Changes to International Nonproprietary Names for antibody therapeutics 2017 and beyond: of mice, men and more

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Changes to International Nonproprietary Names for antibody therapeutics 2017 and beyond: of mice, men and more

Paul W. H. I. Parren, Paul J. Carter, and Andreas Plückthun

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ABSTRACT

Active pharmaceutical substances require an International Nonproprietary Name (INN) assigned by the World Health Organization (WHO) to obtain market authorization as a medicinal product. INNs are selected to represent a unique, generic name for a drug enabling unambiguous identification and labeling. INNs may be requested after initiating clinical development of an investigational drug. Pharmaceutical classes are indicated by a common stem or suffix. Currently, INNs for monoclonal antibody-based drugs are recognized by the suffix, -mab, preceded by a source infix such as -xi- (chimeric), -zu- (humanized) or -u- (human) designating the species from which the antibody was derived. However, many technological advances have made it increasingly difficult to accurately capture an antibody’s source in its name. In 2014, the WHO and the United States Adopted Names (USAN) Council approached this challenge by implementing changes to antibody source infix definitions. Unfortunately, gaps and ambiguities in the definitions and procedures resulted in inconsistent source category assignments and widespread confusion. The Antibody Society, extensively supported by academic and industry scientists, voiced concerns leading to constructive dialog during scheduled consultations with WHO and USAN Council representatives. In June 2017, the WHO announced that use of the source infix will be discontinued for new antibody INNs effective immediately. We fully support this change as it better aligns antibody INNs with current and foreseeable future innovations in antibody therapeutics. Here we review the changes implemented. Additionally, we analyzed antibody INNs recently assigned under the previous 2014 definitions and provide recommendations for further alignment.

Introduction

“The best laid schemes o’ mice an’ men / Gang aft a-gley.” This line of the well-known poem by Robert Burns eloquently expresses the notion that things, even though carefully planned, can often go wrong. In fact, this is what happened with well-intended changes to the definitions used to assign the source infix (substem) for (generic) INN and USAN for antibody therapeutics (see appendix for details). Specific concerns with respect to the changes in the INN and USAN source designations have previously been discussed in detail elsewhere.

Contemporary INNs lack transparency and consistency in source infix designations

The WHO and the USAN Council are not, to our knowledge, planning to change recommended INNs previously issued under the 2014 definitions. Therefore, we considered it important to reinvestigate nomenclature practices for contemporary INNs to identify and highlight shortcomings. We systematically analyzed all INN for antibody therapeutics as they occur in the most recent 2017 INNs Recommended List (RL77). The results summarized in Table 1 reinforce our previous concerns, and show that multiple inconsistencies occur for antibodies with a chimeric or humanized source designation. The four antibodies at the top of Table 1 all received a chimeric (-xi-) or mixed (-xizu-) INN designation; the latter referring to antibodies containing both a chimeric and a humanized heavy or light chain. Dinutuximab beta is based on mouse variable (V) domains fused to human constant (C) domains and therefore represents a genuine chimeric antibody generated via classic domain exchange. The other three antibodies categorized as chimeras or mixed by their INNs, in contrast, were humanized using common methods. The chimeric designation of aneculimab highlights the drawbacks of using linear sequence homology to categorize therapeutic antibodies by source. For this antibody, a humanization procedure was used that employs non-contiguous human framework regions (FRs) aimed at minimizing T cell epitope content and reducing immunogenicity risks. Next, rozanolixizumab represents the INN with the least transparent source designation in RL77. Despite its mixed source -xizu- designation and its annotation as a “humanized and chimeric antibody,” the INN description (i.e. additional information published by WHO) only shows alignments of rozanolixizumab’s variable region sequences.

