CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211733Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 112538

MEETING MINUTES

Pfizer Inc.
Attention: Wendy A. McManus, MS, RAC
Director, US Regulatory Affairs Strategy
One Giralda Farms
Madison, NJ 07940

Dear Ms. McManus:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ibuprofen 125 mg and acetaminophen 250 mg tablet.

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2018. The purpose of the meeting was to discuss your upcoming new drug application submission.

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 Tinya Sensie, Regulatory Project Manager at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Deputy 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:	March 19, 2018 from 3:00 p.m.- 4:00 p.m. (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 112538
Product Name:	ibuprofen 125 mg and acetaminophen 250 mg tablet
Indication:	For the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) (b) (4) muscular aches, and minor pain of arthritis (b) (4).
Sponsor/Applicant Name:	Pfizer
Meeting Chair:	Karen Murry Mahoney, MD, FACE, Deputy Director, Division of Nonprescription Drug Products
Meeting Recorder:	Tinya Sensie, MHA, Regulatory Project Manager, Division of Nonprescription Drug Products

FDA ATTENDEES

Office of Drug Evaluation IV (ODEIV), Division of Nonprescription Drug Products (DNDP)

Karen Mahoney, MD, FACE, Deputy Director
Frank Becker, MD, Clinical Team Leader
Martha Lenhart, MD, Clinical Reviewer
Amanda Pike-McCrudden, MAA, Social Science Reviewer
Betsy Scroggs, PharmD, Associate Director for Labeling
Kevin Lorick, PhD, RAC, Interdisciplinary Scientist Team Leader

Yoon Kong, PharmD, Interdisciplinary Scientist Reviewer
Jane Sohn, PhD, Nonclinical Team Leader
Chibueze Ihunnah, PhD, Nonclinical Reviewer
Tinya Sensie, MHA, Regulatory Project Manager

ODEIV, Immediate Office (IO)

Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Office of Drug Evaluation II (ODEII), Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Joshua Lloyd, MD, Clinical Team Leader
Timothy Jiang, MD Clinical Reviewer

Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)

Grace Jones, PharmD, Reviewer

Office of Biostatistics (OB), Division of Biometrics VII (DBVII)

Rima Izem, PhD, Biostatistics Team Leader
Joo-Yeon Lee, PhD, Biostatistics Reviewer

Office of Biostatistics (OB), Division of Biometrics II (DBII)

David Petullo, PhD, Biostatistics Team Leader
Yan Zhou, PhD, Biostatistics Reviewer

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology II (DCPII)

Srikanth Nallani, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Pfizer

Michael Bailey, Head of Regulatory Affairs, North America & Rx-OTC Switch
Wendy McManus, MS, RAC, Director, US Regulatory Strategy
Mario Cruz-Rivera, PhD, MPH, Senior Director, Global Clinical Research
David Kellstein, PhD., Senior Director, Global Medical Affairs
Seth Minsk, Director, Global Consumer Insights
Dongweon Song, PhD, Director, Global Clinical Research & Pharmacology
Steve Teo, PhD, DABT, ERT, Senior Director, Nonclinical Safety Evaluation/Toxicology

Jennifer Jiangfeng Su, MD, PhD, Medical Director, Safety Risk Lead
Rina Leyva, Senior Manager, Biostatistics & Analysis
Suzanne Meeves, Pharm D, MBA, Director, Global Clinical Research
Tania Thomas, Director, US Regulatory Strategy

1.0 BACKGROUND

FDA had a pre-investigational new drug application (PIND) meeting with Pfizer on September 20, 2011, to discuss the development program for this proposed ibuprofen and acetaminophen fixed-dose combination drug product intended for nonprescription (over-the-counter or OTC) use. The proposed indication is for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, and minor pain of arthritis (b) (4)

Following the PIND meeting, Pfizer conducted a proof-of-concept (POC) dental pain study (Study B5061001) to determine whether one of three different doses of the combination of ibuprofen and acetaminophen was superior to ibuprofen 400 mg alone.

