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August 3, 2005

Subject: Look-alike Sound-alike (LA/SA) Health Product Names: Comments and Responses to the Related Draft Guidances.

The purpose of this note is to inform you that following consultation with stakeholders regarding the two draft guidances, *Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names* and *Marketed Health Product Name Assessment: Look-alike Sound-alike (LA/SA) Health Product Names* and after a careful review of comments received, the LA/SA working group has developed responses to compiled comments. We thank all stakeholders for their constructive feedback and hope that this document responds to all issues raised. The attached document, *Look-alike Sound-alike Health Product Names-Comment and Responses to the Related Draft Guidances* is now available and may be accessed from the Biologics and Genetic Therapies website at http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/index_e.html.

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Thank you for your interest in this issue.

Original signed by

Pierre Charest
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Enclosure

Canada

Look-alike Sound-alike (LA/SA) Health Product Names
Comments and Responses to the Related Draft Guidances.

Prepared by the LA/SA Working Group

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August 3, 2005

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1. General Support

Comments:

We applaud Health Canada's initiative to make our products safer.

Member companies generally are supportive of having guidance documents in place which will support their goal of minimizing confusion in the marketplace by creating distinct individual product names.

We recommend that Health Canada and all stakeholders, including industry, work together in partnership on this issue to further the interest of patient safety.

The Institute of Safe Medication Practices Canada (ISMP Canada) is prepared to assist the Health Products and Foods Branch (HPFB) of Health Canada, as well as manufacturers, with the review and identification of potentially problematic drug names.

Response:

With appropriate pre-market and post-market processes in place within HPFB to respond to potential look-alike sound-alike (LA/SA) health product names, the risk of health product name confusion should be reduced.

It is important that all stakeholders, including sponsors, work together to minimize the potential for confusion between products with names that look or sound alike.

2. Incidence of Medication Errors Attributable to LA/SA Confusion

Comments:

"Name confusion is thought to account for one in every four medication errors." The paper that it refers to states that, in one particular year, one in four errors reported to the USP/ISMP Medication Error Reporting Program listed name confusion as a cause. Reported errors are not the same thing as the number of errors that occur.

The proportion or error *reports* are not the same thing as the proportion of *actual errors*.
The proportion of *actual errors* due to name confusion is not known, although a recent study of US outpatient pharmacies (1) showed that 0.13% of all prescriptions led to "wrong drug" errors. Name confusions are one type of wrong

drug error, so one might validly conclude from this study that name confusions account for no more than 13 errors in every 10,000 prescriptions filled.

Response:

Thank you for the clarification.

Comment:

The extent of LA/SA name confusion leading to medication errors is unknown. We believe it is not possible to use statistics from the available data to determine to what extent medication errors are attributable to name/name similarity. Figures put forth are not based upon sound scientific evaluation, as evidenced by the vastly different figures put forth in different published papers.

Response:

Health Canada has taken on this issue because of longstanding unresolved issues relating to LA/SA health product names, as well as a specific safety issue involving the potential for confusion between two approved biologics.

Health Canada has a responsibility to assess the safety of a health product and to endeavour to prevent LA/SA health product name errors. Health Canada cannot use scientific uncertainty where safety is a concern as reason not to act.

Results of LA/SA studies are different, in part, because they are reporting on different types of figures. Some studies report **actual errors** while others are reporting **error reports** while others still are reporting **deaths attributed to errors**.

3. Other Factors Contributing to LA/SA Medication Errors

Comments:

The nature of the disease, the age and gender of the patient and dosing would reduce the chance of erroneous dispensing.

The frequency with which each drug of a pair is prescribed, dispensed, or administered will make the probability of confusion in one drug more likely than in the other. When the rare drug is presented, the common drug may be mistakenly seen/heard. The opposite will rarely occur.

Frequency is important because it determines the number of errors that are likely to occur. The number of errors is equal to the probability of an error times the number of opportunities for an error. If a name has a 1% chance of being

misperceived, and it is dispensed 100,000 times per year, then one expects 1000 errors. If a name has a 0.1% chance of being misperceived, but it is dispensed 10,000,000 times per year, then you would expect 10,000 errors. The "safer" name, i.e., the one with the lower probability of confusion, actually results in more errors because there are many more opportunities for error.

Response:

Health Canada currently includes the therapeutic category (including the nature of the disease), similar patient populations (including age and gender) and dosing in determining whether the degree of similarity in names is problematic.

One cannot include frequency of dispensing/usage as a contributing factor in the pre-market guidance document because frequency is a variable that is not know prior to a drug being marketed. Furthermore, frequency varies across Canada (i.e. regional prescribing habits) and across locations (i.e. hospital versus pharmacy). Anticipated frequency of use could be included in the list of factors.
Post-market, frequency of dispensing/usage could be considered when assessing risk of harm from potential name confusion among marketed health product names.

Comments:
Errors can arise solely from human central nervous system variability. Errors are in the translation of sensation and perception and this is part of the process of being human.

If the legibility is poor or low, a prescription may be interpreted as something other that what was intended to be written. It is my belief that research on cursive writing be undertaken, or that regulations be employed to forbid the use of handwritten prescriptions. It will be interesting to follow the success of such rules in Florida and other States where recent legislation has forbidden the use of cursive script.

The probability of error in pharmacy operations will go down as the general illumination level goes up.

Response:

There is no denying that other factors cause or contribute to medication errors, however, if one were to deal with all factors at once, the task would be insurmountable.

