CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

PROPRIETARY NAME REVIEW(S)

Memorandum

Date August 2, 2012

From Biological Product Naming Working Group

Subject BLA 125294 – [xxx]-filgrastim

To File

FDA has determined that a unique nonproprietary name will be required for Teva Pharmaceuticals' (Teva) proposed product for which it is seeking approval in BLA 125294 ([xxx]-filgrastim), a biological product submitted in a 351(a) biologics license application (BLA), to distinguish the product from Neupogen (filgrastim), a previously licensed biological product submitted in a different 351(a) BLA by Amgen, Inc. (Amgen) that contains a related drug substance. Specifically, Teva's proposed xxx-filgrastim is indicated for the reduction in the duration of severe neutropenia in patients with non myeloid malignancies receiving myelosuppressive anti cancer drugs associated with a clinically significant incidence of febrile neutropenia. Amgen's Neupogen (filgrastim) was first licensed on February 20, 1991. Neupogen has been indicated:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML
- to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation
- for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

FDA has concluded that a nonproprietary name for Teva's product that is distinct from Amgen's product will help to minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are

indistinguishable from a clinical standpoint. FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "filgrastim" product is dispensed to patients. Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.

Amgen's Neupogen and Teva's proposed xxx-filgrastim are the subject of separate BLAs submitted by different manufacturers, Amgen and Teva respectively. For this reason, FDA has concluded that a unique nonproprietary name is warranted for the subsequently licensed product.

FDA's decision to require a unique nonproprietary name in the form of [prefix]–filgrastim for Teva's product, for which licensure is sought under section 351(a) of the PHS Act, is separate from any decision FDA may make in the future regarding the naming convention for biosimilar and interchangeable products under section 351(k) of the PHS Act. FDA is still considering the appropriate naming scheme for such products, and FDA does not anticipate that any decision on nomenclature for biosimilar and interchangeable products will conflict with FDA's determination regarding the nonproprietary name for this product.

FDA notes that a prefix previously has been used to distinguish one biological product from another biological product that contains a related drug substance, although the prefix was directly appended to the stem (without a hyphen) given the nature of the differences between those products. For example, the nonproprietary names for botulinum toxin products were changed to add prefixes (e.g., onabotulinumtoxinA, abobotulinumtoxinA) to emphasize the non-interchangeable potency units of each botulinum toxin product in an effort to prevent medication errors and serious adverse events. In addition, there is precedent for using a hyphen in biological product nonproprietary names, e.g., interferon alfa-2b.

Amgen and Teva products are the subject of different marketing applications held by different manufacturers. Identifying Teva's xxx-filgrastim with a unique nonproprietary name will reinforce these differences, help to prevent medication errors involving the two products, and facilitate pharmacovigilance. For these reasons, the Teva product will be identified as Neutroval ([xxx]-filgrastim).

In the September 29, 2010 Complete Response letter, FDA described the need to differentiate Teva's product from Amgen's filgrastim product and explained that FDA is requiring the use of a prefix with the "filgrastim" stem. FDA requested that Teva propose a 3-4 letter prefix to be added to the non-proprietary stem, "filgrastim." Teva proposed the following prefixes in their February 29, 2012 submission:

- (b) (4)
- tbo-filgrastim
- (b) (4)
- t (b) (4)

FDA evaluated those names with a hyphen inserted between the proposed prefixes and the filgrastim stem, using the criteria outlined in the September 29, 1010 communication to Teva, and determined that "tbo-" or (b) (4) are acceptable prefixes proposed by Teva. Specifically, FDA made the following determinations:

- (b) (4)
- The second prefix "tbo-" does not appear to raise concerns related to conveying specific meaning, being promotional or looking or sounding similar to a currently marketed product. FDA notes that "tbo" stands for the medical abbreviation, "toluidine blue O.[2]" However, it is not thought that this abbreviation would cause confusion in this context or conflict with the proper name, "tbo-filgrastim" and therefore FDA has no objection to its possible selection. The proposed prefix "tbo-" is acceptable based on the criteria outlined in the July 17, 2012 communication to sanofi.
- (b) (4)
- (b) (4)

Of the four prefixes proposed by Teva, FDA has no objection to:

- tbo-filgrastim
- (b) (4)
-

[1] Oxford Dictionaries Online. http://oxforddictionaries.com/definition/american_english/bio-?region=us&q=bio- Accessed 08/02/2012.
[2] Davis, NM. Medical Abbreviations: 26,000 Conveniences at the Expense of Communication and Safety. 12th edition. p. 348.
[3] Davis, NM. Medical Abbreviations: 26,000 Conveniences at the Expense of Communication and Safety. 12th edition. p. 348.

In a communication dated April 5, 2012, the Division of Hematology Products was informed of a change in sponsorship of BLA 125294 from Teva Pharmaceuticals USA to SICOR Biotech UAB. Teva Global Branded Pharmaceutical Products R&D will serve as the US agent. Therefore, all future communications will be directed to SICOR Biotech UAB and the US agent.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH A CHRISTL
08/02/2012
Memo entered into DARRTS on behalf of the Biological Product Naming Working Group

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	July 16, 2012
Reviewer:	Sarah K. Vee, PharmD, Safety Evaluator Division of Medication Prevention and Analysis
Team Leader	Yelena Maslov, PharmD, Acting Team Leader Division of Medication Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD, MPH Division of Medication Prevention and Analysis
Division Director	Carol A. Holquist, RPh Division of Medication Prevention and Analysis
Drug Name(s) and Strength(s):	Neutroval (XM-02) Injection 300 mcg/0.5 mL, 480 mcg/0.8 mL prefilled syringes
Application Type/Number:	BLA 125294
Applicant/Sponsor:	Teva
OSE RCM #:	2012-951

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

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Neutroval, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 REGULATORY HISTORY

Neutroval was reviewed under IND 103,188 (OSE Review # 2009-1414) and BLA 125,294 (OSE Review # 2010-1) and was found conditionally acceptable. The application received a Complete Response on September 29, 2010. On April 17, 2012, the Applicant resubmitted Neutroval for review and stated that the product characteristics have not changed from the original BLA submission.

