Prevention of errors related to authorised brand names: the EMA can still do more

- In March 2022, Prescrire responded to a public consultation launched by the European Medicines Agency (EMA) in preparation for the 7th revision of its guideline on the acceptability of brand names for drugs authorised via the centralised procedure. The new version of this guideline was published in December 2023.
- For drugs that are the subject of a European marketing authorisation application, the EMA is stepping up its efforts to prevent medication errors related to brand names. But it still does not encourage systematic use of international nonproprietary names.
- While the introduction of a preliminary assessment of brand name-related risks within Europe represents a step in the right direction for patient safety, the requirements for pharmaceutical companies unfortunately still fall far short of those that have been in place for years in the US and Canada.

Drug brand names sometimes cause medication errors. They are owned by pharmaceutical companies who are fiercely protective of their trademarks. Prescrire closely monitors the policies implemented by drug regulatory agencies, in particular in Europe, to prevent errors and adverse effects related to brand names.

Independently of trademark-related issues, which fall outside its remit, the European Medicines Agency (EMA) reviews drug brand names as part of the centralised marketing authorisation procedure (1). In March 2022, Prescrire contributed to a public consultation launched by the EMA in preparation for the 7th revision of its guideline on the acceptability of brand names for drugs (2,3). No other organisation representing patients or healthcare professionals contributed to this consultation (**a**). The new version of the guideline was published in December 2023 (1). What are the main changes introduced?

Umbrella branding no longer acceptable at the European level: a welcome position. The EMA considers that the addition of any segment to a brand name constitutes a new brand name, but explicitly rejects "umbrella" branding, which groups drugs and other health products with different compositions under variants of the same brand name. The EMA notes that the use of umbrella brands makes it harder to correctly identify a medicinal product, and creates a risk of confusion and medication errors (1,3).

This European position is a much-needed step forward in terms of patient safety: Prescrire has called for this change on numerous occasions, and it supports the French Health Products Agency's (ANSM) recommendation to abolish umbrella branding, which has been approved by the Conseil d'État, France's administrative supreme court (4-7). These welcome decisions aim to prevent new umbrella brands from being introduced onto the European market.

Efforts to better anticipate potential errors caused by confusion between brand names. Compared to the previous version published in 2013, this 7th revision of the guideline provides more information about how the EMA Name Review Group (NRG) assesses brand names, and the criteria on which it bases its decisions (1,5). In the meantime, the EMA developed its good practice guide on the prevention of medication errors (8).

For example, in addition to visual and phonetic similarities, the EMA thus requires the assessment of the risk of errors conducted by pharmaceutical companies to take into account potential confusion with other brand names, even if they do not share the same letters in the same order. The assessment must also take into account how the product will be used in practice, the complexity of its handling for healthcare professionals, the particularities of the intended patient populations, and the settings in which the name will be used (see the inset opposite, "Review of drug brand names by the EMA: hundreds of submissions per year") (1).

The EMA requires pharmaceutical companies to propose names that are compatible with the product's packaging and are, for example, short enough to fit on small items of primary packaging (i.e. those directly in contact with the drug), such as vials or blister pockets. It reserves the right to refer cases back to the NRG at the stage of reviewing the packaging mock-ups submitted by companies as part of their marketing authorisation application,

Review of drug brand names by the EMA: hundreds of submissions per year

Within the European Medicines Agency (EMA), review of brand names for drugs is delegated by the Committee for Medicinal Products for Human Use (CHMP) to a specific working group, the Name Review Group (NRG). The NRG is chaired by an EMA representative and made up of representatives from each of the national drug regulatory agencies within the European Union. Representatives from the European Commission and World Health Organization as well as European experts may also participate in its activities (1). According to the statistics included with the minutes of CHMP meetings, the NRG receives many more submissions than the hundred or so authorisations of new substances issued by the EMA each year (2).

