Prescrire’s contribution to the WHO consultation on List 115 of proposed INNs

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Both independently since 1981, and with others as part of the Medicines in Europe Forum, the International Society of Drug Bulletins (ISDB) and the International Medication Safety Network (IMSN), **Prescrire** has been advocating the routine use by healthcare professionals and patients of international nonproprietary names (INNs), which are clearer, safer and more informative than drug brand names (1-6).

**Making INNs safer.** The principles underlying the creation of INNs are the same that apply to the prevention of medication errors: standardisation, differentiation, and facilitation of logic and redundancy checks (7).

However, even with the INN system there is a residual risk of confusion, partly owing to the sheer number of INNs now in circulation. A report from the Council of Europe, which recommends the use of INNs, calls for active participation in the public consultations on proposed INNs organised by the World Health Organization (WHO), in order to identify any risk of confusion during their clinical use (8). Members of **Prescrire**'s editorial staff, including hospital- and community-based health professionals, joined by a pharmacy lecturer, have examined List 115, which was published in June 2016, to participate in the public consultation on this latest list of proposed INNs (a)(9).

**Our critical analysis of the proposed INNs.** Our analysis of the 118 INNs proposed in List 115 and the amendment to an INN proposed in a previous list was based on the following resources: the 2013 list of common stems and its addenda; the INN database and the WHO’s lists of pre-stems, biological and biotechnological substances, and radicals; the list of planned stems proposed by the United States Adopted Names (USAN) Council; a database of drugs marketed in France, which enables searches on both brand names and INNs; a reference database of drugs used throughout the world; and **Prescrire**’s in-house monitoring of the literature (10-17).

**Prescrire** used a two-step Delphi method. First, the participants compiled a list of potentially contentious INNs, along with the reasons for their doubts. For each of the 16 proposed INNs selected for further scrutiny in this first step, and for the amendment, the participants assessed the risk of confusion and/or misunderstanding, along with the potential clinical consequences of such errors. Finally, they proposed comments for each of these 17 INNs, listing their arguments.

**Ever longer lists.** With 118 proposed INNs and 1 amendment, List 115 is the longest **Prescrire** has examined. It contains: 26 novel proposed INNs or stems (22%); 64 proposed INNs whose common stems have been presented in the journal **Prescrire** (54%); 19 proposed INNs whose common stems have not yet been presented in
Prescrire (16%); 9 variants (such as salts and isomers) and INNs that have undergone specific modifications (7%); and 1 amendment to an INN proposed in a previous list (<1%). The graph plotted to monitor Prescrire’s contributions to the WHO’s public consultations on proposed INNs shows that the number of proposed INNs or stems in all these categories, apart from amendments, is higher than in previous consultations.

Our examination of List 115 of proposed INNs also provided an opportunity to familiarise ourselves with some future stems: -brutinib for Bruton tyrosine kinase (BTK) inhibitors; -cetrapib for cholesteryl ester transfer protein (CETP) inhibitors; -estrant for oestrogen receptor antagonists; -gacestat for gamma-secretase inhibitors; the monoclonal antibody sub-stems -ami-, for monoclonal antibodies targeting serum amyloid protein (SAP), and -vet-, for monoclonal antibodies for veterinary use; -orexant for orexin receptor antagonists; -stinel for NMDA partial agonists (agonists/antagonists); and -toclax for BCL-2 (B-cell lymphoma 2) inhibitors (12).

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -bresib for bromodomain inhibitors; -clotide for guanylate cyclase-C agonists; -dnar for DNA fragments that block transcription; and -glivant for glucagon receptor antagonists (15).

The 6 INNs proposed for cell therapy products (audencel, cenplacel, eltrapuldencel, palucorcel, tonogenconcel and vandefitemcel) show the remarkable expansion of this category, since until now only one INN had been assigned, to spanlecortemlocel, proposed in List 112 (18).

Similarly, the number of INNs proposed for gene therapy products has increased, with 4 in this list: elivaldogene tavalentivec, eretidigene velentivec, ofranergene obadenovec (misspelt in French in List 115 as ofranergéne obadénovec instead of ofranergène obadénovec) and vorietigene neparvovec. The participants in our review group did not identify any specific risks associated with these proposed INNs, although they were not entirely familiar with the INNs of gene therapy products (9).

Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 115 was of sufficient concern to warrant 7 formal objections.

All of these objections relate to INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs: aprutumab ixadotin, depatuzumab mafodotin, gentuzumab ozogamicin, lupartumab amadotin, telisotuzumab vedotin and trastuzumab duocarmazine from List 115, and sacituzumab govitecan from List 113, on account of the publication of the proposed INN sacituzumab in List 115. We did not file a formal objection to sacituzumab govitecan in our response to the public consultation on List 113, because at
that time an INN had not been proposed for the naked antibody (19).