The proper name for this product is pending at this time. Although this is a 351(a) stand alone biologic application, this product has the same product characteristics as Neupogen. The discussion regarding the proper name nomenclature is still ongoing, and thus the active ingredient will be referenced as XM-02 throughout this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 10, 2009 proprietary name submission.

- Active Ingredient: XM-02
- Indication of Use: Reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- Route of Administration: subcutaneous injection (b) (4)
- Dosage Form: solution for injection
- Strength: 300 mcg/0.5 mL, 480 mcg/0.8 mL
- Dose and Frequency: 5 mcg/kg/day 1st dose should be administered no earlier than 24 hours following myelosuppressive chemotherapy (b) (4) Daily dosing should continue (b) (4) until neutrophil count has recovered to the normal range.
- How Supplied: 300 mcg/0.5 mL, 480 mcg/0.8 mL single use prefilled syringe
    - Packs of 1, 5, and 10 without a safety needle guard
    - Packs of 1, 5, and 10 with a safety needle guard in trays
    - Packs of 1, 5, and 10 with a safety needle guard in blisters
- Storage: Refrigerated at 36° to 46°F (2° to 8°C), may be allowed to reach room temperature for a maximum of (b) (4)

- Container and Closure Systems: Primary: Type I glass syringe barrel, (b) (4) rubber stopper, steel needle. Secondary: cardboard cartons (1, 5, or 10 syringes)

2. RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Hematology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall safety evaluation.

2.2.1 United States Adopted Names (USAN) Search

The May 7, 2012 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Neutroval, is crafted from the concept of strong neutrophils, utilizing the prefix of the Latin word validus, meaning strong or powerful. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched Adverse Event Reporting System (AERS) database for medication errors involving confusion with proprietary names Neupogen and Neulasta, which would be relevant for this review, because this name pair shares the same beginning letter string, 'neu', as well as similar product characteristics.

The May 4, 2012 search of the AERS database used the following search terms: filgrastim, neupogen, neupo%, filgras%, Medication Errors (HLT), and Product Quality Issues (HLT) with no specific time frame.

Each report was reviewed for relevancy and duplication. Duplicate reports were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 79 reports were not included in the final analysis for the following reasons:

Dose omission	1	Wrong time	2
Duplicate therapy	1	Wrong technique	4
Accidental Exposure	1	Deteriorated drug	5
Intentional overdose	1	Wrong route	7
Underdose	1	Overdose	19
Wrong patient	2	No medication error	32
Near miss (NeoProfen vs. Neupogen)	1	Wrong drug (Neupogen vs. Nutropin)	1
Wrong drug (GM-CSF vs. G-CSF)	1		

Following exclusions, the search yielded six relevant cases of wrong drug errors.

- 3 Cases: Neulasta administered instead of Neupogen

One case reported that the patient was routinely receiving Neupogen but an accidental dose of Neulasta was administered following a chemotherapy cycle. The patient experienced white blood cell count increase. The patient recovered but no further information was provided.

The second case reported that Neulasta 6 mcg was given instead of Neupogen. As a result, the patient's subsequent chemotherapy cycle may have been delayed.

The third case from Italy, involved a pediatric patient where a nurse confused the vial of pegfilgrastim with filgrastim and gave the contents of the entire vial (6 mg) of pegfilgrastim. The patient did not experience any adverse events.

- 2 Cases: Neupogen administered instead of Neulasta

One foreign case from Germany reported that a patient was on Neulasta therapy but filgrastim (Neupogen) was accidentally prescribed and administered. No outcomes were reported for this case.

Another foreign case from Germany reported that a patient received Neupogen instead of Neulasta. The pharmacist reported that the patient did not receive the scheduled dose of Neulasta after the mistaken dose of Neupogen. According to the reporter, Neupogen worked well for the patient and the patient did not experience any adverse event.

None of the five cases reported possible root causes of the confusion. However, given the fact that all patients, with the exception of the pediatric case, were on chemotherapy and both products are indicated for the same patient population, with the same route of administration and product presentation as prefilled syringes, product selection confusion is likely due to the name confusion.

- 1 Case: Neupogen administered instead of Neumega

One case involved a patient receiving a dose of Neupogen instead of Neumega. The reporter commented that "these names are too similar" and that the "nurse should have double checked." This case demonstrates that even though Neumega is a powder for injection and Neupogen is a solution, the name similarity (i.e. same beginning letter string, 'neu'), similar dose (5 mcg/kg/day vs. 50 mcg/kg/day), and same route of administration (subcutaneous) outweighed this difference in product characteristics. .

The report of Neupogen and Neumega confusion demonstrates that minor orthographic differences cannot overcome name similarity in the presence of shared product characteristics.

