

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

PROPRIETARY NAME REVIEW(S)



Memorandum

Date July 27, 2012

From Biological Product Naming Working Group

Subject Memorandum Addendum -- BLA 125418 – Zaltrap ([xxx]-aflibercept) manufactured by sanofi-sintelabo, U.S., LLC

To File

As detailed in a memorandum dated July 15, 2012, FDA determined that a unique nonproprietary name will be required for sanofi-aventis' (sanofi) Zaltrap ([xxx]-aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA by Regeneron Pharmaceuticals Inc. (Regeneron) that contains similar drug substance. In sum, Regeneron's and sanofi's products are the subject of different marketing applications held by different manufacturers; have different indications, different formulations, and different routes of administration; and are manufactured at different sites. Identifying sanofi's Zaltrap with a unique nonproprietary name will reinforce these differences and help to prevent medication errors involving the two products. For these reasons, FDA determined that the sanofi product will be identified as Zaltrap ([xxx]-aflibercept).

FDA communicated this decision to sanofi on July 17, 2012. By email of July 20, 2012 (attached to this addendum), sanofi proposed three nonproprietary names [REDACTED] (b) (4), but objected to the use of an underscore [REDACTED] (b) (4)

FDA has considered sanofi's position on use of the underscore, and has concluded that separating the prefix from the aflibercept stem with a punctuation mark is the appropriate mechanism by which to effectuate the goals underlying the decision to require a distinct nonproprietary name for sanofi's product. As described in the July 15, 2012 memorandum, FDA has determined that the nonproprietary name of a biological product for which licensure is sought under section 351 (a) of the Public Health Service Act (PHS Act) that shares a similar drug substance to a previously licensed product should indicate both distinction from, and relation to, that other product in order to minimize medication errors and facilitate postmarketing safety monitoring. Removal of the mark changes both the visual and auditory impact of the prefix in a way that diminishes the desired effect of the use of the prefix and the clear preservation of the stem.

In addition, appending a prefix directly to the related product's stem for the purposes of distinguishing products in different 351 (a) BLAs submitted by different manufacturers risks significant confusion and potentially could be misleading in light of the United States Adopted Names (USAN) Council's nomenclature practices related to prefix use. Specifically, the USAN Council's practice for naming biological substances uses prefixes directly appended to a stem (b) (4)

(b) (4) For example, darbepoetin, (b) (4) has a prefix "darb" appended directly to the epoetin stem. No such determination has been made here.

However, FDA acknowledges that an underscore is not a mark normally used in handwriting, and that use of an underscore may result in the mark not being easily seen in handwriting and/or computer systems. FDA thus has determined that a prefix should be followed by a hyphen preceding aflibercept rather than an underscore. A hyphen is a common mark used in writing and is a more easily recognized mark.

(b) (4)

(b) (4) In addition, there is precedent for using a hyphen in biological product nonproprietary names, e.g., interferon alfa-2b, as well as in the proprietary and nonproprietary nomenclature of drug products. FDA is not aware of any incompatibility that has resulted from use of the hyphen for interferon products, or more generally, of any inherent incompatibility of using hyphens with prescribing systems.

(b) (4)

FDA's decision to require a unique nonproprietary name in the form of [prefix]-aflibercept for Zaltrap, 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 reviewed the three proper names that sanofi proposed in decreasing order of preference:

(b) (4)

(iii) zivaflibercept

FDA evaluated those names with a hyphen inserted between the proposed prefixes and the aflibercept stem, using the criteria outlined in the July 17, 2012 communication to sanofi, and determined that "ziv-" is the only acceptable prefix provided by sanofi. Specifically, FDA made the following determinations:

(b) (4)

¹ Medical Abbreviations; 14th Edition; Neil M Davis.

² Davis, NM. Medical Abbreviations: 26,000 Conveniences at the Expense of Communication and Safety. 12th ed., at 269.

- The ^{(b) (4)} prefix, "ziv-" does not appear to raise concerns related to conveying specific meaning, being promotional or looking or sounding similar to a currently marketed product. The proposed prefix "ziv-" is acceptable based on the criteria outlined in the July 17, 2012 communication to sanofi.

