DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEETING MINUTES

FDA Docket No. FDA-1975-N-0012

Lonza America, Inc.
Attention: Michael R. Neilson
Assistant General Counsel
90 Boroline Road
Allendale, NJ 07401

Dear Mr. Neilson:

Please refer to your January 14, 2015 correspondence, requesting a meeting to discuss the protocols you have submitted to FDA Docket No. FDA-1975-N-0012 regarding maximal use test studies and screening studies for potential endocrine effects of benzethonium chloride and benzalkonium chloride.

We also refer to the meeting held between Lonza America, Inc. and the FDA on May 6, 2015.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Celia Peacock, Senior Regulatory Project Manager at (301) 796-4154.

Sincerely,

Theresa M Michele, MD

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Date:	May 6, 2015
Time:	11:00 a.m. - 12:00 p.m.
Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Product:	benzethonium chloride and benzalkonium chloride
Indication:	Hand washing products to decrease bacteria on skin
Meeting Chair:	Theresa Michele, MD
Meeting Recorder:	Celia Peacock, RDN, MPH

FDA ATTENDEES

Office of Drug Evaluation IV
Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Division of Nonprescription Drug Products
Theresa Michele, MD, Director
Celia Peacock, MPH, RDN, Senior Regulatory Project Manager
Frank Becker, MD, Medical Team Leader
Wafa Harrouk, PhD, Pharmacology/Toxicology Reviewer
Colleen Rogers, PhD, Interdisciplinary Scientist Team Leader
Pranvera Ikonomi, PhD, Interdisciplinary Scientist
Anita Kumar, PhD, Interdisciplinary Scientist
Michelle Jackson, PhD, Interdisciplinary Scientist
Michelle Walker, PhD, Interdisciplinary Scientist

Office of Regulatory Policy
Deb Livornese, JD, Senior Regulatory Counsel

Office of Clinical Pharmacology-3
Captain E. Dennis Bashaw, PharmD, Director
Doanh Tran, PhD, Team Leader

CDER Office of Communications
Andrea Fischer, Public Affairs Specialist

PUBLIC ATTENDEES

Eliot Harrison, Lewis & Harrison, LLC
Dr. Neil Snyder, Head of Global Product Safety and Toxicology, Lonza, Inc.
Dr. Nicholas Skoulis, Global Head of Toxicology, Lonza, Inc.
Louise Aust, Manager, Product Safety, Henkel North America
Janice Fuls, Manager, Microbiology, Henkel North America

1.0 BACKGROUND

Lonza America, Inc. (Lonza) requested a meeting with the FDA to obtain feedback on Lonza's overall approach for providing a safety database for benzethonium chloride (BZC) and benzalkonium chloride (BAC) as active ingredients in consumer antiseptic hand washes. Lonza received preliminary responses on May 5, 2015.

The sponsor's questions are in **bold** font; FDA's preliminary responses are in *italics*; meeting discussion is in normal font.

2.0 DISCUSSION

Introductory Comments
We note that the Environmental Protection Agency (EPA) regulates alkyl dimethyl benzyl ammonium chloride (ADBAC) ingredients that are also under consideration in the FDA antiseptic monograph rulemaking. Benzalkonium Chloride is a mixture of alkylbenzyldimethyl-ammonium chlorides with various alkyl chain lengths but all variations of ADBAC have the same chemical identifier (CAS # 68424-85-1). ADBAC and BAC are used interchangeably by the sponsor and in this document. We also note that both agencies evaluate acute and long-term toxicity including the potential to cause carcinogenicity and effects on hormonal activity. However, the two agencies approach evaluation in light of the different intended uses of the ingredients under their respective regulatory oversight. The intended use of an EPA-regulated product that contains ADBAC ingredients does not include intentional direct human exposure as is the case for the FDA-regulated antiseptics which are intended to be used directly on human skin. Consequently, EPA is generally looking at the risk associated with accidental human exposure to the ingredient rather than intentional, repeated exposure as is the case with consumer washes. While EPA assessments may provide useful information for the toxicity assessment of ADBAC, they are not generally dispositive for risk assessment for its use as a consumer antiseptic wash.

Question 1
Is the QSAR assessment adequate for bridging or clustering the BZC and BAC safety data bases?

FDA Preliminary Response to Question 1
QSAR assessment strategies have been used for drug products regulated by CDER as a screening tool for identification of relevant structural characteristics, to identify structural alerts or to determine a potential mechanism/mode of action of a target chemical. However, the use of QSAR assessment to bridge or cluster safety databases for two unique chemical entities is not currently an acceptable strategy used by CDER to establish the safety profile of a drug product. Small differences in chemical structure can impact the pharmacology and the function of the ingredient being bridged to a seemingly similar chemical entity. We consider benzethonium chloride and benzalkonium chloride to be two separate chemical entities, and as such complete safety analyses will need to be submitted for each ingredient separately.

Meeting Discussion Question 1
Lonza inquired if there is any way to demonstrate to the Agency that the bioavailability of the BZC and BAC molecules are nearly identical, thus allowing a bridge to demonstrate safety? The Agency reiterated that BZC and BAC are two separate chemical entities. Complete safety analyses will need to be submitted for each ingredient separately.