2.2.4 FDA Name Simulation Studies

Twenty-nine practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Of the 29 participants, 19 identified the name as Neutroval. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, April 27, 2012 e-mail, the Division of Hematology Products (DHP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Neutroval. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Neutroval identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Since Neutroval was evaluated twice previously, this review focused on names that start with the prefix "neu" and its variations, since we identified medication errors involving name confusion between Neupogen and Neulasta name pair and Neupogen and Neumega name pair.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar		Look Similar		Look Similar	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Hectorol	EPD	(b) (4)	EPD	Nexterone	EPD
Neulasta	EPD/Previous review	Neurolite	EPD	Nuedexta	(b) (4)
Neumega	EPD/Previous review	Neutrexin	EPD	Nulecit	EPD
Neupogen	External/Previous review	(b) (4)**	EPD	Nutrament	EPD
Neuramate	EPD	Neutroval***	EPD	Uroxatral	EPD
(b) (4)	(b) (4)				
Sound Similar		**Sound Similar**		**Look and Sound Similar**	
Mebaral	EPD			NeutraSal	EPD

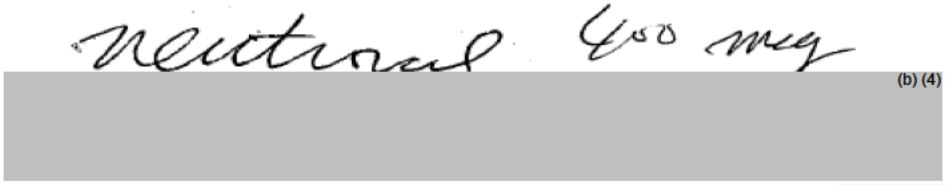
Our analysis of the 18 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined 13 of the 18 total number of names will not pose a risk for confusion as described in Appendix D and E. However, the proposed name could be confused with Neupogen, Neulasta, Neumega, NeutraSal, and (b) (4) The rationale for the risk of confusion between Neutroval and Neupogen, Neutroval and Neulasta, Neutroval and Neumega, and Neutroval and NeutraSal is described below and in section 3.1. The rationale for risk of confusion between pending application name, (b) (4) and Neutroval is described below. Since (b) (4) is not approved, DMEPA cannot provide specifics on the proposed similarity of this name pair to the Applicant, Teva.

The proposed proprietary name, Neutroval, is orthographically similar to and shares product characteristics with an investigational product (IND (b) (4), (b) (4)

(b) (4)

*** This document contains proprietary information that should not be released to the public

The orthographic similarity stems from the fact that the name pair has the same beginning letter string 'Neu' and length (9 letters).



Moreover, the products share product characteristics including (b) (4)

As seen by the medication error cases describing the name confusion between Neupogen and Neulasta, orthographic differences beyond the letter string 'neu' does not eliminate the potential for name confusion when product characteristics overlap. Therefore, if the two products were marketed, medication errors could occur.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Hematology Products via e-mail on June 7, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Hematology Products on June 7, 2012, they stated no additional concerns with the proposed proprietary name, Neutroval.

3 CONCLUSIONS

The proposed proprietary name is acceptable from a promotional perspective but not acceptable from a safety perspective. The proposed name is vulnerable to name confusion with Neupogen, Neulasta, Neumega, NeutraSal, and (b) (4) Therefore, the decision to deny the name will be communicated to the Applicant/Sponsor via letter (See ***section 3.1).***

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

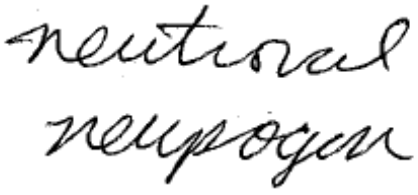
We have completed our review of the proposed proprietary name, Neutroval, and have concluded that this name is unacceptable due to the following reasons.

A. ORTHOGRAPHIC SIMILARITIES WITH NEUPOGEN, NEULASTA, AND NEUMEGA

1. Neutroval and Neupogen

The proposed proprietary name is orthographically similar to Neupogen (filgrastim injection). Neutroval and Neupogen are similar in length (9 vs. 8 letters) and share the

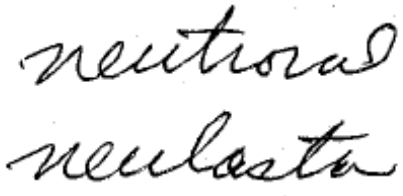
beginning letter string, ‘neu’. Moreover, the name pair has identical product characteristics such as indication (to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever), dosage form (solution for injection), route of administration (subcutaneous (b) (4) strengths (300 mcg/0.5 mL, 480 mcg/0.8 mL), dose (5 mcg/kg/day), frequency of administration (once daily), and product presentation (single use prefilled syringe). However, the two products are not interchangeable.



Although the ending letter strings differ, there is significant overlap with product characteristics. We are concerned with name confusion based on prior errors with name pairs that share the same beginning letter string but end differently (Neutroval vs. Neulasta, Neupogen, or Neumega). These name pairs also shared product characteristics such as dosage form, route of administration, indication, patient population, and product presentation. Thus, confusion between this name pair may result in mediation errors if both are marketed.

2. Neutroval and Neulasta

The proposed proprietary name is orthographically similar to Neulasta (pegfilgrastim injection). Neutroval and Neulasta are similar in shape (3 up strokes), length (9 vs. 8 letters), and share the beginning letter string, ‘neu’. Moreover, the name pair shares product characteristics including dosage form (solution for injection), route of administration (subcutaneous), indication (decrease in incidence of febrile neutropenia), patient population (patients receiving myelosuppressive anti-cancer drugs), and product presentation (single use prefilled syringes).

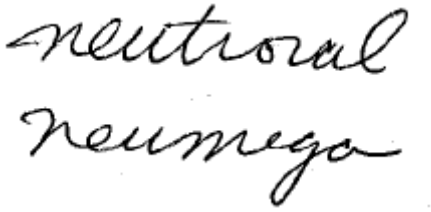


The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in mediation errors if both are marketed as demonstrated by post marketing medication error.

