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Prescrire's comments on QRD Recommendations EMEA/208304/2009
Preventing errors related to the expression of strength on drug packaging

The European Commission has produced detailed definitions of drug strengths because of their impact on the fees paid by pharmaceutical companies (**a**)(1p3-4). These definitions are not intended to apply to the expression of strength in the summary of product characteristics (SPC), the package leaflet or on drug packaging (1p2). However these administrative definitions have entered into normal usage in these various situations, leading to overdoses and confusion between different strengths of the same drug, unnecessarily exposing European citizens to preventable adverse effects.

The European Medicines Agency (EMEA) has produced recommendations on the expression of strength in the name of centrally authorised human medicinal products, "*not only in order to achieve harmonisation across similar medicinal products and pharmaceutical forms, but especially in order to make improvements to medicines labelling to ensure the correct and safe use of medicines and minimise medication errors*" (2).

These draft recommendations are currently the subject of a public consultation (2). They are all the more important since national drug regulatory agencies and the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD) align themselves with the EMEA's position.

Prescrire is responding to this public consultation to push for safer and clearer naming of drugs (3).

The emphasis on concentration is a source of error

As of 2009, in accordance with European Commission guidelines, drugs are labelled with: the brand name + the strength + the pharmaceutical form and, underneath, the international nonproprietary name (INN) (4p.12). But these guidelines are ambiguous. Prescrire's systematic analyses of drug packaging reveal that in fact pharmaceutical companies place greater emphasis on commercial details: invented names, logos and company graphics (5-8).

Prominence given to concentration. The strength of liquid forms in particular is expressed as the amount of active substance in each millilitre (concentration) rather than as the amount of active substance in the total volume. Analyses of the packaging of centrally authorised medicinal products have revealed that the amount of active substance in the total

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volume is usually absent (for example: Naglazyme° (galsulfase), Torisel° (temsirolimus), Ventavis° (iloprost trometamol)) or poorly visible (for example: Abilify° (aripiprazole), Atriance° (nelarabine), Increlex° (mecasermin)) (6).

Furthermore, prominent display of a drug's concentration can cause errors: overdoses, some of which have been fatal, occur when the quantity per millilitre is confused with the total quantity in the container.

Keppra° (levetiracetam): 5-fold overdoses. Overdoses of the injectable form of the antiepileptic drug levetiracetam (Keppra°) were reported in France at the end of 2007, and were caused by the product's ambiguous labelling. Its concentration, "*100 mg/ml*", was displayed prominently on the labelling. Healthcare practitioners could have been led to believe that each vial contained 100 mg of levetiracetam, whereas they contain 5 ml of solution at a concentration of 100 mg/ml, i.e. 500 mg of the active substance. Five-fold doses were therefore injected by mistake (9).

The labelling was modified in 2008. The two largest surfaces of the box and the label on the vials now display "*500 mg/5 ml*" in large red letters, which is a welcome development. Nevertheless, the concentration "*100 mg/ml*" still appears in a highly visible way on the box and the vials, which could give rise to confusion (10).

Kaletra° (lopinavir + ritonavir): 20-fold overdoses. An overdose of the combination lopinavir + ritonavir caused a baby's death in France in 2007: 6.5 ml of oral solution (Kaletra° - Abbott) were given instead of 0.30 ml, i.e. roughly a 20-fold overdose (11). Although neither the French Health Products Safety Agency (AFSSAPS), the EMEA nor the drug company Abbott have made the precise causes of the overdose public, it is probable that where the packaging was labelled "*80 mg/20 mg"*, this was interpreted as the amount of lopinavir (80 mg) in 20 ml of solution, resulting in administration of a 20-fold dose (12).

In October 2007, the expression "*80 mg/20 mg*" was replaced by "*(80 mg + 20 mg)/ml"*, but the syringes supplied with the vials of Kaletra° oral solution are still graduated in ml rather than in units of weight of the two active substances (12). As with many dosing devices supplied with other drugs, the required dose in milligrams needs to be converted into the number of millilitres to be administered, and this is a source of error (8,13).