³ Webster's New World College Dictionary, 4th ed. 1999, at 1043; Stedman's Medical Dictionary, 26th ed. 1995, at 1292.

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/s/

LEAH A CHRISTL

07/27/2012

Memo entered into DARRTS on behalf of the Biological Product Naming Working Group



Memorandum

Date July 17, 2012

From Biological Product Naming Working Group

Subject BLA 125418 – Zaltrap ([xxx]_aflibercept) manufactured by sanofi-aventis, U.S., LLC

To File

FDA has determined that a unique nonproprietary name will be required for sanofi-aventis' (sanofi) Zaltrap ([xxx]_aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA by Regeneron Pharmaceuticals Inc. (Regeneron) that contains similar drug substance. Specifically, Zaltrap ([xxx]_aflibercept), is a solution for infusion for use in combination with irinotecan-fluoropyrimidine-based chemotherapy for treatment of patients with metastatic colorectal cancer (mCRC) who were previously treated with an oxaliplatin-containing regimen. Regeneron's Eylea (aflibercept) was licensed for macular degeneration on November 18, 2011.

FDA has concluded that a nonproprietary name for sanofi's product that is distinct from Regeneron's product will 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 "aflibercept" 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.

Eylea and Zaltrap are the subject of separate BLAs submitted by different manufacturers, Regeneron and sanofi respectively, although we are aware that they have a business relationship. For this reason, FDA has concluded that a unique nonproprietary name is warranted for the subsequently licensed product. In addition, the following factors also support the decision to designate a unique nonproprietary name for Zaltrap.

- Eylea and Zaltrap have different formulations. Eylea is formulated at 2 mg/mL, while Zaltrap is formulated at 25 mg/mL. Zaltrap differs from Eylea in (b) (4) vial size.

-  (b) (4)
As the products are manufactured at different sites under different BLAs held by different manufacturers, there is concern that, among other things, the two products may drift over time.
- Eylea and Zaltrap have different routes of administration. Eylea is administered by intravitreal injection while Zaltrap is administered by intravenous infusion in combination with chemotherapy.
- Eylea and Zaltrap have different indications. Eylea is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), while Zaltrap is indicated in patients with metastatic colorectal cancer.

To differentiate Regeneron's aflibercept product from sanofi's product, FDA is requesting that sanofi propose a 3-4 letter prefix to be added to the non-proprietary stem, "aflibercept."

This decision for the aflibercept products is similar to the decision to revise the nonproprietary names for the botulinum toxin products. The nonproprietary names for botulinum toxin products were changed to emphasize the non-interchangeable potency units of each botulinum toxin product in an effort to prevent medication errors and serious adverse events. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new nonproprietary names (which incorporated a 3-4 letter distinguishing prefix to the "botulinumtoxinA" or "botulinumtoxinB" stem) reinforced these differences and the lack of interchangeability among botulinum toxin products.

Regeneron and sanofi products are the subject of different marketing applications held by different manufacturers; have different indications, different formulations, and different routes of administration; and are manufactured at different sites. Identifying sanofi's Zaltrap with a unique nonproprietary name will reinforce these differences and help to prevent medication errors involving the two products. For these reasons, the sanofi product will be identified as Zaltrap ([xxx]_aflibercept).

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/s/

SUE P LIM

07/17/2012

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--Final

Date: June 18, 2012

Reviewer: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zaltrap (Aflibercept) Injection,
100 mg/4 mL and 200 mg/8 mL

