

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211733Orig1s000

OTHER REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV (ODE IV)
Office of Biostatistics (OB)

Integrated Review

Label Comprehension Study

Application Type/Number	NDA 211733
Drug Name(s)	Advil ® Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets)
Indication(s)	Pain reliever
Applicant/sponsor	Pfizer Inc.
Date(s)	Submission Date: November 21, 2019 PDUFA Goal Date: February 29, 2020
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Executive Summary

A pivotal Label Comprehension Study (LCS) was conducted to determine how well consumers understood a key novel feature of the label for a product containing Advil, (b) (4) the proposed Drug Facts Label (DFL) for Advil® Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets). An additional exploratory question to assess adult consumers' general understanding of the term "dual action" was also evaluated at FDA's request. The overall results from the LCS were satisfactory in the general adult population as well as in the low literacy and adolescent subpopulations.

1. Introduction and Background

1.1 Overview

On January 31, 2019, Pfizer Inc. (the sponsor) submitted a pivotal LCS as part of NDA 211733 that described how well subjects understood key communication messages from the proposed Drug Facts Label (DFL) for Advil® Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets). The proposed indication was "pain reliever (b) (4)." In an advice letter submitted on October 18, 2019, FDA requested that the sponsor modify the DFL (b) (4) to conduct an additional pivotal LCS to verify that subjects understand the revised product "Uses" (as a pain reliever). On October 23, 2019, the sponsor submitted a draft protocol for the additional pivotal LCS. FDA sent two advice letters providing feedback on the protocol. One comment stated that CDISC compliance is not required, provided that within the dataset there are columns for each response (initial and follow-up) showing coding, as well as a column for overall correct / incorrect for each question.

This review evaluates Pfizer's additional pivotal LCS, submitted on November 21, 2019 as a major amendment. The objective of this study was to describe the comprehension of the absence of (b) (4) from the product "Uses" on the proposed DFL by adult and adolescent subjects from the general population. An additional exploratory question to assess adult consumers' understanding of the term "Dual Action" was also evaluated.

1.2 Data Sources

The applicant submitted all NDA files electronically. The November 21, 2019 submission contained the additional pivotal LCS report, the final protocol, the analysis/derived comprehension datasets used for statistical analysis and reporting of comprehension results, the raw baseline and comprehension datasets used as the source to create the analysis dataset, and associated documentation including define files and annotated CRF.

However, the sponsor did not initially submit a derived baseline dataset. Additionally, the comprehension datasets only included the overall scoring for each question based on the initial question and follow-up question. Following an information request from FDA sent on December 4, 2019, the sponsor submitted on December 18, 2019 and January 17, 2020 derived baseline

dataset, derived comprehension datasets and programming specifications that would allow FDA to derive separately the scores for the initial response and the follow-up response.

The raw datasets for the LCS and associated documentation are available at:

- <\\CDSESUB1\evsprod\NDA211733\0023\m5\datasets\pf-06438867-29oct19-044313>

Clarifications on all subjects included/excluded in raw datasets are available at:

- <\\CDSESUB1\evsprod\NDA211733\0024\m1\us\response-gen-advice-04-dec-19-clinical.pdf>

The derived baseline dataset for the LCS and associated documentation are available at:

- <\\CDSESUB1\evsprod\NDA211733\0024\m5\datasets\pf-06438867-29oct19-044313\analysis\legacy\datasets\derived-data>

The derived comprehension datasets for the LCS, and associated documentation are available at:

- <\\CDSESUB1\evsprod\NDA211733\0023\m5\datasets\pf-06438867-29oct19-044313\analysis\legacy\datasets\derived-data>
- <\\CDSESUB1\evsprod\NDA211733\0025\m5\datasets\pf-06438867-29oct19-044313\analysis\legacy\datasets\derived-data>

The programming specifications for the derived comprehension datasets are available at:

- <\\CDSESUB1\evsprod\NDA211733\0024\m1\us>
- <\\CDSESUB1\evsprod\NDA211733\0025\m1\us>

The annotated CRF is available at:

- <\\CDSESUB1\evsprod\NDA211733\0023\m5\datasets\pf-06438867-29oct19-044313\tabulations\legacy>

The pivotal LCS report and final protocol is available at:

- [\\CDSESUB1\evsprod\NDA211733\0023\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-reliever-\(b\) \(4\)\5354-other-stud-rep\pf-06438867-29oct19-044313](\\CDSESUB1\evsprod\NDA211733\0023\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-reliever-(b) (4)\5354-other-stud-rep\pf-06438867-29oct19-044313)

1.3 Data and Analysis Quality

Data submitted following the information request on December 4, 2019 were of sufficient quality and facilitated easy analysis of the study primary, secondary and exploratory endpoints.

2. Study Design

2.1 Study Overview

This was a multicenter pivotal LCS conducted in seven retail shopping mall sites geographically dispersed across the United States. Data for adults and adolescents were collected via structured, one-on-one interviews utilizing scenario-based questions with follow up probes to ascertain rationale for the response. Additionally, adult subjects were asked the meaning of the name “Dual Action.” Interviews were audio-recorded and transcribed for use in analyses.

2.2 Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Males and females 12 years of age and older from the general population.

Exclusion Criteria:

1. Refused to provide explicit consent to collect health and demographic information during screening or re-screening
2. Was less than 12 years old, or was 12-17 years of age and not accompanied to the research site by a parent or legal guardian
3. Was unable to speak or understand English
4. Subject or someone in his or her household worked:
 - For a pharmaceutical or consumer healthcare company
 - As a healthcare professional (HCP) or as part of a healthcare practice
5. Could not see well enough to read information on the label (subject needed contact lenses or glasses to read but did not have them at the time of the visit)
6. Participated in any clinical trial or market research study for healthcare products in the past 12 months
7. Participated in any clinical trial or market research study for pain reliever products in the past 2 years

Additionally, subjects who refused to sign the confidentiality statement or permission-to-audio-record form were excluded, and no further data was collected.

The LCS protocol states that screening for reading ability may also be implemented to ensure adequate representation of adult low-literacy subjects (approximately 30%) in the overall adult sample. For example, if only low-literacy adult subjects were needed to ensure adequate representation for this group, a REALM Test score of 61 or above was implemented as an additional exclusion criterion. No literacy quotas were implemented for adolescent subjects.

Social Science Reviewer Comment:

Inclusion/Exclusion criteria appear acceptable.

2.3 Recruitment

This study utilized both pre-recruitment of subjects by telephone as well as direct-intercept recruitment of subjects from general consumer traffic in the malls. Pre-recruited subjects were contacted approximately 1-2 weeks before the start of the study via telephone to assess their interest in participating and to determine if they qualified to participate. Interested subjects who qualified had an appointment scheduled at the nearest mall site. Parents of adolescent subjects were screened by telephone to ensure that the pre-recruited adolescents would be accompanied to the site by a parent or a legal guardian.

Subjects recruited via direct-intercept from the mall floor were screened for eligibility and then taken directly to the on-site interviewer to complete the interview. During recruitment no information was given about the content of the interview.

Social Science Reviewer Comment:

Recruitment strategy appears acceptable. It is noted that recruitment of adolescents solely through their parents could affect the randomness of the sample.

2.4 Study Objectives

The Primary Communication Endpoint for this study was:

- Uses: Temporarily relieves minor aches and pains due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis

The primary endpoint was considered successful if the lower limit of the 95% confidence interval (CI) equaled or exceeded the 85% a priori performance threshold.

The Secondary Communication Endpoints for this study were:

- Consumer awareness that “Uses” do include a representative minor ache or pain
- Consumer awareness that “Uses” (b) (4)

No performance threshold was set for the secondary endpoints.

The exploratory endpoint for this study was:

- Adult consumers’ understanding of the term “Dual Action”

Social Science Reviewer Comment:

Study objectives are acceptable.

2.5 Study procedures

Obtain Parental Permission and Verify Screening Information:

Adolescent subjects were instructed to arrive at the research site with a parent or guardian who would need to sign a permission form for their child to participate in the study. Parents were asked to accompany their child throughout the interview but to refrain from participation as the interview questions will be addressed to the adolescent. Interviews were conducted in a private interviewing room in the research center. In the interviewing room, the eligibility criteria first evaluated at screening was reviewed once again to ensure that the subject qualified.

Health Literacy Assessment:

The REALM and REALM Teen tests were administered by an interviewer trained in the proper administration of these literacy tests. A score of 60 or less was defined as low literacy for adult subjects. The tests were scored in the EDC system.

REALM Test Grade-Equivalent Reading Levels

REALM	Grade-Equivalent Reading Level
0-18	Third and below
19-44	Fourth to sixth
45-60	Seventh to eighth
61-66	Ninth and above

REALM Teen Test Grade-Equivalent Reading Levels

REALM Teen	Grade-Equivalent Reading Level
0-37	Third and below
38-47	Fourth to fifth
48-58	Sixth to seventh
59-62	Eighth to ninth
63-66	Tenth and above

Confidentiality Agreement and Permission to Audio Record:

Once eligibility was confirmed, subjects were asked to sign a confidentiality statement and a form granting permission to audio record.

Presentation of Product Label:

The proposed DFL and Principal Display Panel (PDP) were displayed on empty packages. Subjects were handed the package and asked to read the information. Subjects were allowed as much time as necessary to review the package. When finished reading, subjects were told they could refer to the information on the package at any time during the interview. The interviewer then began audio-recording the interview.

Comprehension Interview Questions:

Standardized comprehension questions were asked of each subject. Subjects were shown the question in printed format as the interviewer read the question from the computer screen. The printed question remained visible to the subject until a response was given. The printed question, along with the verbal one, was included so that subjects who prefer to read the question instead of hearing it were not at a disadvantage. If requested, the interviewer could repeat a question but paraphrasing or explaining anything about the question was not permitted. Once a question was answered, subjects were not allowed to revise their answer to a previous question.

Adult subjects were asked an additional question regarding the meaning of the term ‘Dual Action’. Basic demographic information was collected from all subjects.

Post-Interview Process:

Following the conclusion of the interview, subjects were compensated for their time.

Social Science Reviewer Comment:

FDA typically requests that parents not be present in the interview room as it can influence adolescents' answers about their attitudes and behaviors.

2.6 Scoring of Endpoints

Scoring criteria for “correct” or “acceptable” responses (when applicable) for each communication endpoint was prespecified in the data collection instrument. The overall score for each endpoint question was determined by reviewing the subject’s combined verbatim narrative including the initial response and the follow-up response (“Could you please tell me why you say that?”).

3. Statistical Methods

3.1 Sample Size

The sponsor proposed a sample size of 300 adults based on a power analysis. Assuming a 2-sided test with $\alpha = 0.05$, an expected correct comprehension rate of 91% and a performance threshold of 85% for the primary endpoint, a sample of 300 subjects would provide greater than 85% power based on the Wald Method for the binomial distribution.

The sponsor proposed a sample size of 50 adolescents. This sample size was not selected based on statistical considerations; the sponsor considered that it was adequate because all analyses regarding comprehension among adolescents were descriptive.

Statistics Reviewer Comment:

Sample size was agreed upon prior to trial initiation and appears acceptable.

3.2 Statistical Analysis

3.2.1 Disposition and Demographic characteristics

Subjects’ disposition and demographic characteristics were summarized for both adults and adolescents using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions for categorical variables (sex, race/ethnicity, age categories, and education level). Frequency distributions were also summarized by literacy level for adult subjects and by reading-grade level for adolescent subjects.

3.2.2 Analysis of Primary and Secondary Endpoints

The analysis estimated the comprehension rate for each communication message in the analysis population, which consists of adult subjects who satisfied inclusion/exclusion criteria and answered at least one comprehension question. The comprehension rate was computed as the number of subjects with an overall correct or acceptable response (including responses mitigated to “acceptable” status) divided by the number of subjects in the analysis population, unless otherwise specified (see subsection below, on ‘Missing Data Handling Rules for Endpoint Calculations’). In addition to point estimates (PEs), two-sided Wilson 95% confidence intervals (CIs) for binomial proportions were reported for primary and secondary endpoints. For the primary endpoint, the communication objective was considered comprehended if the lower bound (LB) of the CI for the comprehension rate was equal to or greater than the 85% pre-defined performance threshold. Secondary endpoints were not evaluated against performance thresholds.

3.2.3 Analysis of Exploratory Endpoints

Exploratory endpoints were not evaluated against performance thresholds. The exploratory endpoints were presented and summarized descriptively, using counts and percentages.

3.2.4 Missing Data Handling Rules for Endpoint Calculations

When a subject’s response was missing due to an inability or refusal to answer, the missing data was reported in a frequency table and included in the denominator for endpoint calculations.

Subjects were identified in a table footnote but not included in the denominator for an endpoint calculation in the following situations:

- The participant’s response was missing due to premature termination of the interview
- The participant was not asked the question due to an unforeseen circumstance, or the response was not properly recorded, and there is no additional information (e.g., data for the entire question series is missing).

Statistics Reviewer Comments:

The sponsor conservatively coded missing responses due to refusal/inability to answer as incorrect but did not count other types of missing data as incorrect. However, this did not impact the study conclusions because there was no subject that started the comprehension interview who did not complete it and there was no subject who completed the comprehension interview who had missing survey responses.

