

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)

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Office of Surveillance and Epidemiology

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Subject: Proprietary Name Review

Drug Name(s): Makena (Hydroxyprogesterone Caproate) Injection,
1250 mg/5 mL

Applicant: Hologic Inc.

OSE RCM #: 2010-2519

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CONTENTS

| | |
|--|---|
| EXECUTIVE SUMMARY | 3 |
| 1 BACKGROUND..... | 3 |
| 1.1 Introduction..... | 3 |
| 1.2 Product Information..... | 3 |
| 1.3 Regulatory History..... | 3 |
| 2 METHODS AND MATERIALS | 3 |
| 2.1 Search Criteria..... | 3 |
| 2.2 Prescription Analysis Studies..... | 4 |
| 3 RESULTS..... | 4 |
| 3.1 Data base and Information Sources..... | 4 |
| 3.2 Expert Panel Discussion..... | 5 |
| 3.3 Prescription Analysis Studies..... | 5 |
| 3.4 Safety Evaluator Risk Assessment..... | 5 |
| 3.5 Comments from the Division of Reproductive and urologic Products (DRUP)..... | 5 |
| 4 DISCUSSION | 6 |
| 4.1 Promotional Assessment..... | 6 |
| 4.2 Safety Assessment..... | 6 |
| 5 CONCLUSIONS AND RECOMMENDATIONS | 6 |
| 5.1 Comments to the Applicant..... | 6 |
| 6 REFERENCES | 7 |
| APPENDICES..... | 8 |

EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of Makena as the proposed proprietary name for Hydroxyprogesterone Caproate Injection. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Makena acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Hologic Inc. dated November 29, 2010 for an assessment of the proposed proprietary name, Makena, regarding potential name confusion with other proprietary or established drug names in the usual practice settings and for promotional assessment.

1.2 PRODUCT INFORMATION

Makena (Hydroxyprogesterone Caproate Injection) is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. The recommended dose is 250 mg (1 mL) as an intramuscular injection once each week beginning at 16 to 20 weeks until 37 weeks of gestation or delivery. Makena will be available as a 250 mg/mL injection and supplied in 5 mL multiple dose vials.

1.3 REGULATORY HISTORY

This is a resubmission to the NDA with 02/28/2011 PDUFA date. DMEPA found the prior proprietary names, Gestiva (OSE #06-0134); (b) (4) unacceptable for this product, which was conveyed to the Applicant in a teleconference, dated November 23, 2010. Subsequent to notification, the Applicant withdrew these names and submitted Makena for further evaluation.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Makena. Section 2.3 identifies specific information associated with the methodology for assessment of the proposed labels and labeling.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'M' when searching to identify potentially similar drug names, as 75% of the

confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{1,2}

To identify drug names that may look similar to Makena, the DMEPA safety evaluators also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (two, capital letter ‘M’, and lower case ‘k’), down strokes (none), cross strokes (none), and dotted letters (none). Additionally, several letters in Makena may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Makena.

When searching to identify potential names that may sound similar to Makena, the DMEPA staff search for names with similar number of syllables (two), stresses (Ma-kee-na), and placement of vowel and consonant sounds. (See Appendix B). The Sponsor’s intended pronunciation (Mah-kee-nah) was also taken into consideration, as it was included in the Proprietary Name Review Request. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies. (See Appendix C for samples and results).

3 RESULTS

The following sections describe the findings from our database searches, expert panel discussion, prescription analysis studies and safety evaluator risk assessment.

3.1 DATA BASE AND INFORMATION SOURCES

The DMEPA safety evaluator searches yielded a total of 17 names as having some similarity to the name Makena.

Fourteen of the names were thought to look like Makena. These include: Mirena, Maxair, Malarone, Nalfon, Nubain, Melanex, Nebcin, Moban, Maxam, Multaq, Maxidone, Marcaine, (b) (4) ***. Three names were thought to look and sound similar to Makena: Makena, Mevacor and Moctanin.

¹ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

² Kondrack, G and Dorr, B. *** This is proprietary and confidential information that should not be released to the public.

