DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS

3 JAN 2017

MEMORANDUM FOR SGCEE
ATTN: CAPT JOHN BENNION

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Dose Uniformity of Topical Corticosteroid Ophthalmic Medications: Flourometholone Acetate 0.1% Suspension and Loteprednol Etabonate 0.5% Lotemax** presented at/published to **Journal of Ocular Pharmacology and Therapeutics** in accordance with MDWI 41-108, has been approved and assigned local file #**17014.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

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4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

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PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol)	3. GME/GHSE STUDENT:	4. PROTOCOL NUMBER:
	John Bennion, Capt, 59th SGC/SGCEE	☒ YES ☐ NO	397493-3

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Dose uniformity of topical corticosteroid ophthalmic medications: flourometholone acetate 0.1% suspension and loteprednol etabonate 0.5%

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:

Dose uniformity of topical corticosteroid ophthalmic medications: flourometholone acetate 0.1% suspension and loteprednol etabonate 0.5%

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Journal of Ocular Pharmacology and Therapeutics

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13. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email)	14. DUTY PHONE/PAGER NUMBER
Bennion, John L; john.l.bennion.mil@mail.mil	210-594-6174

15. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.

LAST NAME, FIRST NAME AND M.I.	GRADE/RANK	SQUADRON/GROUP/OFFICE SYMBOL	INSTITUTION (If not 59 MDW)
a. Primary/Corresponding Author Bennion, John L	Capt	59th TRS SGC/SGCEE	
b. Stevens, Charlton E	Capt	959th CSPS/MCHE-ZDM-M	959 CSPS
c. Caldwell, Matthew C	Lt Col	59th MDW SGC/SGCEE	
d. Townley, James R	Maj	59th MDW SGC/SGCEE	
e. Apsey, Douglas A	Civ	59th MDW SGC/SGCEP	
f. Schwertner, Harvey A	Civ	59th MDW CSPG/SGVU	

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16. AUTHOR'S PRINTED NAME, RANK, GRADE	17. AUTHOR'S SIGNATURE	18. DATE
John Bennion, CAPT, 0-3	BENNION.JOHN.L.1386423454	December 06, 2016
19. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE	**20. APPROVING AUTHORITY'S SIGNATURE**	**21. DATE**
James Richard Townley, MAJ Cornea and Refractive Surgeon	TOWNLEY.JAMES.RICHARD.III.10 13936532	December 13, 2016

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26. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: ☒ NO ☐ YES If yes, give date. _____ ☐ N/A

27. COMMENTS ☒ APPROVED ☐ DISAPPROVED

Draft version of IRB exempt determined study with appropriate disclosures. Approved with pending final revisions for publication

28. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	29. REVIEWER SIGNATURE	30. DATE
Kevin R. Kupferer/GS13/Human Research Subject Protection Expert	KUPFERER.KEVIN.R.1086667270	December 19, 2016

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Journal of Ocular Pharmacology and Therapeutics

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Dose uniformity of topical corticosteroids: A simulated trial fluorometholone acetate 0.1% (Flarex®) and loteprednol etabonate gel 0.5% (Lotemax®)

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Disclaimer: The views expressed are that of the author(s)/presenter(s) and do not reflect the official views or policy of the Department of Defense or its Components.

Correspondence: John Bennion, MD
2200 Bergquist Dr, San Antonio, TX 78236
Tel: 210-292-6583; Fax: 210-292-6569
E-mail: bennion.john@gmail.com
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Dose uniformity of topical corticosteroids: A simulated trial fluorometholone acetate 0.1% and loteprednol etabonate gel 0.5%

Charlton E Stevens[1]

John L Bennion*[2]

Matthew C Caldwell[2]

James R Townley[2]

Douglas A Apsey[2]

Harvey A Schwertner[3]

[1]Intern, San Antonio Military Medical Center, San Antonio, TX 78219

[2]Department of Ophthalmology, Wilford Hall Ambulatory Surgical Center JBSA Lackland, TX 78236

