Clinical Excellence Commission

TGA Medicine Labelling and Packaging Review

August 2012

CLINICAL EXCELLENCE COMMISSION

The Clinical Excellence Commission (CEC) operates as an independent agency which adds value to the NSW public health system through its role in investigating, advising, supplying expertise, facilitating improvement, encouraging clinical input, evaluation and assessment of quality programs.

The CEC's Mission is to build confidence in health care in NSW by making it demonstrably better and safer for patients and a more rewarding workplace.

The CEC's Vision is to be the publicly respected voice providing the people of NSW with assurance of improvement in the safety and quality of health care.

The CEC maintains an active Medication Safety and Quality program, working to enhance patient outcomes and prevent avoidable harm by improving the safety and quality of medicines use. As a component of this work, the CEC advocates work to reduce the likelihood of look-alike, sound-alike medication errors, which have the potential to cause considerable patient harm.

WHY THIS REVIEW IS IMPORTANT

The Clinical Excellence Commission is heartened to see this review being undertaken by the Therapeutic Goods Administration. Whilst the *TGA Best Practice Guideline on Prescription Medicine Labelling* has been in place for a number of years and provides excellent guidance on how medicines can be named, packaged and labelled in such a way as to prevent error, uptake of the recommendations appears variable. This review provides an opportunity to raise the minimum expected standards for the naming, labelling and packaging of medicines.

Medication errors, and associated patient harm, can occur as a result of a number of contributing factors. For over forty years, similarity between medicines names and/or their packaging have been identified as contributing factors in medication errors[1]. Some authors have estimated that as many as 1 in 3 medication errors are related to confusion between two or more medicines caused by similarity between their names, labels or packages[2].

The CEC acknowledges that no single activity will eliminate all problems caused by look-alike, sound-alike products and advocates a multi-faceted approach to their prevention that includes a range of interventions including the use of technology (e.g. barcode scanning), safe product design, education of consumers and health care professionals, and regulatory intervention. The objectives of the review are admirable and fully supported by the Clinical Excellence Commission. The recommendations outlined in the consultation paper, if implemented, will assist in reducing medication errors in the Australian health care system and are largely supported by the Clinical Excellence Commission. Specific comment on each of the proposed regulatory changes and associated questions follows. Additional recommendations have been made as part of this submission for the consideration of the TGA.

GENERAL COMMENTS

Considerable work has been done on reducing look-alike, sound-alike errors across the world. Regulatory bodies in the USA, Canada and Europe and patient safety agencies in the United Kingdom and Denmark have each undertaken work in this field. This work, particularly that listed below, should be given strong consideration when regulatory changes are made by the TGA.

Notable regulations and other work:

- The European Medicines Agency: Guideline on the Acceptability of Names for Human Medicinal Products Processed Through the Centralised Procedure[3]
- Health Canada: Guidance for Industry, Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names[4]
- United States Food and Drug Administration: Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names[5]
- National Patient Safety Agency: A guide to labelling and packaging of injectable medicines[6]
- National Patient Safety Agency: A guide to the graphic design of medication packaging[7]

Additionally, the *TGA Best Practice Guideline on Prescription Medicine Labelling* contains many considered and valuable recommendations. Increasing the strength of a number of these recommendations by including them in revised regulations would be beneficial to patient safety.

The Clinical Excellence Commission was involved in the labelling round table jointly held by the Therapeutic Goods Administration and the Australian Commission on Safety and Quality in Health Care in 2011. The report from this round table contains a number of valuable recommendations that should be considered as part of this review.

RESPONSES TO THE PROPOSED REGULATORY CHANGES

PROMINENCE OF ACTIVE INGREDIENTS ON MEDICINE LABELS

1.1 The active ingredient(s) must be listed immediately below the brand name, with the first letter of the active ingredient directly below the first letter of the brand name.

The standard positioning of the active ingredient name is supported.

The active ingredient name is the most important piece of information presented on the medicines packaging and should be treated as such.

With the increasing use of generic medicines and patients switching between multiple brands of the same medicine[8] the potential for patients to be confused about their therapy and take multiple products with the same active ingredient, has been raised as a concern[9]. This concern is shared by numerous clinicians who frequently provide anecdotes of such medication misadventure.

Standardising the position of the active ingredient name on packaging is one mechanism for assisting consumers to access this information and correctly identify their medicines. Providing a more proscriptive requirement (e.g. the active ingredient(s) must be listed in the top left hand corner of the front panel) may be more beneficial than specifying its position in relation to the brand name.

As the active ingredient name is the most important piece of information, this may be more appropriately positioned above the brand name.

1.2 On the front/main panel of the label, the active ingredient must have equal prominence with the brand name.

As stated above, the active ingredient name is the most important piece of information presented on medicines labels. As such, this information should have **greater** importance than the brand name and should have commensurate prominence. The Clinical Excellence Commission acknowledges that requiring equal prominence is a step forward, but advocates for greater prominence for the active ingredient name than for the brand name.

