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Prescrire's contribution to the WHO consultation on List 123 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 escalating number of INNs now in circulation and the sheer number of applications for new INNs, some of which are never used. 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 other contributors, including lecturers in pharmacy and medicine, has examined List 123 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2020 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 163 INNs proposed in List 123, and 2 amendments to INNs proposed in previous lists, was based on the following resources: the WHO's Stem Book 2018 (and its addendum), INN database, and lists of pre-stems, biological and biotechnological substances, and radicals; the United States Adopted Names (USAN) stem list; databases of drugs marketed in France, which enable 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 123. In each case, the participants then assessed the likelihood and clinical consequences of a medication error and/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.

A huge list. This is a very long list, comprising 163 proposed INNs and 2 amendments. Naming this many new drugs is a real challenge!

Our examination of List 123 identified the use of a number of pre-stems: **-batinib** for BCR-ABL kinase inhibitors; **-bep** for engineered or synthetic protein scaffolds, non-immunoglobulin variable domain derived; **-bresib** for inhibitors of bromodomain proteins; **-cianine** for fluorescent dyes derived from indocyanine; **-espib** for heat shock protein (HSP) 90 inhibitors (other than **-mycin**); **-lintide** for amylin derivatives and analogues; **-meran** for messenger RNA (mRNA); **-metostat** for histone *N*-methyltransferase inhibitors; **-pixant** for purinoreceptor (P2X) antagonists; **-saicin** for analgesics, capsaicin analogues; **-sudil** for Rho protein kinase inhibitors; **-terkib** for ERK (extracellular signal-regulated kinase) inhibitors; and **-vivint** for Wnt signalling inhibitors (12).

This list also features some proposed INNs that include a USAN stem: -cirnon for chemokine receptor (CCR) antagonists, not antivirals; -polstat for DNA polymerases; and -xian for coagulation factor XIa inhibitors (15).

Objections

The risk of confusion or misunderstanding associated with seven INNs proposed in List 123 was of sufficient concern to warrant a formal objection: the prefix "adren-", present in the proposed INN *adrenomedullin pegol*, and six INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs, namely *dafsolimab setaritox*, *grisnilimab setaritox*, *mipasetamab uzoptirine*, *tusamitamab ravtansine*, *upifitamab rilsodotin*, and *zanidatamab zovodotin*.

"adren-": a prefix with a history, to be used with caution. Most of the members of our review group felt that the immediately recognisable prefix "adren-" in the proposed INN *adrenomedullin pegol* could lead to confusion with *adrenaline*, used as a nonproprietary name for *epinephrine* in many countries, including France (19,20). Confusion between these two drugs would expose patients to the opposite pharmacological effect to the one intended — vasodilation with *adrenomedullin pegol*, peripheral vasoconstriction, among other effects, with *epinephrine* — which could have particularly dangerous consequences in a life-threatening emergency. The prefix "adren-" has only been used once before in an INN, namely *adrenalone* (21). In view of the risk of confusion over the pharmacological effect of this drug, it would be better to amend this proposed INN, dropping the prefix "adren-", and possibly making use of the stem **-dil** to indicate the drug's vasodilatory effect.

The abiding risk associated with the naming of monoclonal antibodies conjugated to active substances. We are still deeply concerned about the risks associated with the two-term INNs given to monoclonal antibodies conjugated to cytotoxic drugs. The list of these conjugates continues to grow, creating 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. To give two examples, *trastuzumab emtansine* (List 103), *trastuzumab duocarmazine* (List 115) and

trastuzumab deruxtecan (List 115) all contain the antibody *trastuzumab* but conjugated to different cytotoxic drugs, while the list of compounds containing the cytotoxic moiety *ravtansine* conjugated to an antibody continues to grow: *cantuzumab ravtansine* (List 105), *indatuximab ravtansine* (List 105), *anetumab ravtansine* (List 109), *coltuximab ravtansine* (List 109), *praluzatamab ravtansine* (List 121) and *tusamitamab ravtansine* (List 123)(9,22-26).

