Prescrire’s contribution to the WHO consultation on List 118 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 systematic 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). Our review group, consisting of members of Prescrire’s editorial staff, including hospital- and community-based health professionals, joined by lecturers in pharmacy and medicine from Marseille University Hospital and Marseille School of Pharmacy, has examined List 118 in order to participate in the public consultation on this latest list of proposed INNs, published in January 2018 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 118 INNs proposed in List 118, and one 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 (10-18).

The first step of Prescrire’s collective review was to identify INNs or brand names of marketed drugs that could potentially be confused with the INNs proposed in List 118. In each case, the participants then assessed the likelihood and clinical consequences of a medication error or misunderstanding arising through this mechanism, listing their arguments. When clinical consequences were foreseeable, the participants were also invited to suggest solutions to reduce the risk of confusion.
Another long list. With 118 proposed INNs and 1 amendment, List 118 is one of longest Prescrire has examined.

Our examination of List 118 provided an opportunity to identify some planned stems: -adenant for adenosine receptor antagonists, -caftor for CFTR protein modulators, -calcet/-calce- for calcium-sensing receptor agonists, -fexor for farnesoid X receptor agonists, -golix for non-peptide gonadorelin (GnRH) antagonists, -inurad for urate transporter inhibitors, -ixafor for chemokine CXCR4 antagonists, and -ixibat for ileal bile acid transporter inhibitors.

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -dutide (formerly -modutide) for oxymotudolin analogues; -leuton for 5-lipoxygenase inhibitors; -selen for E-selectin antagonists; -vir tide for antiviral peptides, a combination of the stems vir and -tide; and -vivint for Wnt pathway inhibitors.

Some noteworthy new developments. List 118 also shows how the INN Programme is dealing with the profusion of monoclonal antibodies and the increasing number of fusion proteins, by means of the prefix ef- and now the future stem -fusp.

The suffix -fusp is used for multifunctional fusion proteins, i.e. a protein with several major pharmacological effects that is derived from a single nucleotide sequence; it is preceded by a syllable consisting of a consonant denoting the drug’s pharmacological action and a vowel indicating its targeting (19). The first 5 INNs containing this suffix appear in List 118: bilifakusp alfa, onfekafusp alfa, tagraxofusp, tebentafusp, and valanafusp alfa (9).

The prefix ef- has been used since List 109 to denote fusion proteins containing the constant fragment of an immunoglobulin molecule (Fc), except for INNs using the stem -cept (13,20). Its use is increasing: in 2 INNs proposed in List 116 (efgartigimod alfa, ettilagimod alfa), 3 in List 117 (efepoetin alfa, efizonerimod alfa, ellenogristim alfa), and 4 in List 118 (efvabaleukin alfa, efineptakin alfa, efinopegdtide, and etfinsomatropin alfa). In French, the prefix ef- is sometimes accented: efgartigimod alfa, ettilagimod alfa, eteftin etine alfa, efizonerimod alfa, ellenogristim alfa, efvabaleukine alfa, efineptakine alfa, efinopegdtide, etfinsomatropine alfa. Clarification of the rules governing its accentuation would be helpful.

Some INNs proposed for monoclonal antibodies in List 118 were devised using the revised nomenclature scheme and therefore lack the species substem (21). This change will help maintain sufficient reserves of distinctive INNs to supply this overcrowded drug class for some years to come, but the fact that all the participants identified these proposed INNs as anomalies or errors shows that more needs to be done to effectively inform health professionals when important changes are made. Leaving aside antibody–drug conjugates containing an existing monoclonal antibody, other INNs proposed for monoclonal antibodies in List 118 are based on the old nomenclature scheme (cusatuzumab, flotetuzumab), yet the INN favolixizumab has been amended to favolimab; perhaps these are just oversights.

Although dropping the species substem helps simplify the INNs of monoclonal antibodies, it does not prevent the risk of confusion between naked monoclonal antibodies and those conjugated to pharmacologically active substances. Several of our objections concern this persistent danger.

**Formal objections**

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 118 was of sufficient concern to warrant five formal objections. Three relate to INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs (belantamab mafodotin, enapotamab vedotin and samrotamab vedotin). Prescrire has filed a number of objections concerning drugs of this type in previous consultations (22-27). The fourth is a similar objection to the proposed INN satoreotide tetraxetan. The fifth relates to deutivacafitor, which in French sounds like “two ivacaftor” and could result in serious ivacaftar overdoses.
The current two-term INNs for cytotoxic conjugates are unacceptable. As in our previous contributions, we note with regret the abiding problem of the risk associated with the two-term INNs given to monoclonal antibodies conjugated to active substances (22-27). The number of recommended or proposed INNs for antibody–drug conjugates currently stands at 47 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. Further potential for confusion is created by the two-term INNs given to monoclonal antibodies to indicate differing glycosylation patterns, for example for trastuzumab beta in this list.