Within the Food and Drug Regulations, section C.01.041. (1.1) states that no person shall sell a substance containing a Schedule F drug unless the sale is made persuant to a verbal or written prescription received by the

seller. Revising these regulations requires a regulatory amendment. Furthermore, mandating this is a provincial matter as it falls under the practice of medicine and pharmacy.

Of note, forbidding the use of handwritten prescriptions may have merit in the future but it cannot be implemented as a stand-alone solution because errors can happen either upstream or downstream from the prescription and is only relevant to those drugs sold persuant to a prescription. Furthermore, significant stakeholder investment would be required to comply with this. *The Regulatory Policy (Privy Council Office, Government of Canada)* specifically states that when developing policy "information and administrative requirements are limited to what is absolutely necessary and imposes least possible cost."

4. Other Factors Causing Medication Errors

Comments:
There are many reasons for medication errors and there is no clear consensus that trademarks are the primary cause or are even among the leading causes of errors. LA/SA procedures will not control for poor handwriting on prescriptions, spelling errors, incomplete knowledge of drug names, verbal order errors, or other human errors, all of which may well be more significant contributors to medication errors that product trademarks.

Response:

Health Canada is participating in many areas that fall within its mandate to increase patient safety and to reduce medication errors through its work with the Canadian Patient Safety Institute and the Canadian Medication Incident Reporting and Prevention System. The initiative to reduce the number of LA/SA health product names is just one of the ways that Health Canada is working to maximize the safety provided by the regulatory system for health products.

Longstanding unresolved issues relating to LA/SA health product names, as well as a specific safety issue involving the potential for confusion between two approved biologics prompted the Biologics and Genetic Therapies Directorate (BGTD) to initiate a review and analysis of the issues associated with LA/SA health product names and to recommend an appropriate course of action.

Various associations, including the Canadian Medical Association (CMA), Canadian Pharmacists Association (CPhA), the Canadian Society of Hospital Pharmacists (CSHP) and the Institute for Safe Medication Practices (ISMP), have been concerned about the LA/SA issue for a number of years.

5. Scope/Prioritization

Comments:
We would recommend that Health Canada consider and include the important aspect of pharmaceutical products' packaging and labelling issues as a future part of the product safety initiative. A similar mechanism that is being implemented for drug names should be put in place to review packaging and labelling.

Response:

As medication incidents are considered to be one of the most common preventable causes of patient injury, Health Canada is investing $2 million annually for up to five years in the Canadian Medication Incident Reporting and Prevention System (CMIRPS). This system, now in its design phase, will have the capacity to collect and analyse data regarding medication incidents (including labelling and packaging issues) with a view to understanding why events happen and how they can be prevented in the future. The system will be closely aligned with the Canadian Patient Safety Institute.

6. Trade-marks

Comments:
Pharmaceutical companies share the concern about the issue of LA/SA drug names and undertake a lengthy and thorough process in developing trademarks that will be free from likely confusion with other marks and names.

The Canadian Trade Marks Office already reviews proposed new trademarks, including pharmaceutical trademarks, and has developed expertise in evaluating the legal degree of permissible or impermissible similarity. Thus, Health Canada should carefully consider its role in the reviews already being conducted by other government bodies.

Response:

Health Canada does not infringe upon Industry Canada's role in granting trademarks. It is Health Canada's role to ensure the safety of a health product, including its name, as required under the *Food and Drug Act and Regulations*.

The trademark process within Industry Canada has proven insufficient in preventing LA/SA health product name confusion. This may be because proposed trademarks are considered and reviewed to determine whether they are confusingly similar from a marketing perspective (i.e. protect trademarks from being used by others for financial gain) and not from a safety perspective (i.e. reducing medication errors). As stated by Dr. Levin (Director, Center for Medical Consumers) at the December 4, 2003 FDA meeting of the Drug Safety and Risk Management Advisory Committee, "trademarking has a legal

aspect that is very powerful, and it has a marketing aspect that is extremely powerful. I don't mean to suggest that the safety is disregarded, but trademarking is not a principle or a concept or an activity that was developed in the field of safety management or risk management."

Distinct trademarks may reduce the incidence of medication errors due to safety but this is not always the case. For example, in the U.S., the top four most common LA/SA drug errors between May 2000 - 2002 involved drugs with registered trademark names:

Four Most Common Look-alike Sound-alike Medication Errors[1]

Sarafem® (fluoxetine hydrochloride)	Serophene® (clomiphene citrate tablets, USP)
Lantus® (insulin glargine [rDNA origin] injection)	Lente® Iletin® II (insulin zinc suspension, USP purified pork)
Serzone® (nefazodone HCl)	Seroquel® (quetiapine fumarate)
Depakote® (Divalproex Sodium)	DEPAKOTE® ER (Divalproex Sodium)

Furthermore, it is important to note that in Canada:

- Health product names are not required to have trademarks.
- Trade-marks are not subject to regulation in the marketplace. For example, Industry Canada might refuse registration of a trademark but they cannot refuse the use of the name in the marketplace.
- If one company proposes two trademarks that are similar, the similar trademarks will be granted for both products.

Comment:
Sponsors require some certainty that when it endeavours to clear and protect a mark under relevant trademark law in Canada and that its efforts in this regard will indeed be recognized in some way should another company attempt to circumvent that protection by obtaining prior review of its mark with Health Canada. Health Canada must not ignore the legal rights of trademark holders and Canada's obligations under international treaties regarding trademarks.