Application Type/Number: BLA 125418

Applicant: Sanofi-Aventis

OSE RCM #: 2012-410

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1 INTRODUCTION

This re-assessment of the proposed proprietary name, Zaltrap, is written in response to the anticipated approval of this BLA within 90 days from the date of this review. DMEPA found the proposed name, Zaltrap, acceptable in OSE Review 2011-4363 dated February 13, 2012.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Review 2011-4363. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded 2 new names (Zebeta and (b) (4)***) thought to look or sound similar to Zaltrap and represent a potential source of drug name confusion. Failure mode and effects analysis was applied to determine if the proposed proprietary name could potentially be confused with Zaltrap and lead to medication errors. This analysis determined that the name similarity between Zaltrap and the identified names was unlikely to result in medication error for the reasons presented in Appendix A.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 13, 2012. The Office of Prescription Drug Promotion OPDP re-reviewed the proposed name on May 3, 2012 and had no concerns regarding the proposed name from a promotional perspective.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Zaltrap, did not identify any vulnerability that would result in medication errors with any additional name(s) noted in this review. Thus, DMEPA has no objection to the proprietary name, Zaltrap, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Oncology Products 2 (DOP2) should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

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

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4 REFERENCES

1. **OSE Review # 2011-4363 Proposed Proprietary Name Review for Zaltrap, February 13, 2012.**

2. **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.

3. **USAN Stems** (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?>)

USAN Stems List contains all the recognized USAN stems.

4. **Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request**

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

APPENDIX A: FMEA TABLE

Zaltrap (Aflibercept) Injection 100 mg/4 mL and 200 mg/8 mL 25 mg/mL 4 mg/kg via Intravenous Infusion Once Every Two Weeks	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion: Causes (could be multiple)	Prevention of Failure Mode
(b) (4)		

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<p>Zaltrap (Aflibercept) Injection 100 mg/4 mL and 200 mg/8 mL 25 mg/mL 4 mg/kg via Intravenous Infusion Once Every Two Weeks</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion: Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Zebeta (Bisoprolol) Tablet 5 mg and 10 mg <u>Usual Dose</u> 5 mg or 10 mg orally twice daily</p>	<p><u>Orthographic</u> The letter string ‘Zeb’ can look similar to the letter string ‘Zal’ when scripted. Both names have the cross stroke letter ‘t’ after an upstroke letter.</p>	<p><u>Orthographic</u> The name Zebeta does not have a downstroke letter at the end of the name. The name Zebeta has the letter ‘e’ between the upstroke letter ‘b’ and cross stroke letter ‘t’ where the name Zaltrap has the cross stroke letter ‘t’ immediately after the upstroke letter ‘l’.</p> <p><u>Strength</u> Multiple strengths vs. single strength and no overlap or numerical similarity in strength. Thus, Zebeta’s strength will be specified vs. Zaltrap’s strength may be omitted.</p> <p><u>Dose</u> No overlap or numerical similarity in dose</p> <p><u>Frequency of Administration</u> Twice daily vs. Once every two weeks</p>

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/s/

JAMES H SCHLICK
06/18/2012

TODD D BRIDGES
06/18/2012

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

Proprietary Name Review

Date: February 13, 2012

Reviewer(s): James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Team Leader Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Zaltrap (Aflibercept) Injection,
100 mg/4 mL and 200 mg/8 mL

Application Type/Number: BLA 125418

Applicant: Sanofi-Aventis

OSE RCM #: 2011-4363

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Zaltrap, 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

The proposed proprietary name, Zaltrap, was found acceptable by DMEPA in OSE Review 2010-1837, dated November 30, 2010 under IND 009948. Sanofi Aventis submitted a proprietary name request on February 2, 2012 which is the topic of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 2, 2012 proprietary name submission.

- Established Name: Aflibercept Injection
- Indication of Use: For the treatment of metastatic colorectal cancer in combination with the chemotherapy regimen Fluorouracil, Irinotecan, and Leucovorin (FOLFIRI).
- Route of administration: Intravenous infusion
- Dosage form: Solution for injection
- Strength: 25 mg/mL
- Dose: 4 mg/kg via intravenous infusion over one hour every two weeks
- How Supplied: (b) (4) vials
- Storage: Refrigerated at 2 to 8°C (36 to 46°F)
- Container and Closure systems: Supplied in either 5 mL or 10 mL (b) (4) glass vial, sealed with flanged stopper with flip-off cap (b) (4) containing 100 mg or 200 mg of aflibercept. The 100 mg vial comes in 1 vial or 3 vial cartons and the 200 mg vial comes in 1 vial cartons.

