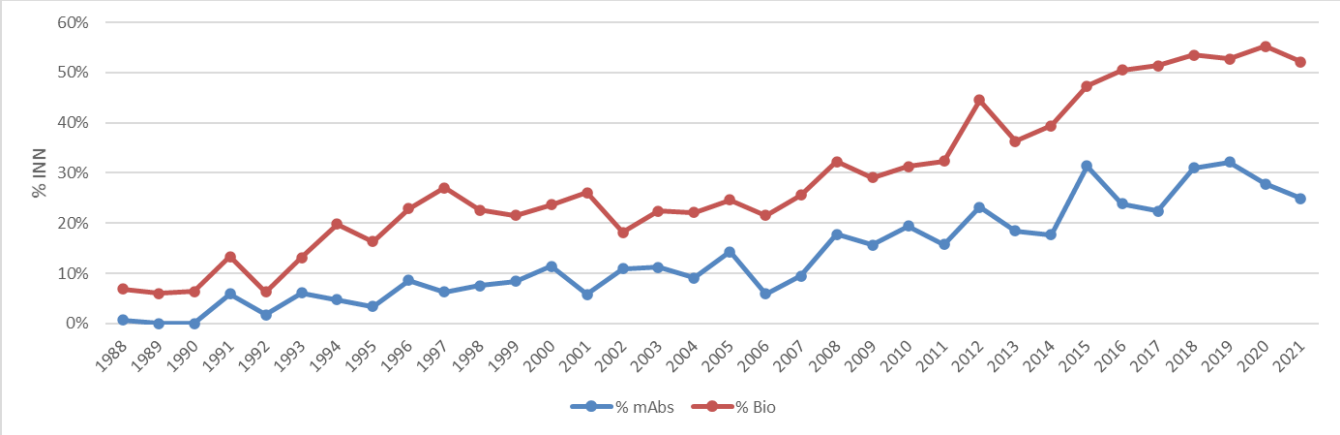

Figure 2: Percentage of published INN for biological requests and monoclonal antibodies through the years.

Figure 2 Alt Text: A line graph plotting the percentage of published INN for biological substances and for monoclonal antibodies from 1988 until 2021. An increase is observed along the years. In 1988, 7% of published INN were for biological substances and 0.7% were for monoclonal antibodies; in 2021, 52% of published INN were for biological substances and 25% were for monoclonal antibodies.