3.2.5 Subgroup Analyses

Estimates of comprehension rates and 95% confidence intervals were summarized separately for adolescents and literacy level (low literacy and normal literacy).

4. Study Results

4.1 Disposition

A total of 410 subjects were screened for participation in the study. Of these, 18 subjects were disqualified during screening. Of the remaining 392 subjects who met inclusion criteria and initial qualification requirements, 33 subjects did not begin the comprehension interview for various reasons documented in Appendix Table 1. The surveyed analysis population thus included 359 subjects (310 adults and 49 adolescents).

4.2 Demographics

A summary of the demographic characteristics of study subjects is provided below in Table 1.

Table 1. Summary of Subject Demographic Characteristics for Adult Subjects and Adolescents		
	Adults, N = 310 Percent % (n)	Adolescents, N = 49 Percent % (n)
Literacy		
Normal Literacy	69.7 (216)	18 (36.7)
Low Literacy	30.3 (94)	31 (63.3)
Sex		
Male	47.4 (147)	53.1 (26)
Female	52.6 (163)	46.9 (23)
Ethnicity		
Hispanic / Latino	26.5 (82)	38.8 (19)
Not Hispanic / Latino	73.5 (228)	61.2 (30)
Race		
White	69.4 (215)	75.5 (37)
Black or African American	19.7 (61)	16.3 (8)
Asian	4.5 (14)	0.0 (0)
Native Hawaiian or Pacific Islander	1.0 (3)	2.0 (1)
American Indian or Alaska Native	4.5 (14)	4.1 (2)
Other	8.1 (25)	14.3 (7)
Refused	0.3 (1)	0.0 (0)
Age		
Mean (SD)	39.4 (15.07)	14.4 (1.83)

4.3 Comprehension Results

4.3.1 Primary Endpoints

For the primary endpoint which tested comprehension of ‘Uses: Temporarily relieves minor aches and pain due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis’, 97.2% of the surveyed population provided a Correct response.

Table 2. Comprehension Results: Primary Endpoint <i>Uses: Temporarily relieves minor aches and pain due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis</i>		
Response	Percent % (n)	95% Confidence Interval
Correct	97.2 (349)	(94.9, 98.7)
Not Correct	2.8 (10)	(1.3, 5.1)

Social Science Reviewer Comment:

The results for this endpoint were acceptable.

4.3.2 Secondary Endpoints

For the secondary endpoint which tested ‘Consumer awareness that “Uses” do include a representative minor ache or pain’, 88.0% of the surveyed population provided a Correct response and an additional 9.8% provided an acceptable response.

For the secondary endpoint which tested ‘Consumer awareness that “Uses” (b) (4)’, 83.3% of the surveyed population provided a Correct response and an additional 12.8% provided an acceptable response.

Table 3. Comprehension Results: Secondary Endpoints		
Response	Percent % (n)	95% Confidence Interval
<i>Consumer awareness that “Uses” do include a representative minor ache or pain</i>		
Total Correct or Acceptable	97.8 (351)	(95.7, 99.0)
Correct	88.0 (316)	(84.2, 91.2)
Acceptable	9.8 (35)	(6.7, 13.3)
Not Correct	2.2 (8)	(1.0, 4.3)
<i>Consumer awareness that “Uses” (b) (4)</i>		
Total Correct or Acceptable	96.1 (345)	(93.5, 97.8)
Correct	83.3 (299)	(79.0, 87.0)
Acceptable	12.8 (46)	(9.5, 16.7)
Not Correct	3.9 (14)	(2.2, 6.5)

Social Science Reviewer Comment:

The coding and results for the endpoint “Consumer awareness that “Uses” do include a representative minor ache or pain” were acceptable.

Overall, the coding for the endpoint “Consumer awareness that Uses (b) (4)” is acceptable. A sensitivity analysis was performed to examine responses for Question 4 to determine if proper coding was utilized. There were instances of responses being miscategorized as acceptable/correct, but not enough to lower the final results significantly. The “4b” column was miscategorized as incorrect when left blank. Some subjects confused “headache” with (b) (4) but not enough to significantly impact results. Results from this endpoint were acceptable.

4.3.3 Exploratory Endpoint

For the exploratory endpoint which tested ‘Adult consumers’ understanding of the term “dual action’, 86.1% of the surveyed adult population provided a Correct response.

Table 4. Comprehension Results: Endpoint <i>Adult consumers’ understanding of the term “dual action”</i>		
Response	Percent % (n)	95% Confidence Interval
Correct	86.1 (267)	(81.8, 89.5)
Not Correct	13.9 (43)	(10.5, 18.2)

Social Science Reviewer Comment:

The results for this exploratory endpoint were acceptable. A sensitivity analysis was performed to examine responses for Question 5 to determine if proper coding was utilized. There were instances of responses being miscategorized as acceptable/correct, but not enough to lower the final results significantly.

4.4 Subgroup Analyses

Among adult subjects, 98.9% of low literacy subjects and 95.8% normal literacy adults provided a Correct response for the primary endpoint.

For both secondary endpoints, more than 90% of low literacy and normal literacy adults provided a Correct or Acceptable response.

For the exploratory endpoint, proportion of subjects providing Correct responses was 91.2 % among normal literacy adults and 74.5% among low literacy adults.

Table 5. Low vs Normal Literacy Comprehension				
	Low Literacy, N = 94		Normal Literacy, N = 216	
Response	Percent % (n)	95% Confidence Interval	Percent % (n)	95% Confidence Interval
<i>Uses: Temporarily relieves minor aches and pain due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis</i>				
Total Correct Responses	98.9 (93)	(94.2, 99.8)	95.8 (207)	(92.3, 97.8)
<i>Consumer awareness that “Uses” do include a representative minor ache or pain</i>				
Total Correct or Acceptable Responses	96.8 (91)	(91.0, 98.9)	99.5 (215)	(97.4, 99.9)
<i>Consumer awareness that “Uses” (b) (4)</i>				
Total Correct or Acceptable Responses	93.6 (88)	(86.8, 97.0)	96.3 (208)	(92.9, 98.1)
<i>Adult consumers’ understanding of the term “dual action”</i>				
Total Correct Responses	74.5 (70)	(64.8, 82.2)	91.2 (197)	(86.7, 94.3)

The proportion of Correct responses for the primary endpoint and the two secondary endpoints was greater than 90% in both adult and adolescent sub-groups of surveyed population.

Table 6. Adult vs Adolescent Comprehension				
	Adult, N = 310		Adolescent, N = 49	
Response	Percent % (n)	95% Confidence Interval	Percent % (n)	95% Confidence Interval
<i>Uses: Temporarily relieves minor aches and pain due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis</i>				
Total Correct Responses	96.8 (300)	(94.2, 98.2)	100.0 (49)	(92.7, 100.0)
<i>Consumer awareness that “Uses” do include a representative minor ache or pain</i>				
Total Correct or Acceptable Responses	98.7 (306)	(96.7, 99.5)	91.8 (45)	(80.8, 96.8)
<i>Consumer awareness that “Uses” (b) (4)</i>				
Total Correct or Acceptable Responses	95.5 (296)	(92.6, 97.3)	100.0 (49)	(92.7, 100.0)

Statistics Reviewer Comments:

The statistical reviewer was able to confirm the results for all endpoints reported by the sponsor in the ‘Quantitative Label Testing Report’.

Low literacy subjects performed better on the primary endpoint than normal literacy and were within acceptable range of normal literacy on the secondary endpoints. Low literacy subjects had a lower comprehension score for the exploratory endpoint. This question required the subject to apply abstract thinking since the answer does not appear on the product labeling. This type of question/answer is one where low literacy subjects typically struggle. Adolescent subjects outperformed adults on the primary endpoint and secondary endpoint 2. They were within acceptable range for the remaining secondary endpoint.

4.5 Summary of Issues

As requested by the FDA, the sponsor conducted an additional pivotal LCS to describe the comprehension of the product “Uses” from the proposed Drug Facts Label (DFL). The study endpoints were related to subjects’ understanding of discrete communication messages from the DFL.

The study also tested as secondary endpoints ‘Consumer awareness that “Uses” do include a representative minor ache or pain’ and ‘Consumer awareness that “Uses” [REDACTED]’ without any target thresholds. The study showed that 97.8% of subjects provided a correct or acceptable response when tested on the former and 96.1% provided a correct or acceptable response when tested on the latter.

Social Science

Overall, the study results showed comprehension (b) (4) the indications for this product and the study primary endpoint was met. While there were coding mistakes made in data analysis, they were not significant enough to impact overall study results.

4.6 Conclusions and Recommendations

Biostatistics

From a statistical standpoint, the sponsor's additional pivotal LCS verified that subjects understand the revised product uses. Specifically, the study verified an understanding of the DFL communication message '*Uses: Temporarily relieves minor aches and pain due to: headache, toothache, backache, menstrual cramps, muscular aches, minor pain of arthritis*'. This is supported by the lower bound of the proportion of correct responses to the test question being greater than the target threshold of 85% overall and in sub-groups of adults, adolescents, low and normal literacy adults.

Social Science

From a Social Science perspective this application is approvable.

5. Appendix

Table 7. Subject Disposition Status

	All Subjects (N=410)
Subjects who started screening	410 (100.0%)
Subject who met exclusion criteria ^[1]	18 (4.4%)
Refused to provide explicit consent to collect health and demographic information during screening	0 (0.0%)
Was less than 12 years old	0 (0.0%)
Was 12-17 years of age and not accompanied to the research site by a parent or legal guardian (or did not sign the parental permission form)	2 (0.5%)
Unable to speak or understand English	0 (0.0%)
Worked (or someone in household worked) for a pharmaceutical or consumer healthcare company	3 (0.7%)
Worked (or someone in household worked) as a healthcare professional (HCP) or as part of a health care practice	6 (1.5%)
Could not see well enough to read information on the label (subject needed contact lenses or glasses to read but did not have them at the time of the visit)	8 (2.0%)
Participated in a clinical trial or market research study for healthcare products in the past 12 months	1 (0.2%)
Participated in a clinical trial or market research study for pain reliever products in the past 2 years	1 (0.2%)
Subjects who met inclusion criteria	392 (95.6%)
Interview completed	359 (87.6%)
Qualified on the mall floor, but elected to leave before receiving Privacy Notice	5 (1.2%)
Qualified, but refused to sign confidentiality statement or Permission-to-Audio-Record form	1 (0.2%)
Qualified, but literacy quota group was full	23 (5.6%)
Qualified, but demographic quota group was full	2 (0.5%)
Qualified, but did not start comprehension questions	2 (0.5%)
Comprehension questions started but not completed	0 (0.0%)
Comprehension questions completed, but survey responses missing (not transcribed) due to malfunction of audio recording	0 (0.0%)
Survey Population ^[2]	359 (87.6%)

Data Source: [Table 14.1](#)

N= number of subjects

[1] Responses are not mutually exclusive. Sum of percentages may be greater than 100%.

[2] Survey population is defined as the number of subjects who met the inclusion criteria and answered at least one comprehension question (which includes “Interview Completed” and “Comprehension questions started but not completed”).

Source: ‘Table 5. Subject Disposition Status’ on page 26 of ‘Quantitative Label Testing Report’ located at
 \\CDSESUB1\evsprod\NDA211733\0023\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-reliever-
 (b) (4) 5354-other-stud-rep\pf-06438867-29oct19-044313

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02/28/2020 10:55:09 AM

Addendum Draft Labeling Review for Advil Dual Action with Acetaminophen Tablets (acetaminophen 250 mg & ibuprofen 125 mg)

SUBMISSION DATES: January 31, 2019; February 18, 2020; February 24, 2020; February 27, 2020

NDA: 211733/Original NDA

ACTIVE INGREDIENTS: Acetaminophen 250 mg and Ibuprofen 125 mg

DOSAGE FORM: Tablets (sold in capsule shape as ‘caplets’)

SPONSOR: Pfizer Inc.
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PROJECT MANAGER: LT Sally Doan, PharmD, OND/ORO/DRO-NPD

I. BACKGROUND

This document is an addendum that completes the labeling review submitted September 23, 2019. That review recommended labeling revisions for labeling submitted January 31, 2019 and was uploaded to meet a PDUFA requirement that all reviews are submitted at the same time. Sections of that review were incomplete since it was uploaded before other disciplines provided their final recommendations. This addendum captures the final clinical recommendations and evaluates the final labeling submission in this application and the labeling revisions that were requested of Sponsor.

The previous review was completed under the premise that the product 1.) would receive a complete response letter, 2.) was considered for (b) (4) pain relief (b) (4) indications, and 3.) would not include any additional instruction to use the medication in a fasting state. Since then, Sponsor was informed that data submitted in their application (b) (4) filed a major amendment (b) (4)

(b) (4) which included changes to the Drug Facts label, and to provide data from a labeling comprehension study showing that consumers understand that Sponsor's product, "Advil Dual Action with Acetaminophen," is only indicated for pain relief. After these significant changes to the product's indication for use and its labeling the review team found the application approvable.

