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April 22, 2015

Celia Peacock, MPH, RDN
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Building 22, Room 5416
10903 New Hamsphire Avenue
Silver Spring, MD 20993

re: **Briefing Document for Feedback Meeting with FDA's Center for Drug Evaluation and Research Regarding the Safety Evaluation of Benzethonium Chloride and Benzalkonium Chloride when used as Active Ingredients in Consumer Antiseptic Handwashes**
Requestor: Lonza Inc.
Meeting Date: May 25, 2016
Docket Number: FDA-1975-N-0012
RIN: 0910-AF69

Dear Ms. Peacock:

On behalf of Lonza, Inc., I am forwarding ten (10) copies of the above noted briefing document in support of the May 25, 2016 meeting between Lonza representatives and FDA staff. An electronic copy of the above documents is also be forwarded to you.

If you have any questions about this request or need further information, please contact me at (202) 393-3903, ext. 114 or by e-mail at eharrison@lewisharrison.com.

Sincerely,

Eliot Harrison
Consultant to Lonza

Briefing Document

For

Meeting with FDA's Center for Drug Evaluation and Research Regarding the Use of Benzethonium Chloride and Benzalkonium Chloride as Active Ingredients in Consumer Antiseptic Handwashes

FDA Docket No. FDA-1975-N-0012

Submitted by:

Lonza, Inc.

April 22, 2016

Introduction

Lonza has scheduled a meeting with FDA's Center for Drug Evaluation and Research (CDER) on May 25, 2016, for the purpose of: 1) obtaining clarification on specific items concerning the human pharmacokinetic study (also known as the Maximal Usage Trial or "MUsT") that were noted in the "General Advice" letter FDA issued on October 15, 2015, and FDA's Memorandum of Meeting Minutes" (undated) for the Lonza-CDER meeting held on May 6, 2015 and 2) obtaining feedback on how the results from the MUsT study will be used in the risk assessment process.

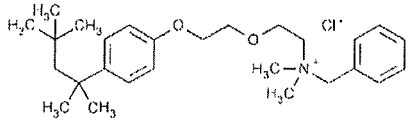
As per FDA instructions for a meeting, Lonza is providing the following information:

1. Product Name:

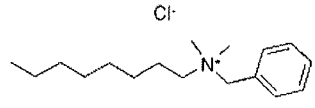
   Consumer antiseptic handwashes

2. Chemical Name and Structure

   Benzethonium chloride and benzalkonium chloride.



Benzethonium Chloride (BZC)



Benzalkonium Chloride (BAC)

3. Proposed Indication:

   Hand washing products to decrease bacteria on skin.

4. Dosage Form, Route of Administration, and Dosing Regimen (frequency and duration):

   Benzethonium chloride and benzalkonium chloride will be used as active ingredients in liquid antiseptic formulations that are applied to the skin multiple times per day for short durations and are rinsed off after use.

5. Meeting Attendees:

   Dr. Neil Snyder (Lonza, Inc). - Head of Global Product Safety and Toxicology.
   Dr. Nicholas Skoulis (Lonza, Inc.) - Senior Consulting Toxicologist.
   Eliot Harrison (Lewis & Harrison, LLC) - Consultant to Lonza, Inc.
   Louise Aust (Henkel Consumer Goods, Inc.) – Manager, Research & Development
   Janice Fuls (Henkel Consumer Goods, Inc.) – Director, Product Development

6. Background Section:

On July 15, 2015, Lonza/Henkel submitted a revised protocol for a human pharmacokinetic study ("A Maximal Use Study to Measure the Systemic Absorption of Benzethonium Chloride after Using the Antimicrobial Soap on Intact and Abraded Skin on Health Volunteers"). The original protocol was submitted on December 13, 2014 and was revised based on FDA feedback at a meeting held on May 6, 2015.

In the General Advice letter, FDA made the following comments about the revised protocol:

- The duration of the protocol is not sufficient. As designed, the protocol includes dosing for only three days. Given that the average healthcare worker works approximately 8 hours per day, five days a week, extend the dosing period to at least five days. This recommendation reflects the upper end of expected use in keeping with the MUsT paradigm.

- While acknowledging that "efforts" will be made to enroll subjects above the age of 65, we recommend that the protocol identify a dedicated cohort (numerically) of subjects within this age group for enrollment purposes.