Question 2
If not, can FDA recommend additional QSAR assessments Lonza should undertake or additional studies that should be provided to bridge the data bases?

FDA Preliminary Response to Question 2
FDA does not recommend additional QSAR assessment in order to bridge the two ingredients. Complete safety data will be required for each of the active ingredients separately.

Question 3
Are additional animal pharmacokinetic/toxicokinetic studies needed on different formulations of BZC and/or BAC based antiseptic handwashes or will the human pharmacokinetic study suffice?

FDA Preliminary Response to Question 3
Maximal use human absorption studies and nonclinical ADME (absorption, distribution, metabolism, and excretion) data are needed that will allow comparison of exposures achieved in toxicity studies to those achieved in humans after maximal use. Exposure data from studies in which animals are treated under the same conditions as the toxicity, DART (developmental and reproductive toxicology) and carcinogenicity studies are used to calculate the margin between the levels at which toxic effects occur in animals and the exposures achieved in humans.

We acknowledge the oral and intravenous ADME data submitted for BAC. However, we have not received ADME data for dermal exposure for either BZC or BAC. Based on the information

provided in the background materials, the Agency is willing to review your proposal to address the ADME data gaps for both ingredients.

Question 4
Are any additional studies necessary for FDA's safety assessment of BZC and BAC?

FDA Preliminary Response to Question 4
A number of studies are still necessary for the assessment of BZC and BAC as it is not possible to bridge data across ingredients. To support the safe use of BZC and BAC as antiseptic products, refer to the table below for the data gaps that still exist:

Study type	Benzalkonium chloride	Benzethonium chloride
Animal ADME	Inadequate (Rat oral and intravenous, but no dermal data)	Inadequate (No data submitted)
Oral carcinogenicity	Adequate (Rat & mouse (submitted 10/2014))	Inadequate (No data submitted)
Dermal carcinogenicity	Inadequate (No data submitted)	Adequate (2013 TFM)
DART	Adequate (Rabbit & Rat 2-generation (submitted 10/2014))	Inadequate (only adequate study is an embryofetal study in rats; No fertility or pre/postnatal toxicity data submitted)
Hormonal effects	Inadequate (No data submitted)	Protocols submitted (this meeting)
Maximal Usage Trial (MUsT)	Inadequate (No data submitted)	Protocols submitted (this meeting)

Meeting Discussion Question 4
Lonza inquired if the Agency had a chance to review the BZC 1995 study done at Argus Labs that was submitted to the docket. FDA agreed to address this in the meeting minutes. See the Post- meeting Addendum at the end of this document.

Lonza asked why an oral carcinogenicity study needs to be performed for a dermal product. The Agency responded that the need for an oral carcinogenicity study will depend on the results of the Maximal Usage Trial (MUsT) study, as the totality of the data will be evaluated to make this decision. If the MUsT study shows a detectable level of exposure in humans, an oral carcinogenicity study will need to be conducted. In response to the question regarding the choice of species to be used in the two carcinogenicity studies, the Agency noted that the oral and the

dermal carcinogenicity studies should not be done in the same species. See the Post-meeting Addendum for further clarification.

Question 5

On December 15, 2015, Lonza submitted protocols for a human pharmacokinetic study ("A Maximal Use Study to Measure the Systemic Absorption of Benzethonium Chloride after Using Antimicrobial Soap on Intact and Abraded Skin in Healthy Volunteers") and two assays ("Uterotrophic Bioassay of Benzethonium Chloride USP by Oral Gavage in Female Rats" and "Hershberger Bioassay of Benzethonium Chloride USP by Oral Gavage in Male Rats" for evaluating potential hormonal effects. The protocols are in Attachment 3.

Are the number of subjects proposed for the study appropriate and are the numbers considered sufficient to support statistical significance?

FDA Preliminary Response to Question 5

The number of subjects enrolled in the protocol for cohort 2 (22 subjects) is inadequate for the assessment of dermal absorption of BZC across the targeted population (adults aged 18 years and above) as outlined in your trial. In addition, the subject population selection criteria should be re-worked to assure that there is an adequate diversity of age in the trial. Aged skin, due to both hormonal changes and the cumulative effect of sun damage, has a different potential for skin absorption than younger skin does. For this reason a dedicated cohort of subjects aged 65 and above should be included in the trial. Therefore, the number of subjects enrolled in the trial needs to be increased if the trial is to be viewed as a definitive assessment. We recommend that the protocol be re-drafted to include two cohorts in adults from 18-64 and 65+, with each cohort to enroll a minimum of 25 subjects with a distribution of ages and gender in each cohort.
In addition, you have not addressed the absorption of either BAC or BZC in the pediatric population. As this product is intended for consumer use, the use of the product in these populations may need to be assessed.

See "Additional Comments" below for further study guidance.