Furthermore, this risk is spreading to other active substances that are produced separately then linked together. This is the case for radicals initially intended to provide chelation sites for radioisotopes but which also have cytotoxic properties, such as satureotide tetraxetan in List 118, and satureotide trizoxetan in List 114, which we missed (28). When coupled to these chelation radicals, the somatostatin receptor antagonist satureotide (List 115) becomes a cytotoxic drug (28,29).

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 second active substance is 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, since they contain stems (such as -dotin, -tecan, -tansine and -xetan).

Why not continue to revise the nomenclature scheme for monoclonal antibodies? Although the WHO INN Programme recognises the problem, it has still not revised the nomenclature scheme used for these conjugated compounds, on the grounds that the rules were established a long time ago (30). This amounts to shifting the task of risk mitigation onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, requiring them to devise measures to reduce the number of patients harmed through confusion between these INNs, such as: aiding discrimination between these products through different packaging or labelling, and aiding discrimination between their INNs, for example by appending the brand name. This leads to the paradoxical situation in which it is safer to use brand names than INNs.

In our previous contributions, we have suggested indicating the conjugated nature of these drugs with a specific prefix, for example “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.

Given that the INN Programme has still not devised a solution to enable healthcare professionals to reliably identify compounds that contain two pharmacologically active substances, we reiterate our request that no more two-term INNs be created for substances conjugated to pharmacologically active substances, and that all such existing INNs be revised.

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; presence of a stem or pre-stem in a brand name; confusion with another INN; or confusion with other stems or pre-stems.

Confusion with a brand name. Some INNs proposed in List 118 could be confused with a brand name, in particular: lenervimab, praconase, satafrastat, tegavivint and tengonermin.

The proposed INN lenervimab is liable to confusion with the brand name Lenvima®, due to their orthographic and phonetic similarity. The entire brand name Lenvima® is present in the proposed INN lenervimab, accounting for 7 of its 11 letters, and their endings are almost identical. Confusion between an antiviral with an antineoplastic could have serious consequences.
A few participants in our review group identified a slight risk of confusion between the proposed INN *parconase* and the brand name *Béconase* through upward displacement of the descender of the letter "p" to form a "b". Similarity to the INN *parconazole* was also identified, but wrong-drug errors are unlikely to occur because *parconazole* is used in veterinary medicine.

The proposed INN *setrafrastat* could be confused in verbal communication with the brand name Agrastat™ (*tirofiban*), a brand name that never should have been permitted as it contains the stem *-stat* (31). In French, *setrafrastat* could be misheard as "c’est Afrastat" (it’s Afrastat) which is phonetically very similar to "c’est Agrastat™". In addition, the INN *tirofiban* was attributed in 1996 and the brand names Agrastat™ and Aggrastat® were attributed between 1998 and 1999 (18). In the United States, Aggrastat® has been confused with the INN *argatroban* and features on a list of pairs of drug names liable to be confused (32).

A slight risk of confusion exists between proposed INN *tegavivint* and the brand name Adavin® (*nicergoline*), marketed in Poland. We already commented on the USAN Council’s proposed stem -vivint for Wnt pathway inhibitors in our response to List 117, due to the risk of confusion between the proposed INN *adavivint* and the brand name Adavin® when selecting drugs from an alphabetical menu. One participant noted a strong resemblance between the proposed INN *tegavivint* and the pre-stem *tegravir*, used for HIV integrase inhibitors, with 6 shared letters. As a result, healthcare professionals might assume that *tegavivint* is an antiviral, yet it is claimed to be an antineoplastic (27).

All 9 letters of the brand name Tenormine® are present in the French proposed INN *tengonermin*. As these names start and end with the same series of letters, and are phonetically similar, a risk of confusion between them cannot be ruled out.

Confusion due the presence of a pre-stem in a brand name. The proposed INNs *cilofexor* and *nidufexor* pose a risk of confusion when written and spoken with the brand name Effexor® (*venlafaxine*), authorised in France since 1994, as they end in the same 5 letters. Healthcare professionals may, by association, mistake *cilofexor* and *nidufexor* for serotonin and noradrenaline reuptake inhibitor antidepressants. However, the use of the pre-stem *-fexor* in a brand name does not exactly contravene resolution WHA46.19, because the suffix *-fexor* appeared later, in List 101 (*turofexorate isopropyl*, the French version of which was amended in List 103 from *isopropyl de turofexorate to turofexorate d’isopropyl*) (31,33,34).