The third premise that my previous review was written under, the product's label would not include any additional instruction to use the medication in a fasting state, was based on preliminary team meetings with the Division Clinical Pharmacology II (ClinPharm), who noted that the food effect for the fixed dose combination (FDC) tablet was more pronounced than some similar products. Information requests were issued to Sponsor to determine if similar delays had been observed for similar OTC pain medication. Upon receiving appropriate justification from Sponsor, ClinPharm determined that the food effect observed with the FDC was not clinically meaningful and the FDC product is bioequivalent to immediate release products of the same strength.

An advice letter containing recommendations from my September 23, 2019 labeling review and the November 15, 2019 labeling review by the Division of Medication Error Prevention and Analysis (DMEPA) was sent to Sponsor February 04, 2020 (see Labeling Advice Letters and Information Requests below). Additional advice was provided for Sponsor's February 06, 2020 inquiry (see February 12, 2020 general advice letter) and Sponsor's February 18, 2020 submission (see February 19, 2020 general advice letter).

Significant revisions were made to the drug facts label (DFL) in the revised labeling that should be preserved in any proposed labeling changes.

- 1.) The "Acetaminophen liver damage warning" is now the first warning of the DFL.
- 2.) The allergy alert subheadings were modified to "Acetaminophen allergy alert" and "NSAID allergy alert."
- 3.) The spacing before and between the allergy alerts was increased.
- 4.) The directions are now displayed in a table format

For a full discussion of #1, #2, and #3 see section **II(A)ii Warnings** under Reviewer's Comments.

For a full discussion of #4 see section **II(A)iii Directions** under Reviewer's Comments.

LABELING ADVICE LETTERS AND INFORMATION REQUESTS

FDA Comment (February 04, 2020):

1. Per 21 CFR 201.326(a)(1)(iii)(A), the liver damage warning, located on the Drug Facts Label (DFL), must be the first warning under the **Warnings** heading. Revise your labeling so that the liver damage warning is the first warning subheading, above the allergy alert warnings in the DFL and immediate container labeling pieces that do not include a DFL.
2. While the print size of the term "**(NSAID)**" in the statement of identity (SOI) on the loose vial's principal display panel (PDP) is at least one-quarter the size of the most prominent printed matter, it is not at least as large as the size of the "Drug Facts" title, per 21 CFR 201.326(a)(2)(i). Increase the type size of the loose vial's statement of identity so that

“(NSAID)” is at least the size of the “Drug Facts” title.

3. Per 21 CFR 201.66(c)(2), change the DFL heading “*Active ingredient (in each caplet)*” to “*Active ingredients (in each caplet)*” because there are two active ingredients in each tablet.
4. Per 21 CFR 201.326(a)(2)(ii), change the format (i.e., move the asterisk) of the term “(NSAID)*” in the statement “Ibuprofen 125 mg (NSAID)*.... Pain reliever” under the Active ingredient section of the DFL to “(NSAID*)”.
5. Change the statement of identity (SOI) to include the dosage form, “Tablets” and move the term (NSAID) so that it immediately follows Ibuprofen. Revise your labeling so that the SOI reads, “Acetaminophen 250 mg and Ibuprofen (NSAID) 125 mg Tablets Pain Reliever”.
6. Provide the annotated labeling for the 24-count (18-ct + 6-ct) immediate container (bottle) in 1.14.1.2 .
7. The tamper evident statement located on the vial immediate containers, “DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED,” can only be viewed if the peel back label is peeled back. The goals of the tamper-evident statement would likely not be achieved if the statement only appears in a peel back or fold out label and is not clearly visible without peeling back or folding out the label. It is important that the consumer view the tamper evident statement before purchase and use of the drug product so that he or she will be better aware of the tamper-evident features and any signs of tampering. Relocate the tamper evident statement so that it is prominently displayed, per § 211.132(c) and the guidance for industry *Labeling OTC Human Drug Products —Questions and Answers* (December 2008).
8. Immediate container labels for bottles and vials without a full DFL separates statements using semi-colons instead of bullets. This format reduces clarity and ease of reading. Use bullets to separate statements under the “liver damage warning,” “stomach bleeding warning,” and “ask a doctor before use” warning on all immediate container labeling. This revision is consistent with approved immediate container labeling for ibuprofen and acetaminophen drug products.
9. Only 82% of the study participants in the pivotal labeling comprehension study were able to identify that the dosing interval was 8 hours. The visibility of the directions can be improved by using a 2 x 2 table (four cells in total) for the **Directions**, “adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist” and “children under 12 years: ask a doctor.” Revise your labeling to include a table like the table provided below.

adults and children 12 years and over	▪ take 2 caplets every 8 hours while symptoms persist
children under 12 years	▪ ask a doctor

10. The labeling for bottles in cartons does not include the graphic image of two tablets marked with “Advil II.” This graphic image was added to reinforce the dosing regimen of two tablets every 8 hours and was included on the 5-panel carton tested in the pivotal

labeling comprehension study. Revise your labeling so that the two-tablet graphic image is included on the PDP for all bottle immediate container labeling that has adequate spacing to accommodate the image.

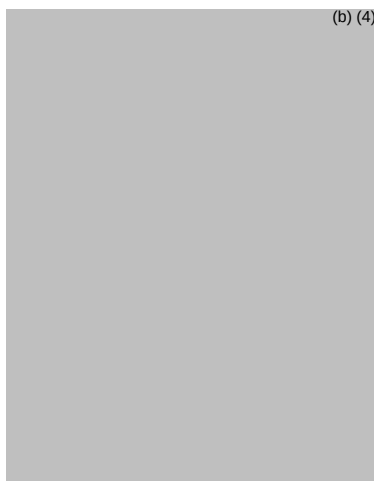
11. Propose an alternate placement for the instant redeemable coupons on the stand-alone bottles that does not obscure the graphic image of the two tablets marked with “Advil II” or any other regulatory information.
12. Submit an actual tablet sample or photograph of actual size tablet to allow for comparison to the graphic image on the PDP.
13. As currently presented, the format for the expiration date is not defined on the container label and carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
14. As currently presented, there’s a large discrepancy between the prominence of “Advil” and “Acetaminophen,” which both describe the active ingredients in your proposed product. To ensure consumers recognize that the proposed product is a combination of two drugs, i.e. ibuprofen (Advil) and acetaminophen, increase the prominence of “Acetaminophen” relative to “Advil” in the proposed proprietary name on the PDP.
15. As currently proposed, the imprint, “Advil II” only makes reference to the active ingredient, ibuprofen. Because the proposed product contains the additional active ingredient, acetaminophen, we recommend changing the imprint on the tablet (caplet) to an imprint that suggests both active ingredients or to a random imprint.

Sponsor Inquiry (February 06, 2020):

(Request #1) Pfizer has no objection to the Agency’s proposal to not have the Allergy Alert first, however, it now appears that the allergy alert only applies to acetaminophen (see example below). Please confirm the Agency would like to move forward with relocating the Allergy Alert?

(Request #8) For the few labels impacted, the additional spacing required to accommodate a bullet is not available, only semicolons can be utilized. Is this acceptable?

(Request #15) Although our current imprint meets 21 CFR 206.10, Pfizer would be willing to consider an imprint change in the future (via a supplement) since this is a considerable process. Please confirm this is not mandatory for approval?

**FDA Comment (February 12, 2020):**

1. Thank you for calling to our attention that the allergy alert appears to be grouped under the acetaminophen liver damage warning after the labeling revisions requested by the Agency in the February 4, 2020, information request. The Agency still believes that the Acetaminophen liver damage warning should be the first warning under the **Warnings** on the Drug Facts Label (DFL) to increase its prominence. Results from the Label Comprehension Study showed that subjects, especially those with low health literacy, struggled to locate the appropriate warning language on the label about what happens if two or more acetaminophen products are taken together and often confused the liver damage warning with the allergy alert warning. Placing the liver damage warning first will enhance the prominence of the warning and clearly separate it from the allergy alerts.

In the labeling sample you provided in your email on February 6, 2020, the space between the liver damage warning and the first allergy alert is greater than the spacing between allergy alerts. Maintain the spacing between the liver damage warning and first allergy alert, and increase the spacing between the allergy alerts to emphasize that the allergy alerts pertain to different active ingredients. Also, place “Acetaminophen” and “NSAID” before the allergy alerts in bold print so the allergy alert subheadings read, **“Acetaminophen allergy alert”** and **“NSAID allergy alert”** to emphasize that the NSAID alerts do not pertain to acetaminophen.

2. The Agency finds the use of semicolons in this case acceptable.
3. It is acceptable to not change the imprint on the tablets at this time. We acknowledge your commitment to change the imprint with a future supplement.

Sponsor Response (February 18, 2020):

(Request #1) Pfizer has adjusted the allergy alert to align with the Agency preliminary [February 12, 2020] comments.

(Request #2) Pfizer has updated the statement of identity as requested.

(Request #3) Pfizer has updated the DFL Active ingredients heading as requested.

(Request #4) Pfizer has updated the NSAID statement as requested.

(Request #5) Pfizer has updated the statement of identity as requested.

(Request #6) See the attached representative labeling: 1.14.1.2 Instructional PAA118181.FDA01 18+6ct Bottle

(Request #7) Pfizer has relocated the tamper evident statement so that it is more prominently displayed as requested.

(Request #8) See the attached representative labeling: 1.14.1.1 Clean 144ct bottle PAA116862.FDA02

(Request #9) Pfizer added the Directions table as requested on each component except the 2 count pouch, which will not have the necessary space.

(Request #10) Pfizer added this two tablet image where adequate spacing is available on each bottle. The image will be proportional to the product graphics and therefore the actual size will not be utilized.

(Request #11) Pfizer provided an actual tablet sample to the FDA Project Manager on 14 February 2020.

(Request #12) Pfizer has proposed an alternate placement for the instant redeemable coupons on the stand alone bottles as requested.

(Request #13) The format to be used is a 2 digit month/ 2 digit year (example: EXP 10/20). This format is utilized at the (b) (4) site for similar products and is controlled by the site's standard operating procedures (SOPs). The format selection is driven by the artwork/labeling configuration and constrained by the size of the smaller packaging components.

(Request #14) Given the Agency feedback, to further reinforce this combination communication, we will adjust the size discrepancy between "Advil" and "Acetaminophen" by decreasing the Advil logo by 5% and increasing the Acetaminophen by 10%. These adjustments will complement the label design measures which Pfizer has already taken to ensure that consumers recognize and understand this "dual" action product contains 2 ingredients:

- A large fifth panel was purposely added to the standard carton to communicate that the product "**CONTAINS 2 MEDICINES**" followed by "**Acetaminophen + Ibuprofen.**" This same call-out appears on the backer cards, stand alone bottles, and the dispenser as well.
- At the top of the inner container labels, both the bottle and vials, the "**CONTAINS 2 MEDICINES**" message appears to reinforce that the product has 2 ingredients.
- Under **Advil DUAL ACTION with Acetaminophen**, the statement of identity lists **Acetaminophen** (bolded) and Ibuprofen (not bolded) to further call attention to the presence of acetaminophen.
- Acetaminophen is listed first on the DFL Active Ingredients and highlighted
- The pivotal label comprehension study results demonstrated that consumers understand the product contains 2 ingredients.

(Request #15) Pfizer will consider your recommendation to change the imprint for the tablet. As we stated in our email response, although our current imprint meets 21 CFR 206.10, Pfizer would be willing to consider an imprint change in the future (via a supplement) since this is a considerable process. The lengthy process of changing the imprint requires the new identifier to be selected, and if it contains any trademarked content it must be assessed by our trademark

team to confirm clearance. After clearance, a new printer tooling would need to be manufactured and print trials conducted to ensure the logo can physically be printed on the tablet surface and that it is clear and legible.

FDA Comment (February 19, 2020):

1. We note that “acetaminophen” has been removed from the Acetaminophen allergy alert. Re-insert “acetaminophen” into the allergy alert so it reads, “Acetaminophen allergy alert: acetaminophen may cause severe skin reactions...”
2. We note that your attempt to prominently display the tamper evident statement on vial containers placed the statement at a location that will be affected by the tamper evident feature of the package. This location is not permitted per 21 CFR 211.132(c)(iii). Is it possible to place the tamper evident statement above the principal display panel by reducing the size of the UPC symbol? Otherwise, propose a location that will prominently display the tamper evident statement, per 21 CFR 211.132(c) and the guidance for industry Labeling OTC Human Drug Products — Questions and Answers (December 2008).
3. We note your attempt to adjust the size discrepancy between “Advil” and “Acetaminophen” by decreasing the Advil logo by 5% and increasing the size of “Acetaminophen” by 10%. However, a large discrepancy still persists, and it appears that there is space to further increase the size of “Acetaminophen.” Further increase the prominence of “Acetaminophen” relative to “Advil” in the proposed proprietary name on the PDP.

Sponsor Response (February 18, 2020):

1. Pfizer added the word “Acetaminophen” (and added “NSAID” for the respective alert) in front of the allergy alert warning as instructed. With limited space, especially on smaller cartons and inner labels, these extra words make this section more dense and this acetaminophen sentence now reads (b) (4) (Acetaminophen allergy alert: (b) (4) may cause severe skin reactions). Therefore we removed this second “(b) (4)” to yield a more succinct statement and conserve space: Acetaminophen allergy alert: may cause severe skin reactions. Please let us know if it is acceptable to keep this succinct statement.
2. Options are quite limited as to where we can place the TE statement, as the UPC cannot be manipulated further, is this preliminary option acceptable?