Elsewhere too. Errors related to highlighting the concentration in the labelling or naming of drugs have been reported in other countries, by medication errors reporting programmes (14,15). Here are a few examples: Torisel° is a concentrate that requires dilution before IV infusion, each vial of which contains 30 mg of temsirolimus, but it is labelled "*25 mg/ml*" (16); each of the different strengths of Metoject° (methotrexate sodium) mentions the concentration "*10 mg/ml*" first, leading to errors of selection when preparing electronic prescriptions (17); Mabcampath° is a concentrate for solution for infusion which, at the time, was supplied as 3-ml ampoules containing alemtuzumab at a concentration of 10 mg/ml (i.e. 30 mg/3 ml) (18); etc.

In summary, expressing a drug's strength in terms of its concentration exposes patients to the risk of errors, usually overdoses, through a failure to differentiate between different strengths of the same drug or by confusing the total amount of active substance present with its concentration. Given these risks, an EMEA initiative to clarify the expression of strength on drug packaging therefore seemed necessary.

Preventing errors related to the expression of strength on drugs: basic principles

Dosing errors are more likely when the drug's strength is expressed on packaging and labelling in an ambiguous way. The mechanisms that "precondition" such errors are well known and form the basis of the principles used to prevent them.

Preconditions to error. The risk of confusing different strengths arises mainly because contradictory information is displayed in the same field of view, even when it is read carefully. Furthermore, the orientation of the text and its prominence in the drug's name tend naturally to give greater importance to the concentration, expressed as the amount of substance per millilitre, which is displayed first. Finally, the layout of drug labelling is left to the discretion of the drug companies and is not adequately standardised, which means that each drug has to be analysed in a different way when searching for the critical information.

In summary, the readability of the expression of the amount of active substance present in drugs on their labelling is variable, complex, and ambiguous. When the total amount of active substance in each unit is not indicated, it systematically blurs the correct perception of its exact strength. This can cause healthcare practitioners and patients to make mistakes, even when they are particularly careful and conscientious.

Principles for preventing dosing errors. The principles for preventing medication errors related to drug packaging are widely available (19-22). Reducing the risk of dosing errors requires critical information to be displayed clearly on the labelling and packaging, and this needs to be taken into account right from the design stage (23). This ergonomic approach is based on basic safety principles, such as: simplification, priorisation and reminders, standardisation, differentiation, redundancies (double-checks), constraints, forcing functions and fail-safes, etc. (19-23).

According to these principles, when preparing doses for administration, the process needs to be simplified and the risk of overdose prevented by using ready-to-use unit-dose packaging or, where this is not possible, by supplying a dosing device that is appropriate to both the substance (graduated in weight units) and the posology. Furthermore the most crucial information for the safe use of the drug must be made immediately obvious, by displaying it first: information about the nature of the substance, by making its international nonproprietary name (INN) more prominent than its brand name (3); information about its strength, by making the total dose in the container more prominent than its concentration; information about the route of administration rather than the pharmaceutical form, etc.

It is also preferable to remove any graphics that are unnecessary or detract from the critical information.

The EMEA's interpretation of the "full name": a nonsense and a constant source of error

National agencies implement these principles for preventing dosing errors, at least in part, by expressing strength in a safer way on all the components of the drug's packaging (24-26). One might have expected the EMEA to have proposed measures along the same lines. Unfortunately, the EMEA's proposals are ambiguous and even counterproductive.

A clear, flexible legal basis. The particulars that need to be included on drug labelling are defined in the European Commission's guidelines, revised in 2009 following amendment of Directive 2001/83/EC by Directive 2004/27/EC (4,27).

According to article 54 of Directive 2001/83/EC: *"The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging: a) the name of the medicinal product followed by its strength and pharmaceutical form and, if appropriate, whether it is intended for babies, children or adults); where the product contains up to three active substances, the international nonproprietary name (INN) shall be included, or, if one does not exist, the common name;* (…)" (27). Article 55 stipulates that these particulars shall appear on "immediate packagings" and specifies that: *"The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed: the name of the medicinal product as laid down in point (a) of Article 54, and, if necessary, the route of administration; the method of administration; the expiry date; the batch number; the contents by weight, by volume or by unit"* (27).