These two-term INNs add to the list of similarly constructed INNs for monoclonal antibodies conjugated to cytotoxic drugs for which Prescrire has filed objections in previous consultations (20-22). Given that the INN Programme has still not devised a solution to enable healthcare professionals to reliably identify compounds containing two pharmacologically active substances, we reiterate our request for the revision of the INNs of all monoclonal antibodies conjugated to cytotoxic drugs.

The current two-term INNs for monoclonal antibodies conjugated to cytotoxic drugs are not safe. As in our previous contributions, we would like to draw the INN Programme’s attention once more to the dangerous current system for naming monoclonal antibodies conjugated to cytotoxic drugs, a risk identified by all of the participants in our analysis (20-22). The number of recommended or proposed INNs for antibody conjugates currently stands at 35 and continues to grow. There is therefore a worrying and ever-increasing risk of confusion between the INNs of: naked antibodies and their conjugated counterparts; conjugates containing the same antibody coupled to different active moieties; and conjugates containing the same active moiety coupled to different antibodies.

If healthcare professionals do not know the precise meaning of the second term, which they may assume refers to a radical devoid of pharmacological activity rather than a second active substance, dosing errors can occur through administration of the wrong product. The fact that the active substances coupled to these antibodies are described in the WHO list of radicals and groups trivialises their dangers (14). It would make more sense to present them more explicitly as active substances, especially since some contain stems or pre-stems (such as -dotin, -tecan, -tansine and -xetan).

It is not enough to acknowledge the risk of error. Following various warnings about confusion between trastuzumab and trastuzumab emtansine, in particular from members of the International Medication Safety Network (IMSN), the WHO INN Programme set up a working group to examine the issue. Its report, submitted in September 2015 and released in April 2016, shows the rising incidence of these errors as the number of marketing authorisations for trastuzumab emtansine increases: according to Roche°/Genentech’s pharmacovigilance data, 12 errors linked to trastuzumab emtansine were reported in countries of the European Union up to 21 February 2015 (7 in Germany, 2 in Greece, 2 in the UK and 1 in Denmark); 3 cases were reported to Health Canada up to 31 March 2015 (23). This patent risk would be compounded by the risk of confusion with the INN trastuzumab duocarmazine, proposed in List 115 (9).

The WHO INN Programme is aware of the problem but refuses to revise the nomenclature used for these conjugated compounds, on the basis that the rules were established a long time ago (24). It is shifting the task of risk mitigation onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, through measures such as packaging and labelling the products differently to aid discrimination, listing them differently in computer systems, etc. Worse still, and paradoxically, the INN Programme advocates the use of brand names to reduce the risk of confusion between INNs it has itself created (23).

The INN Programme admittedly mentioned error prevention strategies such as the introduction of prefixes or suffixes, but only to rebut them, and does not appear to have begun devising naming rules that would reduce this risk of error (23). In our previous contributions, we have suggested for example clearly indicating the conjugated nature of these drugs through a specific prefix, such as “con” or “conj”, possibly combined with a specific typographic sign that clearly differentiates these INNs from those of fixed-dose combinations, for which specific typographic conventions already exist.

We urge the INN Programme once more to devise appropriate measures to make the INNs of conjugates of pharmacologically active substances more distinctive, and to do so urgently before this group of compounds becomes too large to assign them all a safer INN.
Comments

The participants in our review group identified a number of proposed INNs that could generate medication errors for a variety of reasons: confusion with a brand name; confusion with another INN; or confusion between their stem and another stem or suffix.

Risk of confusion with a brand name. One of the proposed INNs, vamorolone, is particularly liable to confusion with the brand name Malarone° (atovaquone + proguanil hydrochloride), due to visual and phonetic similarity. One participant also remarked on its resemblance to amorolfine.

Risk of confusion with another INN. Some of the INNs proposed in List 115 could be confused with existing INNs, in particular: afabicin, pimodivir, poseltinib and valnivudine.

The proposed INN afabicin does not contain a stem, but some participants felt that the suffix “-abicin” could be confused with “-arubicin”, containing the common stem -rubcin, creating a risk of confusion with the INNs aclarubicin and idarubicin. Some participants also pointed out that 5 INNs already begin with “afa-” and that the proposed INN afabin could be confused with the INN afatinib.

Some participants identified a risk of confusing pimodivir with pimozide in scroll-down alphabetical menus in computer systems.

The proposed INN poseltinib could be confused with the INN ponatinib. As they share the same two first letters and the same stem, -tinib, and differ only by 3 letters, our team identified a risk of confusion when these two names are written, spoken and displayed in a scroll-down alphabetical menu.