Response:
Health Canada is not ignoring the legal rights of trademark holders, nor its

[1] Matthew Herper. "FDA Takes on Drug Name Confusion." Forbes.com 5 December 2003. 2 January 2004 <http://www.forbes.com/2003/12/05/cx_mh1205confusion_print.html>

obligations under international treaties regarding trademarks. Instead, it is using its power under the *Food and Drug Regulations* to refuse to issue a DIN and/or NOC, as applicable, when a brand name (with or without a trademark) poses a risk of name confusion with another product which creates a potential safety risk for the drug.

Legal Rights of Trademark Holder:
Granting of a trademark does not entitle the holder of the registered trademark to use the name. In the case of drugs, the right to use is only granted by HPFB upon issuance of a DIN and/or Notice of Compliance, as applicable. As a result, HPFB can enforce the safety standards as required under the Food and Drugs Act without regard to which manufacturer may ultimately be entitled to use a particular name as a matter of trademark law.

International Treaties:
The working group involved in the LA/SA issue has concluded that HC's refusal to authorize the sale of a proposed drug prior to market based on potential LA/SA similarities that could result in safety concerns should not pose concerns regarding international legal agreements under the *Marakesh Agreement Establishing the World Trade Organization* (WTO agreements) and the *North American Free Trade Agreements (NAFTA)*, assuming that rational, objective and nondiscriminatory criteria are developed and applied to respond to these situations.

Based on WTO agreements and NAFTA, once a drug is marketed, it is recognized that HC should consider all other less "trade restrictive" options before moving to request a sponsor to change a drug name and/or stop sale of the drug. As with, the pre-market case, rational, objective and nondiscriminatory criteria should be developed and applied to respond to these situations.

7. Name Review-General

Comments:
Health Canada appears to recognize that it is unclear which, if any, of the assessment techniques it references has value. It thus appears too soon to recommend such methods while their value remains in doubt. Further study and evaluation is needed.

We urge Health Canada not to implement any additional reviews without a validated, reliable, reproducible and standardized method for conducting such reviews.

Response:
Based on the precautionary principle, Health Canada cannot use scientific uncertainty where safety is a concern as reason not to act.

Health Canada believes that the assessment techniques used in the market place to date have value, it is just unsure which has the greatest value in assessing a name for LA/SA similarities. Decisions and direction regarding criteria for sponsor-generated data submissions will be provided as the science develops to assess outcomes data.

The FDA has been reviewing proprietary names for potential LA/SA similarities for the past decade and is still grappling with this same issue. Current FDA methods to evaluate proprietary drug names represent process-based science. An outcomes based scientific method has yet to be developed.

Comments:
What level of name similarity is permissible for health product names?

It is our view that the guidance lacks adequate discussion of the distinction between the situation in which names may be similar-but are not shown to be confusing, and names that are somewhat dissimilar-but may be confusing.

Response:

It is the sponsor's responsibility to satisfy the government when it comes to safety and efficacy of a product. Some examples of products that have resulted in LA/SA errors can be found in the USP Quality Review, April 2004. The link to this document is as follows:
http://www.usp.org/patientSafety/briefsArticlesReports/qualityReview/qr792004-04-01.html

Comments:
What information should be contained in the assessment? What methods will be considered valid for making the assessment?

If sponsors are using different assessment technique to assess names, how can there be consistency in the reviews by HPFB?

Response:

At the Look-alike Sound-alike (LA/SA) Health Product Names Consultative Workshop that was held on October 20-21, 2003, presentations discussed the name review process. For more information, please refer to the following presentation links. These presentations outline some assessment techniques that are acceptable.

Proprietary Name Evaluation at the Food and Drug Administration (FDA).
http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/j_phillips_e.html

Med-E.R.R.S. Name Review Process
http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/s_proulx_e.html

Automatic Detection of Confusable Drug Names
http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/g_kondrak_e.html

As with other portions of a review (re clinical studies) different assessment techniques will be used by sponsors to assess names. Each name assessment will be reviewed on a case by case basis in determining whether or not a name similarity constitutes a potential safety concern.

Comment:
The initial review described in the guidance should be binding. It is the responsibility of Health Canada to ensure that once a name has been approved for use by a sponsor, no other LA/SA product is approved in the period before NOC is granted to the original product.

The first company to file for a new name should have the right to this name. This is consistent with trademark and patent laws.

Response:

The initial review is not binding and needs to be preliminary in nature because it is possible that another product may be approved prior to the proposed product in question that could result in LA/SA confusion. If the preliminary review was binding or if the first company to file for a new name had the right to this name (without having the rest of the submission approved), it would mean that a number of proposed products that were not approved for other reasons would have approved names that could not be known by other sponsors because they had not yet received a DIN and/or NOC. It would be impossible for a sponsor to assess their proposed name against a name of a drug that had not yet been approved because they would be unaware of the name.

As this section of the guidance may have been misinterpreted, it will be reworded to reduce confusion.

Comment:
There is a need for a list of factors that could be considered in a risk-based assessment of proposed self-care health product names.

Response:

In determining whether the degree of similarity in names is problematic for self-care health products, the following contributing factors would be taken into consideration during the review, as applicable:

- the marketing status (OTC use) and setting for use;
- the therapeutic category and the indications;
- the location on the shelf;
- the packaging and labelling; and
- similar patient populations

Other considerations such as the proposed dose and dosing interval, dosage form, routes of administration and strength would not tend to be as significant considerations for self-care health products as for Rx drugs.