KEYWORDS

Chimeric; drug development; immunization; immunotherapy; International Nonproprietary Name; INN; monoclonal antibody; therapeutic antibody; USAN; World Health Organization

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<table>
<thead>
<tr>
<th>Antibody INN</th>
<th>Common name</th>
<th>Heavy chain VH</th>
<th>Light chain VL</th>
<th>Notes</th>
</tr>
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<tr>
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<td>Mus musculus</td>
<td>Mus musculus</td>
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<td>andecaliximab</td>
<td>GS-5745</td>
<td>Mus musculus</td>
<td>Mus musculus</td>
<td>Humanized by Antitope’s Composite Human Antibody technology</td>
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<td>ABT-806</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>Homo sapiens</td>
<td>Humanized rat Ab</td>
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<td>SHR-1210</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
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<td>Homo sapiens</td>
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<td>DAC HYP</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>7E9</td>
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<td>KBO04, IIA4</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>Homo sapiens</td>
<td>Humanized mouse Fab</td>
</tr>
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<td>rosmantuzumab</td>
<td>OMP-131R10</td>
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<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>hR57</td>
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<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
</tr>
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<td>telisotuzumab vedotin</td>
<td>ABBV-399, ABT-700</td>
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<td>Homo sapiens</td>
<td>Humanized mouse Ab; Antibody-drug conjugate</td>
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<td>trastuzumab durcamazine</td>
<td>SYD985, 4D5-8</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab; Antibody-drug conjugate</td>
</tr>
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<td>SHR-1314</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>aprutumab ixadotin</td>
<td>BAY 1179470</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>burosomab</td>
<td>KRN-23, UX-023</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab; Antibody-drug conjugate</td>
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<td>brazikumab</td>
<td>AMG-139, MEDI2070</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<tr>
<td>elezanumab</td>
<td>ABT-555, AE12-1Y</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>lupartumab amadotin</td>
<td>BAY 1129980</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
</tr>
<tr>
<td>remtolumab</td>
<td>D2E7, A-1230717, ABT-122</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab; Antibody-drug conjugate</td>
</tr>
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<td>REGN 2222, SAR4385S4</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab; Antibody-drug conjugate</td>
</tr>
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<td>PF-05082566</td>
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<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
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<td>ranevetumab</td>
<td>NV-01</td>
<td>Homo sapiens</td>
<td>Homo sapiens</td>
<td>Humanized mouse Ab</td>
</tr>
</tbody>
</table>

*Antibody INNs for which a different top hit relative to the species stated in RL77 was found are highlighted in red.*
with *Homo sapiens* VH and VL reference genes with 86.5 and 76% homology, respectively (ref. 3 and Table 1). The IMGT/DomainGapAlign searches saved for rozanolixizumab in IMGT/mAb-DB10,11 also exclusively show the same human reference genes. So if the reference genes are human, then what is the mixed source designation based on? Notably, rerunning the IMGT reference gene database search as described in Methods reveals that the light chain aligns more closely to macaque VL genes with 7 Macaca mulatta reference alleles showing slightly greater homology compared with the first human VL hit (i.e., 77–79% versus 76%, respectively; Table 2). Differences are subtle, however, with rozanolixizumab VL showing 20 amino acid changes in FR1- FR3 compared with both the top macaque (i.e., IGKV1-17’01 with 9 changes in FR1-3 and 11 in complementary-determining region (CDR)1-2) as well as the top human (i.e., IGKV1-17’01 with 8 changes in FR1-3 and 12 in CDR1-2) reference allele hit in IMGT/DomanGapAlign. The lower score for the human references allele can therefore be attributed to a slightly greater dissimilarity of the CDR-L3 which, in fact, was grafted from the parental rat antibody during humanization. Rozanolixizumab’s light chain, therefore, reasonably should also have obtained a humanized source designation. Unexpectedly, it was assigned a mixed chimeric stem instead which, in addition, is at odds with the documentation for the INN. Unexpectedly, it was assigned a mixed chimeric stem instead which, in addition, is at odds with the documentation for the INN. Unexpectedly, it was assigned a mixed chimeric stem instead which, in addition, is at odds with the documentation for the INN. Unexpectedly, it was assigned a mixed chimeric stem instead which, in addition, is at odds with the documentation for the INN. Unexpectedly, it was assigned a mixed chimeric stem instead which, in addition, is at odds with the documentation for the INN.

