

World Health Organization
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Prescrire's contribution to the WHO consultation on List 108 of proposed INNs

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As an active member of the Medicines in Europe Forum, the International Society of Drug Bulletins (ISDB) and the International Medication Safety Network (IMSN), *Prescrire* has long been advocating the routine use, by both healthcare professionals and patients, of international nonproprietary names (INNs), which are more informative, safer and clearer than brand names (1–4).

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 (5).

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 (6). The editorial staff of *Prescrire* and members of the not-for-profit organisation *Association Mieux Prescrire* are participating in this phase of the consultation and have examined List 108 of proposed INNs, published in January 2013 (7).

Our critical analysis of the proposed INNs. Our analysis of the 74 proposed INNs of List 108 was based on the 2011 list of common stems, on the INN database, on a database of drugs marketed in France, which enables searches on both brand names and INNs, and on *Prescrire's* own data search (8–12).

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 25 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 decided for each of these 25 contentious INNs whether a simple comment or a formal objection was more appropriate, and listed their arguments.

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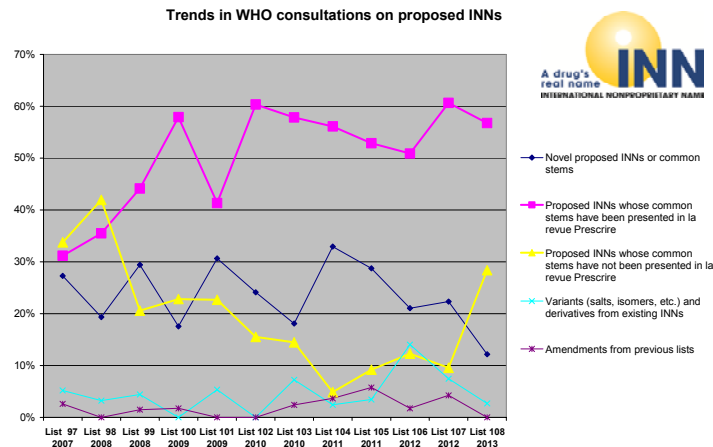
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Less innovation. While the previous list contained 90 proposed INNs and 4 amendments, List 108 is shorter and includes: 42 proposed INNs whose common stems have been presented in la revue *Prescrire* (57%); 21 proposed INNs whose common stems had not yet been presented at the start of our analysis of List 108 (28%); 9 novel proposed INNs or stems (12%); 2 variants, such as salts and isomers (3%); and no amendments to INNs proposed in previous lists. The graph plotted to monitor *Prescrire's* contributions to the WHO's public consultations on proposed INNs shows that, in comparison with previous consultations, List 108 included fewer novel proposed INNs or common stems, but more



proposed INNs containing recently published stems that have not yet been presented in la revue *Prescrire* because no drugs containing these stems have yet been marketed in France.

The examination of a list of proposed INNs provides an opportunity to discover some pre-stems, of which List 108 includes: **-apt-** (in *emapticap pegol*, *lexaptepid pegol* and *olaptosed pegol*) used for aptamers, which are synthetic oligonucleotides, usually RNA, capable of binding to a specific ligand and sometimes of catalysing a chemical reaction on this ligand; **-casan** (in *belnacasan*) for inhibitors of interleukin 1b converting enzyme (caspase); **-lisib** (in *apitolisib*, *copanlisib*, *pilaralisib*, *recilisib* and *voxtalisib*) for antineoplastic phosphatidylinositol 3-kinase inhibitors; and **-orexant** (in *filorexant*) for orexin receptor antagonists (7,10).

Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 108 was of sufficient concern to warrant a formal objection. The risks appear avoidable for 2 INNs proposed for monoclonal antibodies presented as cholesterol-lowering agents.

Monoclonal antibodies: a substem for metabolic targets is lacking. The INNs *evolocumab* and *lodelcizumab* have been proposed for 2 monoclonal antibodies presented respectively as a “hypocholesterolemic” and an “antihypercholesterolemic agent” (7). The sub-stem **-c(i)-** does not explicitly identify these potential uses, as it simply denotes a “cardiovascular” target (11). Although *lodelcizumab* sounds like “low LDL” (low-density lipoprotein), a risk of confusion with cytotoxic monoclonal antibodies was identified and such an error could have serious consequences.

Monoclonal antibodies can of course be developed for all sorts of pharmacological uses, but this risk, created by the absence of a sub-stem for metabolic indications, should be recognised. It could be avoided by establishing a clear rule for naming monoclonal antibodies for metabolic use. We therefore request that these proposed INNs be re-examined, to avoid exposing patients to considerable risks in real-life healthcare situations due to confusion between a cholesterol-lowering drug and a cytotoxic drug.

Comments

Some proposed INNs generate a risk of medication errors, for a variety of reasons: some could be confused with other INNs, possibly when slightly deformed by a slip or lapse (misspelling, mispronunciation, misreading, mishearing or misremembering); some stems are easily confused with other stems; some common stems or INNs are difficult to interpret; and some INNs can be confused with brand names. Hence the following comments.

Confusion with other INNs. Some proposed INNs, such as *aldoxorubicin*, *peginterferon beta-1a*, *ilorasertib*, *ipatasertib*, *telmapitant* and *ulodesine*, could be confused with other INNs. Confusion can arise between INNs containing different common stems or the same common stem.