Of note, Susan Winckler (Vice President, American Pharmacists Association) stated at the June 23, 2003 FDA meeting, entitled *Minimizing Medication Errors- Methods for Evaluating Proprietary Names for Their Confusion Potential*, that "drug name safety testing for all medications — regardless of their class — should be held to the same high standards. Medication errors due to name confusion can occur with proprietary and nonproprietary prescription drugs, as well as OTCs. Consumers selecting an OTC may select the incorrect product due to confusion generated by similar product names or brand name line extensions. Eliminating confusing nomenclature practices for all medication products is an important step toward reducing medication errors of all kinds."

8. Name Review- Mandatory?

Comments:
It is unclear from this document whether a risk assessment is required to be submitted for a proposed product name. Page 2 of the guidance document states "it was recommended that when filing a submission, sponsors provide a name analysis". However, on page 7, it states "a risk assessment and evaluation of the product's brand name supported with studies, data and analysis are encouraged".

It should be the sponsors' discretion as to whether a risk assessment is required or not. If Health Canada raises concerns or rejects a proposed name, the sponsor should then be able to provide their own risk analysis if not previously done.

We recommend that a stepped approach to the analysis be adopted. For example, if based on the contributing factors listed in the guidance (e.g. dose forms or routes of administration, therapeutic category, patient population, etc.) it is determined that the drug is of less concern for medication errors, then a full assessment should not need to be completed.

It is unclear whether all names will be reviewed or whether a name review will only be conducted if the name is "flagged" during the computer screening process.

Response:

The WG reconfirmed that a name review will be mandatory for all drugs. Where this is unclear, the guidance document will be revised accordingly.

At the December 4, 2003 FDA Drug Safety and Risk Management Advisory Committee Meeting, the following two questions were posed:

- Is it possible to triage the drug names into groups that may be handled

differently based on risk?

- Describe circumstances, if any, when it would be appropriate to approve a proprietary drug name contingent on a risk management program being in place.

In response, it was agreed that all drugs should be reviewed because it is unknown as to which ones will pose a problem. Even if a drug appears innocuous, it may not be if another product is used in error.

9. Name Review- Who Should be Involved?

Comments:
We believe that pharmacists and prescribers (and not reviewers or an Inter-Directorate Committee within Health Canada) have by far, the best experience and broadest knowledge to decide whether or not a name may cause confusion. An external committee should therefore be constituted (e.g., the CSHP) to make this assessment, rather than relying on personnel within the Directorates.

We would like to propose that the review process include health care provider participation.

Shouldn't the name evaluation methods be peer reviewed before they are accepted as evidence by HC?

Response:
Sponsors should be consulting with pharmacists and health care providers in preparing name review analysis.
HC does acknowledge that a name reviewer would ideally have a pharmacy background. Of note, HC does have a number of pharmacists and health care providers on staff that currently review drugs.

10. Name Review- Does it Work?

Comment:
The experience of other countries, including the US, does not indicate that such additional reviews create any appreciable improvements in the overall rate of medication errors. Very clear expectations on what a LA/SA procedure can accomplish needs to be assessed.

Response:
Health Canada has a responsibility to assess the safety of a health product and to endeavour to prevent LA/SA health product name errors. Health Canada is

confident that effective policy and risk management to prevent LA/SA medication errors will have a positive outcome.

11. Name Review: Timing

Comments:
It is recommended that the review of a drug brand name be conducted upon the sponsor's first use of the brand name in any submission type (CTA, NDS, SNDS, ANDS, SANDS etc..). Health Canada should also consider providing sponsors with the opportunity to submit a drug brand name for review independent of any submission.

In other jurisdictions, the product name analysis/review is conducted during earlier stages of development (i.e. during phase II/III clinical trials). Health Canada should also allow for the flexibility of accepting name analysis during earlier development stages, in order to match the sponsor's global plan/timeline.

Response:

The statement in the guidance document recommending that a proposed name be introduced at a pre-submission meeting will be removed as it would be premature to conduct a name review at this stage as Health Canada may not be able to assess contributing factors and proceed with a complete assessment at this stage of the review.

Comment:
The draft guidance document recommends that a proposed name be introduced at pre-submission meetings. Those submitting nonprescription drugs or natural health product applications do not hold such meetings.

Response:

Presubmission meetings may be requested for OTC products and NHPs.

Comments:
Page 7 states that the final review will be completed "within 90 days of the anticipated day of approval". Clarification is needed as to whether or not this is intended to be 90 days before the anticipated day of approval.

It is unclear what will trigger this subsequent 90 day re-assessment period as the review will still be underway at this time.

A 90-day target for name review has been proposed in the draft guidance document. However, this greatly exceeds the 45-day target for the pre-market review of Labelling Standards and Category IV Monographs and the 60-day target for the pre-market review of Natural Health Products with monographs.

Response:

Yes, it is intended that the final review is intended to be 90 days before the anticipated date of approval.

With the use of project management tools (i.e. MS Projects), HPFB can better predict the anticipated day of approval with some accuracy.

As Labelling Standards, Category IV Monographs and Administrative NDS submissions have a 45 day review target, it was recognized that a 90 day name review assessment would be a problem. It was agreed that these name reviews would need to be prioritized in the name review workload.