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There may be multiple explanations for the observed inconsistencies. First, there is no precise definition of what constitutes “closer to human than to other species” in the reference database search. Presumably, an INN examiner may determine that a sequence aligns most closely to a human reference gene even if non-human genes score slightly higher but the observed homology is of similar magnitude (see appendix). This may be of particular relevance if the result is affected by differential alignment in CDR sequences. Macaque reference genes, for example, may obtain a higher IMGT/DomainGapAlign score through a closer homology with rodent CDRs or, due to an artifact of the local alignment algorithm by having no identity or similarity in the V gene termini (CDR3 and FR3), even though alignment for the corresponding region in the human counterpart is better. However, such subjectivity in assigning an appropriate source category is highly problematic as discussed above (Table 1). Second, results may vary over time as the composition of the IMGT gene reference database changes due to additional genome sequences becoming available in which specifically the addition of macaque germline reference genes with high allelic variation is of concern. Finally, inconsistencies will occur when an INN for an antibody contained in a novel compound was issued before the 2014 change in source definitions. This is exemplified by gentuzumab ozogamicin. The INN for the antibody portion of this antibody-drug conjugate (ADC) was issued in 2001 without its sequence being made available. In fact, sequences have only been systematically disclosed in the INN description since RL57 released in 2007. The subjectivity and time-dependence of antibody INNs creates undesired uncertainties with respect to predicting and interpreting INN source categories.

As noted, the USAN definition differs from INN by using an 85% sequence cut-off definition for distinguishing chimeric from humanized antibodies (appendix). When using the USAN definition, only 8 of 19 antibody heavy chains and 9 of 19 light chains would have obtained a humanized designation. Interestingly, rozanolixizumab’s nomenclature would be consistent with USAN’s definitions for a mixed source antibody. This antibody however has not been assigned a USAN, so the pre-existence of a USAN cannot explain the discrepancies described.

Examining the 8 human antibodies in RL77, we observe no discrepancies, which is as expected due to the absence of a definition (Fig. 1; appendix). Ironically, the only antibody in RL77 derived from an immune response in a human individual (i.e., the second Fab in the bispecific DVD lutikizumab was cloned from a patient with auto-immune disease) did not earn the antibody a (mixed) human INN.

### Table 2. Inconsistencies in source inflex designations analyzed for antibodies from RL77.

<table>
<thead>
<tr>
<th>Antibody INN</th>
<th>Top hit species (searched May 2017)</th>
<th>Homology to top hit species (%)</th>
<th>If different, homology to closest human (%)</th>
<th>Top hit species (searched May 2017)</th>
<th>Homology to top hit species (%)</th>
<th>If different, homology to closest human (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anecaximab</td>
<td>Mus musculus</td>
<td>82.5</td>
<td>71.1</td>
<td>Macaca mulatta</td>
<td>81.1</td>
<td>80</td>
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<td>86.5</td>
<td></td>
<td>Macaca mulatta</td>
<td>79.0b</td>
<td>76</td>
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<td>camrelizumab</td>
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<td>Macaca mulatta</td>
<td>87.6</td>
<td>87.4</td>
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<tr>
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<td>Homo sapiens</td>
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<td></td>
<td>Macaca mulatta</td>
<td>87.1</td>
<td>86.9</td>
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<td>Macaca fascicularis</td>
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<td>82.7</td>
<td>Homo sapiens</td>
<td>84.0</td>
<td></td>
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<td>85.3</td>
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<td>72.9</td>
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<td>81.9</td>
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<td></td>
<td>Macaca mulatta</td>
<td>82.4</td>
<td>82.1</td>
</tr>
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<td></td>
<td>Macaca mulatta</td>
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<td>92.6</td>
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<td></td>
<td>Macaca mulatta</td>
<td>83.9</td>
<td>83.8</td>
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<td></td>
<td>Macaca mulatta</td>
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<td>86.3</td>
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<td>82.7</td>
<td>Macaca mulatta</td>
<td>81.9</td>
<td>80</td>
</tr>
</tbody>
</table>

*Results that differ from the closest reference gene or allele species shown in RL77 and as referenced in the IMGT/mAb-DB INN database are shown in red. New search was performed as stated in Methods. The homology to the closest human reference gene or allele is provided.*

*bSearch provides 7 Macaca mulatta reference alleles that have greater homology than the Homo sapiens reference allele.*
The wide range of technologies used to access human sequences for generating therapeutic antibodies is noteworthy. These technologies include mRNA-display, multiple distinct phage-display and several distinct transgenic mice platforms (Table 1), and exemplify that therapeutic antibodies can have many origins (Fig. 2). Additional similar technologies, often used in conjunction, are being used to fill early pharmaceutical development pipelines. INNs requests for such antibodies can be expected for submission in the near future.