[3]Clinical Research, Wilford Hall Ambulatory Surgical Center JBSA Lackland, TX 78236

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Keywords: Flourometholone acetate, loteprednol etabonate, Flarex®, Lotemax®, dose uniformity, ophthalmic formulation, simulated dosing

Abstract

Purpose: The purpose of the study was to determine the concentrations of Flarex® and Lotemax® when shaken and not shaken. Many patients fail to shake or inappropriately shake suspensions of corticosteroids prior to instillation as directed. This study was designed to help determine what concentration of corticosteroid these patients are receiving. In addition, independent confirmation of loteprednol etabonate ophthalmic gel dose uniformity was determined and compared as a possible alternative.

Methods: Drug concentrations of shaken versus unshaken Flarex® and Lotemax® were determined over a 20 day simulated tapered course in our institutional laboratory. Collected samples were analyzed by reversed phase high performance liquid chromatography (HPLC) with photodiode array detection at 240 nm.

Results: Flarex® had a mean concentration of 93.7% of the declared concentration when shaken and 7.25% when not shaken. The difference between these groups was statistically significant (p=0.0001). Lotemax® had a mean concentration of 96.74% of the declared concentration when shaken and a mean concentration of 98.97% when not shaken. The difference between these groups was not statistically significant (p=0.194).

Conclusions: Flarex® maintains dose uniformity when shaken. When not shaken it has poor dose uniformity. Lotemax® was consistent whether shaken or not in our study and can be considered to eliminate the variability of poor patient compliance with shaking. The manufactures of both drugs recommend shaking prior to application. ~~Formulations of ocular corticosteroids that do not require shaking such as Lotemax® should be considered to eliminate the variability of poor patient compliance with shaking.~~

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Introduction

Topical ophthalmic corticosteroids are essential in the management of inflammation in the eye including following ocular surgery.[1] They are available in different forms including emulsions, ointments, solutions, gels, and suspensions. The choice of corticosteroid depends on the patient's disease condition, adverse side effect profile, strength of corticosteroid required, target tissue, and patient compliance.[2] Suspension formulations are commonly used, though a limitation is the need for adequate shaking immediately prior so as to ensure homogeneity.[3] Otherwise an unknown dose would be delivered. Apt et al showed that as many as two thirds of patients do not shake the ophthalmic corticosteroids suspensions before administering a dose.[4]

Fluorometholone acetate (Flarex®) (Alcon Laboratories Inc; Fort Worth, TX) is a commonly used corticosteroid suspension that requires vigorous shaking prior to application.[5] Loteprednol etabonate ophthalmic gel 0.5% (Lotemax®) (Bausch and Lomb Inc; Tampa, FL) is a newer formulation with comparable efficacy to other corticosteroids and the manufacturer recommends to invert closed bottle and shake once to fill tip before instilling drops. Lotemax has equal dose uniformity whether shaken or not.[6] Both medications are used in the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.[5,7] They are frequently used following refractive surgery in managing inflammation and modulating wound healing.[1,8]

Loteprednol etabonate (LE) ophthalmic gel 0.5% is a formulation of LE approved by the US Food and Drug Administration (FDA) in 2012. This drug is unique compared

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

to many other ocular corticosteroids in its ability to change from a gel to a liquid upon increased shear stress, thus converting to a liquid form when squeezed from the bottle.[9] After application to the corneal surface it remains liquid owing to its polycarbophil polymer that promotes its more viscous structure on the ocular surface.[9] Lotemax® gel has been shown to have dose consistency after dispersion analysis demonstrated no sedimentation of drug particles.[10]

Due to its gel formulation, Lotemax® remains homogenous and should not require shaking to achieve dose uniformity. This property eliminates dependence on patient compliance to shake before dosing. One previous study demonstrated that LE gel (Lotemax®) has superior dose uniformity compared to prednisolone acetate suspension when not shaken.[10]

The goal of this study was to determine the difference in the concentrations that patients might actually be receiving when corticosteroid suspension Flarex® is adequately shaken versus not shaken. We also sought to independently confirm Lotemax® gel dose uniformity.