*** This is proprietary and confidential information that should not be released to the public.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of December 01, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional name thought to have orthographic or phonetic similarity to Makena.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 PRESCRIPTION ANALYSIS STUDIES

A total of 36 practitioners responded to the prescription analyses studies with eighteen of the participants interpreting the scripted name sample correctly as “Makena,” with correct interpretation occurring in both of the written studies. However, for practitioners interpreting the written prescription for Makena incorrectly, none of the responses overlapped with existing drug product name. In the verbal studies, none of the participants understood the spoken proposed name sample correctly. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in identification of six additional names which were thought to look or sound similar to Makena and represent a potential source of drug name confusion. The names identified to have look-alike similarities are Nalex-A, Mesna, Mykinac, Moxeza, Navane, and (b) (4)

One name “Makena” was not evaluated further since it was identified on the U.S. Patent and Trademark Office website registered to the Applicant likely for this product. Thus, we evaluated a total of twenty two names: 6 identified by the primary safety evaluator, 16 identified in section 3.1 above.

3.5 COMMENTS FROM THE DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

3.5.1 Initial Phase of Review

In response to the OSE, December 03, 2010 e-mail, DRUP did not forward any concerns on the proposed name at the initial phase of the name review.

3.5.2 Midpoint of Review

DMEPA notified the DRUP via e-mail that we had no concerns with the proposed proprietary name, Makena, on December 07, 2010. Per e-mail correspondence from the DRUP on December 07, 2010, they indicated the Division had no other issues with the proposed proprietary name, Makena and had no additional comments.

4 DISCUSSION

Makena is the proposed proprietary name for Hydroxyprogesterone Caproate Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered their comments accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA, and DRUP concurred with the findings of DDMAC's promotional assessment of the proposed name.

4.2 SAFETY ASSESSMENT

DMEPA evaluated 22 names for their potential similarity to the proposed name, Makena. Seven of the twenty two names did not undergo failure mode and effect analysis (FMEA) for the following reasons: products discontinued with no available generics, proposed proprietary names withdrawn by the Applicant, or discontinued proprietary names (see Appendices D-F).

Failure modes and effects analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining 15 names and lead to medication errors. This analysis determined that the name similarity between Makena and all of the identified names was unlikely to result in medication error for the reasons presented in Appendices G and H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Makena, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Makena, for this product at this time. The Applicant will be notified via letter from DMEPA.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Maria Wasilik, project manager, at 301-796-0567.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Makena, and have concluded that the name is acceptable.

Makena will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

6 REFERENCES

1. *Micromedex Integrated Index* (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. *FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]*

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. *Electronic online version of the FDA Orange Book* (<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. *U.S. Patent and Trademark Office* (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or

lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁵ DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

| Type of similarity | Considerations when searching the databases | | |
|--------------------|---|---|---|
| | Potential causes of drug name similarity | Attributes examined to identify similar drug names | Potential Effects |
| Look-alike | Similar spelling | Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics | <ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication |
| | Orthographic similarity | Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics | <ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication |
| Sound-alike | Phonetic similarity | Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics | <ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication |

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent

to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not

⁶ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. . (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

| Letters in Name, Makena | Scripted may appear as | Spoken may be interpreted as |
|----------------------------|------------------------|------------------------------|
| Upper case 'M' | N, U | N, em |
| Lower case 'a' | Any vowel | Any vowel |
| Lower case 'k' | h, la, b | |
| lower case 'e' | Any vowel | Any vowel |
| Upper case 'n' | m, r, u | en |

Appendix C: FDA Prescription Study for Makena

Figure 1. Makena Study Samples (conducted on December 02, 2010)

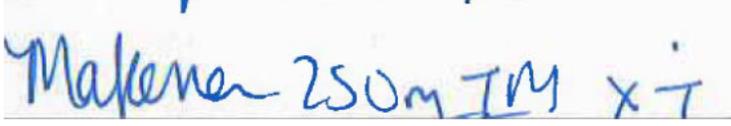
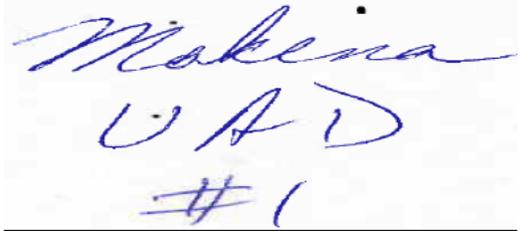
| HANDWRITTEN REQUISITION MEDICATION ORDER | VERBAL PRESCRIPTION |
|---|---------------------|
| <p><u>Medication Order</u></p>  | Makena 20 mg IM x1 |
| <p><u>Outpatient Rx</u></p>  | |