Comments:

The assessment of health product names should not impact the approval time of the submission and should occur in parallel to other activities. Canadian patients should not have to wait for the availability of effective and safe treatments, while the name of a drug is being assessed.

Response:

It is anticipated that the health product name review will occur concurrently with the rest of the product review. In most cases, the health product name review will have no impact on review times.

Comment:

Analyses for name suitability should be done early in the review process. Having to change marketing materials and printed packaging components late in the approval process could add significantly to a company's cost and delay a product launch.

Response:

This concern is understood and this will be considered when implementing LA/SA guidance and related processes.

Health Canada is committed to ensuring that the name review will occur as early as is feasible. It is recommended that the sponsor take precautions to eliminate the potential for LA/SA names before the proposed product is submitted for approval.

Comment:

The guidance should provide sponsors with information on how soon alternative names can be provided, and HC should commit to a target review time for alternative names.

Response:

An alternative name can be provided along with the proposed name when the submission is filed (i.e. with an NDS, SNDS, ANDS (or ABSNDS) SANDS

(or SABANDS), DIN and any administrative submissions that involve a change to the name of a drug). The target review time for the alternate name would be 90 days.

12. International

Comment:

As CBER already has a process for name evaluation in process, alignment with CBER when a product is already approved in the US should be considered.

Response:

Health Canada , in developing its draft guidances, considered other national regulatory agencies' processes for reviewing health product names for LA/SA similarities and has incorporated them into HPFB's draft guidances, where possible.

Of note, HPFB was represented at the two recent meetings in the U.S. regarding LA/SA drugs. In addition, Captain Thomas Phillips, former Associate Director of the Division of Medication Errors and Technical Support in the Office of Drug Safety, was a guest speaker and contributed to discussions held at Health Canada's LA/SA consultative workshop on October 20-21, 2003.

Comments:

International product name consistency is important since industry does not typically have a lot of flexibility in available names that have been approved for use.

There is a small risk that prescribing errors may result from health professionals being exposed to two or more different brand names for the same drug product (i.e. different countries using different brand names for the same drug product).

Response:

Health Canada has no objection to the use of a global trademark so long as it does not create the potential for LA/SA medication errors within Canada.

Health Canada is concerned about the risk of different countries using different brand names for the same drug and advocates that sponsors make a concerted effort not to do this.

Ensuring name consistency internationally is out of Health Canada's mandate. However, this could be an issue that HC could suggest that the World Health Organization might consider taking on.

Comments:

We recommend that Health Canada accept, for its evaluation of the brand name, the information submitted to either the FDA or the EU. The Canadian sponsor

would have to ascertain that the information is applicable to the Canadian environment.

Response:

Health Canada will consider information that has previously been submitted to either the FDA or the EU in its assessment of a name review if it is provided to HC. As mentioned above, the Canadian sponsor would have to ascertain that the information is applicable to the Canadian environment.

Comment:
In order to facilitate the name review, sponsors should provide the regulatory approved drug brand name in other countries.

Response:

Yes, in order to facilitate the name review, sponsors could provide the regulatory approved drug brand name in other countries.

Comment:
What if a name is accepted/rejected by EMEA or FDA? How will this impact on Health Canada's decision-making?

Response:

If a name is accepted/rejected by EMEA or FDA, Health Canada will take this into consideration in its decision along with all other information submitted by the sponsor.

Comment:
Pharmaceutical manufacturers should be required to report to the HPFB any name changes that have been made for the United States market as a result of medication errors detected there. The HPFB would then review the current and changed names and consider whether the same change is required for Canada, if not already submitted. (ISMP)

Response:

Agreed. Health Canada intends to monitor available sources of information, including name changes of marketed health products in other countries that occur as a result on medication errors.

13. LA/SA Computer Application

Comments:
The guidance states that a “complex computer application has been acquired”, but in correspondence with Health Canada it was stated that no such system has yet been acquired.

Response:

Health Canada has not yet acquired a computer application. The draft guidance document will be revised accordingly.

Comment:

If a computer application is to be acquired, perhaps something should be said about its specifications and the process by which it will be selected.

Response:

These details are more suitable for a Request for Proposal (RFP).

Comment:

We would be interested in knowing what information this "complex computer application" system contains, what it measures, what is the standard used by this application and whether it can be validated.

If a computer application is used, which search methods will be used (bigram, trigram, edit distance, etc.)? What database of existing names will be searched? How many different searches (spelling, phonetic, etc.) will be done on each name? If non-name attributes such as strength or route of administration are to be included in computer searches, how will those attributes be weighted? If you will use a numerical cutoff or threshold, how will that cutoff be determined? What sort of validation will be required of methods that are submitted by applicant companies?

Response:

HPFB has not yet acquired a computer application; however, parameters used in the computer-based analysis will be similar to those used by the FDA. Currently, the U.S. FDA uses a computer application that applies proven linguistic methods (i.e. Edit Distance, Soundex, DICE, LCSR, Aline) of comparing names for orthographic (spelling) and phonetic or phonological (pronunciation) similarities. The similarity of health product names is determined based on score results. Furthermore, this application considers similar strengths and dosage forms when looking at a name.

For more information regarding these linguistic measures, please refer to LA/SA consultative workshop presentations given by Dr. Greg Kondrak <http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/g_kondrak_e.html> and/or Dr. Bruce Lambert <http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/b_lambert_e.html>.