Materials

Drugs and chemicals

Fluorometholone acetate ophthalmic suspension, 0.1% (Flarex®) was obtained from Alcon Laboratories, Ft. Worth, TX. Loteprednol etabonate ophthalmic gel, 0.5% (Lotemax®) was obtained from Bausch and Lomb, Inc., Tampa, FL. Fluorometholone acetate USP Reference Standard (200.0 mg) was obtained from US Pharmacopeia,

Rockville, MD. Methanol, (HPLC grade), was obtained from Sigma-Aldrich, ST. Louis, MO.

HPLC analysis of fluorometholone acetate and loteprednol etabonate

HPLC analysis of fluorometholone acetate and loteprednol etabonate was performed on a Waters Acquity Ultra Performance Liquid Chromatographic System equipped with an Acquity Binary Solvent and Sample Manager, Acquity Photodiode Array Detector (PDA), Empower 3 software, and a Phenomenex Luna C18 reversed phase column (2.0 x 150 mm, 5.0 µ, Cat.No. 475946-1). The HPLC mobile phase was methanol (100 %), the chromatographic flow rate was 0.25 mL/min., and the quantitation of both drugs was performed at 240 nm.

Methods

This is an institutional experimental laboratory study without human subjects.

Six commercial bottles of Lotemax® gel (0.5% 5mL container) and six commercial bottles of Flarex® (0.1% 5mL container) were purchased and stored at room temperature. The bottles were individually labeled and then shaken per manufacturer instructions 2 days prior to day 1 of the experiment in order to establish a consistent baseline for when the bottles were last shaken or handled.

Three Flarex® bottles were vigorously shaken for 5 seconds immediately before dispensing, and three designated bottles were unshaken. The unshaken samples were collected by tipping the bottle 180 degrees, dispensing the drops, and then returning the bottle to its original upright position. Two drops were dispensed for each sample. Days 1-5: drops were dispensed 4 times daily but only collected for analysis on the first and

last times. Days 6-10: drops were dispensed 3 times daily but only collected for analysis on the first and last times. Days 11-15: drops were dispensed 2 times daily, both of which were collected for analysis. Days 16-20: drops were dispensed 1 time daily and collected for analysis. Figure 1 illustrates pictures taken of the solution at different points in time.

Similarly, three Lotemax® bottles were shaken and three others were unshaken. Collecting method and course for Lotemax® shaken and unshaken bottles were exactly the same as described for Flarex®. Figure 2 illustrates pictures taken of the solution at different points in time.

Three bottles for each subgroup, of shaken vs unshaken, were tracked independently to account for variability. A 20 day tapered course was chosen to determine the dosing concentrations through the span of a full bottle with a volume of 5mL (which contains approximately 100 drops). The two arms of the study required a total of 420 samples (35 samples from 12 separate bottles) to be analyzed.

Results

The drug concentrations were determined and reported as percent of the declared bottle concentration. The declared bottle concentrations were 0.1% and 0.5% for Flarex® and Lotemax® respectively.

Figure 3 shows the drug concentrations of Flarex® comparing shaken to unshaken samples. The difference between Flarex® shaken and unshaken for the declared concentration was found to be statistically significant (p=0.0001) using repeated measures analysis of variance (RM ANOVA). The average concentration for

the Flarex® NOT shaken was 7.25% of the declared concentration (with a standard deviation of 2.44%) whereas shaken was 93.79% of the declared concentration (with a standard deviation of 2.95%). Figure 1 demonstrates visual appearance of the settling of the solution.