Consumer groups strongly advocate for greater prominence of the generic name on product labelling as a mechanism to facilitate product identification and reduce the opportunity for errors[10].

1.2.1 The intention of 'equal prominence' is for the active ingredient to be as easy to locate and identify on the label as the brand name.

Information regarding the active ingredient should be as easy, or easier to locate and identify than the brand name.

1.2.2 The font size of the active ingredient must be at least 100% of the font size of the medicine brand name on the main/front label.
Principles of graphic design tell us that the prominence of information is related to not only the size of the type, but also the application of colour, bolding, shading and other design techniques. This proposal is supported and additional requirements for equal prominence (as per wording in the *TGA Best Practice Guideline on Prescription Medicine Labelling*) should be considered.
1.2.3 For improved differentiation between the brand name and the active ingredient there should be a difference in font style or letter spacing or font colour.
In Australia, the convention has been to use an initial capital letter for brand names and all lower case for active ingredient names (e.g. Brand, active). If this convention were required in labelling and packaging, there would be no need to use font style, letter spacing or colour to differentiate between the brand and active ingredient names. This approach should be considered.
1.2.4 The active ingredient should begin with an uppercase letter but the remainder should be in lower case.
As above, it is suggested that the active ingredient should always be presented as all lower case.
1.3 Where there are more than 3 active ingredients, the most abundant ingredients must appear on the main label immediately below the brand name and the names, together with the quantities of every active ingredient, are to be included on a side panel/label or on a rear panel/label for the product. (This does not apply to day and night preparations.)
Supported
1.4 For products containing day and night preparations that have different formulations, the composition of each tablet must be provided immediately below the brand name and the font size must be no less than 2mm in height on the main/front panel.
Supported
1.5 The active ingredient must be included with, and of equal prominence as, the brand name on at least 3 non-opposing faces of a carton.
Supported. Inclusion of the active ingredient name on at least 3 non-opposing faces allows for identification of the product when stored in a variety of ways. In addition to the active ingredient name, the strength of the medication should also be present. Health care professionals and patients may be using a variety of faces of the carton to identify the product, it is important that the strength is present.
1.6 Non-prescription medicines that contain paracetamol must include the following information on

the front of the packaging. The information must be presented in bold text in letters of at least 1.5mm high and on a background that contrasts with the rest of the packaging:

"Contains paracetamol. X mg. Consult your doctor or pharmacist before taking other paracetamol products."

The inclusion of a warning statement about the maximum dose of paracetamol is important for patient safety.

In a number of studies, patients and carers have had significant difficulty in determining the contents of pain medicines[11] and over the counter cough and cold medicines[12-13]. The authors often cite labelling as a contributing factor to dose errors made, some of which can lead to serious overdoses. The Clinical Excellence Commission supports the inclusion of a warning statement about taking multiple medications containing paracetamol. This warning statement should be designed and tested in collaboration with communications experts to ensure that it is properly interpreted by the largest possible segment of the community.

1.7 Non-prescription medicines that contain ibuprofen must include the following information on the front of the packaging. The information must be presented in bold text in letters of at least 1.5mm high and on a background that contrasts with the rest of the packaging:

"Contains ibuprofen. X mg. Consult your doctor or pharmacist before taking other medicines for pain or inflammation."

As per above, the risk associated with NSAIDs is acknowledged and the Clinical Excellence Commission supports the inclusion of a warning statement on the packaging of ibuprofen.

It should be noted that other anti-inflammatory medicines, including naproxen, are available as over-the-counter preparations and consideration should be given to expanding the need for warning to these other NSAID products.

Again, the warning statement should be designed and tested in collaboration with communications experts to ensure that it is properly interpreted by the largest possible segment of the community.

General questions on the proposed regulatory changes for the prominence of the active ingredients on medicine labels

What do you think will be the impact of increasing the prominence and standardising the location of the active ingredient on the medicine label?

Standardising the location and increasing the prominence of the active ingredient on the medicines label will have a significant impact on the quality use of medicines. As location is standardised, education campaigns (such as the NPS be Medicinewise campaign) will be able to target consumer education about identifying their medicines. Other benefits are likely to include the increased identification of medicines by their active ingredient names.

Ortiz[8] is quoted earlier in this submission, providing evidence that consumers often switch brands of generic equivalent medicines. Being able to identify the active ingredient is crucial to the quality use of medicines. Where identifying the active ingredient is difficult we enter a situation where it is possible that consumers take multiple brands of the same medicine.

What do you think about the proposed warnings for paracetamol and ibuprofen containing products?

The clinical need for these warnings is clear. The exact wording of the warnings should be prepared and tested by experts in communications.

Are there any other concerns you have with the size or position of brand names and active ingredient?

As noted above.

If the active ingredient name is clear, directly below the brand name and in a large font, what are the additional benefits that you see by making it the same size as the brand name?