Meeting Discussion Question 5

Lonza inquired if a literature search would be adequate to model the pediatric cohort. The Agency noted that there are many different ways to address this issue and encouraged Lonza to develop a plan for Agency review and comment. The Agency emphasized that the need for pediatric studies is a data driven, scientifically-based process and as such will depend first on the determination and establishment of a safety margin in adults. The results obtained in the adult population will determine the next steps in the pediatric plan. The Agency is open to having a dialogue with interested parties on this issue.

Question 6
Are 20 washes per day considered "worst case"?

FDA Preliminary Response to Question 6
The dosing paradigm to be used by subjects enrolled in the study may not be the most extreme. Provide information as to why you selected a dosing paradigm of 20 times a day. We are aware of some information regarding consumer use in a daycare setting where a total of 50 exposures a day was utilized. As the goal of the protocol is to emphasize maximal exposure potential, we believe this latter value to represent the upper limit. Also, left unanswered by the protocol is the issue of whole body exposure. The protocol, as designed, is focusing on the hands and would not allow for extrapolation to bodywashes containing either BAC or BZC. This issue needs further consideration as the use of bodywashes, by design, involves exposure onto the entire body and could (in the case of bathing) result in a duration of exposure of 30-40 minutes or more.
As to the act of bathing itself, the protocol is contradictory with regards to allowing bathing and to what degree. Section 3.4.5 seems to allow for bathing, yet the last sentence in the section disallows it. Revise the protocol to allow for daily bathing/showering with a provided product at a time designed not to interfere with the planned dosing, such as (for example) allowing bathing/showering in the morning prior to breakfast with dosing to occur post-breakfast.

Meeting Discussion Question 6
Lonza noted that they are willing to increase the dosing paradigm to 30 washes per day in subjects with healthy skin based on the Agency Preliminary Response to Question 6. Lonza asked for the reference to the day care study mentioned above in the Preliminary Response to Question 6. FDA agreed to provide this in the meeting minutes. See the Post Meeting Addendum.

Lonza asked why the Agency settled on 25 subjects per cohort for PK studies. The Agency replied that this number is based on previous experience from NDA products. Since these are consumer products, they could potentially be used by hundreds of millions of people and a diversity of population will need to be tested to be sure that these ingredients are safe, and that there is confidence in the results. The Agency considers the MUsT study to be the centerpiece of the entire development program; dermal absorption data will be the key to determining the additional types of studies that will need to be conducted.

The Agency advised Lonza to develop clinical protocols, and to submit draft protocols to the docket for review. If there are specific questions that need to be answered, these should be marked in draft protocols. Draft protocols should be sent to the appropriate docket and a courtesy copy electronically to the project manager. If Lonza has firm timelines (e.g., because of testing facility arrangements), the Agency should be alerted to ensure adequate time for FDA review.

Lonza asked what doses they should test in their MUsT study if no specific concentration was mentioned in the monograph. The Agency replied that dose selection would be Lonza's choice but that a specific maximum dose should be included in the testing protocol. The chosen dose(s) will be used to inform rulemaking.

Lonza asked whether they should conduct MuST studies on competitor's formulations in addition to theirs. The Agency replied that testing competitor's formulations would be encouraged, especially if those formulations contain different inactive ingredients.

Lonza asked if they should conduct a separate study involving whole body exposure. The Agency noted that to support a body wash indication, a study involving whole body exposure would be needed. However, the focus of this discussion is on consumer antiseptic hand wash use.

Lonza inquired if there is a level that the Agency is comfortable with regarding the Limit of Detection (LOD). The Agency noted that its primary concern was that the analytical methods used reflect current technology and capabilities. Thus the LOD varies with the assay and its operating limits. Whichever assay methodology is chosen it should be fully validated and the validation information should be submitted with the study report. As noted in the 2014 Advisory Committee meeting, should the results of the MUsT study demonstrate no detectable plasma levels, then the LOD itself (representing the "worst case" scenario) would be used in establishing the margin of safety relative to the nonclinical exposure data. The Agency asked if Lonza has a validated assay. Lonza replied that they will be using an assay that detects levels in plasma and urine for the MuST study. The Agency recommended to Lonza to submit protocols for the proposed analytical techniques to the Agency for review. See Post-meeting Addendum.

Lonza asked whether the Agency uses LOD in nonclinical studies for risk assessment purposes. The Agency responded that nonclinical studies are usually designed to include a negative control arm as well as a range of treatment doses (low, medium and high) which would result in a range of exposure levels resulting in a range of adverse toxicity signals. The nonclinical exposure profile is then compared to human exposure data (e.g., those obtained from MUsT studies) to derive safety margins above which toxicity signals which are seen in animal studies may be predicted to be seen in humans.

Question 7

The study is designed so that 10 subjects are split out from the main study group to evaluate the pharmacokinetics of individuals with compromised skin. Does FDA agree with this approach and is the 10 subjects subgroup sufficient for a meaningful evaluation?

