CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208288Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076549

MEETING MINUTES

3M Health Care, Infection Prevention Division
Attention: Ann M. Hupperts, M.S., R.A.C.
Regulatory Affairs Specialist
3M Center, Building 275-5W-06
St. Paul, MN 55144-1000

Dear Ms. Hupperts:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 3M™ CHG/IPA Film-forming Patient Preoperative Preparation (2% chlorhexidine gluconate; 70% isopropyl alcohol).

We also refer to the Type B pre-NDA meeting between representatives of your firm and the FDA on January 20, 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, Regulatory Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

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

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 20, 2015 from 12:30 – 1:30 p.m.
Meeting Location:	White Oak Campus, Silver Spring, MD Bldg 22, Conference Room: 1415
Application Number:	IND 076549
Product Name:	3M™ CHG/IPA Film-forming Patient Preoperative Preparation (2% chlorhexidine gluconate; 70% isopropyl alcohol)
Indication:	Patient pre-operative skin preparation
Sponsor/Applicant Name:	3M Health Care, Infection Prevention Division
Meeting Chair:	Theresa Michele, MD
Meeting Recorder:	Celia Peacock, MPH, RDN

FDA ATTENDEES

Division of Nonprescription Drug Products
Theresa Michele, MD, Director
Karen Mahoney, MD, Deputy Director
Jane Filie, MD, Medical Team Leader
Ryan Raffaelli, MD, Medical Officer
Dan Brum, PharmD, Chief, Project Management Staff
Celia Peacock, MPH, RDN, Senior Regulatory Project Manager
Colleen Rogers, PhD, Interdisciplinary Scientist Team Leader
Michelle Jackson, PhD, Interdisciplinary Scientist
Ruth Scroggs, PharmD, Acting Associate Director for Labeling
Cindy Li, PhD, Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment
Danae Christodoulou, PhD, Acting Branch Chief

Division of Anti-Infective Drug Products
David Bostwick, Clinical Reviewer

Division of Dermatology and Dental Products
David Kettl, MD, Clinical Team Leader
Gary Chiang, MD, Medical Officer

Division of Biometrics IV
Christopher Kadoorie, PhD, Statistician

Office of Pharmaceutical Quality/Division of Microbiology Assessment
John Metcalfe, PhD, Microbiology Reviewer

SPONSOR ATTENDEES
Michelle Hulse Stevens, MD, Chief Medical Officer and Medical Director
Nancy Klinger, BS, Clinical Research Manager
Vinod Menon, Senior Product Development Specialist, Chemistry
Terri Busch, BA, Manager of Product Development, Chemistry
Kristy Yates, BA, BAS, Microbiologist, Quality & Sterility Assurance
Dan Morse, MS, Senior Biostatistical Specialist
Susan Woods, BS, MBA, Program Manager
(b) (4)
(CRO)
Dianne Gibbs, BS, RAC, Regulatory Affairs Manager
Ann Hupperts, MS, RAC, Regulatory Affairs Specialist

1.0 BACKGROUND

3M™ CHG/IPA is a film-forming patient preoperative preparation containing 2% chlorhexidine gluconate and 70% isopropyl alcohol (IPA) in combination with an acrylate copolymer. When the solution is applied to the skin, it dries to form a water-insoluble film. 3M Health Care, Infection Prevention Division (3M) plans (b) (4) 3M plans to submit a new drug application (NDA) to the Agency in mid-2015. The objectives for this pre-NDA meeting are to reach agreement between the Agency and the sponsor on the format and content of the NDA with regards to the proposed approach for the clinical, biometrics, and chemistry, manufacturing and controls sections and to confirm previous agreements.

FDA sent Preliminary Comments to 3M on January 16, 2015. In an email dated January 19, 2015, 3M indicated that they would like further clarification on the following questions during the meeting: 3, 4, 5, 10, and 13.

2.0 DISCUSSION

The sponsor's questions are in **bold** font; FDA's preliminary responses are in *italics*, and the meeting discussion is in regular font.

Clinical in vitro (Microbiology) Efficacy Data

Question 1

As the location for in vitro efficacy data is not specified directly in the CTD guidelines, 3M is proposing to provide summaries of the in vitro efficacy data in Module 2 (2.5 Clinical Overview and 2.7 Clinical Summary). The in vitro efficacy study reports will be included in Module 5 along with the clinical reports. The efficacy data in the submission (in vitro and in vivo) are based on a microbiological endpoint (log reduction) and 3M believes that it is important to discuss these data in relation to each other. The Agency informed 3M in an email from Capt. Celia Peacock on December 2, 2013 that this proposal is acceptable. Does the Agency confirm that this proposal is acceptable?