Size is a strong determinant when establishing importance or prominence. If the size of the active ingredient name is smaller than that of the brand name, it will be seen as less important.

What is the smallest size font that you consider readable?

This question should be considered in the context of those members of the public who are most likely to take medicines. Undoubtedly, the elderly who consume more medicines than other sectors of the population and their needs, in terms of readability, should be considered.

LOOK-ALIKE SOUND-ALIKE NAMES AND LOOK-ALIKE PACKAGING

3.1 Sponsors of new medicines will be required to submit evidence of risk assessment of the proposed labelling and packaging. The TGA will work with industry to develop guidance for this assessment, which may include consumer testing or risk assessment checklists similar to those used in other countries. The TGA is investigating methods to electronically screen proposed brand names against already existing brand names to identify potential LASA names.

The introduction of standardised processes for reviewing both proposed medicines names and proposed labeling and packaging is supported by the Clinical Excellence Commission.

One of the major criticisms of risk assessment processes used in other jurisdictions is that they are unpredictable, lack transparency and occur late in the regulatory approval process meaning that rejection of proposed names, labelling or packaging can be costly to the product sponsor[14]. It is important, then, that the processes implemented by the TGA are transparent, available to product sponsors for use early in the product development processes, and as objective as possible.

The harm associated with look-alike, sound-alike medicines names has been described in the TGA consultation paper and has been touched upon in the introduction to this response. The literature is awash with specific cases and examples of drug name confusion, many of which have caused significant patient harm [15-17]. It is approximated that a quarter of incidents reported to voluntary error reporting systems in the United States are caused by drug name confusion [18]. A retrospective analysis of a prescription database in the US state of Idaho used data mining techniques to identify potential

substitution errors made with a group of look-alike sound-alike medicine pairs [19]. In a seven year period, the authors found 1,138 records which they identified as likely representing an error caused by name confusion. This study highlights the magnitude of the problem. True rates of error resulting from drug name confusion are difficult to calculate and accurate data are difficult to obtain but it appears indisputable that naming practices that result in similar and confusable drug names are responsible for considerable avoidable patient harm.

It is imperative that the potential for confusion of a drug's proprietary name is assessed prior to it reaching the market. Despite the considerable efforts made, preventing drug name confusion once products have reached the market has proven difficult. Safeguards including the use of both generic and proprietary name and listing the indication for treatment on prescriptions have not been easy to implement as they rely on those involved in the prescribing process to comply. Electronic prescribing solutions have undoubtedly increased the readability of prescriptions, reducing the contribution of poor handwriting to drug name confusion. However, the use of drop down menus in these systems has introduced a new area where drug name confusion can cause errors [20]. Employing the use of bar code scanners and automation in dispensing and administration processes may also help to lessen the impact of drug name confusion [21], but these systems are not yet universally implemented and rely on the accuracy of information entered into the system. Additionally, these systems and safeguards do nothing to support the consumer in selecting the correct over the counter product.

Various design techniques have been applied to differentiate the names of medicines on product labelling and packaging and in computer systems in an attempt to mitigate the risks associated with drug name confusion. The effectiveness of colour, bolding, and letter capitalisation (specifically Tall Man lettering) in differentiating similar medicines names have all been evaluated [21-24]. These studies have demonstrated modest effects in preventing drug name confusion and demonstrate that techniques such as Tall Man lettering and good labelling and packaging design should be used as components of a holistic solution to problems associated with look-alike, sound-alike medicines names. However, it is clear that the best remedy for look-alike, sound-alike errors is to prevent problematic names from reaching the market. This must be supported by sound regulatory processes.

Word and name similarity is not a problem unique to the pharmaceutical industry. Researchers in the fields of cognitive psychology, psycholinguistics and computation science have also addressed issues of word similarity and findings in these fields offer insights into the attributes of drug name combinations that make them similar and confusable. Unsurprisingly, words constructed of similar letters or sounds are those that are most likely to be confused [25]. The importance of letters at the beginning and end of a word in causing confusion has been shown to be greater than for the remainder of the word [26]. These, and other findings, have been used to derive measures of word similarity from both orthographic (look-alike) and phonological (sound-alike) perspectives [27].

This theoretical framework has been applied to medicines names. Researchers have demonstrated that these principles apply to medicines names [28-29] and that objective measures can be used to quantify the similarity of two medicines names [30-31]. This work has included the development of computerised screening tools which can provide an accurate measure of similarity between drug names [32,33]. These screening tools form an integral part of drug name assessment because of their objectivity and ability to compare proposed names to the vast number of existing names. Such a task could not be facilitated without automation. One of these tools has been adopted by both the FDA and Health Canada in their name assessment processes.