- For inclusion in the monograph, GRAS/E must be established for single ingredient that can be formulated in many different ways and presentations. Therefore, in order to support GRAS/E status of an ingredient, we recommend testing of at least 4 different formulations in the MUsT. Regarding choosing the representative material for testing, we recommend testing formulations anticipated to enhance absorption. *In vitro* testing using a human cadaver skin permeating system (e.g. static or flow-through cells) may be useful in choosing and providing justification of which formulations to test.

- Provide additional details regarding the selection of the antimicrobial hand soaps to be used in this study. Specify whether each formulation is currently marketed formulation or one specifically formulated for this study, the rationale for selecting the formulations, and the composition of the formulation (quantity and function of the active and inactive ingredients).

In an attachment to the Memorandum of Meeting Minutes, FDA provided an article from the published literature[1] that examined the use of an alcohol hand gel in a day care facility in Finland. According to the article, the number of exposures per day was approximately 50.

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[1]Kinnula, S., Tapianen, T., Renko, M., Uhai, M. *Safey of Alcohol Hand Gel Use Among Child and Personnel at a Child Day Care Center.* American Journal of Infection Control. May, 2009: 318-321.

7. Purpose of the Meeting:

The purpose of the meeting is for Lonza to obtain FDA feedback so that the MUsT study can be promptly initiated.

8. Proposed Agenda:

Refer to Attachment 1.

9. Discussion Topics for Meeting and List of Questions:

A. The revised protocol was designed for a consumer antiseptic hand wash product, not a product intended for use by health-care workers. Does FDA consider users in day-care and nursing facilities to be general consumers or health-care workers? In order to limit use to residential/household users, will FDA accept a monograph condition that the consumer antiseptic hand wash products must include a label statement that the product is not for use by workers in day care, nursing and related facilities? If so, is the 3-day time period acceptable for the general consumer population?

B. Lonza believes that consumer antiseptic hand wash products containing benzethonium chloride or benzalkonium chloride as the active ingredient will be a single form and substantially similar in composition. Attachment 2 presents background information, provided by Henkel, that supports this position. Assuming that consumer antiseptic hand wash products are substantially similar in composition, what is the basis for requiring that four (4) MUsT studies be conducted? Lonza's proposed approach is to evaluate the dermal absorption of currently marketed consumer antiseptic hand washes using the *in vitro* methodology presented in Attachment 3 and then select the formulation with the highest skin penetration for the MUsT study. Is this approach acceptable to FDA? Finally, are there any elements from the MUsT study conducted with the acne treatment medication, Differin® Gel, that can be incorporated into the benzethonium and benzalkonium chloride MUsT studies?

C. The literature article referenced by FDA on the frequency of use of antiseptic hand products is specific for an alcohol hand gel. Lonza does not believe that use information for an antiseptic hand gel product is pertinent to an antiseptic hand wash product. Marketing information collected by Henkel Consumer Goods showed that the maximum number of daily uses by residential consumers of antiseptic hand wash products is twenty (20). According to the testing laboratory performing the MUsT study, there are significant concerns about exceeding 30 hand washes per day since skin irritation will likely develop from excessive (>30) handwashes thereby confounding the study results.

It should also be noted that the MUsT study protocol requires 30 daily handwashes at a time-period of 60 seconds per wash resulting in a total exposure of 1800 seconds or 30 minutes per day. If the handwash frequency was increased to 50 per day, at the same length of exposure per wash, the total exposure would be 3000 seconds or 50 minutes per day. Handwashing for 50 minutes per day seems abnormally high and the testing laboratory is concerned about participant fatigue after enduring a 12-13 hour day. What survey or other types of information would FDA consider adequate to substantiate 30 hand washes per day for the MUsT study?

D. How will the MUsT study data be used in the risk assessment process?

ATTACHMENT 1

AGENDA FOR LONZA-FDA MEETING

Date: May 25, 2016
Time: 3-4 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, MD 20903

Agenda Items

1. Introduction of Meeting Participants (5 minutes)

2. Background/Purpose/Objectives of Meeting (5 minutes)

3. Discussion Topics
   -Time period (3 or 5 days) for MUsT study (5 minutes)
   -Number of formulations/types to test (15 minutes)
   -Number of handwashes/day (10 minutes)
   -Risk Assessment Process (5 minutes)

4. Meeting Wrap-Up (10 minutes)

ATTACHMENT 2 – FORMULATION BACKGROUND

For OTC sunscreen products, FDA has recommended that four formulations be tested in a MuST trial. The basis for requiring four studies is the frequent reformulation of sunscreens and the potential for different absorption profiles. In contrast to sunscreens, antiseptic hand wash products do not differ significantly among ingredients and have not been subject to frequent or major formulation changes.