In summary, therapeutic antibody INNs as well as the accompanying description published in the INN Recommended List RL77 lack consistency and transparency in source in fix designations for chimeric and humanized antibodies. Fixing the source infix

On behalf of its members and scientists who signed an online petition, The Antibody Society engaged in discussions with the WHO INN expert group and representatives from the USAN Council and Food and Drug Administration (FDA) during the 62nd open consultation on INN for Pharmaceutical Substances in April 2016 and an ad hoc meeting on Biologicals in September 2016.4,17 The Antibody Society, in collaboration with key stakeholders, developed proposals to revise the INN system to provide scientifically sound, distinguishing names for therapeutic antibodies in current and future development.

Two potential solutions were discussed. The first was to drop the use of the source infix and sequence alignments to categorize antibodies altogether. The second was to improve the current system, for example by generating a new expanded ‘engineered’ source infix which should take current and future developments in antibody generation technologies into account. Although no general consensus was reached at the workshop, dropping the source infix was a favored solution.17 Removing the source infix would, as a side effect, create more flexibility in the assignment of INNs. This is important as it was noted that, due the large increase in applications for biologicals, it is becoming increasingly difficult to design new distinguishable INNs.17

After considering all options, the WHO announced it was decided at the 64th consultation on INN for Pharmaceutical Substances held April 4–7, 2017 in Geneva, Switzerland that they will discontinue the use of the source infix in antibody INNs.18 The make-up of previous and new antibody INN nomenclature rules are summarized in Fig. 3.

Antibody INNs: Beyond the source infix

The target infix (substem A) is determined by the target (molecule, cell or organ) class.17 The information provided by a single syllable can only in very general terms describe the intended target for an antibody, especially as an antibody’s target molecule is often expressed on multiple cells in multiple
Antibody INN ABC

<table>
<thead>
<tr>
<th>prefix</th>
<th>infix</th>
<th>suffix</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-be-ce-</td>
<td>tf(l)i</td>
<td>-mab</td>
</tr>
<tr>
<td>a-be-ce-</td>
<td>xi zu u o</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Antibody INN ABC. The general naming scheme for antibody INN before 2017 is compared with the new system. Prior to 2017, the random prefix was followed by a target infix (substrum A) of which -tu- for tumor, -i(0)- for immunomodulatory, -i(c)- for cardiovascular, and -i(k)- for interleukin represented major classes. The source infix (substrum B) indicated the source of which -xi- for chimeric, -zu- for humanized and -u- for human represented major classes (see the Bioreview (2014) for complete listing). In the new scheme, the source infix designating the species has been discontinued as recommended by the INN expert group during the 64th INN Consultation. To avoid confusion with earlier schemes, -a- now designates tumor antigen. Furthermore, -ba- designates bacterial, -am- serum amyloid protein(SAP)/amyloidosis, -ci- cardiovascular, -fung- fungal, -gros- skeletal muscle mass-related growth factors and receptors, -ki- interleukin, -li- immunomodulating, -ne- neural, -so- bone, -toxa- toxin and -vi- viral. The source infix -vet- for veterinary use antibodies is retained and added to the ‘target’ infix list. The suffix -mab represents the common stem for antibody therapeutics.

In some cases, a prefix may be added to specific antibody products to avoid medication errors and facilitate pharmacovigilance. The FDA, for example, included the prefix "ado-" to the ADC ado-trastuzumab emtansine (Kadcyla) to distinguish it from the non-drug conjugated trastuzumab. This is to mitigate the risk that the name is misread or mislabeled and to avoid administration of the wrong drug, which could lead to serious adverse events. Further use of prefixes for specific drugs should be considered as additional conjugates with the same antibody are being developed (e.g., trastuzumab duocarmazine).