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, they may prescribe, dispense or administer the wrong product, causing dosing errors. The proposed INNs *dafsolimab setaritox*, *grisnilimab setaritox*, *mipasetamab uzoptirine*, *tusamitamab ravtansine*, *upifitamab rilsodotin* and *zanidatamab zovodotin* add to the ever-growing list of similarly constructed INNs for monoclonal antibodies conjugated to cytotoxic agents, against which *Prescrire* has filed objections in previous consultations, mainly due to the risk that the cytotoxic moiety will be mistaken for a pharmacologically inactive radical (27).

For example, the chances of suspecting that *uzoptirine* is a cytotoxic drug are low in the absence of a stem indicative of this property. The ability of healthcare professionals to immediately identify the precise nature of the moiety referred to by the second term is vital, especially when it is pivotal to the conjugate's pharmacological action. Yet it remains very difficult to tell whether the second term refers to a pharmacologically active product or a radical with no particular pharmacological action. Although the other cytotoxic agents conjugated to monoclonal antibodies in List 123 contain a stem indicative of their activity, such as **-dotin** (in *rilsodotin* and *zovodotin*), **-tansine** (in *ravtansine*), and **-tox** (in *setaritox*), their inclusion in the section of List 123 on radicals and other substituent groups underplays their toxicity.

The WHO INN Programme has decided not to improve this particular aspect of the nomenclature for these conjugated compounds, on the grounds that the rules for naming them were established a long time ago and that few errors have been reported (28). And it is content to shift the responsibility for measures to prevent any confusion between INNs onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, requiring them for example to adapt the packaging and labelling of the products concerned, and the way they are listed in IT systems and on prescriptions, to help users tell them apart. Unfortunately, this leads to the paradoxical situation in which it is actually safer to use brand names than INNs.

Comments

Our review group identified a number of proposed INNs that could generate medication errors for a variety of reasons: the potential for confusion with a brand name; confusion with another INN; or uncertainty over their meaning.

Potential confusion with a brand name. Some INNs proposed in List 123 could be confused with a brand name, especially *aldumastat*, *cagrilintide*, *danavorexton*, *firazorexton* and *hepcidin*.

The first three syllables of the proposed INN *aldumastat* and of the brand name Aldurazyme° (*laronidase*) are very similar. This could cause the wrong drug to be selected from an alphabetical menu. In addition, phonetic similarity, in French, was identified between *aldumastat* and the brand name Haldol décanoas° (*haloperidol*).

One member of our review group identified phonetic similarity between the proposed INN *cagrilintide* and the brand name Integrilin° (*eptifibatide*).

A risk of selecting the wrong drug from an alphabetical menu was reported with the proposed INN *danavorexton* and the brand name Danatrol° as well as the INN of Danatrol°'s active substance *danazol*.

Similarly, several participants reported the risk of selecting the wrong drug from an alphabetical menu with the proposed INN *firazorexton* through confusion with the brand name Firazyr° (*icatibant*), which starts with the same 5 letters.

Resemblance was noted between the proposed INN *hepcidin* (especially the proposed French INN *hepcidine*) and Hélicidine°, the brand name of a cough suppressant syrup.

Potential confusion with another INN. Some of the INNs proposed in List 123 could be confused with another existing or proposed INN, especially *valiloxibic acid, asundexian, cagrilintide, dapiglutide, darigabat, flubentylosin, garivulimab, pavunalimab, pavurutamab*, *and tenofovir amibufenamide*.

A minor risk of visual or phonetic confusion was identified between the proposed INN *valiloxibic acid* and the INN *valproic acid*, which could cause the wrong drug to be selected from an alphabetical menu

The proposed INN *asundexian* contains the USAN stem -xian, for coagulation factor XIa inhibitors, preceded by the letters "de", which could cause it to be mistaken for a *dextran*.

One participant noted phonetic similarity between the proposed INN *cagrilintide* and the INN *anagrelide*.