After completing the POC study, Pfizer met with the FDA for an End-of-Phase 2 (EoP2) Meeting on May 15, 2014, to discuss data from the POC study and obtain feedback regarding the next phases of the clinical development program.

Pfizer conducted a series of Label Comprehension Studies (LCS) to gain insight into concerns related to liver toxicity if consumers simultaneously use multiple acetaminophen-containing products.

Pfizer met with the FDA on April 3, 2017, to discuss the proposed pivotal LCS protocol and to clarify if modifications made to labeling are acceptable prior to conducting the study.

Pfizer submitted a Type B pre-NDA meeting request on December 8, 2017, and the associated meeting background information on February 5, 2018. The purpose of the meeting request is to discuss their upcoming NDA submission.

FDA sent the preliminary responses to Pfizer on March 13, 2018.

2. DISCUSSION

Below, the Sponsor's questions are in ***bold italics***, FDA's preliminary responses are in *unbolded italics,* Pfizer's premeeting responses to our preliminary responses follow in **bold nonitalicized** font, and the meeting discussion is in regular nonitalicized font.

2.1. Regulatory

Question 1: ***Table of Contents (TOC): Does the Agency agree with the proposed Table of Contents for the upcoming NDA submission?***

FDA Response to Question 1:

Refer to the comprehensive table of contents headings and hierarchy document available at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm315023.pdf

In general, if you plan to omit eCTD sections that seem otherwise applicable (i.e., required or pertinent), clarify why the section is omitted. For example, upon a cursory review of Module 1, your proposed TOC does not include section 1.3.2 Field copy certification or 1.3.3 Debarment certification. We acknowledge that not all headings are applicable to all submissions or submission types.

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

Discussion:

No discussion occurred.

Question 2: ***For Module 1.9.6; does the Agency align with the revised Pediatric Study Plan (PSP)?***

FDA Response to Question 2:

It is unclear to us when you plan to submit your marketing application as you may be able to submit an Amended Initial Pediatric Study Plan (iPSP) and reach an Amended Agreed iPSP to revise your timeline for studies prior to the submission of your marketing application. However, if your marketing application will be submitted in less than 210 days, then the proposed changes to the due dates for submission of the study protocol and initiation of the study can be negotiated with the Division during the review of your marketing application after it has been submitted and filed.

We note that you have satisfied the requirement under The Food and Drug Administration Safety and Innovation Act to obtain an Agreed iPSP from the Agency for your product that triggers the Pediatric Research Equity Act.

Discussion at Face-to-Face Meeting:

Pfizer will submit a revised Amended Agreed iPSP.

Question 3: ***For Module 1.12.4 Environmental Assessment, a claim for a Categorical Exclusion to the Environmental Assessment will be provided in compliance with 21 CFR Part 25.31(a); does the FDA concur?***

FDA Response to Question 3:

Yes, however, we would like to clarify that the environmental impact information is submitted in eCTD section 1.12.14.

Discussion:

No discussion occurred.

Question 4: ***Module 1.14.1.1 Draft Labeling: Does the Agency have comments related to the proposed Principal Display Panel /Drug Facts Label?***

FDA Response to Question 4:

A determination regarding the acceptability of labeling will be an NDA review issue. It is ultimately up to you to ensure that consumers can use your product safely, in the absence of a healthcare intermediary, based on the Drug Facts label (DFL).

Per the April 3, 2017, meeting minutes under question 3, we note that you have implemented some of our suggested labeling changes. However, we remind you of our additional comments made under the "Discussion at Meeting" section under question 3 regarding the use of highlighting in labeling with respect to deviations from labeling regulations set forth by 21 CFR 201.326. We reiterate that use of nonstandard highlighting should be justified with additional data to support your proposed labeling.