3. Neutroval and Neumega

The proposed proprietary name is orthographically similar to Neumega (oprelvekin for injection). Neutroval and Neumega are similar in length (9 vs. 7 letters) and share the beginning letter string, ‘neu’. The two products have similar product characteristics including route of administration (subcutaneous), patient population (cancer patients),

similarity in dose (5 mcg/kg vs. 50 mcg/kg), and frequency of administration (once daily).



The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in mediation errors if both are marketed as demonstrated by post marketing medication error data.

B. ORTHOGRAPHIC AND PHONETIC SIMILARITIES OF NEUTROVAL WITH NEUTRASAL

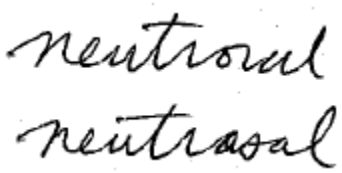
The proposed proprietary name, Neutroval, is orthographically and phonetically similar to the marketed product, Neutrasal.

Neutrasal (powder for supersaturated calcium phosphate rinse) is a 510(k) product marketed as a device. Indications for use are[1]:

- NeutraSal® is also indicated as an adjunct to standard oral care in relieving the discomfort associated with oral mucositis that may be caused by radiation or high dose chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with the amelioration of pain.
- NeutraSal® may be used for relief of dryness of the oral mucosa when hyposalivation results from the following: surgery, radiotherapy near the salivary glands, chemotherapy, infection or dysfunction of the salivary glands; emotional factors such as fear or anxiety; obstruction of the salivary glands; Sjogren's Syndrome .
- NeutraSal® is also indicated for the dryness of the mouth (hyposalivation, xerostomia).
- NeutraSal® is indicated for dryness of the oral mucosa due to drugs such as antihistamines, atropine, and other anticholinergic agents that suppress salivary secretion.

The orthographic and phonetic similarities stem from the fact that the name pair has the same length (9 letters) and are nearly identical with only differences in the two letters as indicated here (Neutr***ov***al vs. Neutr***as***al). Thus the names appear and sound similar when scripted and spoken.

[1] http://neutrasal.com/



The two products also have similar product characteristics such as overlapping patient population (cancer patients) and prescribers.

We carefully considered whether differences in product characteristics such as dosage form, strength, and route and frequency of administration for your product compared to NeutraSal would minimize the potential for error between Neutroval and NeutraSal. We concluded that these aspects will not eliminate the potential for name confusion and medication errors.

Although Neutrasal has some differences in product characteristics, because the name pair has such strong orthographic and phonetic similarities, differences in product characteristics are not enough to overcome the similarities. We identified post marketing confusion between products with different product characteristics when strong orthographic and phonetic similarities exist. For example, ISMP recently published a report where Arixtra (fondaparinux) was confused with Arista (a device used in surgical procedures as an adjunctive hemostatic device to assist when control of capillary, venous, and arteriolar bleeding).[1] The report demonstrates that differing product characteristics cannot overcome overwhelming orthographic and/or phonetic similarities, particularly for products used in the same setting of care.

Thus, confusion between this name pair may result in medication errors if both products are marketed.

C. ORTHOGRAPHIC SIMILARITIES WITH A PENDING PROPRIETARY NAME

The proposed proprietary name, Neutroval, is also vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to orthographic similarity and shared product characteristics.

We acknowledge that the conclusions of this review differ from the March 22, 2010 letter finding your name conditionally acceptable. This difference is accounted for by the recently identified medication error reports among Neupogen and Neulasta as well as Neupogen and Neumega. Because your name is constructed similar to these name pairs and share similar product characteristics, we have determined that these reports indicate your name is prone to confusion with Neupogen, Neulasta, and Neumega. Additionally, two new names (i.e. NeutraSal and pending proprietary name) were identified during this cycle that were not available for review during the previous review cycle. Therefore we conclude that the proposed proprietary name, Neutroval, is not acceptable from a safety perspective.

[1] http://www.ismp.org/newsletters/acutecare/issues/20120517.pdf

4. 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. This database also lists the orphan drugs.

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

   USPTO provides information regarding patent and trademarks.

8. ***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.

9. ***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.

10. ***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.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***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.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

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

14. ***Lexi-Comp (www.lexi.com)***

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

15. ***Medical Abbreviations (www.medilexicon.com)***

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

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). 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. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name 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 misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

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. DMEPA considers the product characteristics associated with the proposed product 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.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA 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.[1]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA 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. DMEPA examines the phonetic similarity using patterns of speech. 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. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing 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).

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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	• 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/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• 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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA 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 searches 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. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses 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, DMEPA reviews 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. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). 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 database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional 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 Simulation 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 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for 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 OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/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 provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

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, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their 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.[1] 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

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

characteristics listed in Section 1.2 of this review. 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? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

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 or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses 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.

Moreover, 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 Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP'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 but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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 generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for 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 Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above 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, confusing, or misleading 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 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

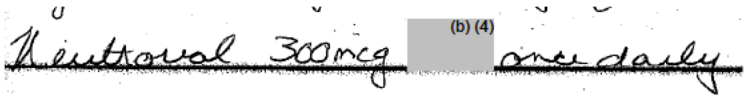
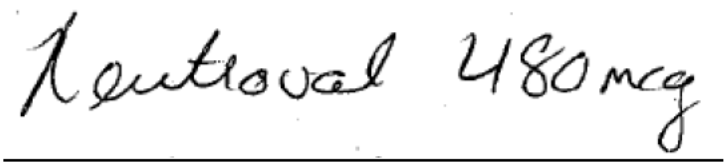
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval 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.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Neutroval	Scripted May Appear as	Spoken May Be Interpreted as
N	h, k, m, u, r, s, v, x	
e	a, i, l, o, u, p	Any vowel
u	c, n, v, w, y, any vowel	Any vowel
t	r, f, x, A	
r	e, n, s, v	
o	a, c, e, u	Any vowel
v	r, u	
a	el, ci, cl, d, o, u	Any vowel
l	b, e, i, s, A, P	