Several participants felt that the proposed INN *dapiglutide* is too similar to the INN *albiglutide*, as they contain the same sequence of vowels.

The proposed INN *darigabat* shares strong visual and phonetic resemblance in French with the INN *dabigatran* and, to a lesser degree, with the brand name Débridat° (*trimebutine*).

Although the construction of the proposed INN *flubentylosin* cannot be faulted, many participants noted the risk of confusion with the INN *flubendazole*, because they share the same prefix, "fluben-".

A high likelihood of confusion was noted between the proposed INN *garivulimab* and the INN *sarilumab*, as they share the same stem, the same sequence of vowels and have 8 letters in common.

Similarly, many members of our review group found the phonetic and visual similarity between *pavunalimab* and *pavurutamab* (both proposed in this list) too strong.

The INN *tenofovir amibufenamide* was proposed in List 123 for a new prodrug of *tenofovir*. Many reviewers were concerned that yet another drug with *tenofovir* in its name would increase still further the risk of confusion that already exists between *tenofovir alafenamide*, *tenofovir exalidex* and *tenofovir disoproxil fumarate* (an alternative name for *tenofovir*), and wondered whether these "copies" offered any real advantages to patients. This risk of confusion is particularly high between *tenofovir amibufenamide* and *tenofovir alafenamide*, due to the similarity of their second terms. Confusion between the two drugs would probably result in dosing errors. It is important that healthcare professionals understand the modulatory role these radicals have on the pharmacologically active substance to which they have been added, whether they convert it to a prodrug or alter its pharmacokinetic or pharmacodynamic properties.

Confusing proposed INNs. Some of the INNs proposed in List 123 confused certain members of our review group, especially *valiloxibic acid*, *icapamespib*, *oplunofusp*, *pirepemat* and *resiniferatoxin*.

It surprised our reviewers that the proposed INN *valiloxibic acid*, described as referring to a $GABA_B$ receptor agonist, lacked the stem **gab**.

Some reviewers, who consider it useful when INNs also reflect the drug's chemical composition, felt that the proposed INN *icapamespib* could have indicated the presence of iodine in its chemical structure more clearly, and would have preferred to see "io" or "iod" in the prefix.

The proposed INN *oplunofusp*, and in particular its infix **-o-**, does not convey this fusion protein's antiviral action. Many of our reviewers would have preferred a more informative INN.

Given *pirepemat*'s chemical structure and the claim that it is a nootropic, one reviewer wondered why this proposed INN lacked the stem **-racetam**. This reviewer also noted that the presence of fluorine and a benzene ring is indicated in the proposed INN *flubentylosin* but not in *pirepemat*.

One reviewer noted the presence of a vanillyl group within the chemical structure of *resiniferatoxin*. This group, present in vanilloids, is also found in the chemical structure of *capsaicin*. If *resiniferatoxin* turns out to be a *capsaicin* analogue, it would be a pity not to have used the stem **-saicin** in its INN.

Welcome amendments. The proposed INN *favezelimab* is a welcome replacement for *mavezelimab*. In our response to List 121, we pointed out that the phonetic and visual similarities between *mavezelimab* and the INN *manelimab* could cause errors (27,29).

Our review group raised no objections to replacing *diroleuton* (List 118) with *daleuton*, but neither did we submit any concerns about *diroleuton* in our response to List 118 (27,30).

In summary. List 123 reflects the continuing rise of complex two- or even three-term INNs, often used, for example, for gene therapy products. Faced with the growing demand for new INNs, we salute the INN Programme for having managed to preserve the system's intrinsic qualities of universality and simplicity, while remaining sufficiently informative for healthcare professionals, able to evolve, and independent of the pharmaceutical industry.

However, our reviewers sometimes expressed surprise, incomprehension, or even disappointment, with comments such as "*Overly complex INN*", "*Impossible to remember*", "*It will be simpler to use the brand name*", "*Three words for one molecule… with 10 or 11 syllables…*". Without knowing how many of these complex INNs will culminate in a marketed product, used perhaps to treat only a handful of patients managed by highly specialised healthcare professionals.