During the development of antiseptic hand wash formulations, the combination of active and inert ingredients needs to be fully understood. Adding or changing ingredients can potentially have a negative effect on the antibacterial activity of a formulation. In addition, major changes to formulations will require additional stability studies as well as the requirement of repeating both *in-vitro* and *in-vivo* efficacy studies. For this reason, changes to antibacterial formulations are limited and restricted to minor changes, such as dyes and fragrances.

Dial Complete foaming hand soap was launched in 2000 as one of the first foaming antibacterial hand soaps. The formula contained the active ingredient triclosan. The development of this formula took several years and resulted in a technology covered by five patents, US: 6,107,261, US: 6,204,230, US: 6451,748 B1, US:6,977,082 B2 and WO 00/78141 A1.

The formula delivered superior efficacy by maintaining a percent saturation with the surfactant and triclosan ratio. This percent saturation range meant that changes to the formulations could be made only within the constraints of the patents and technology. Table 1 shows that while changes were made to the surfactant and triclosan ratios, additional ingredients were not added over the years, other than a dye or fragrance change. The Health care formula which launched in 2001 contained additional skin feel ingredients which are desirable in the healthcare setting. The health care formula did not make any changes other than additional dye or fragrance variants.

Formula History: 2000 - 2015

Table 1

Retail Formula	Timing	Base (Surfactant/%TCS)	Formula History & Change	Efficacy
First Launch	2000 - 2005	0.975% Triclosan/ Ammonium Lauryl Sulfate	• Lowered fragrance from 0.3% to 0.2% • Increased red dye from 0.00005% to 0.000037% • Increased yellow dye 5 from 0.000025% to 0.000037%	HCPHW Time Kill
Mid Lather Formula	2005 - 2008	0.60% Triclosan/ Ammonium Lauryl Sulfate	• Lowered TCS from 0.975% to 0.60% • Lowered ALS by 1% (retain % Saturation)	HCPHW Time Kill
Switch to Health Care Formula	2008 – 2015	0.46% Triclosan/ Ammonium Lauryl Sulfate	• Adopted Health Care Base from 2001	HCPHW Time Kill
Health Care Personnel Handwash Formula	2001 - Current	0.46% Triclosan/ Ammonium Lauryl Sulfate		HCPHW Time Kill

Line Extensions – Fragrance and Dye changes only

The formulation history substantiates that the formulation changes are minor. Moreover, in the case of the healthcare formula, this formula was launched and has remained the same formula for the last 15 years.

Quaternary Antibacterial Formulation:

Henkel, along with other marketers of consumer antiseptic hand washes, are no longer supporting the use of triclosan in antiseptic hand washes. Formula development with alternative actives, such as the quaternary ammonium compounds ("Quats"), began as far back as 2004. In 2014, Henkel launched antiseptic hand wash products containing the active ingredient benzethonium chloride.

The chemistry of the Quats, a cationic active ingredient, requires the development of a new base system that utilizes similar cationic, non-ionic or amphoteric type surfactants and ingredients that do not neutralize the active ingredient. Similar to Henkel's previous formulations, once a system is found to provide the efficacy, safety and the desired aesthetic profile, changes to the formulation will follow the same principle that only minor ingredients (e.g. dyes and fragrances) will change. Henkel is currently marketing two formulations that contain Benzethonium Chloride, foaming and traditional viscous hand wash formulas. Below is a chart listing the ingredients. In addition, a table is provided showing marketed competitor products' ingredient lists. As you will see, because of the specific chemistry of these active ingredients, the selection of inert ingredients is similar. A large variation of main surfactant ingredients does not exist from one formula to the other.

Marketed Formulations

Dial Foaming	Dial Liquid (Viscous)
Benzethonium Chloride – Active (0.2%)	Benzethonium Chloride – Active (0.17%)
Purified USP Water - Solvent	Purified USP Water - Solvent
Lauramine Oxide – Surfactant	Cetrimonium Chloride – emollient
Glycerin – emollient	Glycerin - emollient
Cocamidopropyl Betaine – Surfactant	Citric Acid – pH adjuster
Sunflowereamidopropyl Ethonium Sulfate - emollient	Cocamide MEA - surfactant
Chlorhexidine Digluconate – preservative	Sodium Benzoate - preservative
DMDM Hydantoin – preservative	Parfum (Fragrance)
Methyl Cellulose 40-202 – thickener	Myristamidopropylamine Oxide - surfactant
Fragrance	Sodium Chloride
Citric Acid – pH adjuster	Dimethyl Lauramine - surfactant
Tetrasodium EDTA – chelater	Tetrasodium EDTA - chelater
Zinc Sulfate – anti-irritant	Dimethyl Myristamine - surfactant
D&C Yellow No. 10 – colorant	CI 17200 (Red 33) – colorant
FD&C Green No. 3 – colorant	CI 16035 (Red 40) – colorant
	CI 15985 (Yellow 6) - colorant