3. While it appears there may be more space to increase “acetaminophen” on the larger cartons, we are reaching the limit on the inner and smaller outer cartons, as we do not want to crowd the PDP or impede on the 2 tablet icon image. However, we will add another 5% increase to “acetaminophen”. Pfizer is making every attempt to balance what tested well (when too many elements are the same it is difficult for the eye to trace them), the capacity on the various pack sizes, and the Agency feedback.

FDA Comment (February 19, 2020):

Your proposals from this morning appear reasonable to the review team, at this time. Go ahead and submit your labeling for review.

Submitted Labeling	Dates Submitted
50 x 2-Count Pouch Dispenser	January 31, 2019; February 18, 2020
2-Count Pouch, Front Label	January 31, 2019; February 18, 2020
2-Count Pouch, Back Label	January 31, 2019; February 18, 2020
4-Count Carton (2 x 2-ct packets) Without Drug Facts Label (DFL)	January 31, 2019; February 27, 2020
Peel-Back DFL for 4-Count Carton	January 31, 2019; February 27, 2020
8-Count Loose Vial (“Old DWG” Style)	January 31, 2019; February 18, 2020; February 27, 2020
(b) (4)	
8-Count Loose Vial Shelf Tray	January 31, 2019; February 27, 2020
8-Count Packed Vial (“Old DWG” Style)	January 31, 2019; February 27, 2020
8-Count Packed Vial (“New DWG” Style)	January 31, 2019; February 27, 2020
8-Count Packed Vial Large Backer Card	January 31, 2019; February 18, 2020
8-Count Packed Vial Small Backer Card, Without DFL	January 31, 2019; February 27, 2020
Peel-Back DFL for 8-Count Packed Vial Small Backer Card	January 31, 2019; February 27, 2020
18-Count Outer Carton Without Complete DFL	January 31, 2019; February 18, 2020
18-Count Immediate Container (Bottle)	January 31, 2019; February 24, 2020
24-Count (18+6-Count) Outer Carton with Incomplete DFL	January 31, 2019; February 24, 2020
24-Count (18+6-Count) Immediate Container (Bottle)	January 31, 2019; February 24, 2020
36-Count Outer Carton with Incomplete DFL	January 31, 2019; February 24, 2020
36-Count Immediate Container (Bottle)	January 31, 2019; February 24, 2020
Peel-back DFL for 18-Count, 24-Count (18+6-Count), and 36-Count Outer Carton	January 31, 2019; February 18, 2020
Duplicate Peel-Back DFL for 24-Count (18+6-Count) Outer Carton	January 31, 2019

Submitted Labeling Continued	Date Submitted
72-Count Outer carton with Incomplete DFL	January 31, 2019; February 24, 2020
72-Count Immediate Container (Bottle)	January 31, 2019; February 24, 2020
90-Count (72+18-Count) Outer Carton with Incomplete DFL	January 31, 2019; February 24, 2020
90-Count (72+18-Count) Immediate Container (Bottle)	January 31, 2019; February 24, 2020
Peel-Back DFL for 72-Count and 90-Count (72+18-Count) Outer Carton	January 31, 2019; February 24, 2020
144-Count Outer Carton	January 31, 2019; February 18, 2020
144-Count Immediate Container (Bottle)	January 31, 2019; February 18, 2020
144-Count Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	January 31, 2019; February 18, 2020
162-Count (144+18-Count) Outer Carton	January 31, 2019; February 24, 2020
162-Count (144+18-Count) Immediate Container (Bottle)	January 31, 2019; February 24, 2020
162-Count (144+18-Count) Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	January 31, 2019; February 24, 2020
180-Count Immediate Container (Stand-Alone Bottle)	January 31, 2019; February 24, 2020
216-Count Outer Carton	January 31, 2019; February 27, 2020
216-Count Immediate Container (Bottle)	January 31, 2019; February 27, 2020
216-Count Immediate Container (Stand-Alone Bottle)	January 31, 2019; February 24, 2020
240-Count Outer Carton	January 31, 2019; February 27, 2020
240-Count Immediate Container (Bottle)	January 31, 2019; February 27, 2020
240-Count Immediate Container (Stand-Alone Bottle)	January 31, 2019; February 24, 2020; February 27, 2020
288-Count Immediate Container (Stand-Alone Bottle)	January 31, 2019; February 24, 2020; February 27, 2020
Instantly redeemable coupon (IRC) sticker \$1.00 off any Advil Dual Action 18-ct or larger	January 31, 2019
Instantly Redeemable Coupon (IRC) Sticker \$1.00 Off Any Advil Dual Action 18-ct or Larger	January 31, 2019
IRC Sticker \$2.00 Off Any Advil Dual Action 36-ct or Larger	January 31, 2019
IRC Sticker \$2.00 Off Any Advil Dual Action 72-ct or Larger	January 31, 2019
IRC Sticker \$3.00 Off Any Advil Dual Action 72-ct or Larger	January 31, 2019

Submitted Labeling Continued	Date Submitted
18-Count IRC (Peel-Off PDP) \$1.00 Off	January 31, 2019; February 18, 2020
36-Count IRC (Peel-Off PDP) \$1.00 Off	January 31, 2019; February 24, 2020
72-Count IRC (Peel-Off PDP) \$1.00 Off	January 31, 2019; February 24, 2020
144-Count IRC (Peel-Off PDP) \$1.00 Off	January 31, 2019; February 27, 2020

II. REVIEWER'S COMMENTS

A. Changes to Drug Facts Label

i. Active Ingredient/Purposes

Active ingredients (in each caplet)	Purposes
Acetaminophen 250 mg	Pain reliever
Ibuprofen 125 mg (NSAID)*	Pain reliever
*nonsteroidal anti-inflammatory drug	

FDA Request: Per 21 CFR 201.66(c)(2), change the DFL heading “Active ingredient (in each caplet)” to “Active ingredients (in each caplet)” because there are two active ingredients in each tablet.

Per 21 CFR 201.326(a)(2)(ii), change the format (i.e., move the asterisk) of the term “(NSAID)*” in the statement “Ibuprofen 125 mg (NSAID)*.... Pain reliever” under the Active ingredient section of the DFL to “(NSAID*)”.

Reviewer Comment: Sponsored revised their labeling to include both labeling revisions described above. This labeling revision is acceptable. The **Active ingredients** and **Purposes** section follow the formatting in § 201.66(c)(2) and § 201.326(a)(2)(ii)

ii. Warnings

FDA Request: Per 21 CFR 201.326(a)(1)(iii)(A), the liver damage warning, located on the Drug Facts Label (DFL), must be the first warning under the **Warnings** heading. Revise your labeling so that the liver damage warning is the first warning subheading, above the allergy alert warnings in the DFL and immediate container labeling pieces that do not include a DFL.

Reviewer Comment: The Agency requested that Sponsor revise their labeling so the “Acetaminophen liver damage warning” is the first warning under **Warnings** to increase its prominence. Results from the Label Comprehension Study showed that subjects, especially those with low health literacy, struggled to locate the appropriate warning language on the label about what happens if two or more acetaminophen products are taken together and often confused the liver damage warning with the allergy alert warning. Sponsor revised their labeling so that the liver damage warning is the first warning. However, Sponsor notified the Agency that because of this change and the unique highlighting for the liver damage warning and stomach bleeding warning the

allergy alerts for acetaminophen and ibuprofen appeared to be grouped under the acetaminophen liver damage warning (see labeling example from February 06, 2020 below)

Sponsor's Labeling Example from February 06, 2020 IR Response



To address this concern, the Agency requested four changes to visually decouple the allergy alerts from the liver damage warning (see image below):

1. Place “Acetaminophen” before the allergy alert acetaminophen in bold print so the allergy alert subheading reads, “**Acetaminophen allergy alert**”
2. Place “NSAID” before the second allergy alert for ibuprofen in bold print so the allergy alert subheading reads, “**NSAID allergy alert.**”
3. Maintain the increased spacing between the liver damage warning and the first allergy alert as proposed in Sponsor’s labeling example in their February 06, 2020 response (see above image).
4. Increase the spacing between the allergy alerts to emphasize that the allergy alerts pertain to different active ingredients.

Revised Warnings Labeling

#1 Addition of “Acetaminophen” →

#2 Addition of “NSAID” →

Warnings

Acetaminophen liver damage warning:

This product contains acetaminophen. Severe liver damage may occur if you take:

- with other drugs containing acetaminophen
- more than 6 caplets in 24 hours, which is the maximum daily amount for this product
- 3 or more alcoholic drinks every day while using this product

Acetaminophen allergy alert: may cause severe skin reactions. Symptoms may include:

- skin reddening ■ blisters ■ rash

If skin reaction occurs, stop use and seek medical help right away.

NSAID allergy alert: ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives ■ facial swelling
- asthma (wheezing) ■ shock
- skin reddening ■ rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

← **#3 Increased Space**

← **#4 Increased Space**

These labeling revisions were adopted out of clinical concern to emphasize the liver damage warning and what happens if two or more acetaminophen products are taken together. This labeling is acceptable.

iii. Directions

Directions	
■ do not take more than directed	
adults and children 12 years and over	■ take 2 caplets every 8 hours while symptoms persist
children under 12 years	■ ask a doctor
■ do not take more than 6 caplets in 24 hours, unless directed by a doctor	

FDA Request: Only 82% of the study participants in the pivotal labeling comprehension study were able to identify that the dosing interval was 8 hours. The visibility of the directions can be improved by using a 2 x 2 table (four cells in total) for the **Directions**, “adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist” and “children under 12 years: ask a doctor.” Revise your labeling to include a table like the table provided below.

adults and children 12 years and over	■ take 2 caplets every 8 hours while symptoms persist
children under 12 years	■ ask a doctor

Reviewer Comment: Sponsor revised their labeling to display the directions for “Advil Dual Action with Acetaminophen” in a table format. This labeling revision was made to improve visibility of the directions and reinforce to consumers the dosing regimen of two tablets every eight hours. The table improved the conspicuousness of the **Directions** on this long DFL. They are especially noticeable on the immediate container labeling. This labeling revision is acceptable.

This labeling revision, however, was not implemented in the in the 8-Count Packed Vial (“New DWG” Style) immediate container label. Request that Sponsor revise their labeling so that the Directions are display in a table format in the 8-Count Packed Vial (“New DWG” Style) immediate container label.

B. Changes to Label Outside Drug Facts

Principal Display Panel of 144-Count Outer Carton



i. Statement of Identity

FDA Request: Change the statement of identity (SOI) to include the dosage form, “Tablets” and move the term (NSAID) so that it immediately follows Ibuprofen. Revise your labeling so that the SOI reads, “**Acetaminophen** 250 mg and Ibuprofen (**NSAID**) 125 mg Tablets Pain Reliever”.

Reviewer Comment: Sponsor updated the statement of identity (SOI) (b) (4) include the dosage form, tablets, and moved the term “(NSAID)” so that it immediately follows “Ibuprofen” (see above image of Principal Display Panel). (b) (4) was removed from the SOI following the October 18, 2019 general advice letter and the October 09, 2019 and October 17, 2019 teleconferences.

The dosage form “Tablets” was added to the SOI to complete the established name, since the established name must include the active ingredients, strength, and dosage form. The term “(NSAID)” was moved to immediately follow “Ibuprofen” to improve legibility. The SOI now reads “Acetaminophen 250 mg and Ibuprofen (NSAID) 125 mg Tablets Pain Reliever”

Sponsor chose to display the SOI over three lines:

“Acetaminophen 250 mg and
Ibuprofen (NSAID) 125 mg Tablets
Pain Reliever”

This decision was favorably accepted by the review team. The vertical alignment of the active ingredients should improve the legibility of the SOI and inform consumers that the medicine contains two active ingredients.

This labeling is acceptable. The SOI meets the requirements found in § 201.61, § 201.326, and § 299.4.

ii. Vial Statement of Identity

FDA Request: While the print size of the term “(NSAID)” in the statement of identity (SOI) on the loose vial’s principal display panel (PDP) is at least one-quarter the size of the most prominent printed matter, it is not at least as large as the size of the “Drug Facts” title, per 21 CFR 201.326(a)(2)(i). Increase the type size of the loose vial’s statement of identity so that “(NSAID)” is at least the size of the “Drug Facts” title.

Reviewer Comment: Sponsor updated the SOI on their loose vial’s PDP so that it is at least as large as the size of the “Drug Facts” title, per 21 CFR 201.326(a)(2)(i). This labeling is acceptable.

iii. Proprietary Name

FDA Request: As currently presented, there’s a large discrepancy between the prominence of “Advil” and “Acetaminophen,” which both describe the active ingredients in your proposed product. To ensure consumers recognize that the proposed product is a combination of two drugs, i.e. ibuprofen (Advil) and acetaminophen, increase the prominence of “Acetaminophen” relative to “Advil” in the proposed proprietary name on the PDP.