It should be noted here that similarity between two drug names, in and of itself, is not indicative of potential patient harm. In order to be problematic, similar names must also be confused. The potential for confusion between drug names can be predicted using a range of simulated user tests. Results from such testing provide a measure of the real world likelihood that two medicines will be substituted due to confusion of their names. Importantly, this testing can also take into consideration the impacts of additional factors such as product strength, formulation and indication. Similarities in these attributes can combine to make products more easily confused. For example, products with similar names are more likely to be confused with one another if they are both available in the same dose, in the same dosage form and in the same clinical setting. It is less likely that they will be confused if they do not share other properties.

As this process is about reducing the risk of patient / consumer harm, an evaluation of potential severity should also be considered when assessing the absolute risk of confusion between two medicines names. This process will likely be a more subjective process, relying on expert opinion. Such a review could be undertaken by a body such as the proposed Labelling and Packaging Advisory Committee, provided it had a suitable clinical composition.

Look-alike packaging is associated with its own set of problems. A number of cases[34-35] have shown the catastrophic consequences that can be associated with look-alike packaging. This has recently been an issue highlighted in Australia due to problems associated with the look-alike packaging of Coumadin and Coversyl. This is just one example, and such problems are frequently highlighted by those working in the health system.

As yet, there is no robust mechanism for pre-market assessment of the potential for confusion between the proposed labelling and packaging of a new product and that of an existing product. The Clinical Excellence Commission advocates for development of such risk assessments and would strongly support the application of objective, automated screening tools. It is acknowledged that no such system currently exists, but the development of such a system is considered feasible by leading Australian computer vision researchers. The TGA is encouraged to engage experts in the field of computer vision.

Until such automated screening tools exist, the Clinical Excellence Commission advocates dissemination of proposed packaging to a clinical review panel, representing clinicians who work in a variety of clinical settings. Whilst it is acknowledged that this process cannot possibly identify all potential look-alike products, it is likely that severe issues would be addressed earlier in the product life-cycle, potentially preventing patient harm and considerable cost to the manufacturer.

To summarise:

- The need for objective, pre-market risk assessment of proposed product names, labelling and packaging is strongly supported;
- Risk assessment processes must include subjective measures and must include use of an electronic screening tool endorsed by the TGA;
- Name similarity and confusability are not the same and the potential risk of confusability should be estimated, taking into consideration name similarity as well as other product characteristics;
- Processes should be consistent, robust, transparent and uniformly applied by all product

sponsors, or the TGA.

3.2 In relation to applications to include a new medicine in the Australian Register of Therapeutic Goods (ARTG), if the proposed medicine brand name differs from another product included in the ARTG by three letters or fewer, the presentation of the proposed medicine label and packaging must use colours and designs that contrast with the medicine label and packaging of the existing product. During the implementation of this change, the TGA will work with the medicines industry to develop guidelines to provide clarity about these proposed requirements.

This response should be considered together with our response to 3.1.

The criteria for determining similarity as outlined in this recommendation is overly simplistic and fails to take into consideration a number of factors, particularly the overall length of the medicines' names. More objective measures, founded in the principles of psycholinguistics, as described above, are available and should be applied.

Where the perceived confusability of two names is sufficiently great, or the absolute risk to patients / consumers is considered to be significant, proposed medicines names must be rejected. Whilst risk can be partially mitigated through use of packaging and labelling differentiation and Tall Man lettering, as well as through the application of technological aids such as bar-code scanning, preventing the introduction of a confusable medicine name is a far stronger intervention.

This recommendation should be used where confusion is determined to be possible but is not deemed to be of significant clinical risk to prevent the acceptance of the proposed medicine name.

3.3 In relation to applications to change the labelling and packaging of existing medicines, if the brand name of the medicine differs from another medicine included in the ARTG by less than three letters, the proposed changes must use colours and designs that contrast with the medicine label and packaging of the other medicine.

As noted above, the measure of similarity should be substituted for a more robust and scientifically sound measure.

This recommendation would provide an opportunity to take some action to prevent errors associated with products already on the market and is supported.

The use of colours, packaging design and other interventions to physically differentiate medicines with similar names, would offer some benefit in reducing product confusion. In addition, where the names of the medicines in question are included in the National Tall Man Lettering List of the Australian Commission on Safety and Quality in Health Care[36], application of Tall Man Lettering should also be required.

General question on the proposed regulatory changes for look-alike sound-alike names and look-alike packaging

Do you think the proposed changes to address LASA names and LA packaging will improve medicine safety? Why/why not?