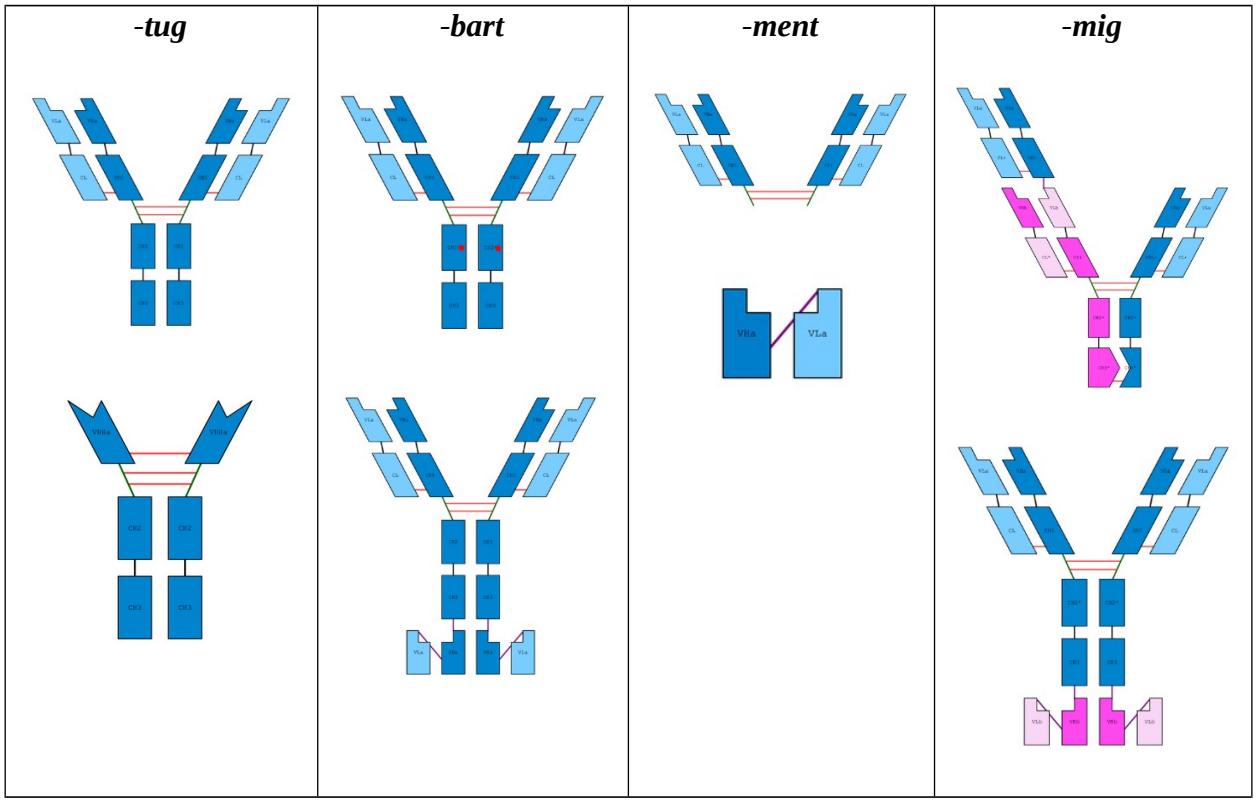

Figure 3: Schematic figures of some possible formats that *-tug*, *-bart*, *-ment* and *-mig* stems can have. VH, Variable Heavy; CH1, Constant Heavy 1; CH2, Constant Heavy 2; CH3, Constant Heavy 3; VL, Variable Light; CL, Constant Light; VHH, camelid heavy chain-only; “red dot” and *, modification.

Figure 3Alt Text: Schematic figures of some possible formats that *-tug*, *-bart*, *-ment* and *-mig* stems can have and that are described in the main text.

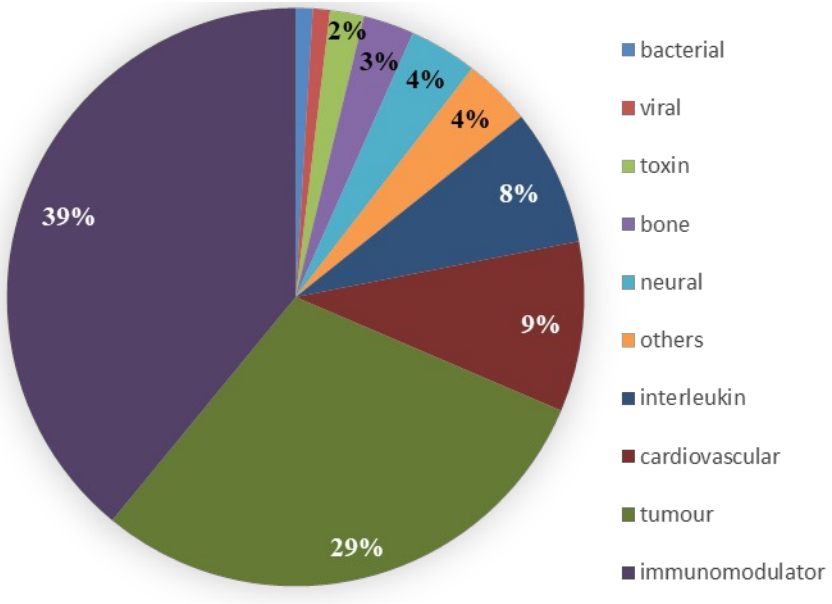

Figure 34: Marketed INN for mAbs by target infix.

Figure 4 Alt Text: A pie chart plotting the current percentage of marketed INN for monoclonal antibodies by target infix. The immunonodulator class is the one with more marketed mAbs with 39%, followed by the tumour one with 29%. Then are the classes of cardiovascular (9%), interleukin (8%), other classes (4%), neural (4%), bone (3%), toxin (2%), viral (1%) and bacterial (1%).