Risk of confusion with another INN. Some proposed INNs *cligosiban* and *nidufexor* pose a risk of confusion with other INNs, in particular: *abeprazan*, *arazasetron*, *cligosiban*, *conteltinib*, *contezolid*, *epeleuton*, *firscostat*, *netorexant*, *netakimab*, *surufatinib* and *tricaprilin*.

The proposed INN *abeprazan* could be confused with the INNs *rabeprazole* and *alprazolam*, a risk that is enhanced by strong phonetic similarity in French and orthographic similarity (7 and 6 letters in common with this proposed INN, respectively).

As *arazasetron* is probably the R-enantiomer of *azasetron*, it may be effective at lower doses: confusion between these two drugs could therefore lead to overdosing or underdosing. While not challenging the prefix ar- or ara-, which has already been used to designate the R-enantiomers of several drugs, we wish to point out that when this prefix is added to an INN that starts with the letter "a", the wrong drug could be selected from an alphabetical menu if the INNs of the racemic substance and its R-enantiomer are listed near to each other. This risk of confusion exists between with the proposed INN *arazasetron* and the INN *azasetron*.

The proposed INN *cligosiban* is liable to confusion with the INN *givosiran* (List 114), since 7 of its 10 letters are present in *givosiran*. The risk is enhanced by the resemblance between the stems *-siban* and *-siran*, a similarity we have already pointed out in previous contributions (28,35,36).

Our reviewers noticed a risk of error when selecting drugs from an alphabetical menu with *conteltinib* and *contezolid*, both proposed in List 118, as they share the same prefix. This is a consequence of the profusion of INNs ending in *-tlinb* and depletion of the supply of available prefixes (116 proposed INNs identified at the time of publication of List 118). Confusion between an antineoplastic and an antibiotic could have serious clinical consequences.

One reviewer felt that the proposed INN *epeleuton* could be confused with the INN *eplerenone* when selecting drugs from an alphabetical menu.
Two reviewers noted a resemblance between the proposed INN *firsocostat* and the INN *febuxostat*, a consequence of the many stems derived from the common stem -stat.

The proposed INN *nedisertib* carries a high risk of confusion with the INN *cenisertib* (List 104), when written and spoken, with which it shares the stem -sertib and 9 out of 10 letters (37).

Similarly, the proposed INN *nemorexant* is similar to the INN *lemborexant* (List 111), with which it shares the stem -orexant and 9 of its 10 letters (38).

The proposed INN *netakimab* and the INN *nebacumab* share orthographic and phonetic similarity. They could be confused when selecting drugs from an alphabetical menu and in verbal communication.

The proposed INN *opinercept* is very similar to the INN *onercept* (List 86), differing only in the addition of one syllable (39).

The proposed INN *surufatinib* shares similarity with 3 INNs of marketed drugs: *afatinib*, *sunitinib* and *sorafenib*. Our reviewers felt that the closest resemblance is with *sunitinib*, with a risk of errors when selecting drugs from an alphabetical menu. They also noted that *surufatinib* contains all but the first letter of the INN *afatinib*, another sign of the overcrowding in the -tinib group.

The proposed INN *tricaprilin* looks and sounds very similar to the INN *ticarcillin*, which starts and ends in an almost identical series of letters. These two INNs could be confused, especially in verbal communication. Its suffix in French, “priline”, could be confused with the pre-stem -pirdine, proposed for serotonin receptor antagonists.

Confusion between stems or pre-stems: anticipating and forestalling risks. The proposed INN *revosimeline* uses the stem -meline, but one reviewer felt that the suffix -simeline could be confused with the pre-stem -sidenib due to phonetic similarity, which could mislead health professionals over the drug’s therapeutic indications.

In summary. Our examination of List 118 confirms the major importance of education to help health professionals and the public decipher and understand INNs. List 118 also shows that the problem with the nomenclature used for combinations of active substances that include a cytotoxic agent has still not been resolved and affects other drug classes too. As anticipated, as the number of these INNs grows, the risk of dangerous drug name confusions will only intensify as more marketing authorisations for such drugs are granted. Strategies to reduce the risk of confusion between the two-term INNs used for drugs containing two pharmacologically active substances are urgently required. The solution lies in safe INN construction by the WHO, rather than in relying on drug regulatory agencies or pharmaceutical companies to devise risk mitigation measures.

To provide quality patient care, health professionals need safe, informative INNs. The fact that the INN Programme has created the stems ef- and -fusp and has dropped the species substem from the INNs of monoclonal antibodies shows that it is capable of changing its nomenclature rules for the better. We urge it to continue by improving the nomenclature used for combinations of pharmacologically active substances.
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