In 2023, the NRG examined 498 brand name submissions, 62% of which were accepted. In the course of these reviews, 1118 objections or comments were made, 749 of which were rejected. The number of objections and comments has increased over the years. In 2023, they mainly concerned similarities with other brand names (77%), followed by similarities with international nonproprietary names (INNs) (7.6%) or inclusion of INN stems (0.8%), and names conveying a promotional message (4.4%) (2).

All in all, while the number of submissions appears to be stable from year to year, activity related to objections and comments seems to be increasing.

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Volume 44 N° 493 • Page 865

1- EMA "Mandate, objectives and rules of procedure for the Name Review Group (NRG) EMA/411943/2014 Rev. 1" 7 October 2019: 6 pages.

2- CHMP "Overview of (invented) names reviewed in April 2024 by the Name Review Group (NRG)" ema.europa.eu accessed 30 December 2024.

and to reject names that do not comply with its guideline (1).

Encouraging companies to accompany their proposed name submissions with a preliminary assessment of the risks related to these names represents a step towards increased safety. However, as of late August 2024, the EMA's new requirements had not been incorporated into the NRG submission form (1,9).

A far less robust review methodology than those used by North American drug regulatory agencies. The new revision of the guideline finally sets out the method the EMA uses to check for similarities between new proposed names and existing names: by providing information about its general rules, setting out its criteria, explaining the process of linguistic review by the national drug regulatory agencies and presenting its own assessment checklist (1). The EMA's similarity analysis is based on a regularly updated dataset extracted from the European medicines database, which has been made publicly available in spreadsheet form since July 2018, and offers limited functionality for searches of this kind (10,11). In response to our request, as part of the consultation, for the provision of a more sophisticated search tool, such as the program made available by the US Food and Drug Administration (FDA) since 2009, the EMA noted that it is in the process of developing its own algorithm for assessing phonetic and orthographic similarities between medicinal product names (3,12).

Since 2006, the development of psycholinguistic and ergonomic methods for analysing the human factors contributing to drug name confusion errors has led the US and Canadian regulators to strengthen their review procedures and their requirements for pharmaceutical companies (5). The FDA review procedure is based on a specific submission dossier that includes the corresponding labelling and packaging, including any administration and measuring devices, accompanied by the name, labelling and packaging assessments conducted by the pharmaceutical company (**b**). The review takes into account the context in which the drug will be used, and includes: searching databases for similar names and producing a similarity analysis using its own publicly accessible "POCA" (Phonetic and Orthographic Computer Analysis) program; listing reported cases of confusion errors; conducting simulation studies for the various phases of medication use; and actively searching for potential causes of confusion using a Failure Mode and Effects Analysis (FMEA) (12,13).

Since 2014, the Canadian drug regulatory agency (Health Canada) has adopted a more methodical procedure, with pharmaceutical companies required to carry out three steps: performing a systematic search for similar drug names that carry a risk of confusion; simulating perception of the drug, in particular in the context of electronic information;

a- *The EMA only received 11 responses to this public consultation, mostly from pharmaceutical companies (including Novartis, Gamida Cell and Gedeon Richter) or organisations responsible for protecting the interests of the pharmaceutical companies, including the Association of the European Self-Care Industry (AESGP), Asociación para el Autocuidado de la Salud, European Federation of Pharmaceutical Industries and Associations (EFPIA), European Industrial Pharmacists Group (EIPG), and specialist brand consultancy firms or organisations, such as Addison Whitney, the Drug Safety Institute and the International Trademark Association (ref 3).*

b- *This "proprietary name review" is included as part of the approval documents published on the FDA website (in the drugs@fda section).*

and producing a synthesis of all their findings, including an FMEA. Health Canada also provides numerous methodological clarifications and examples, including lists of attributes to take into consideration when determining the degree of similarity with brand names that might cause confusion (14).

The methodology set out in the European guideline thus appears to fall far short of those used by the FDA and Health Canada (13,14).