Reviewer Comment: In their November 15, 2019 labeling review, DMEPA recommended increasing the prominence of “Acetaminophen” in the proposed proprietary name “to the extent that space permits” to help communicate that the product under review, “Advil Dual Action with Acetaminophen,” contains acetaminophen. DMEPA determined in their May 02, 2019 review that the proprietary name, “Advil Dual Action with Acetaminophen,” infers two active ingredients, ibuprofen and acetaminophen because “Advil” implies that the product contains ibuprofen and the

modifiers “Dual Action with Acetaminophen” indicate the product contains acetaminophen, thus satisfying 21 CFR 201.6(b). Sponsor originally proposed labeling that contained a large discrepancy between Advil and Acetaminophen.

Sponsor revised their labeling following the February 04, 2020 general advice letter by decreasing the Advil logo by 5% and increasing the size of “Acetaminophen” by 10%. Sponsor was again asked to adjust the size discrepancy in the February 19, 2020 advice letter. Sponsor responded by increasing the size of “Acetaminophen” by 5%.

This labeling revision is acceptable. While Advil is still the most prominent printed material on the PDP, the size discrepancy has been slightly reduced. Moreover, the width of the modifiers “Dual Action” and “with Acetaminophen” are now equal in the PDP (“Dual Action” was significantly longer than “with Acetaminophen” in the originally proposed labeling). These modifiers are the longest statements by total length in the PDP. DMEPA’s recommendations have increased the prominence of Acetaminophen.

iv. Tamper Evident Statement

FDA Request: The tamper evident statement located on the vial immediate containers, “DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED,” can only be viewed if the peel back label is peeled back. The goals of the tamper-evident statement would likely not be achieved if the statement only appears in a peel back or fold out label and is not clearly visible without peeling back or folding out the label. It is important that the consumer view the tamper evident statement before purchase and use of the drug product so that he or she will be better aware of the tamper-evident features and any signs of tampering. Relocate the tamper evident statement so that it is prominently displayed, per § 211.132(c) and the guidance for industry *Labeling OTC Human Drug Products —Questions and Answers* (December 2008).

Reviewer Comment: Sponsor initially proposed relocating the tamper evident statement to the tamper evident seal, a location that would be affected by the tamper evident feature of the package. This location is not permitted per 21 CFR 211.132(c)(iii), because removing the tamper evident seal would also remove the tamper evident statement warning consumers to look for the seal. The Agency requested Sponsor propose another location to prominently display the tamper evident statement.

Sponsor subsequently updated their vial labeling so that the tamper evident statement was directly left of the PDP. This revision required Sponsor to adjust the size of the PDP. However, Sponsor confirmed that although the total area of the PDP was reduced, they did not alter the print size of the statement of identity, the yellow highlighted acetaminophen warning, or the relative print size of “Acetaminophen” in the proprietary name.

The tamper evident statement, “DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED.” is now located to the left of the PDP in blue print in a white box. It identifies the tamper evident feature, is not affected by the

removal of the tamper evident feature, and is prominently displayed. This labeling revision is acceptable, per § 211.132(c).

v. Immediate Container Warnings

FDA Request: Immediate container labels for bottles and vials without a full DFL separates statements using semi-colons instead of bullets. This format reduces clarity and ease of reading. Use bullets to separate statements under the “liver damage warning,” “stomach bleeding warning,” and “ask a doctor before use” warning on all immediate container labeling. This revision is consistent with approved immediate container labeling for ibuprofen and acetaminophen drug products.

Reviewer Comment: The Agency requested that Sponsor add bullets to their liver damage warning, stomach bleeding warning, and ask a doctor before use warnings. Sponsor provided feedback about space considerations for their immediate container labeling, which the review team had accepted. However, per 21 CFR 201.326, bullets are a required part the liver damage warning and the stomach bleeding warning. It is recommended that Sponsor add bullets to the liver damage and stomach bleeding warnings in the final printed labeling.

vi. Graphic Image of Two Tablets Marked With “Advil II”

FDA Request: The labeling for bottles in cartons does not include the graphic image of two tablets marked with “Advil II.” This graphic image was added to reinforce the dosing regimen of two tablets every 8 hours and was included on the 5-panel carton tested in the pivotal labeling comprehension study. Revise your labeling so that the two-tablet graphic image is included on the PDP for all bottle immediate container labeling that has adequate spacing to accommodate the image.

Reviewer Comment: In their January 31, 2019 Sponsor proposed labeling for immediate container bottles (in outer cartons) and vials that did not contain the graphic image of two cream-color tablets marked with “Advil II.” This graphic image was added to the 5-panel outer carton to help communicate the dosing regimen of two tablets every eight hours during the pivotal labeling comprehension study. The Agency requested that Sponsor add this graphic image to all bottle immediate container labeling that has adequate spacing to accommodate the image. Sponsor updated all immediate container bottle labeling to include the graphic image of two tablets marked with “Advil II.” Sponsor also notified the Agency that “the image will be proportional to the product graphics and therefore the actual size will not be utilized.” However, an actual-size graphic image of the tablets is located on all outer cartons and stand-alone bottles. This labeling revision is acceptable and is implemented to reinforce the dosing regimen of two tablets every eight hours.

FDA Request: Submit an actual tablet sample or photograph of actual size tablet to allow for comparison to the graphic image on the PDP.

Reviewer Comment: Sponsor submitted a sample of four tablets in a white-cap (b) (4) vial. These tablets match the graphic image of two cream-color tablets marked with “Advil II.”

vii. Tablet Imprint

FDA Request: As currently proposed, the imprint, “Advil II” only makes reference to the active ingredient, ibuprofen. Because the proposed product contains the additional active ingredient, acetaminophen, we recommend changing the imprint on the tablet (caplet) to an imprint that suggests both active ingredients or to a random imprint.

Reviewer Comment: The Agency acknowledged Sponsor’s commitment to change the imprint.

viii. Instantly Redeemable Coupon Placement

FDA Request: Propose an alternate placement for the instantly redeemable coupons (IRC) on the stand-alone bottles that does not obscure the graphic image of the two tablets marked with “Advil II” or any other regulatory information.

Reviewer Comment: Sponsor proposed a location for the instant redeemable coupons on the stand-alone bottles that does not obscure the graphic image of the two tablets marked with “Advil II” or any other regulatory information. See above image.

III. RECOMMENDATIONS

An APPROVAL letter may be issued to Sponsor for the submitted Advil Dual Action with Acetaminophen (acetaminophen 250 mg and ibuprofen 125 mg) Tablets labeling submitted in NDA 211733 and request final printed labeling with the following corrections.

Labeling that do not require revision:

Request that Sponsor submit final printed labeling (FPL) identical to the labeling listed below (see table below).

Submitted Labeling	Date Submitted
2-Count Pouch, Front Label	February 18, 2020
2-Count Pouch, Back Label	February 18, 2020
4-Count Carton (2 x 2-Count packets) Without Drug Facts Label (DFL)	February 27, 2020
8-Count Loose Vial (“Old DWG”)	February 27, 2020
8-Count Loose Vial Shelf Tray	February 27, 2020
8-Count Packed Vial (“Old DWG” Style)	February 27, 2020
8-Count Packed Vial Small Backer Card	February 27, 2020

Submitted Labeling Continued	Date Submitted
24-Count (18+6-Count) Outer Carton	February 24, 2020
36-Count Outer Carton	February 24, 2020
Peel-back DFL for 18-Count, 24-Count (18+6-Count), and 36-Count Outer Carton	February 18, 2020
72-Count Outer Carton	February 24, 2020
90-Count (72+18-Count) Outer Carton	February 24, 2020
Peel-Back DFL for 72-Count and 90-Count (72+18-Count) Outer Carton	February 24, 2020
162-Count (144+18-Count) Outer Carton	February 24, 2020
162-Count (144+18-Count) Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	February 24, 2020
180-Count Immediate Container (Stand-Alone Bottle)	February 24, 2020
216-Count Outer Carton	February 27, 2020
216-Count Immediate Container (Stand-Alone Bottle)	February 24, 2020
240-Count Outer Carton	February 24, 2020
240-Count Immediate Container (Stand-Alone Bottle)	February 27, 2020
288-Count Immediate Container (Stand-Alone Bottle)	February 27, 2020
Instantly Redeemable Coupon (IRC) Sticker \$1.00 Off Any Advil Dual Action 18-ct or Larger	January 31, 2019
IRC Sticker \$2.00 Off Any Advil Dual Action 36-ct or Larger	January 31, 2019
IRC Sticker \$2.00 Off Any Advil Dual Action 72-ct or Larger	January 31, 2019
IRC Sticker \$3.00 Off Any Advil Dual Action 72-ct or Larger	January 31, 2019
IRC Sticker \$2.00 Off Any Advil Dual Action EZ Open 144-ct or Larger	January 31, 2019
36-Count IRC (Peel-Off PDP) \$1.00 Off	February 24, 2020
72-Count IRC (Peel-Off PDP) \$1.00 Off	February 24, 2020
144-Count IRC (Peel-Off PDP) \$1.00 Off	February 27, 2020

Labeling that Require Minor Revision:

Request that Sponsor submit final printed labeling (FPL) for the 2 x 50-ct count pouch dispenser, 8-count pack vial large backer card, 18-count outer carton, 144-count outer carton, 144-count immediate container (bottle), 144-count stand-alone bottle, and 18-count instantly redeemable coupon (peel-off PDP) with the correction to increase the size of the modifier “with Acetaminophen” within the proprietary name by an additional 5% on the principal display panel (see table below for list of affected labeling).

Submitted Labeling	Date Submitted
50 x 2-Count Pouch Dispenser	February 18, 2020
8-Count Packed Vial Large Backer Card	February 18, 2020
18-Count Outer Carton	February 18, 2020
144-Count Outer Carton	February 18, 2020
144-Count Immediate Container (Bottle)	February 18, 2020
144-Count Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	February 18, 2020
18-Count IRC (Peel-Off PDP) \$1.00 Off	February 18, 2020

Request that Sponsor submit final printed labeling (FPL) for the 18-count, 24-count, 36-count, 72-count, 90-count, 144-count, 162-count, 216-count, 240-count immediate container labeling with a correction to the “Acetaminophen liver damage warning” and the “NSAID stomach bleeding warning” (see table below for list of affected labeling). Per 21 CFR 201.326, bullets are a required part the liver damage warning and the stomach bleeding warning. Use bullets to separate statements under the “Acetaminophen liver damage warning” and “NSAID stomach bleeding warning” on all immediate container bottle labeling.

SUBMITTED LABELING	DATE SUBMITTED
18-Count Immediate Container (Bottle)	February 24, 2020
24-Count (18+6-Count) Immediate Container (Bottle)	February 24, 2020
36-Count Immediate Container (Bottle)	February 24, 2020
72-Count Immediate Container (Bottle)	February 24, 2020
90-Count (72+18-Count) Immediate Container (Bottle)	February 24, 2020
144-Count Immediate Container (Bottle)	February 18, 2020
162-Count (144+18-Count) Immediate Container (Bottle)	February 24, 2020
216-Count Immediate Container (Bottle)	February 27, 2020
240-Count Immediate Container (Bottle)	February 27, 2020

Remind sponsor to change the imprint on the tablet (caplet) to an imprint that suggests both active ingredients or to a random imprint, because the proposed product contains the additional active ingredient, acetaminophen. As currently proposed, the imprint, “Advil II” only makes reference to the active ingredient, ibuprofen.

Per 21 CFR 201.66(d)(5), a visual graphic (e.g., an arrow) shall be used to signal the continuation of the Drug Facts labeling to the next adjacent panel. The “Lift Here” designation is not part of the drug facts label (DFL). Insert an arrow within the second panel of the DFL for the 8-count packed vial small backer card extended label submitted February 27, 2020 and the 90-count immediate container (bottle) extended label submitted February 24, 2020.

Indent the sub-bulleted statements under **Uses** on the peel back drug facts label (DFL) for the 4-count carton (2 x 2 pouches) submitted February 27, 2020. We refer you to Question 21 in *Guidance for Industry Labeling OTC Human Drug Products — Questions and Answers* (December 2008) at <https://www.fda.gov/media/72441/download>.

On the same 4-count carton (2 x 2 pouches) extended label, submitted February 27, 2020, revise the DFL so that the first bulleted warning under **Do not use** is not split between two panels.

Display the **Directions** in table format in the 8-Count Packed Vial (“New DWG” Style) immediate container label. Revise your labeling to include a table like the table provided below.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

ROBERT J BAHDE
02/28/2020 01:09:51 PM

KEVIN L LORICK
02/28/2020 01:25:52 PM
I concur with the review and recommendations.

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 27, 2020
Requesting Office or Division:	Division of Nonprescription Drugs I
Application Type and Number:	NDA 211733
Product Name and Strength:	Advil Dual Action with Acetaminophen (ibuprofen/acetaminophen) tablets, 125 mg/250 mg
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2019-331-1
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Deputy Director:	Danielle Harris, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 18, 2020, February 24, 2020, and February 27, 2020, for Advil Dual Action with Acetaminophen. The Division of Nonprescription Drugs I (DNPDI) requested that we review the revised container labels and carton labeling for Advil Dual Action with Acetaminophen (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented or considered our recommendations and we have no additional recommendations at this time.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Jones, G. Label and Labeling Review for Advil Dual Action with Acetaminophen (NDA 211733). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-331.