FDA Preliminary Response to Question 1
Yes. This proposal is acceptable.

Integrated Summary of Efficacy

Question 2

As required for a submission in CTD format, 3M will provide a Clinical Overview and Clinical Summary in Module 2. In the Clinical Summary of Module 2, 3M will present the efficacy data from the two pivotal efficacy trials conducted at independent test labs as a side-by-side presentation of data to demonstrate that the studies demonstrate substantial evidence of efficacy and, therefore, satisfy the regulatory requirement for approval. 3M does not intend to provide a combined analysis of the two pivotal studies. 3M believes that a combined analysis is not appropriate because each study includes different applicator sizes and solution formulation (tint and colorless). In addition, increasing the sample size by combining the data will decrease the confidence interval and increase the probability of meeting the primary outcome of lower 95% confidence interval greater than 70%. The Agency informed 3M in an email from Capt. Celia Peacock on December 2, 2013 that this proposal is acceptable. Does the Agency confirm that this proposal is acceptable?

FDA Preliminary Response to Question 2
Yes. This proposal is acceptable.

Integrated Summary of Safety

Question 3

Per the agreed upon clinical development program for the product, the in vivo clinical studies are divided into two categories. The first category includes the pivotal efficacy studies evaluating a single application of the test products followed by a short observation period. The second category includes the safety challenge studies designed to evaluate exaggerated application conditions of the product, such as multiple applications over extended periods of time under dressings or after exposure to ultraviolet light. The detailed compilation and interpretation of safety data is also expected to be relatively straightforward and for two of the pivotal studies (one completed study and the one study that was prematurely stopped due to data quality issues) there were no adverse events

reported and no adverse events have been reported to date in the ongoing pivotal efficacy study. Due to the limited amount of safety data and the disparate study designs, 3M does not plan to conduct an integrated analysis of safety. All safety data will be presented in Module 2 separately by study, as well as in the individual study reports in Module 5.

The Agency informed 3M in an email from Ms. Valerie M.D. Gooding, GWCPM, Regulatory Information Specialist, Division of Data Management Services & Solutions (DDMSS), CDER, (with copy to Capt. Celia Peacock) on October 15, 2014 that this proposal is acceptable. Does the Agency confirm that this proposal is acceptable?

FDA Preliminary Response to Question 3
Yes, this proposal is acceptable. As stated in our response to Question 2 from the End-of-phase 2 (EOP2) meeting on June 4, 2013, your NDA also needs to address safety topics of interest historically associated with use of topical chlorhexidine-containing products, i.e., anaphylaxis/hypersensitivity reactions and exposure to vulnerable pediatric populations, particularly premature infants and infants less than 2 months of age. Provide a review of published literature and a summary of related postmarketing safety data from use of your Avagard™ product.

Meeting Discussion – Question 3
The sponsor said they had no clarifying questions or comments.

Data from HRIPT/HCIPT Study

Question 4
3M conducted a HRIPT/HCIPT study of the 2% CHG / 70% IPA film-forming skin prep in both the colorless and tinted formulations versus a positive irritant control (0.4% solution of sodium lauryl sulfate) and a negative control (0.9% sterile saline).
The marketed product, ChloraPrep, was also tested in the study. Per the protocol, approximately 0.1mL of the investigational product was applied, allowed to dry, and then covered with an occlusive dressing which is an exaggerated use of the product for the evaluation of safety.

The summary cumulative irritation scores for all materials tested are provided in the table below (see next page). The result category for both the positive control and the negative control were as expected and the result category for the 3M investigational products, both colorless and tinted, were also as expected as both CHG and IPA are known irritants. ChloraPrep resulted in a lower CIT score than the negative control, which is atypical and unexpected.

