Prescrire's contribution to the WHO consultation on List 116 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, has examined List 116 in order to participate in the public consultation on this latest list of proposed INNs, published in January 2017 (9).

Our critical analysis of the proposed INNs. Our analysis of the 106 INNs proposed in List 116 and the 5 amendments to INNs 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 15 proposed INNs selected for further scrutiny in this first step, and for the 5 amendments, 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 15 INNs and for the 5 amendments, listing their arguments.
Long lists. With 106 proposed INNs and 5 amendments, List 116 is one of the longest *Prescrire* has examined. It contains: 28 novel proposed INNs or stems (25%); 49 proposed INNs whose common stems have been presented in the journal *Prescrire* (44%); 24 proposed INNs whose common stems have not yet been presented in *Prescrire* (22%); 5 variants (such as salts and isomers) or INNs that have undergone specific modifications (<5%); and 5 amendments to INNs proposed in a previous list (<5%). The graph plotted to monitor *Prescrire*’s contributions to the WHO’s public consultations on proposed INNs shows that the numbers of novel INNs and common stems not yet presented in the journal *Prescrire* and the number of amendments to previous lists are higher than in previous consultations.

Our examination of List 116 of proposed INNs also provided an opportunity to familiarise ourselves with some future stems: *ampa tor* for AMPA receptor modulators; *beces tat* for beta secretase inhibitors; *bresib* for bromodomain and extra-terminal motif (BET) inhibitors; *gepant* for calcitonin gene-related peptide (CGRP) receptor antagonists; *inurad* for urate transporter inhibitors; *nexor* for nuclear export inhibitors; *pirdine* for serotonin receptor antagonists; *protafib* for tyrosine phosphatase inhibitors (HPTP); *trigine* for sodium channel blockers, signal transduction modulators; and *vet* for monoclonal antibodies for veterinary use.

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: *borole* for drugs containing boron; *fetamin(e)* for drugs derived from amfetamine; *fexor/fexorate* for farnesoid X receptor agonists; *gliatin* for glucokinase activators; and *sonstat* for s-nitrosoglutathione reductase inhibitors.

The 3 INNs proposed for cell therapy products (*bal lateucl*, *evagenretcel* and *ilixadencel*) show the steady growth of this category of drug, which already counts *spanle cortmilcel*, proposed in List 112, and six proposed in List 115: *audencel*, *cenplacel*, *eltrapul endencel*, *palucorcel*, *tonogenconcel* and *vandefitemcel*.

List 116 also includes 3 INNs proposed for gene therapy products: *betibeglogene daro lentivec*, *donaperminogene sellplasmid* and *valoctocogene roxaparvovec*. Although the participants in our review group were not entirely familiar with gene therapy product INNs, they did not identify any particular risks associated with those proposed in List 116, apart from their seeming complexity.
Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 116 was of sufficient concern to warrant four formal objections. Three objections relate to INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs (azinixizumab vedotin, losatuxizumab vedotin and trastuzumab deruxtecan), adding to the objections filed by Prescrire in previous consultations for drugs of this type (20-23). The fourth objection concerns the proposed INN estetrol, which poses two dangers.

The current two-term INNs for monoclonal antibodies conjugated to cytotoxic drugs are not safe. As in our previous contributions, we note the abiding problem of the risk associated with the naming scheme used for monoclonal antibodies conjugated to cytotoxic drugs, a risk identified by all of the participants in our review group (20-23). The number of recommended or proposed INNs for antibody conjugates currently stands at 38 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 as they contain stems (such as -dotin, -tecan, -tansine and -xetan).

It is not enough to acknowledge the risk of errors. 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 shows the rising incidence of these errors as the number of marketing authorisations for trastuzumab emtansine increases (24). This patent risk would be further compounded by the risk of confusion with the INN trastuzumab duocarmazine, proposed in List 115, and trastuzumab deruxtecan, proposed in List 116 (9,18).

The WHO INN Programme is aware of the problem but refuses to revise the nomenclature used for these conjugated compounds, on the grounds that the rules were established a long time ago (25). 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 medication errors due to confusion between these INNs, such as: aiding discrimination between the names by adding the brand name whenever the INN is listed, and aiding discrimination between the products themselves through different packaging or labelling.