Appendix C: Prescription Simulation Samples and Results

Figure 1. Neutroval Study (Conducted on April 27, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: 	Neutroval 480 mcg (b) (4)
Outpatient Prescription: 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

84 People Received Study

29 People Responded

Study Name: Neutroval

Total	12	8	9	
INTERPRETATION	**INPATIENT**	**VOICE**	**OUTPATIENT**	**TOTAL**
KEUTROVAL	0	0	1	1
NEUTRAVAL	0	3	0	3
NEUTROVAL	11	2	6	19
NUTRAVAL	0	3	0	3
REUTROVAL	0	0	1	1
VEUTROVAL	1	0	0	1
XEUTROVAL	0	0	1	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Neutroval	Failure preventions
Mebaral	mephobarbital	Phonetic	The pair has sufficient phonetic differences.
Neuramate	meprobamate	Orthographic	The pair has sufficient orthographic differences.
[redacted]			(b) (4)
Neutrexin	trimerexate	Orthographic	NDA 20326 withdrawn on 3/13/2009 FR effective
Neutroval***	xxx-filgrastim	Both	The subject of this review
Nulecit	sodium ferric gluconate	Orthographic	The pair has sufficient orthographic differences.

*** This document contains proprietary information that should not be released to the public

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Hectorol (doxercalciferol) - 0.5 mcg, 1 mcg, 2.5 mcg oral capsules - 4 mcg/2 mL solution for injection - Dialysis: 10 mcg by mouth 3 times weekly @dialysis to max of 20 mcg 3 times weekly; - Pre-dialysis: 1 mcg by mouth once daily to max of 3.5 mcg once daily - IV: 4 mcg 3 times weekly (max of 18 mcg/week)	**Orthographic Similarities** - 'Ne' and 'He' may appear similar when scripted **Overlapping Product Characteristics** - Dosage Form (solution for injection) - Units of measure (mcg) (b) (4)	**Orthographic Differences** - 'u' and 'c' does not appear similar when scripted - 'troval' and 'torol' appear different when scripted due to the distance between the 2 up strokes (wider for 'troval' than 'torol' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 0.5 mcg, 1 mcg, 2.5 mcg, 4 mcg/2 mL with no overlap) - Dose (5 mcg/kg * 60 kg = 300 mcg vs. 1 mcg to 10 mcg with no overlap)

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neulasta (pegfilgrastim) - 6 mg/0.6 mL solution in prefilled syringes for injection - 6 mg sub-q injection once per chemotherapy cycle	**Orthographic Similarities** - 'Neut' and 'Neul' may appear similar when scripted **Overlapping Product Characteristics** - Dosage Form (solution in prefilled syringes) - Route of Administration (sub-q)	**Orthographic Differences** - 'roval' appear longer and different than 'asta' when scripted due to the position of the up strokes (9^{th} vs. 7^{th}) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 6 mg/0.6 mL with no overlap) - Dose (5 mcg/kg * 60 kg = 300 mcg vs. 6 mg with no overlap)

Proposed name: Neutroval (XM02/xxx-filgrastim) Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection Usual Dose: 5 mcg/kg/day	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
(b) (4)		

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Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neumega (oprelvekin) - 5 mg/vial powder for injection - 50 mcg/kg sub-q injection once daily - CrCl less than 30 mL/min: 25 mcg/kg	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning **Overlapping Product Characteristics** - Route of Administration (sub-q) - Dose (5 mcg/kg vs. 50 mcg/kg) - Frequency (once daily)	**Orthographic Differences** - 'troval' appears longer and different than 'mega' when scripted due to: 2 up strokes vs. 1 down stroke and 2 more letters in 'troval'
Neupogen (filgrastim) - 300 mcg/1 mL, 480 mcg/1.6 mL solution in vial, 300 mcg/ 0.5 mL, 480 mcg/0.8 mL solution in prefilled syringe for injection - 5 mcg/kg/day	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning **Overlapping Product Characteristics** - All aspects of product characteristics are identical	**Orthographic Differences** - 'troval' appears longer and different than 'pogen' due to: 2 up strokes vs. 2 down strokes

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neurolite (technetium TC-99M Bicisate) Kit - 70 kg patient: 370 MBq to 1110 MBq (10 mCi to 30 mCi)	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning - Both have 9 letters **Overlapping Product Characteristics** (b) (4)	**Orthographic Differences** - 'troval' and 'ralite' appear different when scripted due to the positions of the up strokes (4^{th} & 9^{th} vs. 6^{th} & 8^{th}) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. per batch single strength with no overlap) - Setting of Use (Clinic vs. Radiology Suite) - Units of Measure (mg or mL vs. MBq or mCi where dose must be checked by radioactive callibration system immediately before administering)
NeutraSal (calcium chloride, sodium phosphate) - 510(k) - powder for oral rinse - Dissolve or disperse 1 packet in 30 mL (1 ounce) of tap water. Swish the solution in the mouth thoroughly for 1 min with ½ of the solution and spit out. Repeat with the remaining ½ of the solution. Use 2 to 10 times daily as needed	**Orthographic Similarities** - 'Neutroval' and 'Neutrasal' appear similar when scripted - Both have 9 letters **Phonetic Similarities** - 'Neutro' and 'Neutra' sound the same when spoken - Both names end with 'al'	**Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength with no overlap) - Dose (5mcg/kg/day vs. 1 packet) - Route of Administration (Sub-q (b) (4) vs. oral rinse)

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
(b) (4)		