The proposed INN valnivudine could be confused with the INN lamivudine, which has the same stem, -vudine, and differs by only 2 letters. A slip resulting in inversion of the first 3 letters of valnivudine would produce “lavnivudine”, liable to confusion with lamivudine through visual and phonetic similarity.

Our team identified some other risks of confusion between INNs proposed in List 115 and existing INNs. We will not report all of their comments here, but they involved the possibility of confusion between: agerafenib and regorafenib; apararenone and propafenone; apimostinel and apixaban; elezanumab and elotuzumab; fostemsavir and fosamprenavir; and tirabrutinib and liraglutide.

Risk of confusion between stems. INNs often make drugs’ names meaningful and therefore easier to understand and remember, mainly through the use of informative stems. Stems are therefore the keys to understanding and learning INNs, which is why the participants in our analyses pay particular attention to risks of confusion between stems, pre-stems and the suffixes of INNs that lack a stem or pre-stem.

Some participants pointed out that the stem -citinib, present in the proposed INN itacitinib, is liable to confusion with the stem -citabine and with the suffix “-citidine” in the INN azacitidine, exacerbated by its inconsistency with the stems -citabine and -tidine (10).

A risk of confusion was also identified between the stem -citinib and the suffix “-cinib”, present in the proposed INN asciminit.

Finally, the stem -s(o)-umab present in burosumb could be confused with the stem -zumab, particularly in spoken French, because the letter “s” is pronounced as a “z” when preceded by the letter “o”.

INNs are becoming increasingly informative: educational efforts must continue. Many participants consider the complexity of certain INNs makes them difficult to memorise and pronounce, and hampers communication between health professionals when discussing patient care. Notable examples in List 115 are the gene therapy products elivaldogene tavalentivec, eretidigene velentivec, ofranergene obadenovec and voretigene neparvovec, especially since the participants were not all entirely familiar with the rules governing the naming of these products. In reality, these INNs contain all the information required to understand the nature of the drug. Prescrire helps health professionals learn the INN system through its regular “Common Stem” column. Once they understand the rules of INN construction they can proceed to the next step, that of
investing the effort required to memorise INNs.

Additional help is now available in the form of the INN Programme’s “School of INN”, a welcome initiative to promote education in INN nomenclature for health professionals from their initial university training (25).

**Functions and roles of radicals: an area where more education is required.** List 115 includes the proposed INN tenofovir exalidex, in which tenofovir is esterified by an exalidex radical with no pharmacological activity of its own. As is the case for other salts and esters of drugs, the function of this radical is to modulate the drug’s efficacy. It is probable that tenofovir exalidex will be used at different doses from those used for other tenofovir derivatives. When a drug is modified by a radical with no pharmacological activity, it is important that healthcare professionals understand the modulatory role of the radical, which converts the drug into a prodrug and is likely to alter its pharmacokinetics or pharmacodynamics.

The participants identified a risk of confusion with tenofovir or tenofovir alafenamide, which are already marketed in single-agent and multi-agent products. The risk of confusion between these drugs is compounded by the fact that the INNs of fixed-dose combinations are sometimes truncated or abbreviated in computer systems, because the field provided is too small to display them in full (26).

A very different approach would be required when teaching health professionals about radicals that are pharmacologically active substances, and would need to focus on their toxicity, the risk that underpins our continued objection to the naming rules currently applied to monoclonal antibodies conjugated to cytotoxic drugs.

**Amendments.** Amendments to INNs proposed in previous lists are subjected to risk analysis in the same way as newly proposed INNs. List 115 contained only one such amendment, with ifabotuzumab replacing fibatuzumab (List 113). Our team have no comments to submit about this change, but neither did we submit any concerns over fibatuzumab in our response to the public consultation on List 113 (19).

**In summary.** The main issue with List 115 is that the problem with the nomenclature used for monoclonal antibodies conjugated to cytotoxic drugs remains unresolved. As anticipated, the number of these conjugates continues to grow and the risks of confusion can only intensify as more marketing authorisations are granted.

Strategies to reduce the risk of confusion between the INNs of conjugates containing two pharmacologically active substances are urgently required. They must be based on safer INN construction by the WHO rather than by drug regulatory agencies or pharmaceutical companies. To provide quality patient care, health professionals need the safest and most informative INNs possible.

Prescrire is proud to have contributed for many years to the work undertaken by the WHO to instigate and maintain a common international language for drugs. We trust that the creativity and perseverance of which the INN Programme is capable will be mobilised to address the issues we have raised, in order to improve the quality and safety of drug treatment, in the interest of patients.
- This response was prepared using the resources of the entire Prescrire team.

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