Comment:

The output from a LA/SA computer application system is a tool of limited value and may provide "false positive" information. In a recent U.S. court case, the U.S.

court was provided with computer information evidence risk of confusion between two marks. The Court responded that the evidence was "not a reliable predictor of actual medical substitution, let alone trademark confusion". That court was particularly troubled by the high false positive rate.

Response:

To reduce the incidence of "false positives", a multifaceted approach is proposed for the name review process. The computer application will serve as just one of the screening tools; a precursor to a name review. Names that are flagged will be reviewed further by a Health Canada reviewer.

Comment:

Any computer application programme needs to have very clear instructions for use and expectations so that different users do not use the system in different ways. For example, what level of similarity would be assessed? (e.g. 70% similarity assessed by one reviewer; 80% by another) What triggers would flag a name as being "too similar"?

Response:

The computer application will not provide 100% assurance that all LA/SA cases will be detected. In part, this was one reason to proceed with a multifaceted approach to name review. It must be tested and put into practice in order to determine the appropriate percent settings of similarity to be used during the screening process. In other words, there need to be room for trial and error during the early stages of the application's use.

Comment:

Is it possible to make the computer application available to sponsors, allowing sponsors to conduct a drug name assessment well in advance of having a HC name review?

Response:

This will be considered and Health Canada will work toward making the computer application available to sponsors.

14. Name Hold

Comment:

It is not clear from the guidance at what stage the "Name Hold" takes place (whether during the initial or final review). If the hold occurs during the final abbreviated review, and hence could affect approval timelines, the sponsor should be given options, such a receiving the NOC without a brand name.

Response:

A submission will be placed on name hold when it is the only item outstanding in a review. It would most likely result when an initial proposed name and alternate name have already been rejected and yet another proposed name is being reviewed.

Once an acceptable name is approved, the submission can be taken off name hold. Instead of a name hold, the sponsor could opt to receive the NOC without a brand name.

Comment:
If a full assessment was submitted for the first name (subsequently rejected) and the second name was not submitted with an analysis, would the submission be put on "name hold" until extra studies are complete? What would happen if this subsequent name is rejected?

Response:

A submission will be placed on name hold when it is the only item outstanding in a review. If the subsequent name was rejected then the sponsor could submit another proposed name at that time.

Comment:
Provisions would need to be made so that a brand name could be instituted quickly once the "Name Hold" was resolved.

Response:

Agreed. This will be considered in the implementation plan and related standard operation procedures (SOPs).

Comment:
The "name hold" provision should not be used to handle workload if there is a backlog in this section.

Response:

Agreed. The submission would not be placed on name hold and would be considered behind target and in backlog.

15. Appeal Process

Comments:
Will there be a dispute resolution or an appeal process in place if Health Canada and the sponsor cannot come to a mutual resolution?

It should be stated in this policy (pre-market policy, Section 5) that the sponsor has the right to appeal this name hold and also has the right to address HPFB's concerns by requesting a meeting.

Response:

A sponsor has the right to appeal name review decisions*. When a sponsor disagrees with a Health Canada decision regarding a submission review, they may appeal the decision. The Health Canada Guidance *Appeals Procedures for Drug Submissions* may be referred to for more information regarding appeals.
<http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/appeals_policy_e.pdf>
Of note, this guidance allows sponsors to request a meeting.

* This is assuming that the name review will occur during the submission review

In the future, it is anticipated that the appeal process will be replaced by a dispute resolution process that will apply to the name review process.

16 Phased Scheduling

Comment:

In the interest of public safety, Health Canada should consider implementing these guidance first for OTC and natural health products, then follow with implementation for Schedule C, D and F products. For Schedule C, D and F products, there are health care professionals acting as intermediaries between the receipt of the drug and the patient. For OTC and natural health products, the patient purchases these directly from a store shelf, without any consultation or review by a health professional, who could possibly identify a medication error.

Response:

At the October 20-21, 2003 LA/SA consultative workshop, respondents believed that the LA/SA health product name project should be prioritized as follows:

1. Prescription drugs for human use (including Schedule C, Schedule D and Schedule F drugs)
2. Over-the-counter products for human use
3. Natural Health Products for human use
4. Veterinary Drugs
5. Medical Devices

The respondents general rationale for prioritization was based on:

- risk to human health;
- magnitude of harm (i.e. prescription drugs are more closely controlled for a reason);
- consumer protection;

- incidence and frequency;
- most information available (some problems identified); and
- ability to address / regulate.

The outcome of the workshop concurs with the LA/SA IAS identification of the need to focus specifically on LA/SA issues that appear to pose the most potential for health risk. The LA/SA IAS states that the first priority is to implement both the pre-market and post-market recommendations for Schedule C, D and F drugs.

Comments

Before any such guidance is extended to self-care health products, the look-alike sound-alike issue must be clearly understood for this class of products.

The draft guidance document *Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names* as it is currently presented, focuses almost exclusively on prescription drugs as evidenced by the suggested risk assessment studies, many of which apply only to prescribed drugs. The guidance document as currently presented cannot be extended to self-care health products without major changes.

Other regulatory agencies, such as the Medicines and Healthcare products Regulatory Agency (MHRA) have developed approaches specific to what they term “umbrella segments of product names”, that are relevant to self-care health products. NDMAC has also developed a guidance document on the labelling of products with significant changes, including the introduction of new self-care health products under an existing brand name.