The proposed changes are a positive step for improving patient safety and reducing the risks associated. The objective assessment of similarity / confusability in the pre-market period can potentially prevent high risk product names or packaging and labelling reaching the market.
3.4 Products that are listed on the ARTG cannot be marketed under the same name as a registered medicine.
Supported.
3.5 Medicines that contain the same quantity of active ingredient(s) cannot be selectively differentiated or marketed for a subset of symptoms or uses, unless the medicine has specific characteristics that make it more suitable for a particular symptom. ***For example: Products cannot be marketed as "BRAND headache", "BRAND backache", "BRAND joint pain" if they include the same active ingredients in the same quantity.***
Supported. The differentiation of such products based on therapeutic "target" gives the false impression that these products perform different functions. This then creates an opportunity where consumers may take multiple versions of the same medicine inappropriately, especially when suffering from multiple ailments (such as backache and headache, or pain and fever etc).
3.6 The same brand name cannot be applied to products that have different active ingredients or combinations of active ingredients unless all of the following conditions are met: ***a. The active ingredients are closely related (e.g. different salts of the same pharmaceutical chemical), and*** ***b. The safety profile, efficacy and dosage regimen are similar.***
Supported.
General questions on the proposed regulatory changes for look-alike medicine branding *What benefits, if any, do you think the proposed changes to address look-alike medicine branding will have for consumer safety?* These revisions will enhance consumers' understanding of the medicines that they are taking, and will assist them in identifying products that are the same and those that are different. *Do you understand the proposed changes?* Yes

If you can read the labels and warnings clearly, will these changes reduce the potential for harm?

The use of umbrella branding and brand extension lead to confusion[37] regardless of the clarity of labels and warning statements. These practices should be strongly discouraged by TGA as the regulator. It is acknowledged that these practices may hold potential benefit for the product sponsor in financial terms and that the value of a brand is significant.

STANDARDISED INFORMATION FORMAT: THE MEDICINE INFORMATION BOX

The Clinical Excellence Commission supports the implementation of a standardised medicines information box on products available to consumers over the counter. No comment is made on the specific recommendations (4.1 to 4.6) outlined by the TGA. It is the position of the Clinical Excellence Commission that this information should be based on legislative requirements, and on feedback from consumer groups on what information would be most meaningful to them. Again, the Clinical Excellence Commission advocates for the engagement of experts in communications and design to be involved in setting the minimum standards for this section of medicines labelling. Alternatively, an outcomes based approach to the design should be taken.

General question on the proposed regulatory changes for Standardised Information Format: Medicine Information Box

To what extent do you think a standardised format for information on the labels of over-the-counter and complementary medicines will improve access to information for these medicines?

The introduction of a standardised format for consumer information will improve consumer access to this information largely through standardisation. By standardising the location and format of this information, it will mean that consumers are able to easily and readily find the information they require.

Are there other ways that the presentation of information could be improved?

It is important to consider that the majority of Australian consumers have low health literacy (approximately 60% of all Australians). These low health literacy consumers may have difficulty reading and understanding the information provided. The design of information presented in this box must be constructed in such a way as to maximise its comprehension. This includes the content, graphics, layout and typography and cultural appropriateness of information presented.

Research into the effectiveness of medicines labels shows that consumers have difficulty in both finding and interpreting this information on over the counter[11 38] and prescription medicines[39]. Manufacturers and health care practitioners are both guilty of producing information that is not easily understood. Much of the information included in medicines labelling, such as warning statements, is disregarded or not well understood by consumers[40]. Language that is commonly used by doctors and pharmacists to provide instruction on medicines use is misinterpreted [41]. Statements such as “take two tablets twice daily” are only correctly interpreted by 71% of consumers with adequate literacy skills and by as few as

33% of consumers with literacy problems. These problems can be partially overcome through use of explicit instructions such as "take two tablets in the morning and take two tablets in the evening".

The language within the example provided (Figure 6: An example of a medicine information box) is aimed at consumers with advanced reading skills. International literature suggests that information provided to consumers should be developed to Year 8 reading and comprehension skills. Examples of how this could be amended are:

"Uses" – "Why people use this medication"

"When using this product" – "When using this medicine"

The package title is "medicine information box" it does not mention or describe "product" anywhere

"Gastrointestinal symptoms" – "May occasionally bring about a feeling of illness in your stomach and belly"

"Gastrointestinal" is a complex medical term, and we know that medical terms are not well understood by the majority of consumers.

The Clinical Excellence Commission advocates the formation of consumer focus groups that include consumers from Culturally and Linguistically Diverse (CALD) backgrounds and that have low health literacy to test and review the readability of the material produced for the medicines information box.

Do you think the proposed requirements for products with more than three active ingredients (directions and warnings and allergy information), is sufficient for these products? Please propose an alternative if you don't agree with current recommendation.

- **Warnings and Allergy Information**

  Pharmaceutical terms are not well understood by the majority of the population and may disincentivise consumers with low health literacy to continue reading. We would suggest information like "Not recommended for people with seafood allergies" to be written first (as it is most important to consumers) and then to follow with additional information on glucosamine.

  We believe it is important to provide consumers concise information where they do not have to infer meaning. For example "contains approximately 228mg sodium" does not provide a warning to a consumer, it provides them with information and the consumer is left to infer meaning, as few consumers understand that "sodium" refers to salt. It may be more effective to provide consumers with a reason or an example about why this is important.