Figure 4 shows the drug concentrations of Lotemax® gel comparing shaken to unshaken samples. The difference between Lotemax® gel shaken and unshaken for the declared concentration was not found to be statistically significant ($p=0.194$) using repeated measures analysis of variance (RM ANOVA). The average concentration for the Lotemax® gel not shaken was at 98.97% of the declared concentration (with a standard deviation of 1.39%) whereas shaken was 96.74% of the declared concentration (with a standard deviation of 1.73%). Figure 2 demonstrates visually the lack of the settling of the solution.

The unshaken Lotemax® gel was on average within 1.10% (SD 1.39%) of the declared concentration whereas the unshaken Flarex® was on average within 92.72% (SD of 2.44%) of the declared concentration.

Discussion

Often poor patient compliance leads to improper dosing of topical corticosteroid suspensions such as Flarex® despite clear instructions by manufacturer and prescriber. According to this study, if not shaken, patients would receive only 7.25% of the intended concentration. This much lower dose could have a clinically significant impact. However, when shaken appropriately, a satisfactory concentration is consistently obtained. This reiterates the importance of properly instructing patients to shake the suspension per

manufacturer instructions prior to instillation as well as the need for good patient compliance.

Lotemax® gel 0.5% on the other hand eliminates the reliance on shaking. The ability of the drug to maintain a gel formulation until sheer stress is applied and then remain liquid upon application results in a homogeneous solution that does not require mixing prior to application. This uniform dosing, whether shaken or not, was confirmed in this study. Figure 1 illustrates the settling effect of Flarex® with time. Figure 2 illustrates the preservation of homogeneity of Lotemax® gel with time despite not being shaken.

Results for this study were consistent with a study by Marlow and Davio demonstrating that Lotemax® gel maintains a homogeneous solution. Marlow et al demonstrated that the average percent declared concentration of unshaken Lotemax® gel was 102%.[10] This was compared with unshaken prednisolone acetate 1% (brand name and generic), which demonstrated highly variable drop concentrations and mean concentrations of 18.5% and 22.0% respectively. Our study also showed low mean concentrations when not shaken but did not show the same high variability. The results for their shaken medications were consistent with our study. Their study demonstrated that after being shaken for 5 seconds Lotemax® gel had an average declared concentration of 102%. The prednisolone acetate 1% formulations both had average declared concentrations of 103% when shaken.

Another study done by Stringer and Bryant compared dose uniformity of difluprednate ophthalmic emulsion (Durezol®) with prednisolone acetate (brand name and generic).[11] Similarly, prednisolone acetate 1% brand name and generic showed

high variability when not shaken whereas difluprednate had consistent dose uniformity whether shaken or not.

Clinical correlation of poor dose uniformity has not yet been determined and is an area of possible future investigation. Meanwhile, it is reasonable to assume that having consistent uniform dosing should lead to more predictable outcomes in management. If patients follow manufacturer instructions for either product, no dose non-uniformity is expected. Thus the importance of properly shaking corticosteroid suspensions such as fluorometholone acetate should be stressed, or the need for shaking may be avoided altogether by using other formulations such as loteprednol etabonate gel.