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Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Nexterone (amiodarone) - 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL solution in vials, 150 mg/3 mL solution in prefilled syringe for injection - Initial: 150 mg over the 1st 10 minutes (15 mg/min) then 360 mg over the next 6 hours (1mg/min) then 540 mg over the remaining 18 hours (0.5 mg/min) intravenous infusion	**Orthographic Similarities** - 'Neut' and 'Next' may appear similar when scripted - Both have 9 letters **Overlapping Product Characteristics** - Dosage Form (solution for injection, prefilled syringe) (b) (4)	**Orthographic Differences** - 'roval' and 'erone' appear different when scripted due to the up stroke 'l' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL, 150 mg/3 mL with no overlap) - Dose (5 mcg/kg/day vs. 150 mg to 540 mg)
Nuedexta (dextromethorphan, quinidine) - 20mg/10 mg oral capsules - 1 capsules once daily for 7 days then 1 capsule every 12 hours	**Orthographic Similarities** - 'Neut' and 'Nued' may appear similar when scripted **Overlapping Product Characteristics** - Frequency (once daily)	**Orthographic Differences** - 'roval' appear different and longer than 'exta' when scripted due to the different position of the up stroke (9th vs. 7th) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 20 mg/10 mg with no overlap) - Dose (5 mcg/kg/day vs. 1 capsule)

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Nutrament (nutritional supplement) - Use as directed	**Orthographic Similarities** - Both start with 'N' - 'tro' and 'tra' may appear similar when scripted - Both have 9 letters	**Orthographic Differences** - 'eu' and 'u' appear different when scripted - 'val' and 'ment' appear different when scripted **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength with no overlap) - Dose (5 mcg/kg/day vs. 1 can) - Route of Administration (sub-q, (b) (4) vs. oral)
Uroxatral (alfuzosin) - 10 mg oral tablets - 1 tablet once daily	**Orthographic Similarities** - 'Neu' and 'Uro' may appear similar when scripted - 'val' and 'ral' may appear similar when scripted **Overlapping Product Characteristics** - Frequency (once daily)	**Orthographic Differences** - 'tro' and 'xat' appear different when scripted due to the different position of the up stroke 't' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength (10 mg) with no overlap) - Dose (5 mcg/kg/day vs. 1 tablet) - Route of Administration (sub-q, (b) (4) vs. oral)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K VEE
07/16/2012

YELENA L MASLOV
07/16/2012

CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
07/16/2012

CAROL A HOLQUIST
07/16/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 19, 2010
To:	Patricia Keegan, MD, Director Division of Biologic Oncology Products
Through:	Kristina C. Arnwine, PharmD, Team Leader D.P. Toyer for 3/19/2010 Denise P. Toyer, PharmD, Deputy Director DP. Toyer 3/19/2010. Carol A. Holquist, RPh, Director Carol Holquist 3/19/2010 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator L Holmes 3/19/2010 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name:	Neutroval (b) (4) Injection 300 mcg/0.5 mL and 480 mcg/0.8 mL
Application Type/Number:	BLA 125294
Applicant:	Teva Pharmaceuticals USA
OSE RCM #:	2010-1

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

CONTENTS

EXECUTIVE SUMMARY

Neutroval is the proposed proprietary name for [redacted] (b) (4) Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. 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, Neutroval, conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the BLA.

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 is in response to a December 23, 2009 request from Teva Pharmaceuticals USA for an assessment of the proposed proprietary name, Neutroval, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, the container labels, carton and insert labeling are being evaluated for their potential contribution to medication errors under separate cover (OSE Review 2009-2469).

1.2 REGULATORY HISTORY

DMEPA previously reviewed the proposed proprietary name, Neutroval, under IND 103188 (OSE Review 2009-1414, dated November 10, 2009). We found the name conditionally acceptable at that time.

1.3 PRODUCT INFORMATION

Neutroval is the proposed proprietary name for [redacted] (b) (4) Injection. Neutroval is a granulocyte colony-stimulating factor (G-CSF) indicated for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. The recommended dosage is 5 mg/kg/day subcutaneously [redacted] (b) (4) no earlier than 24 hours following myelosuppressive chemotherapy [redacted] (b) (4) .

Neutroval will be supplied in prefilled syringes (with and without a safety needle guard) containing 300 mcg/0.5 mL or 480 mcg/0.8 mL in 1, 5, and 10-count packages.

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. Section 2.1 identifies specific information associated with the methodology for the proposed proprietary name, Neutroval. We did not repeat the inpatient, outpatient and verbal prescription studies since they were conducted on August 31, 2009.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'N' 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 Neutroval, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), upstrokes (two, lower case letters 't' and 'l'), downstrokes (none), cross strokes (one, lower case letter 't'), and dotted letters (none). Additionally, several letters in Neutroval 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 Neutroval.

When searching to identify potential names that may sound similar to Neutroval, the DMEPA staff search for names with similar number of syllables (three), stresses (NEU-tro-val, neu-TRO-val or neu-tro-VAL), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (see Appendix B). The Applicant provided their intended pronunciation of the proprietary name (nue' troe val) in the proposed name submission and, therefore, it was taken into consideration. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 29 names as having some similarity to the name Neutroval. Nineteen of these names (Neulasta, Neutrexin, Neutracare, Neutralin, Natrova, Introvale, Nutropin, Nutracort, Nizoral, MetroGel, Nicotrol, Neupogen, Nitronal, Naquival, Neutontin, Nortrel, Neutralox, Neoral, and Nutrivit) were identified and evaluated in our previous review and will not be discussed further since the Neutroval product characteristics have not changed since our previous review.