Participants understood *aldoxorubicin* to be a prodrug of *doxorubicin* through linkage to a maleimidocaproyl hydrazone, but were concerned about the risk of prescribing errors due to confusion with *doxorubicin* when both substances become available. They also identified a possibility of confusing *peginterferon alfa-2b* with *peginterferon beta-1a*. The risk is very low because it requires two simultaneous slips, i.e. confusion of “beta” with “alfa” and “1a” with “2b”, but it should be taken into account for healthcare practitioners training. The INNs *ilorasertib* and *ipatasertib* only differ by 3 letters, although the consequences of confusing them would be limited, since the drugs act through the same mechanism. The confusion between *telmapitant* and *telmisartan*, when selecting drugs from an alphabetical list on a computer screen, was considered a more worrying risk in everyday practice. Finally, *ulodesine* and *silodosine* looked and sounded alike to participants, this risk of confusion being compounded by the absence of any recognisable common stem in these INNs.

If these INNs are considered unavoidable, healthcare professionals will require appropriate information to help them avoid errors. This could be achieved for example by stressing the differences between the dosages of *doxorubicin* and *aldoxorubicin*, or between the indications for *telmapitant* and *telmisartan* (bearing in mind that stating the indication on the prescription is not always legal or acceptable). The way in which the differences between INNs are highlighted will depend on the type of confusion anticipated. Bold type or upper-case lettering could be used to emphasise the common stems, e.g. *telmapitant* and *telmisartan*, or to accentuate the parts that differ, e.g. *peginterferon alfa-2b* and *peginterferon beta-1a*, *ALdoxorubicin*, or *ILORasertib* and *IPATasertib*.

Confusion between stems. Some of the proposed INNs could generate errors due to confusion between stems, e.g. between the common stem **-tinib** and the pre-stem **-lisib**, adopted for phosphatidylinositol 3-kinase inhibitors and present in 5 of the INNs proposed in List 108: *apitolisib*, *copanlisib*, *pilaralisib*, *recilisib* and *voxtalisib*. On the other hand, the suffix “ib” is a useful aid to understanding several common stems, by indicating that they are inhibitors: **-anib**, **-coxib**, **-fenib**, **-imibe**, **-tinib** and **-sertib**; it is important that healthcare professionals are taught these helpful tips (13).

While examining the proposed INN *deferitazole*, the participants were concerned about confusion with the many other INNs ending in “azole”. There are currently 157 of them according to our research, since several common stems end in “azole”: **-bendazole** for *tiabendazole* derivatives (15 drugs) (14); **-conazole** for *miconazole* derivatives (43 drugs) (15,16); **-nidazole** for *metronidazole* derivatives (26 drugs) (17); **-piprazole** for psychotropic phenylpiperazine derivatives (9 drugs) (18); and **-prazole** for antiulcer benzimidazole derivatives (21 drugs) (19,20). When la revue *Prescrire* presented these stems, it drew particular attention to the risk of confusion between **-piprazole** and **-prazole** (18,20).

Finally, the examination of List 108 of proposed INNs provided an opportunity to discover some pre-stems proposed by the US drug nomenclature committee (USANC: United States Adopted Names Council): –corat for glucocorticoid receptor agonists (a type of non-steroidal anti-inflammatory drug), in *tomicorat*; –espib to denote heat shock protein (HSP) inhibitors, in *luminespib*; and –parantag for heparin antidotes, in *delparantag*.

Monoclonal antibodies: other effects of overcrowding. List 108 of proposed INNs contains 15 monoclonal antibodies, expanding an already overcrowded group. In addition to the 2 INNs against which we have lodged objections, 4 others could cause confusion: *pidilizumab*, *pinatuzumab vedotin*, *polatuzumab vedotin* and *concizumab*.

Pidilizumab and *ipilimumab* could be confused because they sound and look similar. The same problem was identified for *pinatuzumab vedotin* and *polatuzumab vedotin*, which only differ by 2 letters, prompting many participants to consider lodging a formal objection. Participants did not understand the “vedotin” part of these names, even though it refers to an active moiety. A concerted effort is therefore needed to explain this term to users. It would also be helpful to highlight the parts that differ in these INNs (e.g. *PINatuzumab vedotin* and *POLatuzumab vedotin*) to prevent confusion.

Another source of confusion is when a monoclonal antibody’s potential use is hard to infer from its sub-stem. In the case of *concizumab*, participants did not deduce its haemostatic effect. This creates a risk of confusion with other antibodies that contain the sub-stem –c(i)–, which also act on the vascular system but have very different uses, namely in oncology.

These problems show that the limits of the nomenclature scheme for monoclonal antibodies are being reached due to the sheer size of the group, creating confusion through similarity and generating INNs that are difficult to interpret.

Confusion with brand names. Some of the proposed INNs resemble the brand names of drugs already marketed in France. Participants felt that similarity at the start of the name would be particularly conducive to selection errors when selecting drugs arranged in alphabetical order on a computer screen or shelf, for example: similarity between the antibiotic *brilacidin* and the antiplatelet drug Brilique° (*ticagrelor*) would expose patients to the double risk of bleeding and exacerbation of the infection for which the antibiotic was prescribed; and the similarity between the monoclonal antibody *nesvacumab* and NeisVac°, a meningococcal group C conjugate vaccine supplied in prefilled syringes, is compounded by the fact that they could easily be stored next to each other in a refrigerator.

In summary, our analysis of the INNs proposed in List 108 raises many questions about both INN comprehensibility and the risks of confusion. By identifying problems, we can anticipate some occasionally complex mechanisms through which errors could arise, which should be carefully taken into account when accentuating the differences between INNs and educating healthcare professionals about INNs. Healthcare professionals and patients can only think and act successfully in terms of INNs when these names are devised and taught in a rigorous, consistent and effective way; and if they are presented to them with as legibly as possible.

A handwritten signature in black ink, appearing to read 'Bruno Toussaint', is located in the bottom right corner of the page.

Bruno Toussaint
Publishing Director

Review prepared and translated by the *Prescrire* Editorial Staff with the participation of healthcare professionals from the *Association Mieux Prescrire*.

No conflicts of interest

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