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Oncology Products 2 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 evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

On February 10, 2012 the United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a single word that does not contain any components such as a modifier, route of administration, or dosage form that is misleading or can contribute to medication error. The Applicant notes in their submission that the derivation of the proprietary name has no intended reference to a proposed indication or usage setting.

2.2.3 FDA Name Simulation Studies

Thirty-five practitioners participated in DMEPA's prescription studies. One prescription study name, (b)(4) is a direct match to a currently trademarked name with the US Patent and Trademark Office (USPTO) that was identified by the FDA (see Table 1). Our evaluation of this name can be found in Appendix E. Thirty-one out of thirty-five participants interpreted the written or verbal prescription correctly. The most common misinterpretation was the letter "S" and "X" for the letter "Z" in the voice study. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE, December 13, 2011 e-mail, the Division of Oncology Products 2 (DOP2) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 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 Zaltrap. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Zaltrap, identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified from the FDA Prescription Simulation.

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 and Sound Similar	
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
(b) (4)***	FDA	Zanaflex	FDA	Zelboraf	FDA
Altatapp	FDA	Zantac	FDA	Zentrip	FDA
Betatrex	FDA	Zantryl	FDA	Zaltrap***	FDA
Liotrix	FDA	Zelapar	FDA	(b) (4)***	FDA
Lotapp	FDA	Zeldox	FDA		
Lotrel	FDA	Zoladex	FDA		
Multaq	FDA	Zolinza	FDA		
Salitop	FDA	Zoloft	FDA		
Silapap	FDA	Zolpidem	FDA		
Siltrax	FDA	Zolyse	FDA		
Teldrin	FDA	Zometa	FDA		
Tetracap	FDA	Zomig	FDA		
Val Tran	FDA	Zyvox	FDA		
Valstar	FDA				
Valtrex	FDA				
Valtropin	FDA				
Valtrum	FDA				
Xalkori	FDA				
Zactran	FDA				
(b) (4)***	FDA				
Zaleplon	FDA				
Zalestra	FDA				
(b) (4)***	FDA				

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Our analysis of the 40 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 40 names will not pose a risk for confusion as described in Appendix D through F.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Oncology Products 2 via e-mail on January 9, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Oncology Products 2 on February 13, 2012 they stated no additional concerns with the proposed proprietary name, Zaltrap.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective. The proposed proprietary name, Zaltrap, must be re-reviewed 90 days before approval of the BLA.

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, Zaltrap, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your February 2, 2012 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

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 Pharmacy's Fundamental Reference

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 Book

Medical Abbreviations Book 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.

20. OSE Reviews

Toliver, Kristina. OSE Review 2010-1837: Proprietary Name Review for Zaltrap, November 30, 2010.

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.

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.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.²

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 post marketing 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).

² 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		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, 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 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 Division of Drug Marketing, Advertising, and Communications (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.³ 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

³ 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 possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

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

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

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

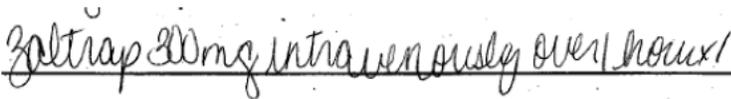
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval 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, NAME	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'Z'	B, X, L, M, T, S, V	C, S, X
lowercase 'z'	g, n, r, m, s, v	c, s, x
Lowercase 'a'	el, ci, cl, d, o, u	Any vowel
Lowercase 'l'	b, e, i, t, d	none
Lowercase 't'	f, l, x	d
Lowercase 'r'	s, n, e, v	none
Lowercase 'a'	el, ci, cl, d, o, u	Any vowel
Lowercase 'p'	yn, ys, g, j, q	b

Appendix C: Prescription Simulation Samples and Results

Figure 1. Zaltrap Study (Conducted on December 12, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p>Medication Order:</p> 	<p>Zaltrap 8 mL vial #2 Bring to Infusion Center</p>

<p><u>Outpatient Prescription:</u> Zaltrap 8mL vial #2 to Outpatient infusion center</p>	
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FDA Prescription Simulation Responses

INPATIENT MEDICATION ORDER	VOICE PRESCRIPTION	OUTPATIENT PERSCRIPTION
ZALTRAP (14)	SALTRAP (1)	ZALTRAP (10)
ZALTRAYS (1)	XALTRAP (1)	
	ZALTRAP (7)	
	ZELTRAP (1)	

Appendix D: Proprietary names determined in OSE Review 2010-1837 not likely to lead to a medication error.