The terms of the directive have been retranscribed in the European Commission's guideline on the readability of the label and package leaflet of medicinal products, as follows: "*Nevertheless, of the information items listed in Article 54 of Directive 2001/83/EC, certain items are deemed critical for the safe use of the medicine. These items are: name of the medicine; strength* ***and, where relevant, total content****; route of administration. Where possible these should be brought together using a sufficiently large type size on the labelling. Having these items* ***together in the same field of view*** *should be considered in order to aid users*" (4p.12).

And the importance of differentiating expressions of strength to maximise patient safety is clearly stated: "*In some cases the packaging may need to contain information on both the quantity per unit volume and on the total quantity per total volume. The total quantity per total volume can be particularly important for safety reasons for injectable products and other medicines available in solution or suspension*" (4p.12).

In summary, the expression of strength is so important to the correct identification of a drug that the European Commission requires it to be displayed immediately after the drug's name. It must be displayed in the same field of view as the brand name, the pharmaceutical form and the international nonproprietary name (INN) (4).

The EMEA's restrictive interpretation. In order to avoid repeating the "*name of the medicinal product as laid down in point (a)* of A*rticle 54"*, the EMEA has created an administrative expression to designate the usual way of naming a drug (its "full name"), and refers to the guideline on summary of product characteristics (4,28). However, there is no reason to apply the principles specific to SPCs to labelling, as each has its own separate guideline (4,28). It is precisely because healthcare practitioners and patients do not read labelling in the same way as they read a package leaflet or SPC, that separate guidelines were produced.

The intention of this jargon is probably to facilitate the handling of Marketing Authorisation (MA) applications by the EMEA and by pharmaceutical companies. In particular, if the concentration alone is given (in "*mg/ml*" for example) rather than the total quantity, different volumes and presentations can be included in the same MA application: this benefits both the EMEA by simplifying the processing of applications, and the drug companies by reducing their licensing fees (**a**)(1,29,30).

The standardisation that has arisen from this confusion between strength and concentration is very inconvenient (**b**). The EMEA is creating new opportunities for errors by recommending that the concentration remain prominently displayed, even if the greater emphasis is given to the total quantity of substance in the total volume, because it increases the risk of confusing the two expressions (2p5note**).

Thus, the priority the EMEA gives to an administrative concept of strength, limited solely to concentration, prevents acceptable practical solutions from being developed. Furthermore, it neither ensures the accuracy of the doses to be administered nor prevents the risk of confusion between different strengths of the same drug, in contrast to its claimed objectives ("*to ensure the correct and safe use of medicines and minimise medication errors"*).

Lack of drug packaging assessement. The use of the administrative expression “full name” for drug labelling and packaging shows the EMEA’s lack of expertise in the field of drug packaging, whereas it should be evaluating packaging systematically before drugs are marketed, in order to anticipate the risks of medication errors (20).

The EMEA needs to review its approach to preventing errors related to drug packaging completely. To improve patient safety, it is essential to conduct a systematic analysis of the risk of foreseeable errors related both to the expression of strength and to the labelling of the final packaging articles and dosing devices. This prospective risk analysis needs to be performed with even greater care for multi-dose forms, whatever their route of administration, and must include checking the effective precision of the dosing devices.

Prescrire’s advice for less ambiguous guidelines

The EMEA must have launched a public consultation process because it wants to remedy its lack of expertise in the risk assessement of packaging-related errors, because it does not perform them systematically on the medicinal products it authorises. It must also be because the disparity among Member States, and even among drug companies, means that unambiguous administrative solutions can no longer be found. Prescrire proposes a pragmatic approach, based on the long experience of its packaging working group.

Make the distinction between single-dose and multi-dose products. For drugs that are supplied in single-dose units, irrespective of their pharmaceutical form, the expression of the strength is unequivocal: the total amount of active substance contained in the dose must be displayed, and that alone. For dosage units that are administered or taken in their entirety, where the individual dose is contained for example in a tablet, a sachet, a unit-dose or an ampoule, etc., there is no reason to express the strength in terms of the total amount of active substance per gram (for semi-solid or powder forms) or per ml (for liquid forms).

