Prescrire's contribution to the WHO consultation on List 117 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 and health professionals from two university hospitals, has examined List 117 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2017 (a)(9).

**Our critical analysis of the proposed INNs.** Our analysis of the 140 INNs proposed in List 117 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 22 proposed INNs selected for further scrutiny in this first step, 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 22 INNs, listing their arguments.
Ever longer lists. With 140 proposed INNs, List 117 is one of longest Prescrire has examined. It contains: 27 novel proposed INNs or stems (19%); 64 proposed INNs whose common stems have been presented in the journal Prescrire (46%); 40 proposed INNs whose common stems have not yet been presented in Prescrire (29%); and 9 variants (such as salts and isomers) or INNs that have undergone specific modifications (6%). The graph plotted to monitor Prescrire’s contributions to the WHO’s public consultations on proposed INNs shows that the number of novel INNs or stems that have not yet been presented in the journal Prescrire is higher than in previous consultations.

![Trends in WHO consultations on proposed INNs](image)

Our examination of List 117 of proposed INNs also provided an opportunity to identify some planned stems: -becestat for beta-secretase inhibitors; -bresib for bromodomain inhibitors; -catib for cathepsin inhibitors; -domide for “immunomodulators” derived from thalidomide; -dustat for hypoxia inducible factor (HIF) prolyl hydroxylase inhibitors; -gacestat for gamma-secretase inhibitors; -laner for antagonists of gamma-aminobutyric acid regulated chloride channels, antiparasitic agents; and -sidenib for isocitrate dehydrogenase inhibitors.

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -aniten for androgen receptor N-terminal domain inhibitors; -forant for histamine H4 receptor antagonists; -netide for peptides and glycopeptides for which neurological uses have been planned; -podect for phosphodiesterase 10 (PDE10) inhibitors; and -vatrep for vanilloid 1 receptor antagonists (15).

There was a notable increase in the number of gene therapy and cell therapy products (8 proposed INNs for each), which accounted for about 11% of the INNs proposed in List 117. Although the participants in our review group were not all entirely familiar with the nomenclature scheme used for these new products, they did not identify any particular risks associated with those proposed in List 117, apart from their seeming complexity (9).

Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 117 was of sufficient concern to warrant ten formal objections. Six objections relate to INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs (camidanlumab tesirine, cofetuzumab pelidotin, iladatuzumab vedotin, ladiratuzumab vedotin, loncastuximab tesirine, and sirtratumab vedotin), adding to the objections filed by Prescrire in previous consultations for drugs of this type (18-22). The other four objections concern excessive
resemblance between INNs proposed for monoclonal antibodies, a symptom of the fact that this class is at saturation point. With all but one letter in common, name-confusion errors would be highly likely between istiratumab and sirtratumab, and between iladatuzumab and ladiratuzumab.

The current two-term INNs for monoclonal antibodies conjugated to cytotoxic drugs are not safe. 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 cytotoxic drugs, a risk identified by all of our reviewers (18-22). The number of recommended or proposed INNs for antibody conjugates currently stands at 44 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, since they contain stems (such as -dotin, -tecan, -tansine and -xetan).

Why not continue revising the monoclonal antibody nomenclature scheme? 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 (23). 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 monoclonal antibodies conjugated to cytotoxic drugs, and that the existing INNs of all such conjugates be revised. The recent decision to drop the source species substem helps simplify the INNs of monoclonal antibodies, but it does not prevent the risk of confusion between monoclonal antibodies and antibody–drug conjugates.

This decision should also help maintain sufficient reserves of distinctive INNs to supply this overcrowded drug class for some years to come. The one-letter differences between the proposed INNs iladatuzumab and ladiratuzumab, and between istiratumab and sirtratumab, illustrate the extent of this overcrowding (24).

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 significant portion of their stem in a brand name; confusion with another INN; confusion between their stem or pre-stem and another stem; or because they lack a stem.

Confusion with a brand name. Some INNs proposed in List 117, such as adavivint, firibastat, lumasiran, parsaclisib, reloxiase, rovazolac and valziflocept, could be confused with a brand name.

The proposed INN adavivint could lead to errors when selecting drugs from an
Confusion due to the presence of a significant portion of the stem in a brand name. The proposed INN *valzilcept* could be mistaken for an antibiotic, due to its resemblance to two brand names for *ofloxacin*: Oflocet® and Monoflocet®. Although these brand names do not contain the whole stem -*cept*, the suffix `-*cet` is phonetically very similar, and the resemblance is heightened by the preceding syllable `*flo-*`.

Another example of this worrying trend is the recent market introduction of Truxima® (*rituximab*), a copy of MabThera® whose brand name includes most of the stem -*lumab*. This could cause confusion with INNs such as *brentuximab vedotin* and *ceftuximab*. The failure of the pharmaceutical company and the European Medicines Agency to follow the rules concerning the protection of INNs and INN stems when devising brand names is worth pointing out (25).