Change the order of the two active ingredients in your proposed product's labeling, such that "acetaminophen" precedes "ibuprofen". It is important that consumers recognize at a first glance at active ingredients that a product contains acetaminophen, because of known problems with consumers accidentally using multiple acetaminophen-containing products at the same time, with consequent serious hepatic injury.

For your proposed statement of identity on the principal display panel and DFL, replace the slash (/) between the ingredients acetaminophen and ibuprofen with the word "and" so that it reads "acetaminophen 250 mg and ibuprofen 125 mg (NSAID)".

Under 21 CFR 314.50(e)(2)(ii), your complete submission is to include all the proposed labels and labeling. This is to include all count sizes with immediate container and carton labeling, including samples, and consumer information leaflet (if proposed). Submit clean

labeling and labeling that is annotated to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling.

In addition to the format and content requirements for over-the-counter (OTC) drug product labeling (21 CFR 201.66), we refer you to 21 CFR part 201 subpart A, General Labeling Provisions; and subpart C, Labeling Requirements for Over-the-Counter Drugs for details of labeling required for packaging (Principal Display Panel (PDP) – 21 CFR 201.60, Statement of identity – 21 CFR 201.61 etc.).

Refer to Guidance for Industry: Labeling OTC Human Drug Products Questions and Answers (December 2008) to assist you in OTC labeling development. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U CM078792.pdf

To facilitate storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents, follow FDA's portable document format (PDF) specifications detailed at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf

Questions regarding the preparation of submissions in electronic format may be directed to esub@fda.hhs.gov. Questions regarding submission of datasets may be sent to edata@fda.hhs.gov.

➢ **PFIZER PREMEETING RESPONSE TO FDA PRELIMINARY COMMENTS:**

Thank you for the Agency's response. Further discussion is needed.

Pfizer would like clarification on the statement "use of nonstandard highlighting should be justified with additional data to support your proposed labeling." As part of the iterative process, after several pretests and the 2015 Pilot Label Comprehension Study (LCS) followed by an additional qualitative pre-test study the corresponding 2016 Pilot LCS label of our fixed dose combination (FDC) was tested after several optimizations were made including:

- **Highlighting the ingredient-specific warning header, and inserted space so the heading was on its own line, separate from the explanatory text, in order to enhance comprehension of all three endpoints, particularly among the low literacy population.**

Post the 2016 Pilot LCS, further modifications were made to the study design and to optimize the final labels tested in the 2017 Pilot LCS. No additional Drug Facts Label changes have been made as Pfizer prepares for the upcoming Pivotal LCS. At the 3 April 2017 meeting, the Agency stated "highlighting proposed by Pfizer is acceptable…" and "FDA will not require side-by-side testing, i.e. with and without highlighting." If side by side testing is not needed and changes were made through the

iterative process, can you please clarify what additional data Pfizer should provide to support the proposed highlighting?

Discussion at Face-to-Face Meeting:

Pfizer noted that it has data to support the effect of highlighting on consumer understanding, and FDA suggested that Pfizer submit the data in the NDA. FDA noted that acceptability of labeling will be determined upon review of the NDA.

2.2. Clinical/Medical- Efficacy

Question 5: ***Does the Agency agree with the proposal to not include an Integrated Summary of Efficacy (ISE)?***

FDA Response to Question 5:

No, we do not agree. The Integrated Summary of Effectiveness (ISE) is a required component of an NDA submission [21 CFR 314.50(d)(5)(v)] and is more than just a pooled analysis of your efficacy data. It is intended to provide a comprehensive, integrated analysis of the effectiveness of a study drug for each claimed indication. Efficacy data need to be pooled to examine the effect of demographics (e.g., age, sex, race, and ethnicity) and other characteristics (e.g., presence of specific concomitant illnesses or treatments), where the individual studies would have too few subjects with these characteristics to support meaningful conclusions.