- **Directions**

  The directions "Take 1 easy to swallow tablet twice daily" may not be easily understand. This statement does not provide an example to the consumer about the times to take this tablet. Additionally, there is no need to include product claims such as "easy to swallow" in the direction statement. Such information decreases comprehensibility and should be excluded.

  It may be more effective to provide an example on titration for example "Take one tablet in the morning and take one tablet at night". This approach is supported by international studies on medicine label comprehension[39 41].

DISPENSING LABEL SPACE

5.1 A designated space of 70 x 30 mm, consistent with international best practice(11), must be provided to accommodate the dispensing label.

The provision of a designated space for application of a pharmacy label is supported. The NPSA outline a series of rational reasons for the inclusion of such an area in their guide to the design of medicines labelling and packaging[7]. The most obvious reason being that providing a designated space allows for the application of pharmacy dispensing label without obscuring information that may be important to the consumer.

The exact measurement of the space provided should be consistent with the standard dispensing labels used in Australia rather than being consistent with international best practice.

5.2 Where a clear space is not practical due to constraints from packaging size and shape, the information should be arranged so that information that is likely to be obscured is the same as the information repeated on the label. The area for placement of the sticker should be illustrated by corner placement marks on the packaging.

Supported.

5.3 For small containers, for example eye drops and ointments, where a designated space of 70 x 30 mm is impractical, a clear space should be provided to affix the edges of a folded dispensing label.

Supported.

General question on the proposed regulatory changes for dispensing label space

Do you support a designated space for the dispensing label on prescription medicines? Why/why not?

Yes. This change will provide consistency in the way in which pharmacists apply dispensing labels and

will minimise the likelihood of valuable information on product packaging being obscured.

BLISTER STRIP LABELLING

6.1 The brand name of the medicine, the active ingredient and amount of active ingredient, batch number and expiry date must be repeated at least once every two units.

This recommended change does not go far enough. Due to a range of factors, including the use of medicines in the hospital sector, blister strips may be broken or cut into individual units. In these instances it is important that each dose is labeled with, at a minimum, the active ingredient name, the amount of active ingredient, batch number and expiry. This is current practice for many medicines on the market in Australia and should be achievable.

There have been case reports where having the medicine details spread across two dose units has caused confusion. One published report from the Netherlands[42] looked at the blister strip labelling of a product that had its name and strength printed across two tablets. In a random selection of 11 nurses, only two correctly identified the amount of active ingredient in each tablet, instead assuming that the amount of active ingredient listed on the blister referred to the two tablets combined. It is likely that this confusion was enhanced by the fact that the blister strip was perforated in such a way as to produce segments of two tablets.

The Clinical Excellence Commission advocates that blister strip labelling contain the brand name of the medicine, the active ingredient and amount of active ingredient, batch number and expiry date repeated on every unit.

It is acknowledged that the physical space on the blister strip limits the amount of information that can be clearly included. This may be problematic for products with multiple ingredients. The following recommendations (6.3 and 6.4) may adequately address these situations. The TGA Best Practice Guideline on Prescription Medicine Labelling also recommends that where it is impractical or not possible to fit this information on individual units due to the small blister size, that the product name and strength should be repetitively printed across the entire blister with batch and expiry on one end.

6.2 Where strips can be segmented, the brand name, the active ingredient and amount of active ingredient, batch number and expiry date is to appear on each segment.

As per 6.1.

6.3 A maximum of 3 active ingredients should be listed on each segment / each 2 units of a blister strip for registered medicines.

As per 6.1.

6.4 Where there are more than 3 ingredients, for example multi-vitamins packaged this way, it may be sufficient to include a single list of active ingredients printed on the foil of each blister strip.

Alternatively, the brand name, together with batch number and expiry date, should be repeated on the foil.

As per 6.1.

6.5 Blister strips that have a "race track format" must include the trade name, the active ingredient(s) and their amount(s), batch number and expiry date in a single location.

This recommendation establishes the basic minimum that would be expected. This is a difficult recommendation to provide comment on since the idea behind the "race track format" or calendar packs is to support the consumer in adherence to their prescribed regimen. The intention of the pack design is well meaning, but for the purposes of identifying individual units it is inadequate. If this change is made, the use of "race track format" blister strips should be controlled and permitted only in situations where it is felt to have benefit for the consumer. Consideration should also be given as to whether information should be repeated more often than once, even if the blister strip is in "race track format".

General question on the proposed regulatory changes for blister strip labelling

Do you think the proposed information for blister strips is sufficient?

No, see comments as per 6.1.

What other changes would you like to see for this type of packaging?

In addition to the recommended changes outlined by the TGA, the Clinical Excellence Commission advocates the inclusion of recommendations made in the NPSA document – A guide to the graphic design of medication packaging[7]. These recommendations include:

- That non-reflective foil should be used for the backing;
- That there should be a strong contrast between the backing colour and the type colour;
- That bold or semi-bold fonts are used;
- That the visual style of the outer packaging should match the blister strip labelling (e.g. especially when colour is used to differentiate between multiple strengths in a product range).