FDA Preliminary Response to Question 7

The use of skin stripping as a model for irritated skin, although interesting, has not been demonstrated to be a suitable model for irritated skin. While tape stripping has been used for assessment of dermal penetration (i.e., dermatopharmacokinetics), in that case it was used to measure the depth of drug penetration by analyzing drug content in the different tape strips. Its use as a regulatory assessment of penetration has never been definitively accepted (it was referred to in a draft dermal bioavailability guidance document that was subsequently withdrawn by the Agency). An alternative model, and one that while not validated either would address the surface area concerns, would be to enroll subjects with a diagnosis of hand dermatitis. While these subjects would not be evaluable for irritation/sensitization, they would

represent a segment of the population that would be at a greater risk for absorption and one for whom the barrier function would exhibit minimal change over the trial duration. Whichever course is adopted, it is noted that in the introduction of the protocol (pages 13 and 14) you note the collection of Trans Epidermal Water Loss (TEWL) measurements in previous "exaggerated use" studies. Should you desire to continue to evaluate absorption in an irritated "disrupted" skin model, you should incorporate TEWL measurements as well in this study both to demonstrate the degree of skin permeability overall, but also as a demonstration of the degree of compromised skin in subjects enrolled with either abraded or hand dermatitis. Because of the exploratory nature of the portion of the study, we recommend you submit the protocol for FDA review and comment to seek concurrence on the design and selection of such a methodology prior to initiation.

Meeting Discussion Question 7

Lonza stated that they would prefer to control the abrasion on the skin for this study using the tape strip method. The Agency reiterated that tape stripping is usually done to test the depth of penetration in a small area. It is difficult to know what we would do with this data, and how it relates to someone with hand dermatitis. A tape stripping study does not show the full range of possibilities of what would happen in people with hand dermatitis with full hand involvement. In addition, the presentation, distribution, and degree of damaged skin varies across disease states such as eczema, sunburn, psoriasis, atopic dermatitis, etc. The extrapolation from a relatively small area of tape stripped skin to the effect of these diseases on absorption is unknown but is unlikely to be relevant.

The Agency agreed that perhaps a pilot study on abraded skin to test preliminary results is a good place to begin should they wish to proceed.

The Agency inquired how industry will determine which formulation will be used for the planned protocols. Lonza responded that they will most likely use a 0.3% aqueous based foam formulation. The Agency found this to be reasonable approach, but recommended also testing other concentrations in an in vitro model to help determine formulation(s) resulting in the highest exposure.

Question 8

Blood samples will be drawn prior to first hand wash and another blood sample will be drawn after the day washes of 10 washes and then again after the 20th wash at the end of the day in the evening. Urine samples will be also taken at the end of the 10th and 20th washes with the continuous urine samples being collected after the final hand wash and through the evening for 12 hours – with the cycle beginning again for days 2-4. Does FDA agree with this regimen for blood and urine sampling?

FDA Preliminary Response to Question 8

The primary objective of this trial is to determine the degree of dermal penetration of BZC; however, the proposed pharmacokinetic sampling scheme is insufficient for this purpose. While limited sampling on treatment days 1-3 may be "acceptable" to demonstrate the attainment of steady-state levels, it will not suffice for determining in vivo absorption potential. To have the

possibility of capturing any meaningful pharmacokinetic data, the proposed plasma sampling for day 4 will need to be revised to include more sampling following the final exposure as the current protocol only calls for two daily samples (single samples taken following the 10th and 20th application) to be taken on each treatment day. We recommend a "front-loaded" sampling scheme with samples being taken just prior to the 20th dose and at 0.5, 1, 1.5, 2, 4, 8, and 12 hours post dosing. You may propose an alternative sampling scheme, provided that it is fit for the purpose of determining an Area Under the Curve for the product.

Question 9

Does FDA have any comments on the protocols for the hormonal effects studies? Should Lonza delay initiating the hormonal effects studies until FDA has completed its review of the developmental, reproductive and chronic toxicity studies performed with BAC since these studies, in conjunction with the BZC studies, may preclude the need for specific hormonal effects studies.

FDA Preliminary Response to Question 9

We have reviewed the submitted hormonal effects protocols and find them acceptable. Hormonal assessment studies are typically conducted prior to conducting the full reproductive toxicity battery to help in determining which endpoints should be enriched in the definitive longer term in vivo reproductive studies. In this particular case, it is possible that data collected from carcinogenicity and DART studies, if the appropriate endpoints are included in such studies, may suffice to address whether BZC and BAC cause adverse effects related to hormonal activity without conducting additional hormonal activity assays.

Question 10

On October 14, 2014, Lonza submitted several safety studies conducted with benzalkonium chloride. The studies included oral oncogenicity, developmental and reproductive toxicity, chronic feeding studies and a metabolism (adsorption, distribution, metabolism and excretion) study.

The individual studies are listed below.

1. **Developmental Toxicity Evaluation of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered by Gavage to New Zealand White Rabbits (179 pg).**
2. **Ninety-Day Dietary Toxicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats (300 pg).**
3. **Developmental Toxicity Evaluation of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered by Gavage to CD Rats (281 pg).**
4. **Ninety-day Subchronic Dermal Toxicity study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats (264 pg.)**
5. **Evaluation of ADBAC in One-Year Chronic Dietary Toxicity Study in Dogs (355 pg).**
6. **Adsorption, Distribution, Metabolism and Excretion Studies of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in the Rat (247 pg).**

7. **Two-Generation Reproduction Study in Sprague-Dawley (CD) Rats with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered in the Diet (492 pg).**
8. **Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats (3 volumes 1671 pg.)**
9. **Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Mice (2 volumes, 1083 pg).**

Have the studies been reviewed by FDA?