Refer to Guidance for Industry: Integrated Summary of Effectiveness, for additional information on preparing an ISE, available at https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf

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

Additional Comments

We note that your pre-NDA meeting package does not include a description of the efficacy data intended to support your proposed submission, and, as such, we cannot provide comments on the adequacy of these data. However, ensure that your planned efficacy analyses address the generalizability of your clinical trial data to a broad population, and the following points, in addition to the primary efficacy analyses:

- *Time-to-onset for your product (e.g., time-to-first perceptible and meaningful pain relief using the double stopwatch method; time-to-request rescue medication; and time-to-request a second dose of study medication. We typically expect that an analgesic drug will have an onset of action within one hour for an OTC product, so that patients do not initiate other medications that could create a safety concern when taken in combination with your product.*

- *Duration of effect/adequacy of the dosing interval, and analgesic efficacy over multiple doses. Because the individual components of your combination product are typically dosed every four to six hours and your proposed combination product is dosed every eight hours, include analyses that evaluate summed pain intensity differences (SPIDs) over the last two to four hours of the dosing interval. Also, provide pain intensity and pain intensity difference over time curves for each of the treatments.*

Include bioanalytical reports along with each pharmacokinetic study report.

➢ **PFIZER PREMEETING RESPONSE TO FDA PRELIMINARY COMMENTS:**

Thank you for the Agency's response. Further discussion is needed.

1.) Pfizer would like clarification on the time interval suggested in the statement "*include analyses that evaluate summed pain intensity differences (SPIDs) over the last two to four hours of the dosing interval.*" Following the previous FDA request, Pfizer assessed SPIDs over 6-8 hours (the last 2 hours interval only) in the individual dental pain studies. Is the Agency aligned that this is still acceptable?

2.) To respond to your overall observation, a total of four efficacy studies were included in the development program: one proof of concept (POC) dental pain efficacy study, one full factorial single dose dental pain study (SDDP), one multiple dose dental pain study (MDDP), (b) (4).

After considering your feedback, Pfizer proposes to provide a comprehensive summary of the individual efficacy study results ((b) (4) dental pain (b) (4)) side by side in the ISE. While Pfizer understands that FDA would like to have a pooled analysis, we believe that there is little *new* information to be gained as compared to presentation of the individual study results as there are minimal data to pool (i.e. 2 treatment arms and 2 subgroups [sex and baseline pain]; see Table A below). A summary table describing the efficacy studies is included in the Appendix (Table B). These tables may help to clarify why we initially proposed to omit the ISE and also why we did not propose pooled analysis.

If the FDA still requires a pooled analysis, then Pfizer proposes to pool efficacy data from the three efficacy dental pain comparing FDC (IBU 250 mg/APAP 500 mg) tablets to placebo through the first 8 hours. These are the only two treatments common to all three dental pain studies (see Table A below).

Table A. Common Treatment Groups in the Three Dental Pain Studies (Highlighted in gray)

STUDY	FDC IBU/APAP (mg) [n]			PBO [n]	IBU (mg) [n]		APAP (mg) [n]	APAP (mg) [n]
	200/500	250/500	300/500		250	400	500	650
B5061001 (POC)	X [90]	X [93]	X [89]	X [30]		X [92]		
B5061003 (SDDP)		X [172]		X [56]	X [175]			X [165]
B5061004 (MDDP)		X* [82]		X* [41]				
n	[90]	[347]	[89]	[127]	[175]	[92]	[0]	[165]

* First treatment period, 0-8 hours only

The integrated efficacy results will be provided for the following parameters to describe the efficacy profile of the FDC product in terms of overall efficacy over 8 hours, and over the last two hours, duration and onset.

- **Sum of pain intensity differences (SPID) over 0-8 hours and 6-8 hours based on the 11-point numerical rating scale**
- **Duration of relief (measured by time to rescue medication)**
- **Time to onset of meaningful relief (through the first 8 hours)**

In terms of subgroup analyses of efficacy based on the pooled data, PCH proposes to include:

- **Gender**
- **Baseline pain severity (moderate vs. severe)**

Note: The well-established third molar extraction pain model uses young healthy volunteers. Therefore, no subgroup analyses based on any disease subgroup or concomitant medication use can be performed. In addition, since the majority (~94%) of the subject population in our studies was comprised of White subjects between the age range of 18-44 years, no subgroup analyses based on race or age will be performed.