SMALL CONTAINERS

7.1 These containers must be enclosed in a primary pack that fully complies with all labelling requirements and that includes a pack insert that provides detailed instructions for use.

Supported.

7.2 The label on the container must include the following details in a letter height of not less than 1.5

millimetres: ***· The brand name of the medicine*** ***· The name(s) of all active ingredients in the medicine*** ***· For ophthalmic preparations the name of any antimicrobial preservatives in the medicine*** ***· Where there are more than three active ingredients, the three most abundant ingredients are to be included on the label of the container and the complete list of ingredients on the primary packaging and the pack insert*** ***· The batch number of the medicine*** ***· The expiry date of the medicine*** ***· If an injection, the approved route of administration*** ***· If an ophthalmic preparation for multidose use, a statement to the effect that the medicine should not be used later than four weeks after the container is first opened*** ***· If a solid ophthalmic medicine for preparing eye drops for multidose use, a statement to the effect that the medicine should not be used later than four weeks after the container is first opened***
Supported.
7.3 A clear space should also be provided to allow a pharmacist to affix a dispensing sticker. This space need not be the size of a standard dispensing sticker (80 x 40 mm), but should allow a folded sticker to be attached like a flag without obscuring information.
Supported.
General question on the proposed regulatory changes for small container labelling *To what extent do you support the proposed changes for small container labels? Please provide details.* *Do you have any further suggestions for how labelling of small containers could be improved?*
Nil comments.
PACK INSERTS
8.1 Advertising material will not be permitted to be included as a separate pack insert or incorporated into an approved pack insert.
Strongly supported.
8.2 A pack insert must be in a form separate to the packaging; i.e. it cannot be printed on the inside of a carton.

The Clinical Excellence Commission has no position on this recommendation, provided that the form of information is usable to the consumer.

General question on the proposed regulatory changes for pack insert requirements

Do you support the proposed changes for pack inserts? Why/why not?

Do you have any further suggestions regarding pack inserts?

Nil comments.

Labels and Packaging Advisory Committee

General question on the proposed establishment of a labels and packaging advisory committee

To what extent do you think that a Labels and Packaging Advisory Committee will assist the TGA to manage consumer health risks associated with medicine labels and packaging?

The proposed establishment of a Labels and Packaging Advisory Committee is supported by the Clinical Excellence Commission.

Whilst there is an obvious need for objectivity in the way in which medicines are assessed prior to their approval for use in Australia, expert review is a necessary parallel process. The proposed use of an expert panel will enhance the TGA capabilities in the areas of labelling and packaging and will help to ensure that risks that may be obvious in the clinical setting are identified earlier in the product approval process.

The Clinical Excellence Commission supports the inclusion of community and hospital practitioners, doctors, nurses and pharmacists and pharmaceutical industry on this panel. In addition, the Clinical Excellence Commission strongly advocates the inclusion of the following members;

- Consumer representatives;
- Experts in communication design;
- Experts in human factors / ergonomics; and
- Experts in the field of medication safety.

Inclusion of these additional groups will ensure that the decisions of the panel are based on input from all relevant experts.

ISSUES NOT SPECIFICALLY ADDRESSED IN THE RECOMMENDED REGULATORY CHANGES

NAMING OF GENERIC MEDICINES

The naming of generic medicines requires careful consideration as part of this regulatory review process.

As outlined in our response to the first section of the consultation paper (location and prominence of the active ingredient name) consumers switch between multiple brands of medicine with the same active ingredient[8] (generic equivalents). Often, these consumers have difficulty identifying these medicines as being the same. This can lead to inadvertent overdose and subsequent harm.

This is important since there are clear benefits to increasing the rate of generic medicine use in Australia.

Strong consideration should be given to the need for generic medicines (i.e. non-innovator products) to be given proprietary names at all. In the event that they are given proprietary names, the TGA should require that this name meet all requirements that would apply to an innovator brand.

Where sponsors choose to use the active ingredient name as the product name, the name should be as it appears in the ARTG and should not be modified.

Graudins and Dooley[43] highlight issues associated with the naming of generic medicines. Particular practices that they highlight as high risk include the use of the company name as a prefix or suffix to the active ingredient name as a brand name. Examples of such names provided by Graudins and Dooley include APO-Alendronate and Simvastatin-Spirit. These authors advocate for the application of standards from the National eHealth Transition Authority (NEHTA) which would see these names presented as the active ingredient name followed by the name of the sponsor company in parenthesis. As Graudins and Dooley correctly point out, the practices of adding company names as suffixes and pre-fixes causes difficulty for consumers and health care professionals alike. Consumers become confused as to what medicines they are actually taking, and health professionals can be confronted with large numbers of medicines names when searching electronic databases, such as those used in prescribing and dispensing systems.