Proprietary Name	Active Ingredient	Similarity to Zaltrap
Valtrex	Valacyclovir	Look and Sound
Valtropin	Somatropin	Look
	Zaleplon	Look
Zantac	Ranitidine	Look
Zentrip	Meclizine	Look and Sound
Zolinza	Vorinostat	Look
Zoloft	Sertraline	Look

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

Proprietary Name	Active Ingredient	Similarity to Zaltrap	Failure preventions
(b) (4)			
Betatrex	Betamethasone Valerate	Look	Lack of convincing orthographic similarity
Liotrix	Active ingredient for Euthroid	Look	Lack of convincing orthographic similarity
Lotapp	Brompheniramine/ phenylpropanolamine	Look	As of November 2000, the United States Food and Drug Administration (FDA) has recommended the removal of phenylpropanolamine from all drug products due to a public health advisory concerning the risk of hemorrhagic stroke associated with its use. The only source this name is located in is Red Book. The electronic version marks its status as "Inactive"
Lotrel	Amlodipine/ Benazepril	Look	Lack of convincing orthographic similarity
Silapap	Acetaminophen	Look	Lack of convincing orthographic similarity
Siltrax	Epinephrine	Look	Coated cotton cord soaked in epinephrine and used in dental extraction procedures. Based on the different practice settings, it is unlikely that confusion will occur with the proposed name.
Zactran	Gamithromycin	Look	Antibiotic approved for use in animals
(b) (4)			
Zanaflex	Tizanidine	Look	Lack of convincing orthographic similarity
Zantryl	Phentermine	Look	Lack of convincing orthographic similarity
Zometa	Zoledronic acid	Look	Lack of convincing orthographic similarity
Zomig	Zolmitriptan	Look	Lack of convincing orthographic similarity
Zyvox	Linezolid	Look	Lack of convincing orthographic similarity
(b) (4)			

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

Proprietary Name	Active Ingredient	Similarity to Zaltrap	Failure preventions
(b) (4)			
Val-Tran	Valerian extract, Vitamin B6, Magnesium Gluconate, Magnesium Oxide	Look	Herbal supplement that is used as a sleep aid. This product will unlikely be written on prescription orders.
Zalestra	Green Tea Extract	Look	Herbal supplement with multiple uses. This product will unlikely be written on prescription orders.
Zaltrap***	Aflibercept	Look and Sound	Trademarked by Regeneron Pharmaceuticals. Regeneron is a partner in developing this drug product with Sanofi-Aventis, who is the Applicant for this NDA

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

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

<p style="text-align: center;">Zaltrap (Aflibercept) Injection</p>	<p style="text-align: center;">100 mg/4 mL and 200 mg/8 mL 25 mg/mL</p>	<p style="text-align: center;">4 mg/kg via Intravenous Infusion Once Every Two Weeks</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes</p>	<p>Prevention of Failure Mode</p>
<p>Multaq (Dronedarone) Tablet 400mg <u>Usual Dose</u> 400 mg orally twice daily with morning and evening meals</p>	<p><u>Orthographic</u> Both names begin with similar letter strings ‘Mul’ and ‘Zal’ Both names have similar letter strings at the end of each name ‘aq’ and ‘ap’ <u>Dose</u> 400 mg vs. 160 mg to 600 mg based on weight</p>	<p><u>Frequency of Administration</u> Twice daily vs. Once every two weeks <u>Storage</u> Room Temperature vs. Refrigerator</p>
<p>Salitop (Salicylic acid) 6% Cream and 6% Lotion <u>Usual Dose</u> Apply to affected area at night; place under occlusion and wash off in the morning.</p>	<p><u>Orthographic</u> Both names contain the letter string ‘al’ in the same location. Also, the letter strings ‘top’ and ‘trap’ look similar when scripted.</p>	<p><u>Orthographic</u> The first letter ‘S’ in Salitop is unlikely to be confused with the first letter ‘Z’ in Zaltrap when scripted. <u>Frequency of Administration</u> Once daily at night vs. Once every two weeks <u>Dose</u> Apply cream as directed vs. 160 mg to 600 mg based on weight <u>Storage</u> Room Temperature vs. Refrigerator</p>