Summary of Cumulative Irritation (CIT) Scores

CIT Score	Indications from Test	Description of Responses	Treatment Group Result (all subjects)
0 to 723	**Mild material – no experimental irritation**	**Essentially no evidence of cumulative irritation under**	**ChloraPrep (70.0) Negative control (195.5)**

		conditions of use	
724 to 2939	**Probably mild in normal use**	**Evidence of slight potential for very mild cumulative irritation under conditions of use**	**3M colorless (1899.5)** **3M tinted (2060.0)**
2940 to 6610	**Possibly mild in normal use**	**Evidence of moderate potential for mild cumulative irritation under conditions of use**	
6611 to 8538	**Experimental irritant**	**Evidence for strong potential for mild-to-moderate primary or cumulative irritation under conditions of use**	**Positive control (6679.0)**
8539 to 9270	**Experimental irritant**	**Evidence of strong potential for moderate-to-marked primary pr cumulative irritation under conditions of use**	

Does the Agency agree to accept this study in primary support of safety, regardless of the unexpected ChloraPrep result?

FDA Preliminary Response to Question 4
The primary safety evaluation of your topical product will be assessed in the pivotal trials, using the final formulation in a manner consistent with proposed labeled usage. Dermal safety studies are recommended to detect the potential for local dermatologic events with fewer subjects than would be needed in larger clinical trials, with focus on irritation and sensitization. They are conceived to be provocative in nature, with product applications that may be more frequent or for longer durations than proposed clinical dosing, and are frequently done under occlusion.

Given the marketing history of ChloraPrep, we do not recommend that a repeat cumulative irritation study be conducted given the information provided. There is no discussion in the briefing document, however, regarding any explanation for the low CIT score for ChloraPrep and whether an evaluation for issues with conduct of the study was undertaken or discovered. In your application, include a discussion of your analysis of the study results and provide an explanation as to why this atypical result occurred, and whether this result has implications for interpretation of other irritation trial results, as well as any implications for eventual product labeling. Your application may include references to dermal safety studies previously conducted with this product to support any recommendations for labeling.

Meeting Discussion - Question 4
The sponsor said they are continuing to inspect the results of the HRIPT/HCIPT study to better understand the unexpected low CIT score for ChloraPrep. The Agency reminded the sponsor to include in the NDA a discussion of their analysis of the study results and to provide an explanation as to why this atypical result occurred, whether this result has implications for interpretation of other irritation trial results, and any implications for eventual product labeling.

The sponsor asked for clarification on the Agency preliminary comment in response to Question 4 which stated "*Your application may include references to dermal safety studies previously conducted with this product to support any recommendations for labeling.*" The Agency clarified that the sponsor should submit data that supports overall safety to inform labeling, and not just dermal safety.

Validation of Neutralization Results from Pivotal Studies

Question 5

The results of the neutralization validation for the pivotal studies will be included in the body of the clinical reports and a summary of the data will be included in an appendix to the clinical reports. The electronic data will not be included in the submission. Does the Agency agree with this proposal?

FDA Preliminary Response to Question 5
No, we do not agree. Submit neutralization validation data electronically.

Meeting Discussion Question 5
The sponsor noted that because the dataset was very small, the neutralization validation results were not recorded in an electronic database. However, the sponsor will submit the results as part of the NDA in eCTD format. The sponsor also agreed they will provide raw plate count data for the clinical simulation study reports.

Evaluations Conducted to Confirm Selection of Sampling Solution

Question 6

In evaluations to identify the appropriate sampling solution, 3M first evaluated spore recovery to select a sampling solution that was capable of dissolving the polymer to release any viable organisms trapped within the film. After selection of the sampling solution, additional evaluation was done using vegetative organisms to confirm that the sampling solution did not demonstrate antimicrobial activity. A description and summary of this work will be included in the CTD Clinical Summary of Efficacy along with a link to the full report. Does the Agency agree with this proposal?

FDA Preliminary Response to Question 6
Yes. This proposal is acceptable.

Case Report Forms

Question 7

Although it is unlikely that there will be any case report forms (CRFs) to include in the NDA submission, 3M intends to submit any CRFs in electronic format only, in accordance

with FDA *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (January 2013, rev 3)*. Each CRF will be included with the corresponding clinical study report and will be referenced by the report's Study Tagging Files (STF), individually tagged as "case-report-forms." All other case report forms will be available by request. Does the Agency agree with this proposal?

FDA Preliminary Response to Question 7
Yes. This proposal is acceptable.