The INN Programme has admittedly mentioned error prevention strategies such as the introduction of prefixes or suffixes, only to rebut them, and does not appear to have begun devising naming rules that would reduce this risk of error (24). Worse still, and paradoxically, the INN Programme has recommended using brand names to reduce the risk of confusion between INNs it has itself created (24). In our previous contributions, we have suggested clearly indicating the conjugated nature of these drugs through 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 for the revision of the INNs of all monoclonal antibodies conjugated to cytotoxic drugs, with the hope that this revision could be conducted at the same time as the simplification of the naming scheme for monoclonal antibodies, which was discussed at the 63rd Consultation on INNs (26).
The two dangers of estetrol. There is a high risk of confusion between the oestrogen estetrol and the brand name Ezetrol® (ezetimibe): they end in the same five letters, they start very similarly, due to phonetic resemblance and the graphical resemblance between the letters “s” and “z”, and six of the eight letters of this proposed INN are present in this brand name, in the same order. The risk of confusion is enhanced by the fact that Ezetrol® is marketed in many countries as a cholesterol-lowering drug. The second danger of this proposed INN is that, as the drug is an oestrogen, its INN would be expected to contain the common stem -estr-, yet it has no stem at all, making it difficult for healthcare professionals to understand and identify. There are already too many INNs without stems; when an easily identifiable stem exists, it would be better to use it.

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 another INN; confusion between their stem or planned stem and another stem; or because they lack a stem.

Risk of confusion with another INN. Some of the INNs proposed in List 116 could be confused with existing INNs, in particular: lanifibranor, letolizumab and olendalizumab.

The risk of confusion between lanifibranor and elafibranor (List 113) derives from the fact that they share the identical suffix “-fibranor”, which as we discuss below resembles a stem, and because 10 of the 12 letters of lanifibranor are present in elafibranor (27).

The proposed INN letolizumab could be confused with mepolizumab and vedolizumab, which have the same stem -izumab, because their random prefixes also contain the same sequence of vowels. As a result, 9 of their 11 letters are identical.

The proposed INN olendalizumab replaces lendalizumab (List 114), but it could be confused with omalizumab, especially when written, and mistaken for olanzapine when selecting drugs from an alphabetical scroll-down menu. Our review group also identified similarities between oleclumab (List 116) and alemtuzumab (9,28).

Other similarities between INNs were noticed by some participants in our review group, such as: brivoligide with brimonidine and brimapitide (List 114); gedivumab with golimumab; and miransertib with mianserin, especially when written, a risk of confusion that is enhanced by the presence of the same sequence of vowels (28).

Confusion between stems or planned stems: anticipating and forestalling risks.

Some of the proposed INNs contain stems or planned stems that could be confused with other stems, in particular: cavosonstat, dorazigilatin, landipirdine, timapiprant and tinostamustine.

In cavosonstat, the planned stem -sonstat for s-nitrosoglutathione reductase inhibitors, a USAN stem constructed from the common stem -stat, could be confused with the stem -inostat, used for cytotoxic drugs of the histone deacetylase inhibitor group.

The proposed INN dorazigilatin contains the planned stem -glatin for glucokinase activators, a USAN stem constructed from the common stem -gli-, liable to confusion with the stem -gliptin, used for oral antidiabetics of the dipeptidyl aminopeptidase-IV inhibitor group.

These two cases illustrate the need to select very distinctive prefixes when the confusion generated by the orthographic and phonetic similarity of these types of stem would have serious consequences, because one of the drugs concerned is highly toxic, especially if it is a cytotoxic agent.

In landipirdine, the pre-stem -pirdine, used for serotonin receptor antagonists, could be confused with the stem -dipine, used for calcium channel blockers, leading to confusion between this proposed INN and lercanidipine for example. This risk of confusion was already mentioned in Prescrire’s response to the consultation on List 102 of proposed INNs, in relation to latrepirdine, but was not taken into account since this USAN stem is how listed as an INN pre-stem (29).