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
<p>Altatapp (Brompheniramine/Pseudoephedrine) Elixir 2 mg/5 mL – 12.5 mg/5 mL</p> <p><u>Usual Dose</u></p> <p>6-11 years old: 10 mL every 6 hours 12 years and older: 20 mL every 6 hours</p>	<p><u>Orthographic</u></p> <p>Both names have the letter string ‘alt’ in similar locations</p> <p>Both names have a ‘t’ and ‘p’ in similar locations</p>	<p><u>Orthographic</u></p> <p>The first letter ‘A’ in Altatapp is unlikely to be confused with the first letter ‘Z’ in Zaltrap when scripted.</p> <p><u>Frequency of Administration</u></p> <p>Every 6 hours vs. Once every two weeks</p> <p><u>Dose</u></p> <p>10 to 20 mL or 4 mg/25 mg to 8 mg/50 mg vs. 160 mg to 600 mg based on weight</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p>
<p>Teldrin (Chlorpheniramine) Tablet 4 mg</p> <p><u>Usual Dose</u></p> <p>Children 6-11 years old: 2 mg orally every 4-6 hours</p> <p>Children 12 years and older and Adults: 4 mg orally every 4-6 hours</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Teld’ and ‘Zalt’</p>	<p><u>Orthographic</u></p> <p>The last letter ‘n’ in Teldrin does not have a down stroke where the last letter ‘p’ in Zaltrap has a down stroke.</p> <p>The second to last letter ‘i’ in Teldrin has a raised dot when scripted while the second to last letter ‘a’ in Zaltrap does not.</p> <p>The fourth letter ‘d’ in Teldrin does not have a cross stroke when compared to the fourth letter ‘t’ in Zaltrap</p> <p><u>Frequency of Administration</u></p> <p>Every 4 to 6 hours vs. Once every two weeks</p> <p><u>Dose</u></p> <p>2 to 4 mg vs. 160 mg to 600 mg based on weight</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p>

<p style="text-align: center;">Zaltrap (Aflibercept) Injection</p>	<p style="text-align: center;">100 mg/4 mL and 200 mg/8 mL 25 mg/mL</p>	<p style="text-align: center;">4 mg/kg via Intravenous Infusion Once Every Two Weeks</p>
<p>Tetracap (Tetracycline hydrochloride) Capsule 250 mg</p> <p><u>Usual Dose</u></p> <p>Children 8 years or older: 250 mg three times daily to 500 mg four times daily</p> <p>Adults: 500 mg twice daily to 500 mg four times daily</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Tet’ and ‘Zal’</p> <p>Both names have the same letter strings at the end of each name ‘ap’</p> <p><u>Dose</u></p> <p>250 to 500 mg vs. 160 mg to 600 mg based on weight</p>	<p><u>Orthographic</u></p> <p>The third and fourth letters ‘tr’ in Tetracap have only one up stroke while the third and fourth letter ‘lt’ in Zaltrap have two up stroke letters.</p> <p><u>Frequency of Administration</u></p> <p>Twice a day to four times per day vs. Once every two weeks</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p>
<p>Valstar (Valrubicin) Intravesical Instillation Vial 200 mg/5 mL</p> <p><u>Usual Dose</u></p> <p>800 mg intravesically weekly for 6 weeks</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Val’ and ‘Zal’</p> <p><u>Storage</u></p> <p>Both are stored in the refrigerator</p> <p><u>Setting</u></p> <p>Both products are used in oncology</p>	<p><u>Orthographic</u></p> <p>The last letter ‘r’ in Valstar does not have a down stroke where the last letter ‘p’ in Zaltrap has a down stroke.</p> <p>Valstar has the letter ‘s’ between the letters ‘l’ and ‘t’, Zaltrap does not have a letter between ‘l’ and ‘t’.</p> <p>The last letter ‘p’ in Zaltrap has a down stroke when scripted. The last letter ‘r’ in Valstar does not have a down stroke when scripted.</p> <p><u>Frequency of Administration</u></p> <p>Once weekly vs. every two weeks</p> <p><u>Dose</u></p> <p>Fixed 800 mg dose vs. 160 mg to 600 mg based on weight</p>