Response:

Prior to implementation of this guidance for self care products, Health Canada will review the guidance to ensure that it is applicable to self care products. In carrying out this task, Health Canada would be interested in reviewing NDMAC’s guidance document on the *Labelling of products with significant changes*, including the introduction of new self-care health products under an existing brand name and incorporate applicable information, where possible.

Susan Winckler (Vice President, American Pharmacists Association) stated at the June 23, 2003 FDA meeting, entitled *Minimizing Medication Errors- Methods for Evaluating Proprietary Names for Their Confusion Potential*, that “drug name safety testing for all medications — regardless of their class — should be held to the same high standards. Medication errors due to name confusion can occur with proprietary and nonproprietary prescription drugs, as well as OTCs. Consumers selecting an OTC may select the incorrect product due to confusion generated by similar product names or brand name line extensions. Eliminating confusing nomenclature practices for all medication products is an important step towards reducing medication errors of all kinds.”

17. Post-Market - Changing Brand Names

Comment:
It is critical that brand name LA/SA issues for any given product be resolved prior to market introduction. Changing a marketed product's brand name would directly impact the sponsor by harming a significant portion of brand equity thereby necessitating significant investment by the sponsor to market their product under the new name. Moreover, one must consider the potential confusion for patients, possibly leading to compliance issues, should names be changed after market introduction has occurred.

Response:

Health Canada concurs with this suggestion, since it is in the best interests of stakeholders, health care practitioners and consumers that health product names not be prone to confusion either through LA/SA similarity or through re-introduction as a new name.

Health Canada has considered the costs to a sponsor of changing a product name post-market. The pros and cons to this option are outlined in the LA/SA IAS Appendix B: post-market option #6. In the analysis of this option, it was concluded that requiring the sponsor to change the name of a product post-market would result in significant economic burden for sponsors (recalls, loss of brand recognition etc.). All effort will be made to resolve the potential LA/SA health product name pre-market. Since the health and safety of Canadians is of foremost importance for Health Canada, as a last resort, a name may need to be changed or modified to avoid confusion.

Comment:
Under section 5. Policy, the last paragraph: Available sources of information will be monitored (medication error reports…. ..) should read *(medication error reports received by the Canadian Medication Incident Reporting and Prevention System (CMIRPS) and other patient safety organizations, incidents reported through media.*…).

Response:

The guidance will be revised to better reflect Health Canada's post-market role.

Health Canada provides a leadership role, and continues to actively participate in, the development and implementation of a national medication incident reporting and prevention system. This system, the Canadian Medication Incident Reporting and Prevention System (CMIRPS) has the objective of reducing preventable medication incidents. The CMIRPS project, currently in the design phases, will have an impact on, as well as help to define, how Health Canada can most

effectively collaborate with other organizations, and how to best respond to post-market safety issues related to health product naming.

Comment:
The post-market guidance states (section 6, Procedures) that HPFB will assess the suggestions generated by MAHs and sponsors will be notified of the agreed upon strategy. What are the timelines for this assessment?

Response:

At this time, a specific timeline has not been determined. In general, the time taken to review the assessment will depend upon the complexity of the suggestions generated and the urgency of the problem (re risk to Canadians).

Comment:
The post-market guidance (section 6, Procedures) states that communications should be filed to MHPD (for health professional communications) and BGTD (for Biologics). The scope also describes the inclusion of Schedule F products as well. There should be instructions to direct communications to the appropriate directorate.

Response:

Instructions will be provided to MAHs as to whom they should communicate with in correspondence. In most cases, it is envisioned that MHPD will be taking the lead role in coordinating the resolution of post-market name similarity issues; whether they be for Schedule F products or Biologics. As applicable, the guidance will be revised to clarify this.

Comment:
The guidance states that all affected MAHs will be advised of concerns with potential safety issues and HPFB will work to facilitate a satisfactory solution which is as “fair” as possible. We would appreciate a more clear explanation of this term “fair”. If a product has been on the market for over 10 years and a concern is signalled with a name which has only been on the market for a few years, will the length of time a product name is on the market affect HPFB’s decision in determining what is a fair solution?

The post-market guidance does not provide any detail regarding how a dispute between two MAHs with products having similar names would be resolved. The proposed guidance does not begin to address the factors that might be considered, nor does it specify any of the actions that might be taken (beyond ``health professional communication``or ``a submission``). If this type of information is not included in the guidance, then there is question on the value of having any guidance in place regarding this topic.

Response:

HPFB has dedicated resources to investigating avenues by which Health Canada

can work together with the pharmaceutical industry, health care professionals and related organizations in responding to health product-related post-market safety issues arising from medication incidents, with the goal of preventing medication incidents, and improving patient safety. This collaborative approach has potential to give rise to options that are both reasonable and agreeable to stakeholders, and the knowledge gained may, in some cases, contribute to development of specific product safety guidance documents. The desired outcome is to complement existing regulatory requirements related to health product naming, labelling and packaging in order to strengthen the safe use of health products in the context of day-to-day use in the practice environment.

The results of this work, in combination with other consultation and analysis will provide the basis for defining the specific details that are currently not available in the post-market guidance document.

Comment:
Will new post-market activities be implemented by HPFB as a result of this guidance?

Response:

Yes. Work is currently in progress to investigate exactly how to operationalize and bring consistency to the post-market response for patient safety issues arising from medication incidents related to LA/SA product naming.

Comment:
Health Canada should globally monitor name changes of marketed health products that occur as a result of medication errors.

Will post-marketing surveillance be used to track the success of your name review initiatives?