Marketed Formulations

(Competitor Product X) (Viscous)	(Competitor Product Y) (Viscous)
Benzalkonium Chloride – Active (0.13%)	Benzalkonium Chloride – Active (0.13%)
Purified USP Water - Solvent	Purified USP Water - Solvent
Cetrimonium Chloride – emollient	Cetrimonium Chloride – emollient
Glycerin – emollient	Glycerin - emollient
PEG -150 Disterate	Lauramidopropylamine oxide - surfactant
Lauramine Oxide – surfactant	Cocamide MEA - surfactant
Cocamide MEA - surfactant	Sodium Chloride
Propylene Glycol - emollient	Peg-120 methy glucose dioleate
Citric Acid – pH adjuster	Fragrance
Fragrance	Citric Acid – pH adjuster
Tretaadodium EDTA – chelater	Tetrasodium EDTA - chelater
Sodium Chloride	Methylchloroisothiazolinone – preservative
Hydrolyzed Collagen - thickener	Methylisothiazolinone – preservative
PPG-12-Buteth	FD&C red No. 40
Magnesium Nitrate	FD&C yellow No. 5
Nitrate Butylene Glycol	FD&C red No. 33
Phenoxyethanol – preservative	
Methylchloroisothiazolinone- preservative	
Magnesium Chloride	
Ethylhexylglycerin	
Methylisothiazolinone - preservative	
FD&C Yellow No. 5	
FD&C Yellow No. 6	

Ingredient Type

Surfactants	Emollients	Preservative	Other
Cocamidopropyl Betaine	Glycerin	Sodium Benzoate	Citric Acid
Myristamidopropylamine Oxide	Cetrimonium Chloride	DMDM Hydantoin	EDTA
PEG -150 Disterate	Propylene Glycol	Phenoxyethanol	Sodium Chloride
Lauramine Oxide		Methylchloroisothiazolinone	Mag. Chloride
Cocamide MEA		Methylisothiazolinone	Red 40
Lauramidopropylamine oxide		Chlorhexidine Digluconate	Yellow 5
Peg-120 methy glucose dioleate			Yellow 6
Dimethyl Lauramine			Red 33
Dimethyl Myristamine			Yellow 10

ATTACHMENT 3

IN VITRO PERMEATION TEST (IVPT) STUDY

Evaluation of the Percutaneous Absorption of Benzalkonium Chloride and Benzethonium chloride from Antimicrobial Topical Formulations, *In Vitro*, using the Franz Human Skin Finite Dose Model

14 April 2016
Prepared by Paul A. Lehman
Vice President, Dermal and Transdermal Research Services
QPS, LLC

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INTRODUCTION

Benzalkonium chloride and Benzethonium chloride are common quaternary ammonium compounds used in topical hand washing antimicrobial formulations. The goal of this study is to compare and contrast the rate and extent of Benzalkonium chloride and Benzethonium chloride absorption *in vitro* through *ex vivo* human skin, when used in commercial consumer antiseptic hand washes.

The *in vitro*, Franz, human skin, finite dose model has proven to be a valuable tool for the study of percutaneous absorption and the determination of the pharmacokinetics of topically applied drugs, noxious chemicals and formulation excipients. The model uses *ex vivo*, human skin mounted in specially designed diffusion cells allowing the skin to be maintained at a temperature and humidity that match typical *in vivo* conditions.[1] A finite dose (for example, 2 mg/cm^2 – 10 mg/cm^2) of formulation is applied to the outer surface of the skin and drug absorption is measured by monitoring its rate of appearance in the receptor solution bathing the inner surface of the skin. Data defining total absorption and rate of absorption, can be accurately determined in this model. The method has historic precedent for accurately predicting *in vivo* percutaneous absorption kinetics.[2,3]

CORE STUDY DESIGN

Ex vivo, dermatomed, human skin, without obvious signs of skin disease or damage, will be used in this study. The skin will have been provided to the testing facility as having been dermatomed, and sealed in a water-impermeable bag with continuous storage at ~ -70°C. Prior to use it will be thawed in ~37°C water and then rinsed in distilled, de-ionized water (ddH_2O) to remove any adherent blood or other material from the surface.