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/s/

GRACE JONES
02/27/2020 02:43:24 PM

DANIELLE M HARRIS
02/27/2020 02:49:36 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

Date of Consult Request: February 14, 2019
From: Division of Nonprescription Drugs I (DNPD I)
Office of Nonprescription Drugs (ONPD)
NDA Number: 211733
Drug: Ibuprofen (125 mg)/Acetaminophen (250 mg) Fixed
Dose Combination (FDC) tablet
Applicant: Pfizer, Inc.
Proposed Indication: Temporary relief of minor aches and pains (b) (4)
(b) (4) in patients 12 years of
age and older

DNPD I submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) pediatric team on February 14, 2019 requesting our attendance at review meetings for this NDA. This application is subject to the Pediatric Research Equity Act (PREA) because the product is a new active ingredient (i.e., new combination). The Applicant submitted an Agreed initial Pediatric Study Plan (iPSP)² as part of its NDA submission.

Although the Applicant's original proposed indications included both temporary relief of minor aches and pains (b) (4) and the Agreed iPSP addressed both the pain (b) (4) indications, DNPD I determined that the data submitted are adequate to support the temporary reduction of pain indication only. As such, the requirements under PREA for this application are limited to the pain indication.

Based on PREA requirement discussions with the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) reviewers, DPMH and the Pediatric Review Committee (PerC), DNPD I will:

¹ The full proposed indication is "the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4) (b) (4)

² FDA acknowledged the agreed iPSP on January 6, 2016

- Grant a partial waiver for studies in pediatric patients birth to less than 6 months of age because the product would be ineffective and/or unsafe in this population for over-the-counter use without a learned intermediary;
- Grant a deferral for pediatric patients 6 months of age to less than 12 years of age because the product is ready for approval in adults;
- Consider the pediatric assessment for pediatric patients 12 to less than 18 years fulfilled and label this product for use in patients 12 years of age and older.

DNDP I agreed to extrapolate analgesic efficacy from adults to patients 2 years to less than 12 years of age, and will require a PK and safety trial in this age group. DNDP I will require a PK, safety and efficacy trial in patients 6 months to less than 2 years because the Applicant has not submitted adequate data to support that efficacy can be extrapolated from adults or older pediatric patients to patients in this age group. DNDP I will require a Labeling Comprehension study, and based on the results of this study, a Self-Selection study, an Actual Use study, or both (see Appendix: PREA Required Studies for NDA 211733). FDA identified challenges in studying patients 6 months to less than 2 years of age with pain. DNDP I communicated to the Applicant that FDA will work with them on the design of their pediatric trial.³

DPMH participated in the team meetings (March 2019 through February 2020), the PeRC discussion (January 14, 2020) and the teleconference discussing the PREA requirements with the Applicant (February 25, 2020). DPMH participated in the development of the language and due dates for the PREA requirements.

DPMH Pediatric Team Medical Officer - Elizabeth L. Durmowicz, MD
DPMH Pediatric Team Leader- Mona Khurana, MD
DPMH Deputy Division Director- John J. Alexander, MD, MPH
DPMH RPM- Jacqueline Yancy, Ph.D.

³ This information was communicated to the Applicant during the February 25, 2020 teleconference to discuss the PREA requirements for this application.

Appendix: PREA Required Studies for NDA 211733⁴

####-#

Pediatric pharmacokinetic and tolerability study in children 2 years to < 12 years of age with acute pain suitable for treatment with an OTC analgesic

The objective of the study is to characterize the PK profile and tolerability of IBU/APAP fixed-dose combination in children 2 years to < 12 years with acute pain suitable for treatment with an OTC analgesic.

Final Protocol Submission	12/2020
Study Completion	06/2022
Final Report Submission	12/2022

####-#

Pediatric pharmacokinetic, efficacy, and safety study in children with acute pain suitable for treatment with an OTC analgesic 6 months to < 2 years of age

The objective of the study is to evaluate analgesic efficacy, PK and tolerability of IBU/APAP fixed-dose combination in children 6 months to <2 years of age with acute pain suitable for treatment with an OTC analgesic.

Final Protocol Submission	03/2021
Study Completion	09/2022
Final Report Submission	03/2023

####-#

Pediatric targeted Label Comprehension Study for caregivers of children from birth to < 12 years of age.

The objective of the study is to ensure that caregivers of children under the age of 12 adequately understand the drug label of Advil Dual Action with Acetaminophen.

Final Protocol Submission	09/2023
Study Completion	09/2024
Final Report Submission	03/2025

####-#

Pediatric Self-Selection Study.

The design of this trial will be based on the results of the Label Comprehension Study (PMR #####).

⁴ These PREA PMRs and due dates were discussed with the Applicant on February 25, 2019. DNDP I communicated that the PREA requirements are not negotiable; however, DNDP I is willing to entertain modification of the deadlines to ensure the deadlines are reasonable. As such, the PREA PMR deadlines listed in this review may be modified.

Final Protocol Submission	09/2025
Study Completion	09/2026
Final Report Submission	03/2027

####-#

Pediatric Actual Use Study.

The design of this trial will be based on the results of the Pediatric Label Comprehension Study (PMR #####).

Final Protocol Submission	09/2025
Study Completion	09/2026
Final Report Submission	03/2027

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/s/

ELIZABETH L DURMOWICZ
02/26/2020 01:45:40 PM

MONA K KHURANA
02/26/2020 02:29:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health
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ADDENDUM TO MEMORANDUM TO FILE

Date of Consult Request: February 14, 2019
From: Division of Nonprescription Drug Products (DNDP)
NDA Number: 211733
Drug: Ibuprofen (125 mg)/Acetaminophen (250 mg) Fixed Dose Combination (FDC) tablet
Applicant: Pfizer, Inc.
Proposed Indication: Temporary reduction of pain (b) (4) in patients 12 years of age and older

DNDP submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) pediatric team on February 14, 2019 requesting our attendance at review meetings for this NDA.

In anticipation of DNDP issuing a Complete Response letter for this application, DPMH entered a Memorandum to File into DARRTS on November 19, 2019 to document DPMH's involvement in this application and close out this consult request. However, the applicant submitted a major amendment on November 21, 2019, providing new consumer use data to support approval of the pain indication, and DNDP granted a review extension on November 21, 2019.

As such, this consult is reopened and DPMH will continue to be involved in the review of this application.

DPMH Pediatric Team Medical Officer - Elizabeth L. Durmowicz, MD
DPMH Pediatric Team Leader- Mona Khurana, MD
DPMH Deputy Division Director- John J. Alexander, MD, MPH
DPMH RPM- Jacqueline Yancy, Ph.D.

¹ The full proposed indication is "the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4) ".
(b) (4)

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/s/

ELIZABETH L DURMOWICZ
12/10/2019 08:22:42 AM

MONA K KHURANA
12/11/2019 10:31:45 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM TO FILE

Date of Consult Request: February 14, 2019
From: Division of Nonprescription Drug Products (DNDP)
NDA Number: 211733
Drug: Ibuprofen (125 mg)/Acetaminophen (250 mg) Fixed Dose Combination (FDC) tablet
Applicant: Pfizer, Inc.
Proposed Indication: Temporary reduction of pain (b) (4) in patients 12 years of age and older

Consult Request:

DNDP submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) pediatric team on February 14, 2019 requesting our attendance at NDA review meetings.

Brief Summary

On January 31, 2019, the applicant submitted NDA 211733 seeking marketing approval for a new FDC oral tablet containing ibuprofen and acetaminophen for the temporary reduction of pain (b) (4) in patients 12 years of age and older.¹ The Prescription Drug User Fee Act (PDUFA) goal date for this product is November 22, 2019.

FDA and the applicant have had ongoing discussions about the pediatric development program for this product in pediatric patients 6 months to less than 12 years of age and the pediatric study requirements under the Pediatric Research Equity Act (PREA).² The

¹ The full proposed indication is “the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4) (b) (4) ”.

² Pediatric development discussions have focused on the ability to extrapolate adult efficacy data to pediatric patients 6 months to less than 2 years of age to support the (b) (4) pain indications in this

Agency issued an Amended Agreed initial Pediatric Study Plan (iPSP) to the applicant on January 6, 2016. The applicant submitted the agreed iPSP to the NDA on May 2, 2019 (see Appendix I).³

(b) (4)

Although DNDP determined the data support effectiveness for the pain indication, DNDP intends to issue a Complete Response (CR) because additional consumer testing is needed to ensure that consumers understand the proper use of this product.

DPMH participated in internal team meetings with DNDP from March 2019 to October 2019.

DPMH has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Pediatric Team MO Reviewer- Elizabeth L. Durmowicz, MD
DPMH Pediatric Team Leader- Mona Khurana, MD
DPMH Associate Division Director- John J. Alexander, MD, MPH
DPMH RPM- Jacqueline Yancy, Ph.D.

age cohort. See IND 112538, the IND for this FDC tablet product,

(b) (4)

³ The applicant did not submit the correct iPSP document as part of the original NDA submission. The applicant submitted the agreed iPSP document, specifically the January 6, 2016 Amended Agreed iPSP document, on May 2, 2019 (eCTD Seq # 0010).

(b) (4)



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/s/

ELIZABETH L DURMOWICZ
11/18/2019 05:05:39 PM

MONA K KHURANA
11/19/2019 10:35:51 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 15, 2019
Requesting Office or Division:	Division of Nonprescription Drug Products (DNBP)
Application Type and Number:	NDA 211733
Product Name, Dosage Form, and Strength:	Advil Dual Action with Acetaminophen (ibuprofen/acetaminophen) tablets, 125 mg/250 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	January 31, 2019
OSE RCM #:	2019-331
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA review process, the Division of Nonprescription Drug Products (DNBP) requested that we review the proposed Advil Dual Action with Acetaminophen container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS OF THE MATERIALS REVIEWED

Our review finds that the proposed Advil Dual Action with Acetaminophen container labels and carton labeling may be improved to ensure safe use of the product and to minimize potential medication errors.

4 RECOMMENDATIONS FOR PFIZER INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels & Carton Labeling

1. To ensure consumers recognize that the proposed product contains acetaminophen and to clearly communicate this additional active ingredient acetaminophen in the proposed product, increase the prominence of “Acetaminophen” in the proposed proprietary name on the PDP to the extent that space permits. As currently presented, there’s a large discrepancy between

the prominence of “Advil” and “Acetaminophen”, which are both active ingredients in your proposed product.

2. Ensure that the tablet (caplet) graphic image when presented on the container labels and carton labeling represents a true depiction of the actual tablet (caplet). The image should reflect the true tablet (caplet) size, color, and imprint of the actual tablet (caplet). Furthermore, as currently proposed, the imprint, “Advil II” only makes reference to the active ingredient, ibuprofen. Because the proposed product contains the additional active ingredient, acetaminophen, we recommend changing the imprint on the tablet (caplet) to an imprint that suggests both active ingredients or to a random imprint.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Advil Dual Action with Acetaminophen received on January 31, 2019 from Pfizer Inc.

Table 2. Relevant Product Information for Advil Dual Action with Acetaminophen	
Initial Approval Date	N/A
Active Ingredient	ibuprofen/acetaminophen
Indication	temporarily relieves minor aches and pains due to: • headaches • toothache • backache • menstrual cramps (b) (4) • muscular aches • minor pain of arthritis (b) (4)
Route of Administration	oral
Dosage Form	tablets
Strength	125 mg/250 mg
Dose and Frequency	• adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist • do not take more than 6 caplets in 24 hours; unless directed by a doctor • children under 12 years: ask a doctor

How Supplied	2-count pouch 50 x 2-count pouch dispenser 4-count (2 x 2-count pouch) 8-count vial (loose and packed) 18-count bottle 24-count bottle (18 + 6) 36-count bottle 72-count bottle 90-count bottle (72 + 18) 144-count bottle 144-count EZ open bottle 162-count bottle (144 +18) 162-count EZ open bottle (144 +18) 180-count bottle 216-count bottle 240-count bottle 288-count bottle
Storage	• store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Advil Dual Action with Acetaminophen labels and labeling submitted by Pfizer Inc.

- Container labels received on January 31, 2019
- Carton labeling received on January 31, 2019

G.2 Label and Labeling Images

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV (ODE IV)
Office of Biostatistics (OB)

Integrated Review

Label Comprehension Study

Application Type/Number	NDA 211733
Drug Name(s)	Advil ® Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets)
Indication(s)	Pain reliever (b) (4)
Applicant/sponsor	Pfizer Inc.
Date(s)	Submission Date: January 31, 2019 PDUFA Goal Date: November 22, 2019
Reviewers	Amanda Pike-McCradden, MAA, Social Science Analyst, Division of Nonprescription Drug Products (DNDP) Elande Baro, PhD, Statistical Reviewer, Division of Biometrics VII (DB7)
Concurring Reviewer	Yong Ma, PhD, Team Leader, DB7 Jody Green, MD, Clinical Team Leader, DNDP
Tertiary Reviewer	Mat Soukup, PhD, Deputy Director, DB7 Karen Mahoney, MD, Deputy Director, DNDP
Project Manager	Kristen Haslam, BSN/RN, DNDP

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Executive Summary

This integrated review from DNDP Social Science and DB7 Statistics evaluates the consumer behavior study in NDA 211733. Pfizer Inc. (the applicant) submitted an application (NDA 211733) for Advil ®Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets) for over-the-counter (OTC) use. A pivotal Label Comprehension Study (LCS) was conducted to determine how well consumers understood key communication messages from the proposed Drug Facts Label (DFL) for Advil ®Dual Action with Acetaminophen.