Beyond INN

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The WHO decision to discontinue the use of the source infix in antibody INNs is an important step forward and addresses the

organ's Fc receptor IIIa binding and antibody-dependent cell-mediated cytotoxicity. Finally, the second word 'pegol' indicates PEGylated antibodies, e.g., certolizumab pegol.

The stem -mab has been used in INNs for all antibody-containing substances. However, the intention to introduce INNs for antibody-fusion proteins consisting of a single word containing the stem -fusp has been discussed. Although general consensus was not reached, it was decided to test the -fusp stem on 2 outstanding requests.

For recombinantly expressed polyclonal antibodies (also known as designer polyclonals), each antibody in the mixture will usually require a separate INN. However, this may not be appropriate for recombinant polyclonal antibodies manufactured using single batch production strategies. In a USAN, the suffix -pab may then be used, such as in rozrolimupab, which comprised 25 different recombinant anti-rhesus D antibodies. A suffix for such recombinant polyclonal drug substances is not available for INNs, but in view of future development should likely be considered.
concerns and objections raised by The Antibody Society on behalf of many academic and industry scientists in the antibody field. The new naming scheme accepted at the 64th Consultation has swiftly been implemented by WHO as we have learned that it has already been adopted in INNs currently proposed to applicants. Since the shortcomings of the 2014 source definitions extend to the Additional Information provided in the INN description (e.g., as in RL77 discussed here), we urge the WHO INN expert group to completely retire the use of categorizing therapeutic antibodies for source by using sequence alignments. The WHO announced that the INN description is envisioned to contain more extensive information on the antibody’s origin and that information regarding the species on which the antibody’s sequence is based will continue to be included in the definition for antibody INN. We fully support the inclusion of more precise information of the antibody’s origin and generation in the INN description. However, continuing the practice of describing antibodies as chimeric, humanized and human in the INN description on the basis of ambiguous and inconsistent definitions, in spite of discontinuing the source infix in the actual INN, would be a very poor solution that should be reconsidered. Going forward, we request the WHO to consider omitting the source infix from antibody INNs currently under discussion (e.g., INNs in the 2016 Proposed List PL116), as well as to review anomalies in previously assigned INNs. Most importantly, discontinuing the use of sequence alignments to determine an antibody’s origin in the INN description would allow the most complete resolution of the issue.

Methods

Database analysis of antibody INNs

The antibody names in the Recommended INN: List 77 were examined. The assigned VH and VL reference genes or alleles were searched in IMGT/mAb-DB using the INN as “General Query” and examined in the IMGT/2D structure-DB card for the INNs using the link provided in the Table on the respective IMGT/mAb-DB result page. The saved IMGT/DomainGapAlign results were accessed using the links provided at the bottom in the box designating the V-domain of the heavy and light chain, respectively. This link provides the top 5 “Closest reference gene and allele(s) from the IMGT V domain directory.” The top hit corresponds to the reference gene and species listed in RL77. The top hit and percentage homology are noted in Table 1 in this manuscript. Next, a new IMGT/DomainGapAlign search against the current database was performed by scrolling to the top of the page and executing “Align and IMGT -gap my sequence(s).” Searches were performed against the database available in weeks 17 and 18 (2017). Antibodies for which a different top hit relative to the species stated in RL77 was found are highlighted in red in Table 1 and further details are provided in Table 2. Patent applications and patents can be accessed via https://worldwide.espacenet.com/.

Web-based materials

All links and searches in this manuscript were checked for accuracy at the time of writing. Since links may become inoperative or linked information may be retired or changed, relevant copies are being kept on file at The Antibody Society and may be accessed in the “member’s only” area on The Antibody Society’s website (http://www.antibodyociety.org) or directly requested from the authors.

Disclosure of potential conflicts of interest

The authors are employees (PWHIP and PJC) or are associated (AP) with companies that have a commercial interest in therapeutic antibody products and antibody engineering technologies.