Risk of confusion with another INN. Some proposed INNs, such as *alobresib*, *garvagliptin*, *ianalumab*, *imlifidase*, *leflutrozole*, *milademetan*, *olorofim*, *sultimotide alfa*, *tibulizumab*, *tisellizumab* and *veldoreotide*, could be confused with other INNs.

The proposed INN *alobresib* is liable to confusion with the INN *molibresib* (List 116) due to orthographic similarity, since 7 of its 9 letters are present in *molibresib*. Some reviewers also noticed a resemblance to the brand name *Alopecia*® (*minoxidil*), with which it shares an identical prefix and a phonetically similar suffix (26).

The proposed INN *garvagliptin* resembles the brand name of another gliptin: *Galvus*® (*vildagliptin*). One reviewer reported its similarity, when written, to the INN *galapentin*.

A risk of confusion, especially when written, was identified between the proposed INN *ianalumab* and the INN *lanadelumab* (List 114), because a capital "i" is easily confused with a lower-case "i" (27).

There is also a risk of confusion between the proposed INN *imlifidase* and the INN *infliximab*.

Although the proposed INN *leflutrozole* appears to be correctly constructed, with "-flu-" appearing to denote the addition of a fluorine to the INN *letrazole*, our reviewers noticed their strong similarity but could not be sure whether confusion of these two drugs would have serious clinical consequences. A risk was also identified of confusing *leflutrozole* with the INN *leflunomide*, when selecting drugs from an alphabetical menu. The INN "*fleutozole*" might be a safer option.

The proposed INN *milademetan* shares the prefix "*mil-*" and suffix "*an" with *milnacipran*, resulting in phonetic similarity that would enhance the risk of confusion between these two INNs, which belong to very different pharmacological classes.

There is a risk of confusion between the proposed INN *olorofim* and the INN *amorolfine*, as well as with the brand name *Orofluc®* (*flucanazole*).

Similarly, a risk of confusion was identified between the proposed INN *sultimotide alfa* and the INN *sultipride*, yet they belong to very different pharmacological classes.

The similarity between the proposed INNs *tibulizumab* and *tisellizumab* was considered excessive by our reviewers, and is yet another illustration of the overcrowding of the monoclonal antibody class and of the importance of revising their nomenclature.

The proposed INN *veldoreotide* is too similar to the INN *edotretotide*, differing only by the addition of two letters.
Confusion between stems or planned stems: anticipating and forestalling risks.

Some of the INNs proposed in List 117 contain stems or planned stems that could be confused with other stems, in particular: -becestat, -ciclib, -citinib and -gacestat.

Our reviewers were concerned by the risk of confusion between the pre-stems -becestat, proposed for beta-secretase inhibitors, and -gacestat, proposed for gamma-secretase inhibitors, present in the proposed INNs atabecestat, crenigacestat and elenbecestat, given that so few resources are invested in helping health professionals and the public decipher and understand INNs.

The stem -citinib, adopted for Janus kinase inhibitors and used in the proposed INN delgcitinib, could be confused with the stem -citabine.

Similarly, the stem -ciclib, adopted for cyclin-dependent kinase inhibitors and used in the proposed INN trilaciclib, is liable to confusion with the stem -cycline, especially in French since “y” is pronounced “i”. We have reported this risk to the INN Programme many times in our previous responses to consultations. The similarity between these stems creates a risk of confusion between the proposed INN trilaciclib and the INN tigecycline (18,28,29).

Risk of confusion because the proposed INN lacks a stem. The proposed INN re-mapirazin, which appears to lack a stem, and especially the French version relmapirazine, could be confused with drugs of the phenothiazine class that end in “-azine” (chlorpromazine, thioridazine, periciazine, levomepromazine, cyamemazine, thioproperazine, fluphenazine, pipotiazine, trifluoperazine, etc.). The suffix “-azine” also has similarity to the common stems -dralazine and -salazine.

In summary. List 117 shows that the problem with the nomenclature used for monoclonal antibodies conjugated to cytotoxic drugs remains unresolved. As anticipated, the number of these conjugates is growing and 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 conjugates 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 source species substem has been dropped from the INNs of monoclonal antibodies confirms that it is perfectly possible to revise the INN Programme’s rules on nomenclature, and that this process could be usefully extended to improve the nomenclature used for combinations of pharmacologically active substances.

List 117 also confirms the importance of effective support for educational efforts, to help health professionals and the public decipher and understand INNs.

We hope that the creativity and perseverance of which the INN Programme is capable will continue to improve the quality and safety of drug treatments, in the interest of patients.

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