Is the Agency aligned with proposal to not include a pooled analysis in the ISE? If not, does the Agency agree with the proposed pooling strategy, parameters and subgroups?

Discussion at Face-to-Face Meeting:

1) FDA noted that, because the individual components of the product are typically dosed every 4 to 6 hours, it is important to confirm that the analgesic effect of the proposed product persists over the entire dosing interval. FDA stated that the prespecified SPID assessed over 6 to 8 hours could be acceptable to address this issue. However, FDA may ask for additional post-hoc analyses (e.g., SPID4-6, SPID4-8) during the NDA review to address any concerns identified based on the overall pain intensity and pain intensity difference curves. Additionally, FDA recommended that the Sponsor evaluate rescue

medication use during the latter part of the dosing interval to support any conclusions regarding persistence of the analgesic effect over the entire dosing interval.

2) The Sponsor proposed providing a comprehensive summary of the individual efficacy study results ((b) (4) dental pain (b) (4)) side by side in the ISE and pooling efficacy data only for the purposes of conducting subgroup analyses to assess for any differences in effect by sex and baseline pain. FDA found the proposal to be acceptable but noted that the Sponsor should include the rationale in the ISE for not conducting other subgroup analyses (e.g., age and race).

   FDA stated that it would be acceptable to not pool the overall primary efficacy data because FDA plans to evaluate the data from each study intended to support a finding of effectiveness.

2.3. Clinical/Medical- Efficacy/Safety Datasets

Question 6: ***Module 5: Pfizer will submit the individual PK study datasets, the individual efficacy/safety study datasets, and the pooled safety datasets in CDISC (Clinical Data Interchange Standards Consortium) formats. Does the Agency agree?***

FDA Response to Question 6:

The proposed data submission plan appears acceptable. We recommend that the pharmacokinetic and efficacy/safety study datasets, annotated case report forms (aCRF), and data definition files comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards, respectively.

Include subject unique identifiers of all study participants, SDTM datasets and analysis-ready datasets, along with a thorough data definition file. All derived variables for the primary and secondary efficacy analyses should be included in the analysis-ready datasets. We emphasize that traceability is an important factor in the submission of data. Reviewers should be able to navigate from CRFs to tabulation data to analysis data.

Refer to standardized clinical and nonclinical study data requirements available at:

- *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm*
- *https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm199599.pdf*
- *http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm*

➢ **PFIZER PREMEETING RESPONSE TO FDA PRELIMINARY COMMENTS:**

Thank you for the Agency's response. Brief discussion is needed.

Pfizer acknowledges your recommendations and will provide the following:

- **aCRF: CRF annotated with the SDTM variables**
- **SDTM and ADaM, and their respective documentations (Define.XML, reviewer's guide), using the latest CDISC standards**

Discussion at Face-to-Face Meeting:

Pfizer's approach appears reasonable from FDA's perspective.

FDA emphasized the definitions of all derived variables should be clearly described in the define file. In addition, FDA stressed the importance of traceability in the data submission.

2.4. Clinical/Medical- Efficacy/Safety

Question 7: ***For Module 2.7.4 (Summary of Clinical Safety, SCS); does the Agency agree with the proposed pooling strategy for the Summary of Clinical Safety?***

FDA Response to Question 7:

It is difficult to provide a definitive answer in the absence of topline results from completed clinical studies. In general, formatting with sub-pools that provide breakouts for different doses of the same treatment and individual analyses for different doses of the same treatment need to be performed.

Consider submitting your table shells for review in advance of the NDA submission.

➢ **PFIZER PREMEETING RESPONSE TO FDA PRELIMINARY COMMENTS:**

Thank you for the Agency's response. Brief discussion is needed.