FDA Preliminary Response to Question 10
We have reviewed the studies listed above. We have specific comments for some of the studies (see answer to Question 11 below). In general the studies were suboptimal because they were conducted in the 1980s prior to the current ICH guidelines, and they do not conform to FDA's current standards for drug regulation. We also note that the studies were designed to meet the EPA's regulations which follow the Organization for Economic Cooperation and Development (OECD) study guidelines.

Question 11
If so, does FDA have any comments, questions or issues with the studies?

FDA Preliminary Response to Question 11
We have no further comments for the following studies and find them to be acceptable:

- *Developmental Toxicity Evaluation of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered by Gavage to New Zealand White Rabbits*
- *Ninety-Day Dietary Toxicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats*
- *Developmental Toxicity Evaluation of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered by Gavage to CD Rats*
- *Evaluation of ADBAC in One-Year Chronic Dietary Toxicity Study in Dogs*
- *Absorption, Distribution, Metabolism and Excretion Studies of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in the Rat*
- *Two-Generation Reproduction Study in Sprague-Dawley (CD) Rats with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered in the Diet*

We have the following comments for the 90-day dermal toxicity study and the carcinogenicity studies:

Ninety-day Subchronic Dermal Toxicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rat)

- *We note that ADBAC was applied only for 5 days, which is the standard procedure for OECD protocols but is not acceptable for ICH-compliant studies. The lack of toxicokinetic analysis prevented the reviewer from characterizing the systemic exposure*

of ADBAC and correlating the no-observed-adverse-effect level (NOAEL) to systemic exposure.

- *We are not requesting additional subchronic toxicity studies. For further clarification, we refer you to the December 2013 Proposed Rule where specific data gaps were identified for BAC and BZC.*

Carcinogenicity Studies

Both carcinogenicity studies have been reviewed by the executive carcinogenicity assessment committee (CAC) which provided the following recommendations:

- *For both carcinogenicity studies, a short-term bridging study could be conducted to provide an estimate of the systemic exposure following dietary administration, with the feed prepared in a manner similar to that in the carcinogenicity studies.*

- *In addition, dermal carcinogenicity studies are necessary to characterize the potential carcinogenic risk that is relevant to the clinical dermal use of this ingredient.*

Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats.

- *The CAC concurred that the study was acceptable. The reduced weight gain/lower absolute body weights at the highest dose were minimal and not considered to adversely affect the ability to interpret the data. Deficiencies with the study include the absence of a measure of systemic exposure and unknown content of the test article in the feed (as mentioned below for the mouse). The absence of systemic effects and the absence of toxicokinetic data lead to uncertainty about systemic test-article exposure in the animals.*

- *The CAC concurred that there were no drug-related neoplasms in the study.*

Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Mice.

- *The CAC found that the 78-week study was suboptimal, being shorter than the two years expected for assessing the lifetime exposure for a pharmaceutical by current standards. Deficiencies with the study included: lack of measurement of drug levels in the animals to confirm exposure; the exact amount of the components of the test material in the feed (i.e., the amount of ethanol remaining in the feed after mixing); and incomplete histopathology assessment (low and mid dose groups were not fully examined). The cause of the lower body weights was unclear.*

- *The CAC concurred that there were no drug-related neoplasms in this suboptimal study.*

Question 12
What is the process for obtaining time extensions?

FDA Preliminary Response to Question 12
We have received your request for extension. Confirm that you will be addressing all data gaps identified in the December 2013 proposed rule for each ingredient for which you are requesting an extension.

Meeting Discussion Question 12
The Agency stressed that the final rule has a strict due date. FDA recommended that Lonza give FDA their proposed timelines and reiterated that all data gaps identified in the December 2013 proposed rule must be addressed in order to support a request for extension.

Question 13
Should time extensions for individual studies be part of an overall time extension – linked to extensions for efficacy and resistance studies?

FDA Preliminary Response to Question 13
We are in the process of determining the best way to communicate our expectations for the time period during which necessary studies are being conducted.

Clinical Pharmacology Additional Comments
One of the precepts for a Maximal Usage Trial (MUsT) as done for New Drug Applications is for it to be done in the final or to-be-marketed formulation. In the case of an OTC monograph ingredient this is not possible as there is not one definitive formulation. Prior to conducting the MUsT for these active ingredients, we recommend that the sponsor first embark on an in vitro testing program using either Franz or Bronaugh diffusion cells using cadaveric skin. The formulation that provides the greatest permeation using this model can then be taken forward into the MUsT program.

It should also be noted that while the package treats BZC and BAC as interchangeable entities for the purposes of meeting the informational burden, they are in fact different chemical entities. As such they will each need their own separate assessment to include individual MUsT.