The stem -piprant present in timapiprant and used for non-prostanoid prostaglandin receptor antagonists, could be confused with the stem -pilant, used for neurokinin NK1 (substance P) receptor antagonists. This could lead to confusion between timapiprant and aprepitant or telapilant, due to the presence of other identical letters.

In tinostamustine, the stem -mustine preceded by the syllable “-sta-” is vaguely
reminiscent of the stem -vastatin (especially in French, where the stem is -vastatine), potentially leading to confusion between a cytotoxic alkylation agent and a cholesterol-lowering agent.

**Risk of confusion because the proposed INN lacks a stem.**

The proposed INN olodanrigan has no stem and ends with the syllable “-gan” which sounds similar to the stem -xaban used for direct factor Xa inhibitors and the stem -gatran for thrombin inhibitors. This phonetic resemblance was the basis of the potential confusion identified by our review group between olodanrigan and apixaban, rivaroxaban or dabigatran, and could lead health professionals to wrongly deduce that olodanrigan is an antithrombotic.

In lanifibranor, the suffix “-fibranor”, which is not a stem, brought to mind the brand name Lipanor° (ciprofibrate), a product marketed in a number of countries including France. This type of unconscious connection made between a brand name and an INN is another error mechanism to bear in mind.

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 116 are the gene therapy products betibeglogene darolentivec, donaperminogene seltoplasmid and valoctocogene roxaparvovec, 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. When health professionals understand INN construction, they are better able to commit INNs to memory.

Additional help is now available in the form of the INN Programme’s “School of INN”, to promote education in INN nomenclature for health professionals, right from their initial university training. This is a welcome initiative, because the survey conducted by the INN Programme among lecturers, students and others revealed that the majority of respondents knew what an INN was, but that the rules governing their construction are still not well known (26,30).

**Functions and roles of radicals: an area where more education is required.**

List 116 includes the proposed INN etoposide toniribate, in which etoposide is esterified by a toniribate 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. Healthcare professionals may be confronted with the situation in which etoposide toniribate is to be used at doses that differ from those used for etoposide. 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 might alter its pharmacokinetic or pharmacodynamic properties.

The education provided to health professionals about such conventional radicals would therefore be very different to the approach required when teaching them about radicals that are pharmacologically active. The latter would need to focus on the risk of toxicity when two pharmacologically active substances are combined, 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 were subjected to the same risk analysis as newly proposed INNs.

Our review group has no objections to amending sapelizumab to satralizumab, but neither did we submit any concerns when sapelizumab was proposed in List 114.

We filed an objection to the name nalbuphine sebacate when it was proposed in List 114 and welcome the proposal to rename the drug dinalbuphine sebacate, which signals the presence of two molecules of nalbuphine in each molecule of the drug. This more explicit INN should draw health professionals' attention to the risk of overdose.

The potential confusion we pointed out in our response to the public consultation on List 114 between pogalizumab and plozalizumab (List 113) or omalizumab, because they contain the same sequence of vowels, has been solved by renaming it vonlerozumab.
Amending lendalizumab to olendalizumab forestalls the risk of confusion between lendalizumab and benralizumab (List 102) pointed out in our response to the public consultation on List 114 (since 10 of their 12 letters are identical). However, as we discuss above, olendalizumab could be confused with other INNs, especially omalizumab (22,27,28,31).

In summary. The main issue with List 116 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 will only intensify as more marketing authorisations for such drugs are granted. Strategies to reduce the risk of confusion between the INNs of 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. Simplification of the naming scheme for monoclonal antibodies was discussed at the 63rd Consultation on INNs, with the aim of ensuring that the INN Programme does not run out of novel INNs to assign to monoclonal antibodies in the coming years. It should be an opportunity to investigate solutions to prevent the risks posed by the current naming scheme for monoclonal antibodies conjugated to cytotoxic drugs.

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. The WHO undertakes this role in a fully transparent fashion, allowing all interested parties to bring their expertise to bear to improve the INN language, whether they work at an institution, a regulatory agency, a pharmaceutical company or an association for health professionals.

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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