The topline results from the completed clinical studies are included in the Appendix (Table B and C) under "results." The sub-pools and analysis that provide breakouts for different dose levels within the same treatment will also be incorporated in the SCS, rather than combining different doses in the same treatment.

Additionally, Pfizer has provided the table shells of SCS for review in this Response (Appendix Tables D, E, F, G, H, I, J). With the corresponding information available, does the Agency agree with the pooling strategy for the SCS?

Discussion at Face-to-Face Meeting:

Pfizer agreed with FDA's suggestion on subpooling in the SCS. FDA agreed with the combination arm. However, FDA may request additional information if questions arise on dose dependence of AEs and if data from individual component medications are needed.

FDA requested inclusion of age greater than 64 as an age demographic subgroup for WHO Vigibase and literature reviews.

Question 8: ***For Module 2.7.4 (Summary of Clinical Safety, SCS); does the Agency agree with the proposed subgroups that will be presented for the Summary of Clinical Safety?***

FDA Response to Question 8:

Yes, inclusion of age, gender and race subgroups is appropriate.

Discussion:

No discussion occurred.

Question 9: ***For Module 5.3.5.3.2 (Integrated Summary of Safety, ISS); Pfizer is proposing to focus on the combination only and use only the WHO Vigibase database, does the Agency agree with the extent of the post-marketing safety data to be analyzed and submitted with the NDA?***

FDA Response to Question 9:

Yes, your proposal to focus NDA postmarketing safety data analyses on the combination product and WHO Vigibase database is acceptable.

Provide a list of countries in which the combination product is marketed as a nonprescription product, including dose/package size, English translations of nonprescription labeling, and a list of countries in which the drug has been withdrawn for safety reasons. Identify countries that require pharmacist dispensing ("behind-the-counter") status for products with this combination of ingredients, and those that have nonprescription status similar to that of the US (i.e. on retail shelves without pharmacist or other healthcare provider intervention). Identify countries that limit the package size of products with this combination of ingredients, and specify the maximum number of doses per package permitted in each country. Identify adverse events most likely to occur with your proposed combination in a nonprescription consumer population.

Include data analyses and summaries as described below. For each subset, identify a biological mechanism of action for the most frequently occurring adverse events and any serious adverse events. Identify the frequently occurring and serious adverse events that are more than likely related to the combination product based on biological mechanism. Use your analyses to consider the likelihood of these adverse events occurring in the US

nonprescription population. Provide a detailed summary of your decisions and the rationale and data supporting those decisions.

- *Dose-Response:*

  Analyze the safety data by dose from lowest dose to highest dose. Identify the most frequently occurring adverse events for each dose and any serious adverse events for each dose. Compare the safety profile of each dose with the safety profile of other doses.

- *Age:*

  Analyze the safety data for each age grouping. Identify the most frequently occurring adverse events for each age group and any serious adverse events. Compare the safety profile of each age group with the safety profiles of the other age groups.

- *Gender:*

  Analyze the safety data by gender. Identify the most frequently occurring adverse events for each gender and any serious adverse events. Compare the safety profile for each gender.

- *Time-to-Onset:*

  Analyze the safety data by time to onset. Identify the most frequently occurring adverse events for time to onset. Identify the most frequently occurring adverse events for each timeframe and any serious adverse events.

- *Accidental or Intentional Overdose:*

  Using the analyses for dose response, age, gender and time-to-onset together, identify adverse events most likely to occur with accidental or intentional overdose in the OTC population. Provide a detailed summary of the biological mechanism, the dose, and the adverse events.

- *Dose and Duration:*

  Using the analyses for dose response, age, gender and time to onset together, identify adverse events most likely to occur with the labeled dose and duration in the OTC population. Provide a detailed summary of the biological mechanism, the dose, and the adverse events.