This was a multicenter, single-visit, LCS in consumers aged 12 years and older. A total of 563 subjects met study inclusion/exclusion criteria and completed at least one comprehension question. The analysis population used for the prespecified primary analyses consisted of the adults (n=482), of which 28.8% were low literacy.

The LCS included two primary communication objectives with 90% pre-specified performance threshold, two secondary communication objectives with 80% pre-specified performance threshold, and two other communication objectives (no thresholds) to evaluate subject's comprehension of specific warnings and directions on the proposed DFL. Each of these objectives was tested by an initial question and one or more follow-up questions in the questionnaire. Comprehension was evaluated based on pre-specified correct/acceptable answers to designated questions in the survey and a post-study transcript review to identify acceptable answers (mitigation). Additional exploratory questions to assess adult consumers' general understanding of the term "dual action," the active ingredients in common OTC pain reliever medicines, and adolescent behavior regarding the purchase and use of OTC medications were also evaluated at FDA's request.

For Primary Endpoint 1 "Do not use with any other drug containing acetaminophen", the adult comprehension rate was 95.4% with 95% two-sided Wilson confidence interval (CI) (93.2,97.0) thereby satisfying the 90% threshold.

For Primary Endpoint 2 "Take 2 tablets (per dose)", the adult comprehension rate was 91.7% with 95% CI (88.9,93.8), just below the 90% threshold. The most common incorrect answer for this endpoint was '6 tablets in 24 hours', which signals a potential confusion with the dosing instructions.

For Secondary Endpoint 1 "Severe liver damage may occur if you take with other drugs containing acetaminophen", the adult comprehension rate was 84.8% with 95% CI (81.3,87.8). Although the 80% threshold was met, comprehension of this endpoint was low for the low literacy subgroup, with point estimate 67.4% and 95% CI (59.2,74.6).

For Secondary Endpoint 2 "May cause severe stomach bleeding", the comprehension rate was 92.1% with 95% CI (89.3,94.2), thereby satisfying the 80% threshold.

The overall results from the LCS were satisfactory, although there were two primary areas of concern regarding subject comprehension of the acetaminophen liver damage warning and the

dose/dosing instructions. Changes to labeling are suggested in Section 5.2 to address these issues of comprehension.

1. Introduction and Background

1.1 Overview

The purpose of this study was to determine how well subjects understood key communication messages from the proposed Drug Facts Label (DFL) for Advil ®Dual Action with Acetaminophen (Ibuprofen 125 mg / Acetaminophen 250 mg Tablets). The label tested in this study was developed and refined based on information from a series of previous pilot label comprehension studies (LCSs) and advice received in a series of pre-submission meetings between the sponsor and FDA. Additional exploratory questions to assess adult consumers' understanding of the term "dual action," the active ingredients in common over-the-counter (OTC) pain reliever medicines, and adolescent behavior regarding the purchase and use of OTC medications were also evaluated at FDA's request.

1.2 Data Sources

The applicant submitted the NDA electronically. The submission for the LCS study contained the report and addendum, the analysis datasets used for statistical analysis and reporting by the sponsor, the SDTM datasets used as the source to create the analysis dataset, and associated documentation including define file, annotated CRF, Analysis Data Reviewer's Guide and Study Data Reviewer's guide.

The analysis datasets (adsl.xpt and addq.xpt) for the LCS, and associated define files and Analysis Data Reviewer's Guide are available at:

<\\cdsesub1\evsprod\NDA211733\0001\m5\datasets\pf-06438867-18apr2018-100614\analysis\adam\datasets>

The SDTM datasets (dm.xpt, dq.xpt, ds.xpt, qs.xpt, sc.xpt, ti.xpt, ts.xpt, suppdm.xpt, suppdq.xpt) for the LCS and associated define files and Study Data Reviewer's Guide are available at:

- <\\cdsesub1\evsprod\NDA211733\0001\m5\datasets\pf-06438867-18apr2018-100614\tabulations\sdm>
- <\\cdsesub1\evsprod\NDA211733\0013\m5\datasets\pf-06438867-18apr2018-100614\tabulations\sdm>

The annotated CRF is available at:

<\\cdsesub1\evsprod\NDA211733\0013\m5\datasets\pf-06438867-18apr2018-100614\tabulations\sdm>

The LCS report and addendum are available at:

- [\\cdsesub1\evsprod\NDA211733\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-reliever-\(b\)\(4\)\5354-other-stud-rep\pf-06438867-18apr2018-100614](\\cdsesub1\evsprod\NDA211733\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-reliever-(b)(4)\5354-other-stud-rep\pf-06438867-18apr2018-100614)

- [\\cdsesub1\evsprod\NDA211733\0013\m1\us](#)

1.3 Data and Analysis Quality

The statistical reviewer was able to reproduce the LCS study results for the primary and secondary endpoints as well as disposition and baseline characteristics, using the submitted data. No major data quality issue was found.

2. Study Design

2.1 Study Overview

This was a multicenter, single visit, pivotal label comprehension study (LCS) conducted in 12 retail shopping mall sites located in different geographic areas of the United States. Data for adults and adolescents were collected via structured, one-on-one interviews utilizing scenario-based questions with follow up probes to ascertain rationale for the response. Additionally, adult subjects were asked about previous use of pain medications (active ingredient recognition), the meaning of the name “Dual Action,” and adolescents were asked about their medication purchase and use behaviors. Interviews were audio-recorded and transcribed for use in analyses.

2.2 Key Inclusion/Exclusion Criteria

Inclusion Criteria:

Subjects must have met the following inclusion criterion to be eligible for enrollment in the study:

- Males and females 12 years of age and older from the general population.

Exclusion Criteria:

Subjects with any of the following characteristics/conditions were not included in the study:

- Refused to provide explicit consent to collect health and demographic information during screening or re-screening.
- Was less than 12 years old, or was 12-17 years of age and not accompanied to the research site by a parent or legal guardian.
- Was unable to speak or understand English.
- Subject or someone in his or her household worked:
 - For a pharmaceutical or consumer healthcare company;
 - As a healthcare professional (HCP) or as part of a healthcare practice
- Could not see well enough to read information on the label (subject needed contact lenses or glasses to read but did not have them at the time of the visit).

- Participated in any clinical trial or market research study for healthcare products in the past 12 months.

Additionally, subjects who refused to sign the confidentiality statement or permission-to-audio-record form were excluded, and no further data was collected.

The LCS protocol states that screening for reading ability may also be implemented to ensure adequate representation of adult low-literacy subjects (approximately 30%) in the overall adult sample. For example, if only low-literacy adult subjects were needed to ensure adequate representation for this group, a REALM Test score of 61 or above was implemented as an additional exclusion criterion. No literacy quotas were implemented for adolescent subjects.

Social Science Reviewer Comment: *Inclusion/Exclusion criteria appear acceptable*

2.3 Recruitment

This study utilized both pre-recruitment of subjects by telephone as well as direct-intercept recruitment of subjects from general consumer traffic in the malls. Pre-recruited subjects were contacted approximately 1-2 weeks before the start of the study via telephone to assess their interest in participating and to determine if they qualified to participate. Interested subjects who qualified had an appointment scheduled at the nearest mall site. Parents of adolescent subjects were screened by telephone to ensure that the pre-recruited adolescents would be accompanied to the site by a parent or a legal guardian.

Subjects recruited via direct-intercept from the mall floor were screened for eligibility and then taken directly to the on-site interviewer to complete the interview. During recruitment no information was given about the content of the interview.

Social Science Reviewer Comment: *Recruitment strategy appears acceptable. It is noted that recruitment of adolescents solely through their parents could affect the randomness of the sample.*

2.4 Study Objectives

The Primary Communication Endpoints for this study were:

- Do not use with any other drug containing acetaminophen
- Take 2 tablets (per dose)

Each primary endpoint was considered successful if the lower limit of the 95% confidence interval (CI) equaled or exceeded the 90% performance threshold.

The Secondary Communication Endpoints for this study were:

- Severe liver damage may occur if you take with other drugs containing acetaminophen

- May cause severe stomach bleeding. The chance is higher if you take other drugs containing prescription or nonprescription non-steroidal anti-inflammatory drugs (NSAIDs)

An *a priori* performance threshold of 80% was set for the secondary endpoints.

The Other Communication Endpoints for this study were:

- Take (a dose) every 8 hours
- Take no more than 6 tablets in 24 hours

Exploratory endpoints for this study were:

- Adult consumers' understanding of the term "Dual Action"
- Adult consumers' understanding of the active ingredients in common over-the-counter (OTC) pain reliever medicines

A post hoc endpoint for this study was:

- Adult consumers' understanding if they have used a product in the past containing acetaminophen

Social Science Reviewer Comment: *The study endpoints appear acceptable.*

2.5 Study procedures

Obtain Parental Permission and Verify Screening Information:

Adolescent subjects were instructed to arrive at the research site with a parent or guardian who would need to sign a permission form for their child to participate in the study. Parents were asked to accompany their child throughout the interview but to refrain from participation as the interview questions will be addressed to the adolescent. Interviews were conducted in a private interviewing room in the research center. In the interviewing room, the eligibility criteria first evaluated at screening was reviewed once again to ensure that the subject qualified.

Health Literacy Assessment:

The REALM and REALM Teen tests were administered by an interviewer trained in the proper administration of these literacy tests. The tests were scored in the EDC system.

REALM Test Grade-Equivalent Reading Levels

REALM	Grade-Equivalent Reading Level
0-18	Third and below
19-44	Fourth to sixth
45-60	Seventh to eighth
61-66	Ninth and above

REALM Teen Test Grade-Equivalent Reading Levels

REALM Teen	Grade-Equivalent Reading Level
0-37	Third and below
38-47	Fourth to fifth
48-58	Sixth to seventh
59-62	Eighth to ninth
63-66	Tenth and above

Confidentiality Agreement and Permission to Audio Record:

Once eligibility was confirmed, subjects were asked to sign a confidentiality statement and a form granting permission to audio record.

Presentation of Product Label:

The proposed DFL and Principal Display Panel (PDP) were displayed on empty packages. Subjects were handed the package and asked to read the information. Subjects were allowed as much time as necessary to review the package. When finished reading, subjects were told they could refer to the information on the package at any time during the interview. The interviewer then began audio-recording the interview.

Comprehension Interview Questions:

Standardized comprehension questions were asked of each subject. Subjects were shown the question in printed format as the interviewer read the question from the computer screen. The printed question remained visible to the subject until a response was given. The printed question, along with the verbal one, was included so that subjects who prefer to read the question instead of hearing it were not at a disadvantage. If requested, the interviewer could repeat a question but paraphrasing or explaining anything about the question was not permitted. Once a question was answered, subjects were not allowed to revise their answer to a previous question.

Adult subjects were asked additional questions regarding previous use of pain relievers, knowledge of active ingredients, and the term Dual Action. Adult subjects were assigned to 1 of 2 groups (or arms) in alternating, 1:1 fashion for the ingredient recognition portion of the interview. The group assignment was generated within the electronic data capture (EDC) system which identified all subjects with an odd identification number to be assigned to Group 1 and prompted the on-site interviewer to show the subject a list of over-the-counter pain relievers. The system prompted the interviewer to show all subjects with an even identification number in Group 2 the package front images of over-the-counter pain relievers.

Additionally, adult subjects were assigned in alternating, 1:1 fashion to an ingredient recognition question order. The system assigned subjects a second identification number; all subjects with an odd second identification number were assigned to Order A and they received the acetaminophen ingredient recognition question first, followed by the NSAID recognition question. The system assigned subjects with an even second identification number to Order B

and they received the NSAID ingredient recognition question first, followed by the acetaminophen recognition question.

Next, debriefing questions were asked about the reasons for any incorrect responses; information gathered from the debriefing questions was not used to mitigate incorrect responses. The interviewer ended the audio recording at this point. Adolescent subjects were asked questions about their typical medication decision-making regarding purchase and use. Basic demographic information was collected from all subjects.

Post-Interview Process:

Following the conclusion of the interview, subjects were compensated for their time.

Social Science Reviewer Comment: FDA typically requests that parents not be present in the interview room as it can influence adolescents' answers about their attitudes and behaviors

2.6 Scoring of Endpoints

Scoring criteria for “correct” or “acceptable” responses (when applicable) for each communication endpoint was prespecified in the data collection instrument. Responses that were not correct or acceptable were independently reviewed by two trained reviewers. If both reviewers agreed, the subject’s response was mitigated to acceptable status. Any discrepancy between the two reviewers was resolved through review by a supervisor.