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The WHO provides International Nonproprietary Names (INNs) to therapeutic antibodies. A complete and current list of INNs for therapeutic antibodies approved or under regulatory review in the US and EU can be found on The Antibody Society’s website. The INN is composed of a random, unique prefix of several syllables, a first infix (substem A), which is defined by the target, and second infix (substem B), which is defined by the source, and the suffix (stem) -mab. The source infixes were developed during 1991–1993, and, although definitions were refined over the years, the delineations between the various categories remained the same until 2014 (see Fig. 1). The most common infix indicating the source is: -o- for all mouse sequence-derived antibodies, -u- for all human sequence-derived antibodies, -xi- for antibodies in which the mouse-derived variable region were combined with a human constant region (variable domain exchange) and -zu- for antibodies in which the mouse-derived complementarity determining regions were combined with a human variable region framework and human constant region. The origin of the antibody or the technology used to generate the therapeutic antibody defined the infix unequivocally in the early years.

Progress in antibody technologies, however, has increasingly blurred boundaries between the various source categories, resulting in an antibody landscape consisting of a continuum of sequences. Through these advances, therapeutic antibodies with the characteristics that are required for modern biopharmaceuticals can be generated with sequences derived from a myriad of in vitro and in vivo technologies, distinct animal species and transgenic animals or even fully synthetic sources. These further changes include the introduction of defined point mutations for optimizing binding, the mitigation of manufacturability and developability liabilities (such as replacing amino acids prone to undesired post-translation modifications) and the removal of T-cell epitopes (to lower the antibody’s immunogenicity risk profile). Finally, many technologies to optimize the therapeutic antibodies’ functionality are being applied (see Table 1). The existing nomenclature system, therefore, was becoming outdated, which was a challenge that the WHO INN expert group attempted to address by developing new infix definitions.

The WHO updated definitions for the source infix released in 2014 handled the distinction between chimeric antibodies and humanized antibodies in a novel and unprecedented way. The new definitions included a sequence alignment procedure whereby the source infixes were now defined by the sequence of the end product and not their factual origin. In 2015, the INN expert group clarified that alignments need to be performed using the IMGT/DomainGapAlign tool. Finally, many technologies to optimize the therapeutic antibodies’ functionality are being applied (see Table 1). The existing nomenclature system, therefore, was becoming outdated, which was a challenge that the WHO INN expert group attempted to address by developing new infix definitions.

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Appendix. The INN source infix explained

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by the INNs applicant. This creates a necessity for an arbitrary
definition regarding whether an antibody with a fully human
sequence derived from 1) a library of natural genes, 2) a library of
synthetic genes, 3) from transgenic animals, or 4) from human
patients would automatically receive the -u- infix, and potentially
blurs the boundary between the -u- and -zu- infix.

Although INNs are used worldwide, several countries use a
separate system of non-proprietary names, one example of
which is the United States Adapted Names (USAN). The
USAN council is administered by the American Medical Asso-
ciation (AMA), and includes members of several agencies, e.g.,
the Food and Drug Administration (FDA). Interestingly, the
post-2014 assignment of source infixes has also generated
debate between the INN expert group and the USAN Council.
In contrast to the INN top hit procedure explained above, the
source designation for a USAN is defined by an 85% sequence
cut-off (with >85% human sequence content designating a
humanized antibody and a <85% content a chimeric). This
discrepancy has further confused the field. During the 62nd
open consultation on INN, the FDA and INN expert group
representatives acknowledged the difference and indicated that
harmonization is essential because therapeutic antibodies in
development may have either an INN or a USAN and about
half have both. We note that all USAN for therapeutic anti-
bodies issued in 2017 thus far are also registered with INNs. In
contrast, of the 27 INNs published in 2017, only 9 also carry a
USAN.

The flaws in determining "humanness" of antibody sequen-
ces by alignment approaches were analyzed and debated by us
and others elsewhere. Overall, the notion that an antibody’s
origin can be captured in a single syllable has lost its validity
due to the increasing complexity of the antibody landscape
(Fig. 2). Moreover, the once useful information that was carried
in this one syllable can become outright misleading. The cut-
off value of a USAN according to human sequence content at
precisely 85% is highly questionable, as is an INN assigned
according to the top homology hit being a macaque or almost
identical human sequence. The source designation in antibody
INNs therefore became a highly disputed issue, and its resolu-
tion was awaiting an urgent deployment.