- *Misuse and Abuse:*

  Identify the adverse events most likely to be seen in the OTC population if the duration of use is extended beyond what is labeled; if the labeled dose is exceeded; and if the labeled dose AND duration of use are exceeded. Provide a detailed summary of the biological mechanism, the dose, and the adverse events.

Discussion:

No discussion occurred.

Question 10: Module 5.3.5.3.2 (Integrated Summary of Safety, ISS): Regarding the post-marketing safety data, a cumulative literature review of published clinical safety data for only the combination of IBU/APAP (not to include the search on single ingredients) will also be included in this NDA submission. Does the Agency agree this is acceptable?

FDA Response to Question 10:

Yes, a cumulative literature review of published clinical safety data for only ibuprofen and acetaminophen combination products is acceptable for inclusion as part of the ISS postmarketing safety data.

If you rely in part on the published literature to support safety and its generalization to a broad population (including an older and more racially diverse population than enrolled in the clinical studies), explain the relevance of each publication to the safety and generalization of your proposed product, include a list of retrieved references, and provide articles in full-text in the English language. Include a table for literature referenced with the type of study, objectives, population and principal results.

If you submit literature from countries that require pharmacist dispensing ("behind-the-counter") status for products with this combination of ingredients, note that dispensing status for each article, and address this issue in your literature summary. If you submit literature from countries that limit the package size of products with this combination of ingredients, note that package size limitation for each article, and address this issue in your literature summary.

Discussion:

No discussion occurred.

Question 11: ***For the Module 5.3.5.3.2 (Integrated Summary of Safety, ISS) post-marketing safety data dose groups; does the Agency agree this approach is acceptable?***

FDA Response to Question 11:

The proposed fixed-dose combination groups are acceptable.

Tabulate, summarize, and analyze postmarketing adverse event data by the following:

- *Seriousness and outcome for each case*
- *Relationship to the drug exposure*
- *Concomitant drugs*
- *Underlying medical conditions*
- *Product specific attributes (dose, dosage strength and duration of use)*
- *Event year*
- *Subject demographics (age sub-groups, sex, race)*

Consider submitting your table shells for review in advance of the NDA submission.

Discussion:

No discussion occurred.

Question 12: ***Does the Agency agree the special safety topics identified for Module 5.3.5.3.2 (Integrated Summary of Safety, ISS) post-marketing safety data are acceptable?***

FDA Response to Question 12:

Include the following System Organ Classes (SOCs) in your special safety topics:

- *Cardiac disorders*
- *Gastrointestinal disorders*
- *Hepatobiliary disorders*
- *Immune system disorders*
- *Injury, poisoning and procedural complications*
- *Nervous system disorders*
- *Renal and urinary disorders*
- *Respiratory disorders*
- *Skin and subcutaneous disorders*
- *Vascular disorders*

Discussion:

No discussion occurred.

Question 13: ***Module 5.3.5.3.2 (Integrated Summary of Safety, ISS): Regarding the external data safety cutoff, since some external databases (including the WHO Vigibase) are updated quarterly, is a 6-month safety cut-off date of 30 March 2018 acceptable for a planned 30 November 2018 NDA submission?***

FDA Response to Question 13:

Yes, an external safety database cut-off date of 6 months prior to NDA submission is acceptable.

Discussion:

No discussion occurred.

Question 14: ***Regarding the 4-Month (120-Day) NDA Safety Update, does the Agency agree that this approach is acceptable?***

FDA Response to Question 14:

The expectation is that all your studies will be complete, and that full study reports will be included with your NDA submission. The 120-Day safety update should contain new safety information derived from postmarketing databases and published literature.

Discussion:

No discussion occurred.

2.5. Non-Clinical

Question 15: For Module 2.4 Nonclinical Overview; does the Agency agree with this abbreviated approach?