Solid, effective INN teaching programmes are as important as ever.

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Publishing Director

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References

1- Prescrire Editorial Staff "Think INN, prescribe INN, dispense INN: good professional practice" *Prescrire Int* 2000; **9** (50): 184-190.
2- Prescrire Editorial Staff "Informed decisions: think of the INN" *Prescrire Int* 2005; **14** (78): 122.
3- Prescrire Rédaction "Patients-soignants: priorité à la DCI" http://www.prescrire.org/cahiers/dossierDciAccueil.php
4- International Society of Drug Bulletins (ISDB) "Special issue on INNs" *ISDB Newsletter* November 2006; **20** (3): 27 pages.
5- International Medication Safety Network (IMSN) "Improving the safety of international non-proprietary names of medicines (INNs)" November 2011; 5 pages.
6- Prescrire Rédaction "Ordonnance: la dénomination commune internationale (DCI) au quotidien" *Rev Prescrire* 2012; **32** (346): 586-591.
7- Prescrire Editorial Staff "Drug regulatory agencies maintain confusion between brand names" *Prescrire Int* 2008; **17** (94): 83-86.
8- Council of Europe - Expert Group on Safe Medication Practices "Creation of a better medication safety culture in Europe: building up safe medication practices" Initial version of the report published online 19 March 2007: 257 pages.
9- WHO "Proposed international nonproprietary names: List 123" *WHO Drug Information* 2020; **34** (2): 263-452.
10- WHO "The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances" WHO/EMP/RHT/TSN/2018.1 + Addendum July 2020; 220+5 pages.
11- WHO "International nonproprietary names (INN) for pharmaceutical substances" mednet.who.int.
12- WHO "Pre-stems: Suffixes used in the selection of INNs" July 2020; 6 pages.
13- WHO "International Nonproprietary Names (INN) for biological and biotechnological substances" Update 2019.1; 96 pages.
14- WHO "International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others - Comprehensive list" Update 2015.1; 80 pages.
15- United States Adopted Names Council "USAN Stem List" https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-approved-stems
16- ANSM: Répertoire des Spécialités Pharmaceutiques. http://agence-prd.ansm.sante.fr/php/ecodex/
17- CNHIM Base de Données Thériaque. http://www.theriaque.org
18- Martindale: The Complete Drug Reference. https://www.medicinescomplete.com
19- Aronson JK ""Where name and image meet"—the argument for "adrenaline"" *BMJ* 2000; 320 (7233): 506-509.
20- Prescrire Editorial Staff "Obstacles to the universal application of INNs" *Prescrire Int* 2014; **23** (153): 248-251.
21- WHO "Proposed international non-proprietary names: List 1" *Chronicle of the World Health Organization 1953*; **7** (10): 299-324.
22- WHO "Proposed international nonproprietary names: List 103" *WHO Drug Information* 2010; **24** (2): 125-198.
23- WHO "Proposed international nonproprietary names: List 105" *WHO Drug Information* 2011; **25** (2): 151-218.
24- WHO "Proposed international nonproprietary names: List 109" *WHO Drug Information* 2013; **27** (2): 135-209.
25- WHO "Proposed international nonproprietary names: List 115" *WHO Drug Information* 2016; **30** (2): 241-357.
26- WHO "Proposed international nonproprietary names: List 121" *WHO Drug Information* 2019; **33** (2): 233-392.
27- Prescrire "Prescrire's responses to the WHO's consultations on proposed INNs" https://english.prescrire.org/en/79/549/49236/4221/ReportDetails.aspx
28- Robertson J et al. "The INN global nomenclature of biological medicines: A continuous challenge" *Biologicals* 2019; **60**: 15-23.
29- WHO "Proposed international nonproprietary names: List 121" *WHO Drug Information* 2019; **33** (2): 233-392.
30- WHO "Proposed international nonproprietary names: List 118" *WHO Drug Information* 2017; **31**(4): 635-754.