International nonproprietary names: the EMA does not favour their use in brand names. In its contribution to the consultation, Prescrire suggested that the EMA might encourage pharmaceutical companies to use brand names made up of the international nonproprietary name (INN) combined with the name of the marketing authorisation holder. Prescrire noted that there is no obligation to use an invented name in the European Union, and that this solution should be imposed when a brand name proposed by a pharmaceutical company is rejected (**c**). This could act as an incentive by providing a fast-track option with lower fees for pharmaceutical companies and agencies (1,3).

This proposal was opposed by the EMA which, despite claiming it does not want to discourage the use of INNs, requires names made up of the INN combined with a company or brand name to undergo the same review process as invented names; the EMA also rejected the idea of adopting this solution if no invented name is accepted by the NRG (1,3,4). Its reasons for doing so include: the claim that this would act as an obstacle to free trade (which would in fact be facilitated by the use of global brand names); the lack of evidence that medication errors are reduced when INNs are used in medicinal product names; and the length of the resulting brand names, which could be incompatible with labelling on small packaging items and could carry a risk of selection error in electronic lists, particularly for fixed-dose combinations (1,3).

By definition, name similarity scores are unfavourable to INNs that include a common stem shared by a group of drugs, even though this makes it easier to recognise their relationship. The new EMA guideline sets the threshold for review of orthographic similarity between a brand name and an INN at 50% (1).

Strong influence of commercial considerations in relation to brand names. Unlike INNs, different brand names can be assigned to the same drug in different indications (1). This is the case with *semaglutide*, which is authorised under the name Ozempic® in type 2 diabetes and Wegovy® in obesity.

Pharmaceutical companies invest considerable resources in developing brand names that are easy to remember and thus easy to promote. This process often involves experts from specialist agencies, some of whom actively contributed to the consultation on this guideline (**a**)(3).

The section of the guideline setting out details of the review procedure and the conditions under which the EMA NRG makes its decisions has been considerably expanded (1). For example, proposed names are considered to be "*conditionally accepted*" where there is a risk of confusion between two candidate names undergoing review; the first one to obtain marketing authorisation is retained while the other is rejected. In such cases, the EMA may, at the request of one of the two pharmaceutical companies concerned, put these companies in direct contact with one another for the purposes of negotiation, without further involvement in this discussion (1,3).

The guideline also incorporates a position developed by the NRG in 2011 on the reuse of brand names that have already been marketed, which was not the case when the 6th revision of the guideline was published in 2013 (15). Although the NRG claims to take into account aspects related to product awareness and safety issues when reviewing a reused name, this represents a risk to patient safety (1,3). Brand names that are identical or very similar to those used in other countries, but contain different substances, create confusion that can lead to wrong-drug errors or to users consulting information on the wrong drug. Various cases have been identified in Europe and elsewhere, including Candazol® (corresponding to *sertaconazole* in France, but *omeprazole* in Greece), and Previscan® (corresponding to *fluindione* in France, but *pentoxifylline* in Argentina) (3,16,17).

IN PRACTICE **Still room for improvement.** In its response to the public consultation, Prescrire welcomed the improvements made to the guideline on brand names authorised via the centralised procedure. But it is a shame, for example, that pharmaceutical companies are merely encouraged to directly report errors related to the names of their drugs to the NRG, given that anyone who becomes aware of such an error is expected to report it to pharmacovigilance systems (1). While the introduction of a preliminary assessment of brand name-related risks by pharmaceutical companies represents a step forward for patient safety, the requirements unfortunately still fall far short of those that have been in place for years in the US and Canada.

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Volume 44 N° 493 • Pages 864-867

c- *Article 1 (20) of the European directive defines the "name of the medicinal product" as "the name given to a medicinal product, which may be either an invented name or a common or scientific name, together with a trade mark or the name of the manufacturer; the invented name shall not be liable to confusion with the common name" (ref 18).*

Selected references from Prescrire's literature search

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2- Prescrire Editorial Staff "Consultation on proprietary drug names" *Prescrire Int* 2023; **32** (246): 82.