Table 1: Responses to Prescription Study

| Outpatient Prescription | Inpatient Medication Order | Voice Prescription |
|--------------------------------|-----------------------------------|---------------------------|
| Makina | Makena | Metkina |
| Makena | Makena | Mesina |
| Makena | Makena | Meclina |
| Makina | Makena | Madena |
| Makena | Makena | Metina |
| Makena | Makena | Mckeena |
| Makena | Mekna | Matina |
| Makena | Makener | Nikina |
| Makena | Makener | |
| Makina | Makena | |
| Makena | Makener | |
| Makena | Makener | |
| | Makene | |
| | Makena | |
| | Makena | |
| | Makener | |

Appendix D: Discontinued products with no available generics

| Proprietary Name | Similarity to Makena | Status |
|---|----------------------|--|
| Moxam (Moxalactam Disodium) Injection | Look | Discontinued products with no available generics |
| Moctanin (Monoctanoin) perfusion Liquid | Sound | Discontinued products with no available generics |
| Moban (Molindone Hydrochloride) Capsules, Tablets and Oral Solution | Look | Discontinued products with no available generics |

Appendix E: Proposed proprietary names

| Proprietary Name | Similarity to Makena | Status |
|------------------|----------------------|--------|
| (b) (4) | | |

Appendix F: Discontinued proprietary names for which the established name or other proprietary names are used in usual practice settings.

| Proprietary Name | Similarity to Makena | Status |
|------------------|----------------------|--|
| Mykinac | Sound | Trade name for Nystatin cream. Preliminary usage data indicates that the name Mykinac is not utilized. |
| Nebcin | Look | Discontinued trade name for tobramycin injection. Preliminary usage data indicates that the name Nebcin is not utilized. |

*** This is proprietary and confidential information that should not be released to the public.

Appendix G : Products with orthographic, phonetic and/or multiple differentiating product characteristics minimize the risk for medication errors