It is also logical to assume that as more products are given unique proprietary names, the probability that these names will cause confusion with existing names increases. There is a finite number of "unique" or discrete names that can be chosen[44]. The use of brand names for generic products should, therefore, be discouraged.

USE OF SUFFIXES

In addition to the use of company names (or components of company names) as suffixes, a number of other suffixes are used. Often these suffixes are used to convey meaning about the release properties of a particular product (for example CR for controlled release). There appears to be no consistency in the choice of suffix or its application. Health professionals are frequently confused about the meaning of suffixes.

Consideration should be given to the development of a standard list of suffixes.

EXPRESSION OF DOSE STRENGTH FOR LIQUID MEDICINES

The consultation document prepared, and the proposed regulatory changes focus heavily on the naming of medicines, and look-alike, sound-alike issues. These are important issues and must be considered. There are additional factors related to medicines labelling and packaging that contribute to error. Significant among these is the way in which dose strength or quantity is described, especially for liquid medicines.

Health professionals and consumers can have significant difficulty in interpreting product strength, as there is no standardised way of presenting this information. The use of ratios and percentages to express the strength of a medicine has long been known to cause confusion amongst health professionals. Wheeler and Wheeler[45] provide a succinct review of the issue, citing many studies that have shown that doctors make considerably more calculation errors when medicines are expressed as ratios or percentages rather than as milligram per millilitre (mg/mL)[46]. Simpson and colleagues confirmed these findings in an Australian teaching hospital, showing that junior doctors make significantly more errors with percentages and ratios that with mg/mL strength expression. Simulation studies have shown that expressing a dose as concentration (mg/mL), quantity (total mg in packaging), and volume (total volume in packaging) can improve safety[47]. Standardising the way in which strength is presented should be strongly considered as a mechanism to improve safety.

It is acknowledged that the use of percentages to express dose is a long-standing practice in some environments (e.g. theatres). The Clinical Excellence Commission advocates that where percentage is used to express dose, a concentration is also provided in mg/mL.

For oral liquid medicines, where multiple doses are almost always withdrawn from a larger volume, the Clinical Excellence Commission advocates for dose to be consistently expressed as mg/mL.

Although injectable medicines are more complicated, consideration should be given to establishing a consistent format for the presentation of strength. The inclusion of both mg/mL and total mg per unit of packaging is advocated as a starting point.

MECHANISMS FOR REPORTING ISSUES WITH NAMING, LABELLING OR PACKAGING

The adverse drug reaction reporting program of the TGA is well established and most health care professionals are aware of the types of information that they should be providing to the TGA with respect to adverse reactions. However, there is seemingly no parallel process for reporting adverse drug events that may have resulted from issues associated with labelling and packaging or other issues beyond simple adverse drug reactions.

Information associated with errors, including those that are contributed to by medicines name, labelling or packaging, is not centralised, and is often not acted upon. When these errors occur in the acute care sector, they may be reported to a hospital based incident reporting system. When they occur in the community, there is no obvious place for them to be reported on. In either case, there appears to be no obvious mechanism for acting upon information related to these errors.

As a jurisdictional organisation that is notified of errors occurring in the NSW public hospital system, the Clinical Excellence Commission would benefit from a clear pathway for escalating concerns about labelling and packaging that are raised by clinicians. There is also a clear need to establish a mechanism for all health professionals and consumers to report issues related to the naming, labelling or packaging of medicines. It is likely that the TGA is the organisation best suited to receiving and acting upon this information.

SPECIFIC SAFETY RISKS FOR CONSIDERATION

As part of the TGA Best Practice Guideline on Prescription Medicine Labelling, a number of specific Australian considerations are presented. For example, it is recommended that all vinca-alkaloids carry the warning statement – “for intravenous route only, fatal if given by any other route”.

All of the recommendations in the Best Practice Guideline should be incorporated into regulatory statements.

Additional high risk products where particular safety warnings should be considered include;

- Neuromuscular blocking agents – these paralysing agents should carry a warning to that effect. For example “Caution, paralysing agent”.
- Local anaesthetic agents such as ropivacaine and bupivacaine should carry warnings regarding the harm caused if they are injected via the intravenous route.

Such warnings should be limited to situations where the perceived or documented risk is significant. Any warning statements should be developed and tested in collaboration with experts in communication and design.

PHYSICAL PRESENTATION

Case reports have been received in Australia where medicines have been administered via the wrong route due to their physical presentation. Such errors were particularly noted with products such as Mucomyst® (now discontinued) that was intended for inhalation but was presented in an ampoule. Due to the product appearance, it was frequently injected. Similar difficulties have been reported with other products.

It is recommended that the physical presentation of the product is considered as part of the labelling and packaging review. Additionally, where ancillary devices are included in medicines packaging (such as oral dose measuring devices in infant pain relief), these devices should be safe. This would include the requirement that such devices are unable to be connected to systems commonly used for intravenous administration (e.g. Luer-lok and Luer-slip systems).

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