The skin from each donor will be cut into multiple smaller sections large enough to fit on nominal 1 or 2 cm^2 static Franz diffusion cells. For the Pivotal study, the actual thickness of each skin section will be measured in triplicate using a Digital Pocket Thickness Gauge. Each skin will then be mounted onto a diffusion cell.

The dermal receptor compartment will be filled to capacity with an appropriately selected receptor solution (such as phosphate buffered saline). The epidermal chamber (also known as the chimney or donor compartment) will be left un-occluded with exposure to the ambient laboratory environment. The cells will then be placed within a rack system and attached to a water circulation system from which the receptor solution will be stirred magnetically at approximately 600 RPM and its temperature will be maintained to achieve a skin surface temperature of 32.0°C ± 1.0°C. One additional skin section per donor will be prepared and will undergo all study activities, but will not be dosed, to serve as a negative sample control. Prior to use, each skin will be assessed for barrier integrity by measuring its trans-epidermal water loss (TEWL).

Follow dose application, at each scheduled sampling time point (as determined from the pilot study and the final dosing regimen), the receptor solution will be removed in its entirety, refilled with stock receptor solution, and an aliquot of the collected sample saved for subsequent analysis.

Benzalkonium chloride and Benzethonium chloride concentrations in the receptor solution will be quantified using an HPLC/MS/MS analytical method developed, optimized and validated by the Dermal and Transdermal Research Laboratory.

SPECIFIC STUDY DESIGN CONSIDERATIONS

Skin

The primary choice of skin would be the back of the hand and/or palmar skin to reflect the actual site of use in the consumer environment. However, if there are a significant number of formulations, to be initially screened, and considering the relatively limited surface area of hand skin, it is recommended that initial screening be performed on trunk skin with a follow-up study with selected formulations on hand skin.

To obtain a reasonable representative absorption profile, it is recommended that skin from at least 4 different donors be used with each formulation being tested on 4 replicate sections from each donor.

Pilot Study

An initial pilot study consisting of 1 or 2 selected formulations dosed to 6 – 12 skin sections from one donor will be performed. The purpose of the pilot study is to 1) obtain actual samples to assess needed limits of detection for the analytical method to be used, 2) monitor for potential interfering compounds which may necessitate a refinement to the analytical method, 3) to determine a sampling schedule to ensure appropriate characterization of the absorption profile, and 4) to evaluate different receptor solutions to ensure appropriate diffusion sink conditions are met.

Dose

Dosing and duration of exposure are still under consideration. The available options (or combinations thereof) are:

1. Single dose application without wash-off.
2. Single dose application with wash-off.
3. Multiple sequential dose applications, with wash-off after each, at defined durations (e.g. 10 min intervals, 20 min intervals, etc.).

Statistical Considerations

Replicates within donors will be averaged and the standard deviation calculated for each key parameter. Within donor averages will then be collated and the across donor population mean with standard error will be calculated. Differences between formulations may be evaluated using the Student's t-test or other suitable ANOVA methods for each measured sample. Outliers will be evaluated using the Dean and Dixon Outlier Test.

Deliverables

Deliverables will consist of preliminary, un-audited summary data (tabular) of the information obtained early in experimentation, which consists of flux data and amount-penetrated data. These data will be transmitted to the Sponsor upon request. If preliminary un-audited data is provided to the Sponsor, the Sponsor understands that these data are subject to change and may be incorrect or inaccurate.

Deliverables will also consist of a detailed, final report containing all the data in tabular and graphic form, as well as copies of the intermediary calculated data that were used to generate the final results. A draft of the final report will be sent electronically to the Sponsor and the final report should be sent on completion of the study.

REGULATORY CONSIDERATIONS

This study will be conducted in accordance with FDA Good Laboratory Practices (Title 21-Food and Drugs, Chapter I-Food and Drug Administration, Subchapter A- General, Part 58).

Study conduct will be compatible with the recommendations of the OECD Test Guideline 428: Skin Absorption: *in vitro* Method (2004b).

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1 Franz, TJ. 1975. Percutaneous absorption: on the relevance of in vitro data. J Invest Derm 64:190-195.

2 Franz TJ. 2008. The cadaver skin absorption mode and the drug development process. Pharmacopeial Forum 34(5): 1349-1356.

3 Franz TJ, Lehman PA, Raney S. 2009. Use of excised human skin to assess the bioequivalence of topical products. Skin Pharmacol Physiol 22:276-286.