Of the ten remaining names, seven were thought to look like Neutroval (Natrecor, Nausetrol, Neuradiab, Nitro-Dur, Nitro-Bid, Retrovir, Neutrospec). One name, Notrel, was thought to look and sound similar to Neutroval and two names (Nutr-E-Sol and Neutrosol) were thought to look and sound similar to Neutroval.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of January 31, 2010.

3.2 CDER EXPERT PANEL DISCUSSION

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

DDMAC had no concerns regarding the proposed name from a promotional perspective, however, they commented that "Neutroval may sound like the existing trade names Neulasta and/or Neupogen".

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[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. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

3.3 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in identification of four additional names which were thought to look and/or sound similar to Neutroval and represent a potential source of drug name confusion. The names identified to have look-alike similarities are Nutrivir and (b) (4) The names, Neuroval (foreign) and Neuroval (domestic), were identified to have look-alike and sound-alike similarities.

When compiling the list of potentially similar drug names, we were unable to identify the drug name, Notrel, in any common drug references. We determined the name was misspelled during the transcription process and should have been Nortrel. Since Nortrel was evaluated in our previous review, it will not be discussed further.

Therefore, 13 new names were considered for their potential similarity to Neutroval.

4 DISCUSSION

4.1 PROMOTIONAL REVIEW

DDMAC did not find the name Neutroval promotional. The Division of Biologic Oncology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY REVIEW

The review team (e.g., clinical, chemistry, etc.) did not express any concerns with the proposed name.

Since the time the name was reviewed in the IND phase, 13 new names were identified as potential sources of confusion. DMEPA did not identify other aspects of the name that could function as a source of error. Five of the twelve names were not evaluated further for the following reasons: two names are foreign products, one name is a discontinued product, one name is an orphan drug product that has not been approved for marketing, and one name had only limited information available and could not be found in DMEPA's commonly used references (see Appendices C through F).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining eight names and lead to medication errors. This analysis determined that the name similarity between Neutroval was unlikely to result in medication errors with any of the eight products for the reasons presented in Appendices G and H.

5 CONCLUSIONS AND RECOMMENDATIONS

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

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Neutroval, and have concluded that it is acceptable. Neutroval will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

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

Drug Facts and Comparisons is a compendium organized by therapeutic course; 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)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

Provides information regarding patent and trademarks.

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

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. 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)

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)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

A web-based searchable version of the Drug Information Handbook.

16. 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

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[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.

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 existing and proposed drug products because similarly in 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 Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

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

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	• 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-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
,nd-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• 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. 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 convinced that the names posses 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:

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

"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 Applicant 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 Applicant 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 Applicant. 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), Joint Commission on Accreditation of Hospitals (JCOAH), 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 Applicant 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. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant 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 Applicants' 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).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name **"Neutroval"**	**When scripted may appear as:**	**When spoken may be interpreted as:**
Capital 'N'	'V', 'M', lower case 'h'	M
Lower case 'e'	'a', 'i', 'l', or 'o'	
Lower case 'u'	'a', 'm', 'n', 'o', 'v', or 'w'	you
Lower case 't'	x', 'l' (if uncrossed)	
Lower case 'r'	'n', 's', 't', or 'v'	
Lower case 'o'	'a', 'e', or 'u'	'oh'
Lower case 'v'	upper case 'L', 'n', 'r', or 'u'	
Lower case 'a'	'e', 'ci', 'ce', 'o', or 'u'	Combination letters 'au' or 'aw'
Lower case 'l'	'e' or 'i'	
Combination letters '-eu-'	'cu' or 'w'	'u' or combination letters 'ew', 'oo'
Combination letters '-tr-'		Combination letters 'ch'
Combination letters 'Neu-'		Combination letters 'Nu', 'New', or 'Pneu'

Appendix C: Proprietary or Established Name used only in a Foreign Country

Proprietary Name	**Similarity to Neutroval**	**Country**	**Description/Comments**
Neuroval••• (Dipyrone and Diazepam)	Look and Sound	Indonesia	No additional product information available.
Neutrosol (Electrolyte infusion)	Look and Sound	Venezuela	No additional product information available.

••• There were two different products identified with this name, one foreign and one domestic.

Appendix D: Drug name not found in commonly referenced databases (See Section 6, References 1 through 16)

Name	Similarity to Neutroval	Comments
Neuroval••• (Phenobarbital)	Look and Sound	This name could not be found in Red Book, the NDC Directory, Facts and Comparisons, Drugs@FDA, the Orange Book, or Clinical Pharmacology Online. This name was found at the webmd.com and healthsquare.com websites via a Google search. These websites are not among our commonly referenced databases. The active ingredient is phenobarbital, however, the only information available about the product at these websites was general information concerning oral phenobarbital. There was no product specific information available. DMEPA was unable to determine the manufacturer of this product or its availability.

Appendix E: Drug product that is discontinued and no generic equivalent is available

Proprietary Name	Similarity to Neutroval	Status and Date
(b) (4)	Look	(b) (4)

••• There were two different products identified with this name, one foreign and one domestic.