Correspondence: John Bennion, MD

2200 Bergquist Dr, San Antonio, TX 78236

Tel: 210-292-6583; Fax: 210-292-6569

E-mail: bennion.john@gmail.com

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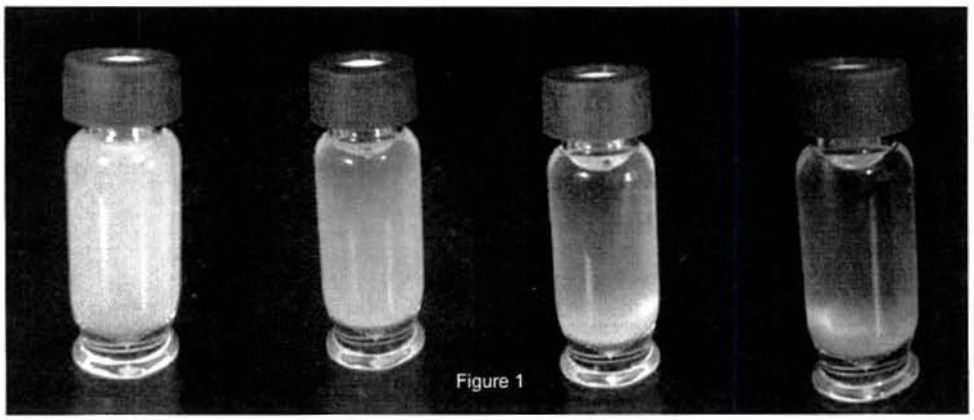
Figures

Figure 1: Settling affect of Flarex® with time. From left to right immediately following shaking, four hours after being shaken, eight hours after being shaken, twelve hours after being shaken. The picture is a collection of individual images.

Figure 2: Non-settling effect of Lotemax® gel with time. From left to right immediately following shaking, four hours after being shaken, eight hours after being shaken, twelve hours after being shaken. The picture is a collection of individual images.

Figure 3: Drug concentrations in drops of Flarex® comparing shaken immediately prior to simulated dosing to NOT shaken

Figure 4: Drug concentrations in drops of Lotemax® gel comparing shaken immediately prior to simulated dosing to NOT shaken



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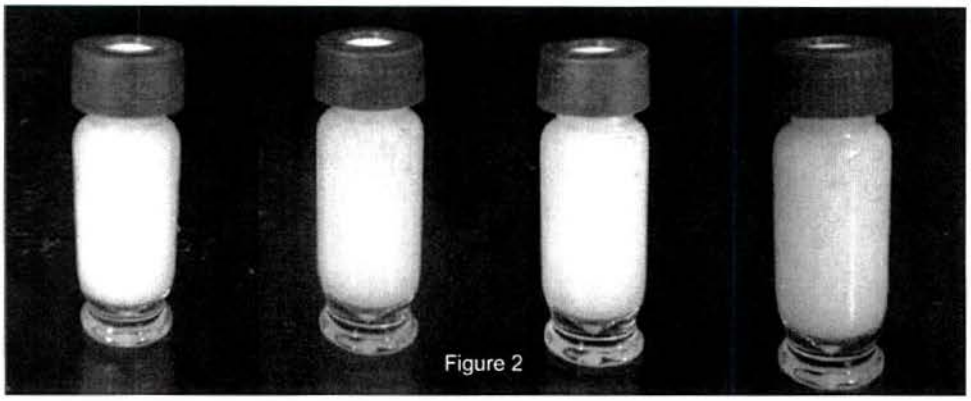

Figure 2

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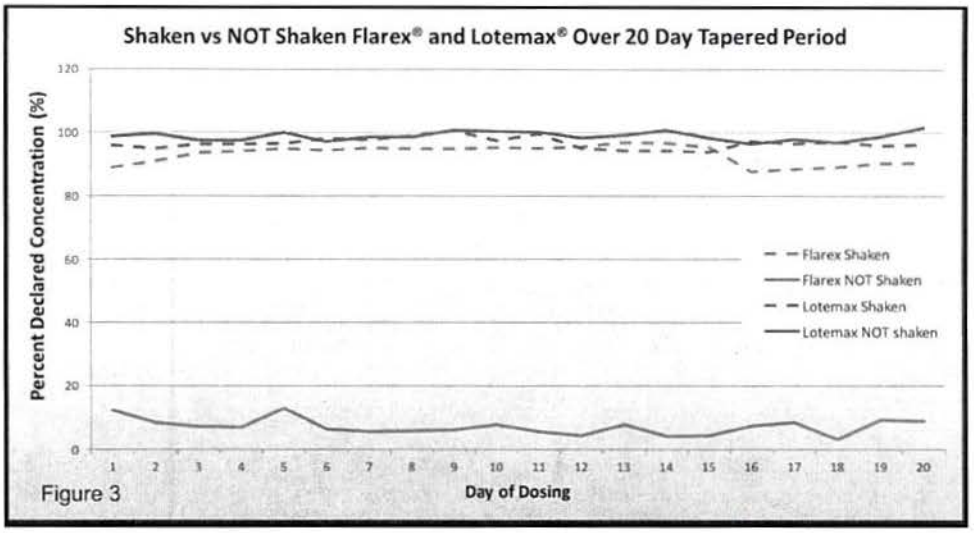