3- EMA "Overview of comments received on draft 'Guideline on the acceptability of names for human medicinal products processed through the centralised procedure' (EMA/CHMP/287710/2014 – Rev. 7)" 15 December 2023: 105 pages.

4- Prescrire Editorial Staff "Prescrire's advice: brand names: reorient the EMEA draft guidelines towards patients' interests" *Prescrire Int* 2008; **17** (94): 85.

5- Prescrire Rédaction "Noms commerciaux: la sécurité des patients doit primer sur la promotion des marques" *Rev Prescrire* 2014; **34** (368): 462.

6- Prescrire Rédaction "Gammes ombrelles: vers leur arrêt sur initiative de l'ANSM" *Rev Prescrire* 2018; **38** (417): 506-507.

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8- EMA "Good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014)" 18 November 2015: 41 pages.

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13- Food and Drug Administration, Center for Drug Evaluation and Research "Best Practices in Developing Proprietary Names for Human Prescription Drug Products. Guidance for Industry" December 2020; 42 pages. fda.gov accessed 10 February 2024.

14- Health Canada "Guidance Document for Industry - Review of Drug Brand Names" 2 July 2014: 44 pages.

15- EMA "NRG position paper re-use of invented names of medicinal products (EMA/648795/2009)" 23 May 2011: 5 pages.

16- Prescrire Editorial Staff "Drugs' brand names are a source of confusion" published online at https://english.prescrire.org 2009: 1 page.

17- Merchant L et al. "Identical or similar brand names used in different countries for medications with different active ingredients: a descriptive analysis" *BMJ Qual Saf* 2020; **29** (12): 988-991.

18- "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use": 62 pages.

Artificial intelligence: perpetuating bias and stereotypes

● Since "generative" artificial intelligence (AI) tools produce content based on information that is freely available online, they contribute to spreading the biases present in these online materials. Their developers have a responsibility to correct these biases.

With its ability to rapidly synthesise a large amount of data, artificial intelligence (AI) is being touted as a source of progress in numerous fields, including health care. But this is dependent, among other things, on the reliability and completeness of the data processed by AI tools (1).

According to France's Defender of Rights (a civil rights ombudsman), "*the databases processed by algorithms must be representative of the population in order to prevent these algorithms from generating discriminatory biases based on this information, in particular with regard to gender differences, and different social determinants of health such as region, life history or socioeconomic status*" (our translation) (2).

The United Nations Educational, Scientific and Cultural Organization (Unesco) has also warned that "generative" AI can produce information reflecting the prejudices that run through society. A group of researchers studied the generative AI tool ChatGPT 3.5 alongside GPT-2 and Llama 2, two open-source "large language models" (or LLMs, a form of AI) used by numerous generative AI tools. They found that in the texts generated by these LLMs, female names were associated with the words "home", "family", "children", "marriage", "prostitute" and "waitress", while male names were associated with the words "business", "executive", "salary" and "career". GPT-2 and Llama 2 also often generated negative content about homosexual subjects, though this was not the case with ChatGPT (3).

According to Unesco, AI can "*reinforce stereotypes, biases and violence against women and girls*", and cause them tangible harm, in particular when used in tools for job recruitment, determining loan approvals or insurance premiums, or even medical diagnosis (3).

Unesco is calling on AI developers and policy makers to work to prevent AI from "*perpetuat*[ing] *(and even scal*[ing] *and amplify*[ing]*) human, structural and social biases*". The fact that ChatGPT 3.5 does not perpetuate the negative prejudices against homosexuality present in the GPT LLM on which it is based shows that human intervention (in the form of "reinforcement learning from human feedback") remains essential for identifying and correcting biases in the algorithms used by AI tools (3).

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