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

Appendix F: Orphan drug that is not approved for marketing

Proprietary Name	Similarity to Neutroval	Status and Date
Neurodiab (Anti-tenasin 81c6 Monoclonal Antibody Labeled with I 131)	Look	This is an orphan drug that has not been approved for marketing

Appendix G: Products with no numerical overlap in strength, dose and/or route of administration

Product name with potential for confusion	Similarity to Neutroval	Strength	Signa
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day administered as a daily subcutaneous injection** (b) (4) (b) (4)
Nitro-Bid (Nitroglycerin Ointment)	Look	2%	½ inch to 2 inches to skin twice daily
NutriVir Nutritional Supplement Over-the-Counter (OTC) product	Look	Each serving contains: (whey protein concentrate, fructose, dextrose, malto dextrin, vanilla and vanillin, "Enzyme Blend (amyloglucosidase, amylase, arotease, acid protease, cellulase, lipase), Vitamin A 5,000 IU, Vitamin C 1000 mg, Vitamin D 200 IU, Vitamin E 400 IU, Thiamin 1.5 mg, Riboflavin 1.7 mg, Niacin 10 mg, Vitamin B-6 25 mg, Folate 800 mcg, Vitamin B-12 1000 mg, Biotin 300 mcg, Pantothenic Acid 50 mg, Calcium 160 mg, Phosphorus 120 mg, Iodine 35.5 mcg, Magnesium 240 mg, Zinc 5.25 mg, Selenium 200 mcg, Manganese 2 mg, Chromium 200 mcg, Molybdenum 11.25 mcg, Sodium 180 mg, Potassium 160 mg, Medium Chain Triglycderides 6 g, N-Acetyl Cysteine 2 g, L-Cartinitine Magnesium Citrate 1g, Taurine 500 mg, Alpha-Lipoic Acid 100 mg, Choline 100 mg, Inositol 100 mg, Inosine 50 mg, Pyridoxine Alpha-Ketoglutarate 25 mg, Lutein 6 mg, Lycopene 3 mg, Boron 1.5 mg, and Vanadium 50 mcg.	5 tablespoonsful in 8 oz. of cold beverage once daily

Product name with potential for confusion	Similarity to Neutroval	Strength	Signa
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day administered as a daily subcutaneous injection** (b) (4) (b) (4)
NeutroSpec [Technetium (99m Tc) Fanolesomab] Injection *Marketing and sales of this product were suspended in 2005 due to reports of serious adverse events. There are no generics available.*	Look	0.25 mg	Adults: 75 mcg to 125 mcg labeled with 10 mCi to 20 mCi intravenously once Children (5 years of age and older): 0.21 mCi/kg to a maximum of 20 mCi.

Appendix H: Products with overlap in strength, dose or achievable dose with multiple differentiating product characteristics

Product name with potential for confusion	**Similarity to Neutroval**	**Strength**	**Signa**	**Differentiating Product Characteristics (Neutroval vs. Product)**
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously (b) (4) (b) (4) (b) (4) to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Retrovir (Zidovudine) Capsules Tablets Syrup Injection	Look	Capsules: 100 mg Tablets: 300 mg Syrup: 50 mg/5 mL Injection: 10 mg/mL	Adults: 600 mg per day in divided doses orally or intravenously	The beginning portion of Neutroval appears longer in length ("Neu" vs. "Re") which helps to differentiate the names. Additionally, the ending letter "l" in Neutroval has an upstroke characteristic which also helps to differentiate the names. *Frequency of administration*: Once daily vs. two or three times per day
Nutr-E-Sol (Vitamin E) Oral Liquid OTC product	Look	400 IU/15 mL	15 mL (1 tablespoonful) once daily	The beginning portion of Neutroval appears longer in length because it contains three letters whereas Nutresol contains two ("Neu" vs. "Nu"). *Dosage form*: Injection vs. oral liquid *Route of administration*: Subcutaneous (b) (4) vs. oral *Status*: Prescription vs. OTC

Product name with potential for confusion	**Similarity to Neutroval**	**Strength**	**Signa**	**Differentiating Product Characteristics (Neutroval vs. Product)**
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously (b) (4) (b) (4) (b) (4) to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Nausetrol Solution OTC Product	Look	Dextrose 1.87 g, Fructose 1.87g, and Phosphoric Acid 21.5 g per 5 mL	5 mL, 10 mL, 15 mL or 30 mL every 15 minutes until nausea is gone; take no more than 5 doses in one hour or a maximum of 5 doses	Both names contain the letters "tro". However, these three letters are in the middle portion of Neu**tro**val and in the ending portion of Nause**trol** which helps to differentiate the names. Additionally, the letters "tro" are followed by three letters ("val") in Neutroval and one letter ("l") in Nausetrol which further differentiates the names. *Dosage form*: Injection vs. oral solution *Route of administration*: Subcutaneous (b) (4) vs. oral *Frequency of administration*: Once daily vs. every 15 minutes *Status*: Prescription vs. OTC
Nitro-Dur (Nitroglycerin Transdermal Patch)	Look	0.1 mg/hr, 0.2 mg/hr, 0.3 mg/hr, 0.4 mg/hr, 0.6 mg/hr, and 0.8 mg/hr patches	0.2 mg/hr to 0.8 mg/hr patch applied to skin once daily, on for 10 to 12 hours then off for 12 to 14 hours	Both names contain the letters "tro". However, the letters ("eu" vs. "i") in the beginning of the names look different. The ending letters ("val" vs. "dur") look different as well due to the upstroke characteristic of the letter "d". *Dosage form*: Injection vs. transdermal patch *Route of administration*: Subcutaneous (b) (4) vs. topical

Product name with potential for confusion	**Similarity to Neutroval**	**Strength**	**Signa**	**Differentiating Product Characteristics** **(Neutroval vs. Product)**
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously (b) (4) (b) (4) (b) (4) to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Natrecor (Nesiritide) for Injection	Look	1.5 mg vial	2 mcg/kg intravenous bolus then 0.01 mcg/kg/min intravenous infusion	The beginning portion of Neutroval appears longer in length because it contains three letters whereas Natrecor contains two ("Neu" vs. "Na"). Additionally, the ending letters of the names look different ("val" vs. "cor"). *Dose:* 5 mcg/kg vs. 2 mcg/kg and 0.01 mcg/kg/min *Frequency of administration*: (b) (4) (b) (4) vs. a continuous infusion.