Figure 3

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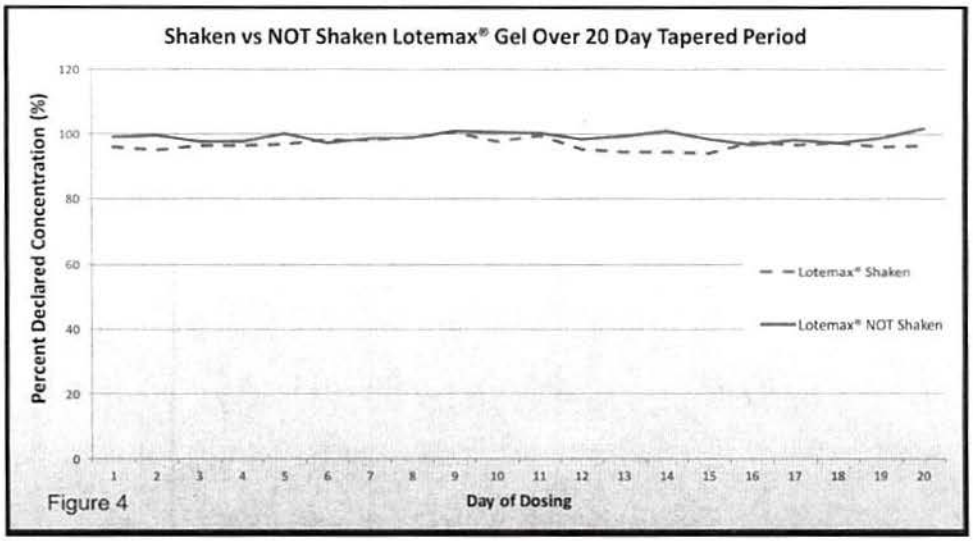

Figure 4

108x60mm (300 x 300 DPI)

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26 Feb 14

FINAL DETERMINATION

Determination Date: 24 Feb 2014

Project Lead: Capt John Bennion/SGVT

Reference Number: FWH20140054N (IRBNet ID: 397493-1)

Project Title: Dose uniformity of topical corticosteroid ophthalmic medications: flourometholone acetate 0.1% suspension, loteprednol etabonate 0.5% suspension, and loteprednol etabonate 0.5% gel

Your project was determined on 24 Feb 2014 to be considered **not human research** as defined by DoD regulations at **32 CFR 219 and FDA regulations at 21 CFR 56**. You are not required to obtain IRB approval for this activity. The proposed project does not include non-routine intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction, nor do the researchers obtain private, identifiable information about living individuals.

If the goals and/or activities of the project change during the course of the project, or if new activities are proposed that would constitute human subjects research, re-contact the Protocol Office so that a regulatory expert may determine whether or not the revised plan involves human subject research activities.

Additional items reviewed and approved by the WHASC/IRB include:

Intramural Funding Support Document
Letter of Support- CRD Lab

DOMINGUEZ.MARIA.E.1231107742

Digitally signed by DOMINGUEZ.MARIA.E.1231107742
DN: c=US, o=U.S. Government, ou=DoD, ou=PKI, ou=USAF, cn=DOMINGUEZ.MARIA.E.1231107742
Date: 2014.02.26 14:31:58 -06'00'

Maria Dominguez, CIV, DAF
Clinical Research Protocol Assistant