3.0 POST MEETING ADDENDUM

1. In response to Question 4 regarding the rat embryofetal toxicity study that was conducted with benzathonium chloride at Argus Labs, FDA refers the sponsor to the 2013 Proposed Rule for Consumer Washes (78 FR 76444 at 76464–76465), where this study was discussed on page 76464. "An embryo-fetal rat study with sufficient detail for evaluation was submitted (Ref. 174)". The conclusion for the DART battery for BZC was summarized on page 76465 of the same document, "Overall, the DART data are not adequate to characterize all aspects of reproductive toxicity and we propose that studies are needed to assess the effect of benzethonium chloride on male and female fertility and on pre- and postnatal endpoints."

2. A systemic carcinogenicity study will not be required for a particular ingredient if a human pharmacokinetic maximal use (MUsT) study results in a steady state blood level less than 0.5 ng/mL and an adequately conducted toxicology program demonstrates that there are no other signals for the ingredient or any known structurally similar compound indicating the potential for adverse effects at lower levels. The threshold value of 0.5 ng/ml is based on the principal that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose.

   To fulfill this requirement, the MUsT study should fulfill appropriate design standards utilizing the highest concentration sought under the monograph in formulations expected to produce the highest *in vivo* absorption. The assay used in the MUsT should be properly validated according to current Good Laboratory Practices and consistent with FDA Guidance for Industry: Bioanalytical Method Validation (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf)

   We expect that the 0.5ng/mL concentration will be sufficiently above the assay's limit of quantitation-limit of detection (LOQ-LOD) to allow a signal: noise ratio that assures confidence in the derived concentrations (in the case of "exaggerated" values) or lack of concentrations.

   Studies to assess fertility and pre/postnatal toxicity may be waived if a human MUsT study shows absorption that results in a steady state blood level less than 0.5 ng/mL and there are no signals indicating the ingredient or any known structurally similar compound interacts with related pathways, such as endocrine function or signaling pathways related to growth and development.

3. For inclusion in the monograph, GRASE must be established for a single ingredient that can be formulated in many different ways and presentations. Therefore, in order to support GRASE 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 permeation system (e.g., static or flow-through cells)[1] may be useful in choosing and providing justification of which formulations to test.

4. Regarding Question 6, the reference showing up to 50 hand washes per day in a consumer daycare setting may be found at: Kinnula *et al*, 2009 "Safety of alcohol hand gel use among children end personnel at a child day care center" American journal of infection control 37, 318-321.

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[1] Bronaugh R and Stewart F, 1985, Methods for In Vitro Percutaneous Absorption Studies IV: The Flow-Through Diffusion Cell, J. Pharm. Sci, 74(1), 64-67.

Safety of alcohol hand gel use among children and personnel at a child day care center

Sohvi Kinnula, MD, Terhi Tapiainen, MD, Marjo Renko, MD, and Matti Uhari, MD, MSc
Oulu, Finland

Background: Alcohol hand gels (AHG) have been used by children in child day care centers (CDCCs) to prevent the transmission of microbes. Because parents and personnel have been concerned about the safety of AHGs, we conducted a trial to assess this.
Methods: A total of 82 children age 3.5 to 7.2 years (mean, 5.7 years) at 2 CDCCs rubbed their hands with AHG. Alcohol concentrations in expiratory air were measured using an official police alcometer after 15 and 60 minutes. We also conducted a questionnaire survey asking how commonly AHGs were used in CDCCs, obtaining 128 answers from 68 CDCCs (with more than 1 person responding in 6 CDCCs).
Results: All of the alcometer readings were $< 0.01‰$, although up to 30 contacts with the mucous membranes (mean, 2.4) occurred during the first 15 minutes. An AHG was used in all 68 CDCCs, but only by adults at 11 of them. The most common occasions for using an AHG were before serving food and after cleaning secretions. One case of fire occurred when a worker lit a fire while his hands were covered with AHG. Personnel were most concerned about situations in which children put their fingers into their mouth or eyes after using an AHG.
Conclusion: The use of an AHG in CDCCs is safe. Even though children tend to put their hands into their mouth after disinfection, no significant amount of alcohol is absorbed.

(Am J Infect Control 2009;37:318-21.)

Children attending a child day care center (CDCC) are at increased risk for diarrhea and respiratory tract infections.[1,2] Although hand disinfection with alcohol-based hand gels (AHGs) containing 60% to 90% alcohol has an important role in preventing the transmission of such viruses, only recently have AHGs been accepted for this purpose.[3-5] Improved infection control practices in CDCCs, including the use of an AHG, was shown to reduce the number of episodes of any infection among children significantly in our previous intervention study.[6] Based on these results, AHGs have been recommended for use by both personnel and children in CDCCs in Oulu.

Parents and CDCC personnel have raised concerns about children's use of AHGs. Skin disinfection with methylated ethanol before umbilical arterial catheterization was shown to lead to skin necrosis and percutaneous absorption of alcohol in a preterm infant.[7] In another case, the use of preoperative wrapping with ethanol and boric acid caused alcohol intoxication in a 2-year-old girl, reaching a blood alcohol concentration of $0.8‰$.[8]

We conducted a questionnaire survey among all of the CDCCs in Oulu to evaluate the use of AHGs and an experimental trial at 2 CDCCs in February 2006 to evaluate the safety of AHG use among children.