Statistical and Electronic Datasets

Question 8

3M intends to submit the NDA in electronic Common Technical Document (eCTD) format with the following XML definition files. On October 15, 2014, the Agency informed 3M in an email from Ms. Valerie M.D. Gooding, GWCPM, Regulatory Information Specialist, Division of Data Management Services & Solutions (DDMSS), CDER (with copy to Celia Peacock) that the proposal to use the versions below is acceptable.

eCTD Supportive Files	Version
ICH eCTD DTD	3.2
ICH-STF DTD	2.2
US regional DTD	2.01

3M intends to include Case Report Tabulation (CRT) as part of the NDA submission. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM 1.2 IG 3.1.2). In addition, the Sponsor plans to submit Analysis Data published in scientific data set (SDS 1.6 – ADaM IG 1.0) format along with Source Data published in SDS 1.6 (ADaM IG 1.0, SAS .XPT) format for the 3 pivotal studies only.

Does the Agency agree with the proposed outline regarding the scope, format, and documentation of the electronic datasets to be submitted and that the CRT, Analysis Data, and Source Data will be submitted for the 3 pivotal studies only?

FDA Preliminary Response to Question 8
Yes. This proposal is acceptable.

Clinical Study to have Limited Presentation in the CTD

Question 9

3M conducted a foreign pilot in vivo (groin only) efficacy study at a test lab in Romania with a related formulation that was evaluated in our Toxicology studies. This early formulation was qualitatively the same but slightly different quantitatively than our final current formulation. The data from this foreign study will not be included in the Module 2, but the full report will be included in Module 5 for reference. Does the Agency agree with this proposal?

FDA Preliminary Response to Question 9
Yes. This proposal is acceptable.

CHEMISTRY, MANUFACTURING AND CONTROLS

Addition of HEDTA to Formulation

Question 10

As communicated in Serial Number 040 submitted to IND 76,549 on May 23, 2014, 3M added one arm to our pivotal clinical study (EM-05-013260 / BSL 140537-103, approximately 100 subjects) that included our formulation containing a trace amount (b) (4) of HEDTA in order to directly compare it to our non-HEDTA solution. 3M expects the study will provide not only the efficacy data required by the Agency for product approval, but would also substantiate the addition of a trace level of HEDTA to the formulation from a safety and efficacy perspective. (b) (4)

Does the Agency agree that the arm added to the pivotal clinical study is sufficient to bridge the safety and efficacy between the formulations with and without a trace amount of Trisodium HEDTA and that no additional clinical and safety studies are required?

FDA Preliminary Response to Question 10
It appears reasonable from a nonclinical perspective. However, final determination of the nonclinical studies required to support your NDA submission will only be determined after completion of review of all data in the NDA submission. In your submission, provide a comprehensive nonclinical review of your proposed product.

It also appears reasonable not to conduct additional clinical safety trials prior to NDA submission, but whether your product with the HEDTA ingredient is safe for use in the nonprescription setting is a matter for the review of an NDA. We remind you of your data submission commitments as described in your letter of July 2, 2014 in response to FDA's related questions.

Meeting Discussion - Question 10
The sponsor clarified that all of the nonclinical studies were conducted with the non-HEDTA formulation. However, one of the pivotal clinical studies is currently being conducted using both the HEDTA formulation and the non-HEDTA formulation. Close to 500 subjects, not 100 as stated in the meeting materials will receive the HEDTA final formulation in this pivotal clinical study from which skin irritation and overall safety data will be gathered.

Stability Data

Question 11

3M plans to submit stability data in the NDA for the following 13 clinical lots of our formulation manufactured under production conditions. These studies were conducted per ICH under real time conditions of 25˚C/60%RH and 30˚C/75%RH, and accelerated condition of 40˚C/75%RH (6 months). Based on our target NDA submission date around the end of June 2015, the following data would be included in the original submission. Additional stability data would be submitted via amendment to the pending NDA during

the course of review.

Final formulation:

LOT #	Applicator Volume	With HEDTA? (Y/N)	Tinted/ Untinted	CHG Lot #	IPA Lot #	Data available for original submission / pull point
CLIN A	**10.5 ml**	**No**	**Untinted**	**A120181**	**20021**	**18 mo. (Apr 2015)**
CLIN B	**10.5 ml**	**No**	**Tinted**	**A120181**	**20021**	**18 mo. (Apr 2015)**
CLIN E	**10.5 ml**	**No**	**Untinted**	**A130290**	**20025**	**9 mo. (Mar 2015)**
CLIN C	**26 ml**	**No**	**Untinted**	**A120181**	**20021**	**18 mo. (Apr 2015)**
CLIN D	**26 ml**	**No**	**Tinted**	**A120181**	**20021**	**18 mo. (Apr 2015)**
CLIN G	**26 ml**	**No**	**Tinted**	**A130398**	**20026**	**9 mo. (Mar 2015)**
CLIN H	**10.5 ml**	**Yes**	**Untinted**	**A130290**	**20025**	**12 mo. (May 2015)**
CLIN J	**10.5 ml**	**Yes**	**Tinted**	**A130398**	**20026**	**9 mo. (Mar 2015)**
CLIN L	**10.5 ml**	**Yes**	**Tinted**	**A140056**	**20028**	**6 mo. (Mar 2015)**
CLIN P	**10.5 ml**	**Yes**	**Tinted**	**A130398**	**20026**	**6 mo. (Mar 2015)**
CLIN K	**26 ml**	**Yes**	**Tinted**	**A130398**	**20026**	**9 mo. (Mar 2015)**
CLIN M	**26 ml**	**Yes**	**Tinted**	**A140056**	**20028**	**6 mo. (Mar 2015)**
CLIN Q	**26 ml**	**Yes**	**Tinted**	**A130398**	**20026**	**6 mo. (Mar 2015)**

Question 11A

Does the Agency agree that the submission of stability data for the above 13 lots will be sufficient to support approval of 3M's formulation with HEDTA (b) (4)?

FDA Preliminary Response to Question 11A

We strongly encourage you to submit 12-month stability data in the NDA, at least for your two lots CLINJ and CLINK, applicator volume 10.5 mL and 26 mL respectively. Note that expiration dating will be assessed during NDA review, based on all your available data from lots containing the proposed commercial formulation and supporting data and principles of the ICH Q1E guideline.

Meeting Discussion - Question 11A
The sponsor plans to submit their NDA to the Agency at the end of June, 2015. However, there are two lots, CLINJ and CLINK, of the HEDTA formulation that will not be ready for submission until the end of July 2015. The sponsor inquired if it would be acceptable to send in the data on CLINJ and CLINK within one month after the planned end-of-June NDA submission (i.e., by the end of July). The Agency found this proposal to be acceptable. The sponsor will provide additional stability updates to the NDA during review if requested by the Agency.

Question 11B
Assuming the stability trending at the time of submission substantiates a two year shelf life, does the Agency agree that the above stability data will support an expiry of two years?

FDA Preliminary Response to Question 11 B
See response to Question 11A.

Process Validation Plan
Question 12
In order to validate the solution manufacturing process for the 3M™ CHG/IPA Film-forming Patient Preoperative Skin Preparation, 3M intends to manufacture 3 batches of the tinted formulation and 1 batch of the untinted formulation, all containing trace amount of Trisodium HEDTA. The solution manufacturing process steps are identical between the untinted and the tinted formulations, with the exception of dye addition in the tinted formulation.

The packaging validation including validation of ampule filling, applicator assembly, and pouching will be designed to reflect routine manufacturing. The number of units produced per configuration will be based on the number of units anticipated for routine production, but may vary to meet the demands of the validation protocol. 3M will target producing (b) (4)

3M commits to place the first 3 production batches of each configuration on accelerated (6 months) and long term stability. The full process validation plan will be provided in the Pre-NDA meeting package.

Does the Agency agree with our process validation strategy?

FDA Preliminary Response to Question 12
Your approach to process validation strategy appears reasonable.

(b) (4)

Reprocessing Strategy

Question 13A

(b) (4)

Does the Agency agree that these analytical data will support (b) (4) ?

FDA Preliminary Response to Question 13A

To obtain Agency approval of a reprocessing strategy (b) (4) submit validation data for both the (b) (4) with the NDA submission. In the he validation data for (b) (4) include demonstration of package integrity.

Meeting Discussion - Question 13A

The sponsor proposed that the data to support (b) (4) . See Post Meeting Addendum for additional information.

Validation Package Timing

Question 13B

Based on an agreement by the Agency in a Type C Guidance teleconference held on February 3, 2014 with Dr. John Metcalfe, Senior Review Microbiologist, and Dr. Stephen Langille, Product Quality Microbiology Reviewer, and as documented in 3M's meeting minutes submitted to IND 76,549 on February 5, 2014 (SN034) plus reference to the Agency correspondence provided by e-mail from Ms. Rebecca McKnight on January 28, 2014, 3M intends to file the (b) (4) approximately 3 months after NDA submission. As requested by Dr. Metcalfe, 3M will include reference to this agreement in our NDA cover letter in order to avoid "Refusal to File."