Multi-dose products should be addressed separately, and the issue of their safe use must be approached in a more coherent manner, depending on their pharmaceutical form. Incidentally, partial use of a single-dose container, particularly of an injectable form, is associated with the same problems as multi-dose containers, whenever the posology mentioned in the SPC means that the unit will not systematically be administered in its entirety (for example when the posology is expressed in mg/kg or in mg/m²).

Drugs for reconstitution: the final concentration is only hypothetical. Expressing the strength of a preparation for reconstitution in terms of the concentration obtained after it has been reconstituted as described in the SPC does not help achieve this concentration, and does not guarantee the actual final concentration. Irrespective of the pharmaceutical form, reconstitution of a drug just prior to use requires knowing at least the nature and the volume of solvent to use, and sometimes the dose to be administered has to be calculated, making it difficult to foresee the concentration obtained.

Rather than displaying the final concentration after reconstitution, the total quantity of active substance in each container should be displayed prominently, especially for injectable forms, or failing this, the quantity of active substance likely to be measured when adequate precautions are taken to guarantee the concentration of the reconstituted solution, for example for oral solutions.

Multi-dose forms: the dosing device is key. The precision of the dosing device authorised with the drug is not adequately addressed in the proposed guidelines, but it should dictate how the strength is expressed and should correspond to the posologies stated in the SPC (13). The strength must therefore be expressed in terms of the amounts likely to be measured, rather than as the concentration in mg/ml alone. In this context, the proposed guidelines mention expressions of strength that have no relation to how the drug will be used and which are unhelpful, for example the amount of active substance in mg/g for oral forms, topical solid forms, creams or gels.

The fact that the EMEA refers to household spoons, when they patently cause dosing errors, shows its lack of experience in this field; while precisely graduated syringes for oral administration offer a level of accuracy that is appropriate to the task (31). Not only should the particulars displayed on dosing devices be set out in detail so as to harmonise them with those on the labelling and in the package leaflet, but stricter guarantees of their precision and their ability to prevent the risk of overdose ought to be provided in specific guidelines, which should include prohibiting the graduation of dosing devices in terms of kg of body weight (32).

It is high time, in 2009, that dosing devices were incorporated clearly in the regulations relating to medicinal products, and the first step would be to add this notion to the definitions in Directive 2001/83/EC (Title I, article 1) as soon as possible. The ambiguity surrounding the status of dosing devices associated with or incorporated into pharmaceutical products that require MA, which lies somewhere between the status of medical devices and medicinal products, is dangerous and harmful to patients.

Drugs for injection: closer to reality. Whether they are supplied in a unit-dose container (for example: a ready-to-use syringe or a ready-to-infuse bag) or in a multi-dose liquid form, requiring reconstitution or dilution, it is always preferable to express strength in terms of the total amount of active substance in the total volume (i.e. in a relative manner). This expression is the closest to reality and indicates the total dose in the container.

In contrast, displaying only the concentration can lead to accidental overdose whenever the volume of the container is greater than the unit of volume used to express the concentration. Highlighting a drug's concentration must therefore be prohibited, and its systematic use even more so. Nevertheless, it should be considered acceptable to display the concentration when the strength is also expressed as the total amount of active substance in the total volume, on condition that the concentration appears in a smaller font and in a separate area (22). In summary, the layout of such additional information must be standardised.

The same is true where it is traditional to express strength as a percentage: it is preferable that it is displayed as additional information, to facilitate understanding of the strength. For example, Prescrire's "Preventing the Preventable" programme received a report of a confusion between two strengths of injectable lidocaine because the percentage had been removed from the label in accordance with the French drug agency (AFSSAPS)' guidelines (25).