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METHODS

Theoretically, a subject's blood alcohol level would increase significantly after using a hand gel containing 70% ethanol if this were totally absorbed through the skin. Ethanol is equally distributed in all body fluids.[9] Thus, the maximum rise in the blood alcohol level of a child weighing 10 kg would be about $0.15‰$ after using 1.5 mL of AHG and double that if 3 mL were used. These blood alcohol levels are high enough to be both measurable and harmful. Correspondingly, the value would be $0.075‰$ with a 1.5-mL dose for a child weighing 20 kg and $0.0375‰$ for a child weighing 40 kg.

A total of 82 children varying in age from 3.5 to 7.2 years (mean, 5.7 years; standard deviation, 1.1), 37 of whom were males, participated in the experiment in 2 CDCCs in Oulu. The children were asked to rub their hands with AHG, and all contacts between the hands and the mucous membranes (eyes, mouth, nostrils) were observed and counted during the first 15 minutes afterward (Fig 1). Alcohol concentrations in expiratory

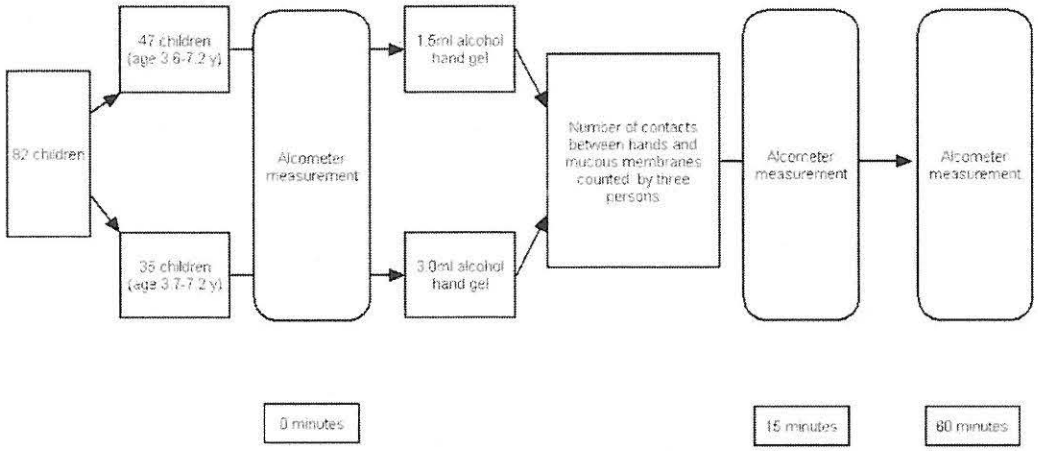

Fig 1. The design of the experiment.

air, reflecting the absorption of alcohol through the skin, were measured using an official alcometer as issued to the police (Alco-Sensor III; identification number 1062558) before and 15 and 60 minutes after AHG use. The alcometer's measurement threshold was 0.01‰. The AHG dose used was 1.5 mL at one CDCC and 3.0 mL at the other. Each child's participation in the trial was voluntary and subject to written consent from the parents. The study protocol was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District.

The use of AHGs in CDCCs was evaluated with a questionnaire asking about the frequency of use, the occasions on which this occurred, and possible risky situations. The attitudes of the personnel regarding AHG use were evaluated using a Likert scale with respect to ease of use (1 = easy; 5 = difficult), convenience, and usefulness. Medians were used to describe these data, because they were not normally distributed.

One questionnaire was sent to each of the 70 CDCCs in Oulu and to each member of the staff of 6 randomly selected CDCCs, so that in the end we received 128 completed questionnaires representing 68 CDCCs. The respondents' working experience varied from 1 month to 26 years (mean, 10 years; SD, 7.3 years) and the group size ranged from 8 to 28 children (mean, 19; SD, 5.2). The analyses of data concerning the features of AHG use in each CDCC were done using only 1 randomly selected answer from those CDCCs in which more than 1 person responded. The attitudes and personal practices of the personnel were analyzed using all 128 completed questionnaires.

RESULTS

In the experimental trial, 47 children rubbed their hands with 1.5 mL of AHG, and 35 children used 3.0 mL of AHG. All of the alcometer readings were below the measurement limit of 0.01‰, suggesting minimal or no alcohol absorption from the AHG. The number of contacts between the hands and the mucous membranes varied from 0 to 30 per child in 15 minutes (mean, 2.4; SD, 4.3).

According to the questionnaires, AHGs were used in every CDCC, only by adults in 11 of the 68 CDCCs (16%) and also regularly by the children in 50 of them (74%). In the remaining 7 CDCCs, the children used AHGs only at times of epidemics. The mean time of AHG use in the CDCCs was 7.4 years (SD, 3.3). The most common occasions for use by personnel were before serving food and after cleaning secretions, whereas handwashing with soap was most common after toileting. The children most commonly used an AHG before eating and washed their hands with soap after toileting (Table 1).