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|---|---|
| Makena (Hydroxy-progesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Mesna Injection Solution | Look alike | Single strength 100 mg/mL | <p>Short infusion standard-dose ifosfamide (<2.5 g/m²/day): Mesna dose is equal to 60% of the ifosfamide dose given in 3 divided doses (0, 4, and 8 hours after the start of ifosfamide).</p> <p>Continuous infusion standard-dose ifosfamide (<2.5 g/m²/day): Mesna dose is equal to 20% of the ifosfamide dose, followed by a continuous infusion of mesna at 40% of the ifosfamide dose, continue mesna infusion for 12-24 hours after completion of ifosfamide infusion</p> | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Makena has an additional upstroke 'k' in the name which is absent in Mesna</i></p> <p><u>Frequency:</u> <i>Three times daily for 24 hours vs. once weekly</i></p> <p><u>Setting of use:</u> <i>Mesna is a uroprotectant to reduce the incidence of ifosfamide-induced hemorrhagic cystitis and administered only when Ifosfamide is administered.</i></p> |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|--|--|
| Makena (Hydroxy-progesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Maxair (Pirbuterol) Inhalation Aerosol | Look alike | Single strength 200 mg/actuation | Two inhalations every 4-6 hours | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Makena has an additional upstroke 'k' in the name which is absent in Maxair</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Inhaler vs. injection solution</i></p> <p><u>Strength:</u> <i>Two inhalations vs. 1250 mg/5 mL</i></p> <p><u>Frequency:</u> <i>Every 4 to 6 hours vs. once weekly</i></p> |
| Malarone (Atovaquone and Proguanil) Tablets | Look alike | 250 mg/100 mg 62.5 mg/25 mg | <p>Adults: Prevention of malaria: 250 mg/100 mg once daily Treatment of acute malaria: 1 g/400 mg as a single dose, once daily for 3 days. Pediatrics: 31.25/12.5 mg to 1g/400 mg once daily</p> | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Malarone (8 letters) appears longer than Makena (6 letters) when scripted.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Tablets vs. injection solution</i></p> <p><u>Frequency:</u> <i>Once daily vs. once weekly</i></p> |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|---|---|
| Makena (Hydroxyprogesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Nalex-A (Chlorpheniramine, Phenylephrine, and Phenyltoloxamine) Oral Solution and Tablets | Look alike | Oral Solution: 2.5 mg-5 mg-7.5 mg per 5 mL. Tablets: 4 mg-20 mg-40 mg per tablet | 10 mL every 4-6 hours OR 1 tablet 2-3 times/day | Differences in product characteristics minimize the likelihood of medication error in the usual practice setting. <u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i> <u>Dosage form:</u> <i>Tablets or oral solution vs. injection solution</i> <u>Dose:</u> <i>One tablet or 10 mL vs. 250 mg</i> <u>Frequency:</u> <i>Every 4-6 hours or 2-3 times daily vs. once weekly</i> |
| Moxeza (Moxifloxacin) Ophthalmic Solution | Look alike | Single strength 0.5 % | 1 drop in affected eye twice daily | Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic:</u> <i>Makena has an additional upstroke 'k' in the name which is absent in Moxeza.</i> <u>Route of Administration:</u> <i>Ophthalmic vs. intramuscular injection</i> <u>Dosage form:</u> <i>Ophthalmic solution vs. injection solution</i> <u>Dose:</u> <i>One drop vs. 250 mg</i> <u>Frequency:</u> <i>Twice daily vs. once weekly</i> |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|--|---|
| Makena (Hydroxy-progesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Navane (Thiothixene) Capsules | Look alike | 1 mg 2 mg 5 mg 10 mg | Adults: 2 mg to 60 mg three times daily Pediatrics: 0.25 mg/kg/day in divided doses | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Makena has an additional upstroke 'k' in the name which is absent in Navane.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Capsules vs. injection solution</i></p> <p><u>Strength:</u> <i>1 mg, 2 mg, 5 mg, and 10 mg vs. 1250 mg/5 mL</i></p> <p><u>Frequency:</u> <i>Three times daily vs. once weekly</i></p> |
| (b) (4) | | | | |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|--|---|
| Makena (Hydroxy-progesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Nalfon (Fenoprofen) Tablets | Look alike | 200 mg 400 mg 600 mg | 200 to 600 mg every 4-6 hours or 2-3 times daily | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Nalfon has an additional upstroke 'f' in the name which is absent in Makena.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Tablets vs. injection solution</i></p> <p><u>Strength:</u> <i>200 mg, 400 mg and 600 mg vs. 1250 mg/5 mL</i></p> <p><u>Frequency:</u> <i>Two to three times daily vs. once weekly</i></p> |
| Melanex (Hydroquinone) Topical Solution | Look alike | Single strength 3 % | One application twice daily | <p>Differences in product characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Route of Administration:</u> <i>Topical vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Topical solution vs. injection solution</i></p> <p><u>Dose:</u> <i>One application vs. 250 mg</i></p> <p><u>Frequency:</u> <i>Twice daily vs. once weekly</i></p> |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|---|----------------------|--|---|--|
| Makena (Hydroxy-progesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Multaq (Dronedarone) Tablets | Look alike | 400 mg | 400 mg twice daily | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Multaq has an additional upstroke 't' and a downstroke 'q' in the name which is absent in Makena.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Tablets vs. injection solution</i></p> <p><u>Dose:</u> <i>200 mg, 400 mg and 600 mg vs. 1250 mg/5 mL</i></p> <p><u>Frequency:</u> <i>Twice daily vs. once weekly</i></p> |
| Maxidone (Hydrocortisone and Acetaminophen) Tablets | Look alike | Single strength 10 mg/750 mg | 1 to 2 tablets every 4 to 6 hours as needed | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>The upstrokes in the two names are in different positions.</i> <i>Maxidone (8 letters) appears longer than Makena (6 letters) when scripted.</i></p> <p><u>Dosage form:</u> <i>Tablets vs. injection solution</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dose:</u> <i>1 to 2 tablets vs. 250 mg</i></p> <p><u>Frequency:</u> <i>Every 4 to 6 hours as needed vs. once weekly</i></p> |