Multiple strengths left out. In practice, the expression of strength as the total amount of active substance in the total volume helps distinguish between the various strengths of a drug that all have the same concentration. The risk of dosing errors due to confusion between different strengths of the same drug means ensuring that when multiple strengths exist, the graphic design of their labelling makes it possible to tell them apart easily. The EMEA's proposed recommendations, like the European Commission's guidelines, say nothing about this issue, give no indication of the EMEA's requirements and do nothing to encourage pharmaceutical companies to design clearly differentiated packaging (2,4).

Transdermal patches: don't just look at the release rate. Transdermal patches are labelled with the quantity of active substance released over a specified time but this is insufficient for an appreciation of all the packaging-related risks, for example in the event of accidental ingestion. The labelling should also include (on the outer or secondary packaging at least) clear and legible details of the total amount of active substance contained in the patch, as well as the predicted residual quantity after use, in support of the information on the precautions for their use. Furthermore, the backing layer of a transdermal patch should always be identified and mention the strength.

Here again, when different strengths exist, efforts should be made to clearly differentiate them.

Assess labelling and packaging safety before granting marketing authorisation. The EMEA states in these proposals that its decisions are taken on a "*case-by-case basis"*, but it does not reveal the methods it uses to assess the labelling and packaging of the drugs that it authorises. This suggests that the EMEA does not perform such assessments systematically and provides some insight into why it is not recommending principles for the design of labelling and packaging that would increase patient safety, like those developed by the National Patient Safety Agency (NPSA) (22).

Rather than listing various examples in a disorganised table which imply that there is only one way of expressing the strength of drugs, it is essential to make the distinction between the critical information that should be displayed in the same field of view, such as the total amount of active substance, and additional information such as concentration or percentage. A drug regulatory agency is expected to assess the pertinence of any additional information that is displayed and when it is deemed necessary, to make sure that it does not create confusion. This can be achieved by displaying it in an area that is clearly separate from the critical information, with less prominence and in a way that does not interfere with the understanding of the critical information.

In practice, these recommendations are incapable of ensuring the safety of European patients

The role of drug regulatory agencies is to ensure the safe use of drugs, starting with clear and unambiguous identification that can be fully and immediately understood by healthcare professionals and patients. This especially applies to the information that is most critical to the safe use of the drug: information about the nature of the substance, giving greater prominence to its international nonproprietary name (INN) than its brand name (3,33); information about its strength, giving greater prominence to the total dose in the container than its concentration.

In addition to the many inadequacies in the EMEA's concept of drug labelling, the mediocrity of its policy on preventing errors related to drug packaging is shown by the absence of any incentive to drug companies to manufacture ready-to-use presentations, to carefully differentiate different strengths from the same range, to ensure precise delivery of the doses stated in the SPC by designing suitable, accurate dosing devices, etc. It is a poor offering that presages many dosing errors ahead.

The EMEA must review its rules on the expression of drug strength so that drug labelling ceases to expose European patients to unacceptable risks of medication errors.

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For Prescrire Editorial Staff
(no conflicts of interest)

a- *These definitions were devised as part of the rules governing marketing authorisation extensions and variations through centralised or mutual recognition procedures (ref. 1). They are reproduced in the EMEA's advice to drug companies applying for Marketing Authorisation (MA) through the centralised procedure (ref. 29). They greatly affect the fees payable by pharmaceutical companies. Indeed, by expressing the strength as a concentration, the fee for an additional presentation requested at the same time as the first authorisation is only 6300 euros, compared to 25 200 euros for an additional strength; furthermore, adding a new strength is considered as an extension of the MA (with a fee of 75 500 euros), whereas the fee for a new presentation at a concentration that has already been authorised is considered as a type II variation for injectable forms (fee of 75 500 euros) or a type Ib variation for other forms (fee of 6300 euros) (ref. 1,30).*

b- *The rules governing MA procedures have also given rise to the distinction between "partial use" and "total use" of a container, which is not defined by the European Pharmacopoeia. It allows the EMEA systematically to place emphasis on the drug's concentration rather than adhering to the total amount of substance in the total volume or in the dose to be measured (ref. 1,2). "Total use" is a particularly illusory concept since in everyday practice caregivers frequently need to divide the available presentations for dose adjustments (depending on the patient's age or on a variety of clinical situations).*

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