Of the 128 respondents, 43 (34%) always washed their hands with soap before using an AHG, and 120 (94%), used soap when their hands were visibly dirty. Seventeen children (13%) always washed their hands with soap before using the AHG. The day care workers used an AHG from 0 to 50 times per day (mean, 6.7; SD, 6.8), and the children used an AHG from 0 to 8 times per day (mean, 2.4; SD, 1.7).

The personnel found the use of an AHG easy. The median assessment score for ease was 1.2 (interquartile range [IQR], 1.0 to 1.4), and the median score for usefulness was 1.2 (IQR, 1.0 to 1.4), with a score of 1 on the Likert scale indicating either easy or useful. The median score for convenience was 2.4 (IQR, 1.2 to 3.0).

One case of a fire occurred when a worker lit a fire while his hands were still wet with the AHG. In addition, 25 of the 128 respondents (20%) reported consequences of AHG use that they believed to be dangerous or harmful. The most common of these (15 comments)

Table I. Use of an AHG and soap in different situations by personnel and children at 68 CDCCs

	Personnel (n = 68)		Children (n = 68)	
	AHG	**Soap***	**AHG**	**Soap***
At the start of a shift, n (%)	40 (59)	39 (57)	34 (50)	38 (56)
Before serving food, n (%)†	59 (87)	47 (69)	51 (75)	45 (66)
After serving food, n (%)†	10 (15)	25 (37)	1 (1.5)	35 (51)
Before changing diapers, n (%)‡	7 (12)	6 (10)	0 (0.0)	2 (3.4)
After changing diapers, n (%)‡	47 (81)	36 (62)	9 (16)	22 (38)
Before blowing nose, n (%)	5 (7.4)	5 (7.4)	0 (0.0)	1 (1.4)
After blowing nose, n (%)	53 (78)	33 (49)	22 (32)	22 (38)
After cleaning secretions, n (%)	61 (90)	52 (76)	—	—
After going to toilet, n (%)	49 (72)	59 (87)	29 (43)	60 (88)
At the end of a shift, n (%)	26 (38)	31 (46)	4 (5.9)	3 (4.4)

*Washing of hands with soap and water or only with water.
†The questions for the children were "before eating" and "after eating."
‡There were 58 persons taking care of children who wore diapers.

was that children put their fingers in their mouth or eyes after using the AHG. Three respondents reported skin problems from AHG use. Other reported problems were splattering of the gel during application (6 comments) and children sniffing their hands after using the gel (1 comment). The reasons for using alcohol for hand disinfection were well understood by the personnel; 98 persons (77%) said it was to prevent the spread of infectious diseases or to improve hygiene. Four respondents (3%) did not know why an AHG was used.

DISCUSSION

Alcohol was not absorbed when the children at the CDCCs used an AHG for hand disinfection in the experimental trial, even though there were as much as 30 contacts between the hands and the mucous membranes. There was no sign of any elevated alcohol concentration in the children's alcometer measurements, although theoretically the amount of alcohol in the AHG could have caused a measurable rise in blood alcohol level.[9]

Attendance at a CDCC is a significant risk factor for infectious diseases such as diarrhea, common colds, otitis media, and pneumonia.[10,11] It is possible to reduce the number of infections at CDCCs by improving the practices of the personnel in changing diapers, serving food, and especially hand hygiene,[6] and the most effective way of achieving the latter and preventing the spread of viruses is to use AHGs.[3] We found this to be safe.

Two cases of toxic absorption of alcohol in children have been described previously, that of a preterm infant[7] (whose preterm status may explain the toxic absorption of alcohol and resulting skin damage), and that of a 2-year-old girl in whom a keloidal scar was exposed overnight to a wrapping containing alcohol.[8] Cases of percutaneous absorption of disinfectants have been documented after skin cleaning with hexachlorophene and chlorhexidine in newborn and premature babies,[10-12] and this issue has recently been reevaluated in connection with the wider use of chlorhexidine in obstetrics and neonatal care in developing countries to reduce neonatal mortality.[13]

In Finland, the use of AHGs is common in CDCCs and was officially recommended by the Ministry of Social Affairs and Health in 2005 in light of our experiences.[6,14] The reasons for using AHGs are well understood by CDCC personnel, and their use is considered a significant improvement. It has been shown that secondary transmission of infections to family members can be reduced by using an AHG at home if there are children who attend a CDCC,[15,16] and a recent review of the role of AHGs in hand hygiene in home and community settings recommended its active use to prevent the transmission of infectious diseases.[17]

Our study confirms the safety of ethanol in AHGs. Other ingredients in the hand gels are glycerin and, commonly, glyceryl cocoate. These skin-conditioning agents are commonly used in cosmetic products and have been found to be safe in animal and clinical tests.[18] We conclude that the use of AHGs at CDCCs is safe and can be recommended for the children as well as the staff, because all of the alcometer readings were below the measurement threshold.

We thank the Oulu Police Department for lending us their official alcometer to measure the alcohol concentrations. We also appreciate the active participation of CDCC personnel in Oulu in our questionnaire survey, and thank the 2 CDCCs that were involved in the experimental trial.

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