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
<p>Valtrum (Camphor 3%/Menthol 3%) Ointment</p> <p><u>Usual Dose</u></p> <p>Apply to affected area every 6 hours</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Valtr’ and ‘Zaltr’</p>	<p><u>Orthographic</u></p> <p>The last letter ‘p’ in Zaltrap has a down stroke when scripted. The last letter ‘m’ in Valtrum does not have a down stroke when scripted.</p> <p><u>Frequency of Administration</u></p> <p>Every 6 hours vs. Once every two weeks</p> <p><u>Dose</u></p> <p>Apply to affected area as directed vs. 160 mg to 600 mg based on weight</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p>
<p>Xalkori (Crizotinib) Capsule</p> <p>200 mg and 250 mg</p> <p><u>Usual Dose</u></p> <p>250 mg twice daily</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Xal’ and ‘Zal’</p> <p><u>Setting</u></p> <p>Both products are used in oncology</p> <p><u>Dose</u></p> <p>250 mg twice daily vs. 160 mg to 600 mg based on weight</p>	<p><u>Orthographic</u></p> <p>The last letter ‘p’ in Zaltrap has a down stroke when scripted.</p> <p><u>Frequency of Administration</u></p> <p>Twice daily vs. Once every two weeks</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p>

<p style="text-align: center;">Zaltrap (Aflibercept) Injection</p>	<p style="text-align: center;">100 mg/4 mL and 200 mg/8 mL 25 mg/mL</p>	<p style="text-align: center;">4 mg/kg via Intravenous Infusion Once Every Two Weeks</p>
<p>Zelapar (Selegiline) Oral Disintegrating tablet (ODT) 1.25 mg</p> <p><u>Usual Dose</u></p> <p>1.25 mg to 2.5 mg daily</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Zel’ and ‘Zal’</p>	<p><u>Orthographic</u></p> <p>The fourth letter ‘t’ in Zaltrap has an up stroke. The fourth letter ‘a’ in Zelapar does not have an up stroke.</p> <p>The last letter ‘p’ in Zaltrap has a down stroke when scripted. The last letter ‘r’ in Zelapar does not have a down stroke when scripted.</p> <p><u>Frequency of Administration</u></p> <p>Once daily vs. Once every two weeks</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p> <p><u>Dose</u></p> <p>1.25 mg to 2.5 mg vs. 160 mg to 600 mg based on weight</p>
<p>Zelboraf (Vemurafenib) Tablet</p> <p>240 mg</p> <p><u>Usual Dose</u></p> <p>960 mg twice daily</p> <p>720 mg twice daily</p> <p>480 mg twice daily</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings ‘Zel’ and ‘Zal’</p> <p><u>Phonetic</u></p> <p>The letter string ‘zel’ and ‘zal’ sound similar when spoken</p> <p><u>Setting</u></p> <p>Both products are used in oncology</p> <p><u>Dose</u></p> <p>480 mg and 720 mg vs. 160 mg to 600 mg based on weight</p>	<p><u>Frequency of Administration</u></p> <p>Twice daily vs. Once every two weeks</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p> <p><u>Phonetic</u></p> <p>Zelboraf has three syllables when spoken while Zaltrap has two syllables when spoken.</p> <p>The letter string ‘boraf’ in Zelboraf does not sound similar to ‘trap’ in Zaltrap when spoken.</p>