Does the Agency confirm the agreement to allow 3M to submit the product (b) (4) at approximately 3 months after the NDA is submitted?

FDA Preliminary Response to Question 13B

Applications are expected to be complete at the time of original submission of the application. We strongly encourage you to submit complete (b) (4) validation data in the initial NDA. We cannot guarantee review of a major amendment that is submitted after the review clock

has begun. A major amendment to an original application submitted at any time during the review cycle may extend the goal date by three months.

Meeting Discussion - Question 13B

The sponsor is timing their initial NDA submission such that (b) (4) would be ready to submit within 3 months after submission of the NDA. The Agency strongly encouraged the sponsor to submit complete (b) (4) validation data at the time of submission of the initial NDA. The Agency reminded the sponsor that a filing determination is made by the signatory authority who takes into consideration the recommendations of the review team. The decision to file the application or the decision to review a (major) amendment can only be made at the appropriate times.

Question 14

3M anticipates that the 3M CHG/IPA Skin Prep will be the first NDA-approved preoperative skin preparation to claim a sterile solution.

Based on this product innovation, does the Agency agree that expedited review of our NDA will be granted?

FDA Preliminary Response to Question 14

The review classification (priority or standard) will be determined after the NDA is submitted, and will be communicated to you upon filing (by day 60 for priority review and by day 74 for standard review). An application for a drug that treats a serious condition AND, if approved would provide a significant improvement in safety or effectiveness is eligible for priority review. See Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 358301.pdf). Given that the indication for preoperative antiseptics states "helps reduce bacteria that potentially can cause disease" and that nonsterile preoperative antiseptics have not been found to be unsafe, provide strong justification to support a request for priority review in the cover letter of your NDA.

Meeting Discussion - Question 14

The Agency reiterated that the review classification (priority or standard) will be determined after the NDA is submitted, and will be communicated upon filing (by day 60 for priority review and by day 74 for standard review).

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

The sponsor plans to:

- include a discussion of their analysis of the HRIPT/HCIPT study results in their NDA, and will provide an explanation as to why atypical results may have occurred, whether these results have implications for interpretation of other irritation trial results, and any implications for draft product labeling;
- submit neutralization validation data electronically (e.g., PDF) in the NDA; and
- submit the data to support the (b) (4)

6.0 POST MEETING ADDENDUM

Post Meeting Addendum - Question 13A
The Agency agrees that the appropriate submission category for this supplement (b) (4).

7.0 ADMINISTRATIVE COMMENTS

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

LABELING REGULATIONS AND GUIDANCES

As you develop your label and labeling, we call your attention to the following pertinent labeling regulations and guidances:

Regulations under the Code of Federal Regulations (CFR)
When you prepare your NDA for submission to FDA include the following:

1. All of the proposed labels and labeling (i.e., all count sizes with immediate container and carton labeling, including samples, and consumer information leaflet if proposed) as required under 21 CFR 314.50.
   a. "clean" labeling and marked up labeling (i.e., annotated) defining the information in the summary and technical sections of the application that support the inclusion of each statement in the proposed labeling.
   b. font and format specified under 21 CFR 201.66 as part of the annotated labeling or detailed in a separate document.

2. In addition to the format and content requirements for over-the-counter (OTC) drug product labeling (21 CFR 201.66), we refer you to the following:
   a. 21 CFR, Part 201 Subpart A-General Labeling Provisions and

b. Subpart C-Labeling Requirements for Over-the-Counter Drugs, which provides the labeling required for packaging (Principal Display Panel (PDP)-21 CFR 201.60 and statement of identity- 21CFR 201.61 etc.).

Guidances

1. See "Guidance for Industry– Labeling OTC Human Drug Products –Questions and Answers" (December 2008) for assistance with OTC labeling development. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf

2. In addition to submitting your label using the Structured Product Labeling (SPL) format, we recommend that you formally submit your proposed labeling in portable document format (PDF) electronically to your NDA.

    a. To ensure electronic storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents (i.e., OTC labeling usually has complex graphics and large file size), follow FDA's portable document format (PDF) specifications detailed in the document found at the following URL: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf

    b. For complete information on preparing your electronic submissions refer to the following URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

    c. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov.

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/s/

THERESA M MICHELE
02/22/2015