Under what circumstances will companies be asked to change their names? After 1 error, 10 errors? One fatality? Ten fatalities?

Response:

As mentioned in section 5 of the guidance *Marketed Health Product Name Assessment: Look-alike Sound-alike (LA/SA) Health Product Names,* Health Canada intends to investigate how it can best monitor available sources of information, which will ultimately include name changes of marketed health products in other countries that occur as a result of medication incidents.

Once the name review process is in place, it will be evaluated. Details of the evaluation plan have yet to be developed.

In the case of medication incident data, reported cases will undergo a risk assessment to detect sentinel events. A "sentinel event" has been defined as "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof." (Cohen, MR editor. Medication Errors, p 20.1, American Pharmaceutical Association, Washington, DC, 1999.) There is no formula, method or specific number of reports required before mitigating strategies involving the market authorization holder may be considered. Medication system and process-based factors that may have contributed to the incident will need to be investigated in addition to product-related labelling/packaging/naming issues before prevention strategies are considered.

Comment:
Will HC use their new name evaluation method to examine existing names?

Response:

Generally this will not be done. HPFB will rely on the guidance, *Marketed Health Product Name Assessment: Look-alike Sound-alike (LA/Sa) Health Product Names*, for direction post-market. It is anticipated that the computer application could be used to examine and/or flag existing names for LA/SA name similarities; however, this is not currently a priority.

18. Other Solutions

Comments:
Medication errors can be multi-causal; therefore, we also recommend that Health Canada fund and support implementation of the use of standardized (universal) product codes in hospitals and pharmacies for easy product identification to reduce medication errors.

Response:

The use of bar codes is not a guarantee that error will not occur. For example, recently a California health care agency labelled thousands of prescriptions incorrectly due to a computer error. <http://www.mercurynews.com/mld/mercurynews/news/5418874.htm>

Bar coding is a measure that could be used to help prevent medical error and was considered as a post-market option in the LA/SA IAS. The pros and cons to this option are outlined in the LA/SA IAS Appendix B: post-market option #4. In the analysis of this option, the LA/SA WG concluded that bar coding has a number of drawbacks including the following:

- it cannot be a stand-alone solution since errors can happen upstream from bar coding (i.e. when an Rx is written and misunderstood by the pharmacist); and

- significant stakeholder investment would be required in bar coding. *The Regulatory Policy* specifically states that "information and administrative requirements are limited to what is absolutely necessary and imposes least possible cost."

  The FDA estimates it will cost U.S. hospitals more than $7 billion US to implement bar coding technology.[2]

Comment:
Health Canada should consider implementing computerized prescribing, improving storage and working conditions at retail pharmacies, and implementing computerized systems for dispensing medications in hospital settings.

Response:

Electronic prescribing was considered as a post market option in the LA/SA IAS. The pros and cons to this option are outlined in the LA/SA IAS Appendix B: post-market option #5. In the analysis of this option, electronic prescribing had some of the same drawbacks as bar coding.

Health Canada advocates improving storage and working conditions at retail pharmacies and that computerized systems for dispensing medications be used in hospital settings. Health Canada cannot directly affect these changes because these issues are outside of Health Canada's mandate and because it is a matter that falls under provincial jurisdiction.

Comment:
The Health Canada draft guidance document discourages suffixes in brand names, while other guidances acknowledge this practice as long as they do not give rise to inappropriate impressions of superiority or ambiguity.

Response:

Because abbreviations can be misinterpreted or misunderstood, resulting in serious errors, all abbreviations and unclear orders or prescriptions should be questioned to avoid errors and the possibility of harm to patients. Please refer to the following link for more information regarding abbreviations:

http://www.usp.org/patientSafety/briefsArticlesReports/qualityReview/qr802004-07-01.html

If abbreviations are to be included in a proposed drug name, appropriate

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[2] Stephen Nicolls, "Eliminating drug name mixups target of new federal program", Medical Post, 13 January 2004; Canadian Medical Association Journal, 4 March. 2003; 40(2) p. 1.

justification for their inclusion should be provided.

Comment:
Will the agency do any other in-house testing, other than computer searches? What about tests of visual perception, auditory perception, or short term memory?

Response:
In addition to computer searches for in-house testing, HPFB will also be conducting name reviews. Besides this, HPFB does not currently have the resources to do any additional in-house testing of names (i.e. prescribing simulation testing).

19. Miscellaneous Comments

Comment:
The Institute for Safe Medical Practices (ISMP) should be written as: the Institute for Safe Medication Practices Canada (ISMP Canada).

Response:
The guidance will be revised accordingly.

Comments:
In sections 5 and 6 of the draft guidance, there are terms used and procedures described which are vague and require clarification in order to be implemented or applied. There is no standard given for what is a "similar" name (i.e. there are names that may be similar, but not confusingly similar).

Response:
The WG will try to find a definition for what is "similar".
Similarity is not only based on the name, it's a multi-factorial concept and all the factors need to be assessed.

Comment:
As the term "proprietary drug name" is used throughout the guidance, the definitions section should define this term.

Response:
The guidance will be revised accordingly. The definition for "proprietary drug name" will be included in the guidance document.

Comment:
The last sentence for Product Line Extensions, which states "This practice has arisen as a marketing strategy to take advantage of familiarity of an original product name" should be deleted since it is merely conjecture and in no way

provides a complete analysis of the potential therapeutic benefit of having related products identified by related names.

Response:

The guidance document will be revised accordingly.