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
<p>Zeldox (Ziprasidone) - Canadian Brand Name</p> <p>Capsule: 20 mg, 40 mg, 60 mg, 80 mg</p> <p>Injection: 20 mg powder for injection</p> <p><u>Usual Dose</u></p> <p>Oral: 20 mg to 80 mg daily</p> <p>Injection: 10 mg to 20 mg every 2 to 4 hours. Max 40 mg per day</p>	<p>Both names begin with similar letter strings 'Zel' and 'Zal'</p>	<p><u>Frequency of Administration</u></p> <p>Once daily or Every 2 to 4 hours vs. Once every two weeks</p> <p><u>Dose</u></p> <p>20 mg to 80 mg vs. 160 mg to 600 mg based on weight</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p> <p><u>Orthographic</u></p> <p>The last letter 'p' in Zaltrap has a down stroke. The last letter 'x' in Zeldox does not have a down stroke.</p>
<p>Zoladex (Goserelin) Injection for Implant 3.6 mg monthly implant, 10.8 mg 3 month implant</p> <p><u>Usual Dose</u></p> <p>3.6 mg every month or 10.8 mg every 3 months</p>	<p><u>Orthographic</u></p> <p>Both names begin with similar letter strings 'Zol' and 'Zal'</p> <p><u>Setting</u></p> <p>Both products are used in oncology</p>	<p><u>Frequency of Administration</u></p> <p>Every month or Every 3 months vs. Once every two weeks</p> <p><u>Dose</u></p> <p>3.6 mg or 10.8 mg vs. 160 mg to 600 mg based on weight</p> <p><u>Storage</u></p> <p>Room Temperature vs. Refrigerator</p> <p><u>Orthographic</u></p> <p>The last letter 'p' in Zaltrap has a down stroke. The last letter 'x' in Zoladex does not have a down stroke.</p>

<p style="text-align: center;">Zaltrap (Aflibercept) Injection</p>	<p style="text-align: center;">100 mg/4 mL and 200 mg/8 mL 25 mg/mL</p>	<p style="text-align: center;">4 mg/kg via Intravenous Infusion Once Every Two Weeks</p>
<p>Zolpidem (Ambien) Tablet (Sublingual, Biphasic) and Spray Tablet: 5 mg, 6.25 mg, 10 mg, 12.5 mg Oral Mucosal Spray: 5 mg per actuation <u>Usual Dose</u> 5 mg to 12.5 mg or 1 to 2 sprays daily at bedtime</p>	<p><u>Orthographic</u> Both names begin with similar letter strings ‘Zol’ and ‘Zal’</p>	<p><u>Frequency of Administration</u> Once daily at bedtime vs. Once every two weeks <u>Dose</u> 5 mg to 12.5 mg or 1 to 2 sprays vs. 160 mg to 600 mg based on weight <u>Storage</u> Room Temperature vs. Refrigerator <u>Orthographic</u> The fourth letter ‘p’ in Zolpidem has a down stroke. The fourth letter ‘t’ in Zaltrap has an upstroke. The last letter ‘p’ in Zaltrap has a down stroke where the last letter ‘m’ in Zolpidem does not.</p>
<p>Zolyse (Chymotrypsin) Ophthalmic Solution for Injection 750 Units per vial; 150 units/mL after reconstitution <u>Usual Dose</u> 0.25 mL to 2 mL or 37.5 mg to 300 mg once via irrigation to the eye during eye surgery</p>	<p><u>Orthographic</u> Both names begin with similar letter strings ‘Zol’ and ‘Zal’</p>	<p><u>Orthographic</u> The fourth letter ‘t’ in Zaltrap has an upstroke. The fourth letter ‘y’ in Zolyse has a down stroke. The last letter ‘p’ in Zaltrap has a down stroke when scripted. The last letter ‘e’ in Zolyse does not have a down stroke when scripted. <u>Frequency of Administration</u> Once during eye surgery vs. Once every two weeks <u>Storage</u> Room Temperature vs. Refrigerator</p>

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

/s/

JAMES H SCHLICK
02/14/2012

TODD D BRIDGES
02/14/2012

CAROL A HOLQUIST
02/14/2012