| Product name with potential for confusion | Similarity to Makena | Strength | Usual Dosage and Administration | Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described. |
|--|----------------------|--|--|--|
| Makena (Hydroxyprogesterone Caproate) Injection Solution | N/A | Single strength 1250 mg/5 mL (250 mg/mL) | 250 mg given Intramuscularly once weekly | N/A |
| Mevacor (Lovastatin) Tablets | Look alike | 10 mg 20 mg 40 mg | 10 mg to 80 mg once daily | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Makena contains an additional upstroke 'k' which is absent in Mevacor.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscular injection</i></p> <p><u>Dosage form:</u> <i>Tablets vs. injection solution</i></p> <p><u>Dose:</u> <i>10 mg to 80 mg vs. 250 mg</i></p> <p><u>Frequency:</u> <i>Once daily vs. once weekly</i></p> |
| Marcaine (Bupivacaine) Injection Solution | Look alike | 0.25% 0.5% 0.75% | Dose varies with procedure, depth of anesthesia, vascularity of tissues, duration of anesthesia, and condition of patient. Ranges from 2 mL to 50 mL given once during procedure | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Makena contains an additional upstroke 'f' which is absent in Marcaine.</i> <i>Marcaine (8 letters) appears longer than Makena (6 letters) when scripted.</i></p> <p><u>Strength:</u> <i>0.25%, 0.5%, and 0.75% vs. 1250 mg/5 mL</i></p> <p><u>Frequency:</u> <i>Once during procedure vs. once weekly</i></p> |

Appendix H: Risk of medication errors due to product confusion minimized by dissimilarity of the names or specified product characteristics

| Proposed name: Makena (Hydroxy progesterone Caproate) Injection Solution | Strength: 1250 mg/5 mL (250 mg/mL) | Usual Dose: 250 mg given intramuscularly once weekly |
|---|--|---|
| Failure Mode: Name confusion | Causes | Prevention of Failure (name confusion) Leading to a Medication Error |
| <p>Mirena (Levonorgestrel) Intrauterine Device</p> <p><u>How supplied/Strength:</u> 52 mg/device</p> <p><u>Dose:</u> To be inserted into uterine cavity</p> | <p>Orthographic Similarities: Both names start and end with similar looking letters. Both names contain the same number of letters.</p> <p>Overlap in setting of use: Both products will be available at the Ob/Gyn office to be administered directly to the patient</p> | <p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: <i>Makena has an additional upstroke 'k' in the name which is absent in Mirena</i></p> <p><i>Mirena is a device, which will be inserted by the HCP at the clinic. Makena is an intramuscular injection intended to be administered to the patient either by HCP or by the patient.</i></p> <p><i>Makena is dosed as 250 mg once every week and the dose will be documented. Mirena does not have a dose and is inserted once in 5 years.</i></p> <p><i>Mirena is not available in the retail setting.</i></p> |
| <p>Nubain (nalbuphine) Injection Solution</p> <p><u>How supplied/Strength:</u> 10 mg/mL 20 mg/mL</p> <p><u>Dose:</u> Intramuscular, Intravenous or Subcutaneous: 10 mg/70 kg every 3-6 hours; Intravenous only: 0.25 to 0.5 mg/kg every 3-6 hours as needed</p> | <p>Orthographic Similarities: Both names start with similar looking letters. Both names contain the same number of letters and have the same shape.</p> <p>Overlap in dosage form: Both products are injection solution</p> <p>Overlap in route: Both products can be given intramuscularly</p> | <p>Differences in product characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: <i>Both products have different frequency of use. Nubain is dosed on a as needed bases for pain control every 3-6 hours vs. Makena is dosed once every week.</i></p> <p><i>The two products do not have any overlapping doses. Nubain is dosed on a mg/kg bases and the maximum single dose of Nubain is 20 mg. Makena is dosed as 250 mg</i></p> |

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