FDA Response to Question 15:

Your proposed approach appears reasonable regarding the active ingredients. However, the safety of your final formulation will be a review issue. The use of any novel excipient exceeding levels in currently approved oral products will need to be qualified for safety as described in the guidance for industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients. Adequate justification of proposed excipient levels addresses the maximum daily dose, duration of use, and the intended consumer population of your proposed product. Information from the Inactive Ingredient Database alone may not provide sufficient information to provide adequate justification. If you intend to use an approved product to justify your proposed level for specific excipient, include in your justification how the maximum daily dose, the route of exposure, duration of use, and the intended consumer population is relevant to the level you propose in that excipient.

Provide your proposed level for each excipient, and the level supported by comparable approved products or by nonclinical data. Refer to the sample table below for a suggestion of how to present information from approved products and data from submitted study reports. Include in the text of your application the calculation for the maximum daily dose of each excipient in your proposed product, and how the maximum daily dose supported was calculated from approved products, or from nonclinical studies.

Excipient Name	*Proposed Product Maximum Daily Dose (mg)*	*Comparable Product*			*Supported Level from appropriate nonclinical studies*	
		Maximum daily dose (mg)	*Intended Consumer Population*	*Indication and Duration of use*	*Maximum daily dose (mg)*	*Justification*

Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH guidance [ICH Q3A(R2) and ICH Q3B(R2)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as having mutagenic structural alerts need to be at or below acceptable qualification thresholds to support an NDA as described in the ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

Discussion:

No discussion occurred.

***Question 16:* For Module 2.6 (Nonclinical Written and Tabulated Summaries); based on the substantial nonclinical data for both ibuprofen and acetaminophen, no Module 2.6 will be submitted. Does the Agency agree with this approach?**

FDA Response to Question 16:

Refer to the response for Question 15. If nonclinical information is submitted to support the safety of your formulation, Module 2.6 may be needed.

Your plan to discuss likelihood of drug-drug interactions in the nonclinical summary is acceptable.

Discussion:

No discussion occurred.

2.6. Behavioral

Question 17: ***Module 1.14.1.4 (Label Comprehension Study (LCS)): While the Pivotal Label Comprehension Protocol, Data Collection Instrument (DCI) and LCS correspondences will be provided in Module 1.14.1.4, should the LCS report be provided in Module 5?***

FDA Response to Question 17:

Yes, providing the LCS report in Module 5 is acceptable.

Discussion:

No discussion occurred.

Question 18: ***For Module 5: Pfizer will submit the pivotal LCS datasets, the transcribed verbatim responses, as well as mitigation responses in CDISC formats. Does the Agency agree?***

FDA Response to Question 18:

Yes, we agree. In addition to the dataset in CDISC format, provide analytic dataset with one record per a subject so that responses from the same subject to different questions will be in different columns. Submit the protocol for comment prior to fielding study.

Discussion:

No discussion occurred.

Additional Discussion at Face-to-Face Meeting:

Combination Rule Discussion:

According to the Sponsor:

- There was a statistically significant treatment effect compared to placebo and to each of the individual components in the pain studies
- (b) (4)

The Sponsor asked whether its proposed fixed-dose combination product must demonstrate a statistically significant treatment effect compared to each of the individual components for (b) (4) the pain (b) (4) indications. (b) (4)
(b) (4)

(b) (4)

The Sponsor asked if the observed findings would preclude submission of the NDA, and FDA reiterated that these findings would not preclude submission of the NDA, and that FDA would consider a weight-of-evidence approach based on all available data. FDA noted that both ibuprofen and acetaminophen are associated with adverse effects and that it will be critical to demonstrate that both components (b) (4)

(b) (4)

The Sponsor asked if FDA would consider labeling the product for the pain indication only (b) (4)

(b) (4) FDA responded that this would be a review issue.

Label Comprehension Study Discussion

FDA could not provide preliminary feedback on the Label Comprehension Study because it was recently received. FDA will provide comments in the official written response only (WRO).

3.0 OTHER IMPORTANT MEETING INFORMATION

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.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's

finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

- Pfizer response to FDA Preliminary Comments

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

/s/

KAREN M MAHONEY
04/18/2018