3. Statistical Methods

3.1 Sample Size

The sponsor proposed a sample size of 470 adults based on a power analysis. Assuming a 2-sided test with $\alpha = 0.05$, an expected correct comprehension rate of 94% and a performance threshold of 90%, a sample of 470 subjects would provide approximately 88% power based on the Wald Method for the binomial distribution.

The sponsor proposed a sample size of 80 adolescents. This sample size was not selected based on statistical considerations; the sponsor considered that it was adequate because all analyses regarding comprehension among adolescents were descriptive.

Statistics Reviewer Comment: Sample size was agreed upon prior to trial initiation and appears acceptable.

3.2 Statistical Analysis

3.2.1 Disposition and Demographic characteristics

Subjects' disposition and demographic characteristics were summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions for categorical variables. The demographic characteristics were summarized for adults, adolescents, and by literacy level for adult subjects.

3.2.2 Analysis of Primary and Secondary Endpoints

Prespecified Analyses

The analysis estimated the comprehension rate for each communication message in the analysis population, which consists of adult subjects who satisfied inclusion/exclusion criteria and answered at least 1 comprehension question. The comprehension rate was computed as the number of subjects with an overall correct or acceptable response (including responses mitigated to "acceptable" status) divided by the number of subjects in the analysis population, unless otherwise specified (see subsection below, on 'Missing Data Handling Rules for Endpoint Calculations'). In addition to point estimates (PEs), two-sided Wilson 95% confidence intervals (CIs) were reported. If the lower bound (LB) of the CI for the comprehension rate was equal to or greater than the pre-defined performance threshold for the communication message (90% for primary endpoints and 80% for secondary endpoints), it was considered that the objective was comprehended.

The sponsor additionally prespecified that:

- Question 6-6b (used to test Secondary Endpoint 1: Severe liver damage may occur if you take with other drugs containing acetaminophen) would be applied as mitigation for Question 4-4b (used to test Primary Endpoint 1: Do not use with any other drug containing acetaminophen), and vice versa, due to the similarity in the structure and content of the questions.
- Multiple follow-up questions ('Why do you say that' and 'Is there anything else you would like to add about this topic before we move on?') would be used for Questions 4-6, rather than a single follow-up question.

Post-Hoc Analyses

In post-hoc analyses, the sponsor conducted additional mitigations by evaluation of responses from related questions as follows:

- Post-hoc mitigations for Question 4-4b (used to test Primary Endpoint 1: Do not use with any other drug containing acetaminophen) and Question 6-6b (used to test Secondary Endpoint 1: Severe liver damage may occur) were conducted using Question 5-5b. Question 5-5b (used to test Secondary Endpoint 2: May cause stomach bleeding) did not use responses from other questions.
- Post-hoc mitigations for Question 7-7a (used to test Primary Endpoint 2: Take 2 tablets per dose) were conducted using Questions 8-8a and 9-9a responses. Similarly, post-hoc mitigations for Question 8 (used to test Other Endpoint 1: Take a dose every 8 hours) were conducted using Questions 7-7a and 9-9a responses. Question 9-9a (used to test Other

Endpoint 2: Take no more than 6 tablets in 24 hours) did not use responses from other questions.

Additionally, per FDA request, the sponsor conducted the following post-hoc analyses:

- Analysis of Question 4-4b with no cross scoring from Question 6-6b
- Analysis of Question 6-6b with no cross scoring from Question 4-4b
- Analysis of Questions 4-6 with a single follow-up question (4a, 5a, or 6a) and no cross-scoring. The sponsor did not conduct any mitigation for this analysis.

Social Science and Statistics Reviewers Comments:

- *FDA agreed with the use of Q6 to mitigate Q4 (and vice versa) due to the similarities between endpoints for these two questions, as documented in the May 9, 2018 Written Response Only Meeting Minutes. However, this cross-scoring strategy is normally discouraged, as it could lead to errors in scoring. This is also against the FDA LCS guidance recommendation, which states that each question should address a single item or issue. Responses for Questions 4 and 6 required an additional examination by the FDA Social Science reviewer to ensure proper mitigations were applied (See Social Science reviewer comments under Sections 4.3 and 4.4).*
- *The sponsor applied additional cross-scoring in their post-hoc analysis. However, FDA is examining endpoints on their own, without the addition of the post-hoc cross-scoring.*
- *FDA only agreed with the use of multiple follow-up questions for Question 4. The use of multiple follow-up questions could be leading, as it may suggest to a participant that there is something else to add. The FDA Social Science reviewer assessed the impact of the use of multiple follow up questions on scoring (See Social Science reviewer comments under Section 4.3).*

3.2.3 Analysis of Other and Exploratory Endpoints

Other and exploratory endpoints were not evaluated against performance thresholds. For other endpoints, comprehension rates and Wilson 95% CIs were calculated. The exploratory endpoints were presented and summarized descriptively, using counts and percentages.

3.2.4 Missing Data Handling Rules for Endpoint Calculations

Subjects were not included in the denominator for an endpoint calculation in the following situations:

- The participant's response is missing due to premature termination of the interview
- The participant was not asked the question due to an unforeseen circumstance, or the response was not properly recorded, and there is no additional information (e.g., data for the entire question series is missing).

Statistics Reviewer Comments:

To be conservative, missing response were coded as incorrect. One participant

started the interview but did not complete it, and one participant completed the interview but his responses were missing due to a malfunction of the audio recording. Because there were only 2 participants with missing data, this will not impact the study conclusions.

3.2.5 Subgroup Analyses

Estimates of comprehension rates and 95% confidence intervals were summarized separately for adolescents and by literacy level (low literacy and normal literacy).

4. Study Results

4.1 Disposition

A total of 661 subjects were screened, of which 563 subjects met study inclusion/exclusion criteria and completed at least one comprehension question. One eligible subject started the interview but did not complete all comprehension questions and one participant completed the interview but his responses were missing due to a malfunction of the audio recording. For additional disposition information, see Table 8 in Appendix.

4.2 Demographics

The study population included a total of 482 adults and 81 adolescents. As shown in Table 1 below, 28.8% of the adults were of low literacy. The mean age of the adults was 41.6, with 42.7% older than 45. There were similar proportions of males (~47%) and females (~53%). Participants were predominantly white (~75%); ~16% were African American and ~4% were Asian. The adult educational levels were primarily composed of those who had a high school degree, GED, or certificate (~28%), some college or technical school (~39%), a college degree (~19%), and post-graduate degree (~8%).

Among the adolescents, 43% had 10th and above grade equivalent reading level. The mean age of the adolescents was 15.2, with 67.9% ages 15-17. There were similar proportions of males (~49%) and females (~51%). Participants were predominantly white (~75%). The adolescent educational levels were primarily composed of those 11th grade (junior in high school) or lower.

Social Science Reviewer Comment: *The low literacy sub-population for the study fell short of the FDA requested 30%*

Table 1. Summary of Subject Demographic Characteristics for Adult Subjects and Adolescents (12-17 years of Age)

Responses	All Adult Subjects (N=482)	Normal- Literacy Adults (N=343)	Low-Literacy Adults (N=139)	Adolescents (N=81)
Gender				
Male	227 (47.1%)	158 (46.1%)	69 (49.6%)	40 (49.4%)
Female	255 (52.9%)	185 (53.9%)	70 (50.4%)	41 (50.6%)
Refused	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic/Latino or not Hispanic/Latino				
Hispanic/Latino	91 (18.9%)	49 (14.3%)	42 (30.2%)	28 (34.6%)
Not Hispanic/Latino	390 (80.9%)	294 (85.7%)	96 (69.1%)	52 (64.2%)
Refused	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.2%)	0 (0.0%)	1 (0.7%)	1 (1.2%)
Race ^[1]				
White	362 (75.1%)	272 (79.3%)	90 (64.7%)	61 (75.3%)
Black or African American	76 (15.8%)	50 (14.6%)	26 (18.7%)	18 (22.2%)
Asian	20 (4.1%)	14 (4.1%)	6 (4.3%)	3 (3.7%)
Native Hawaiian or Other Pacific Islander	9 (1.9%)	4 (1.2%)	5 (3.6%)	1 (1.2%)
American Indian or Alaska Native	20 (4.1%)	15 (4.4%)	5 (3.6%)	5 (6.2%)
Other	31 (6.4%)	14 (4.1%)	17 (12.2%)	4 (4.9%)
Refused	1 (0.2%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Missing	1 (0.2%)	0 (0.0%)	1 (0.7%)	1 (1.2%)
Adult Education Level	N=482	N=343	N=139	
8th grade or less	2 (0.4%)	0 (0.0%)	2 (1.4%)	
Some high school	27 (5.6%)	10 (2.9%)	17 (12.2%)	
High school graduate, GED, or certificate	133 (27.6%)	75 (21.9%)	58 (41.7%)	
Some college or technical school	190 (39.4%)	143 (41.7%)	47 (33.8%)	
College graduate	93 (19.3%)	82 (23.9%)	11 (7.9%)	
Post-graduate degree	36 (7.5%)	33 (9.6%)	3 (2.2%)	
Refused	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Missing	1 (0.2%)	0 (0.0%)	1 (0.7%)	
Adolescent Education Level				N=81
7th grade or less				13 (16.0%)
8th grade				12 (14.8%)
9th grade (freshman in high school)				16 (19.8%)
10th grade (sophomore in high school)				19 (23.5%)
11th grade (junior in high school)				16 (19.8%)
12th grade (senior in high school)				2 (2.5%)
High school graduate, GED, or certificate				2 (2.5%)
Some college or technical school				0 (0.0%)
College graduate				0 (0.0%)
Refused				0 (0.0%)
Missing				1 (1.2%)
Adolescent Grade-Equivalent Reading Level				N=81
3rd and below ^[2]				2 (2.5%)
4th to 5th ^[3]				8 (9.9%)

Responses	All Adult Subjects (N=482)	Normal- Literacy Adults (N=343)	Low-Literacy Adults (N=139)	Adolescents (N=81)
6th to 7th ^[4]				21 (25.9%)
8th to 9th ^[5]				15 (18.5%)
10th and above ^[6]				35 (43.2%)
Age Category				
Ages 12-14	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (32.1%)
Ages 15-17	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (67.9%)
Ages 18-44	276 (57.3%)	185 (53.9%)	91 (65.5%)	0 (0.0%)
Ages 45+	206 (42.7%)	158 (46.1%)	48 (34.5%)	0 (0.0%)
Age Distribution				
Mean (SD)	41.6 (14.2)	43.0 (14.0)	38.1 (14.0)	15.2 (1.7)
Median	42.0	43.0	38.0	15.0
Range	18 - 86	18 - 86	18 - 72	12 - 17

Data Source: [Table 14.3.1.1](#)

N=number of subjects, GED=general educational development, SD=standard deviation

[1] Responses are not mutually exclusive. Sum of percentages may be greater than 100%.

[2] REALM-Teen Score 0-37

[3] REALM-Teen Score 38-47

[4] REALM-Teen Score 48-58

[5] REALM-Teen Score 59-62

[6] REALM-Teen Score 63-66

Subject 4011-00026 completed the Label Comprehension Assessment and Subject 4070-00025 only responded to the first Label Comprehension Question. But neither completed all of the demographic questions, they are identified as 'Missing' where applicable.

Source: Table 7 of the pivotal LCS report

4.3 Comprehension Results

4.3.1 Primary Endpoints

Table 2 below shows the results for Primary Endpoint 1 ‘Do not use with any other drug containing acetaminophen’ among the adults. Based on the prespecified analysis, Primary Endpoint 1 met the 90% performance threshold, with comprehension PE 95.4% and 95% CI (93.2, 97.0). This pre-specified analysis used two follow-up questions and cross-scoring from Q6. In a sensitivity analysis that used a single follow-up question, no cross-scoring from other questions, and no mitigation, comprehension for Primary endpoint 1 was not met (88.1% PE, 85% LB). For the LB to meet the 90% threshold under this sensitivity analysis, 22 (39%) out of the 57 incorrect answers would need to be mitigated to acceptable.

Social Science Reviewer Comment: Overall, the coding for this endpoint is acceptable. The Social Science reviewer examined responses for Question 4 to determine if proper coding was utilized. Cross-scoring was applied appropriately with subjects either showing understanding that acetaminophen products should not be taken together or expressing that they would need to consult a doctor before taking a second acetaminophen product. Responses to the additional follow-up question provided minimal information regarding rationale.

Table 2. Comprehension Results: Primary Endpoint 1 (Do not use with any other drug containing acetaminophen)

	n* (%)	Wilson Score 95% CI
Pre-specified primary analysis ¹	459 (95.4%)	(93.2,97.0)
Analysis without cross-scoring from Q6 ¹	454 (94.4%)	(92.0,96.1)
Analysis with a single follow-up question and no cross-scoring from Q6 and no mitigation	424 (88.1%)	(85.0, 90.7)

Source: Reviewer Table, derived from Table 9 of the pivotal LCS report and Table 3 of Information Request Response 4 dated 15 April 2019

CI=confidence interval

* The sample size for the analysis population is 481. One low literacy subject among the adults did not respond to this question

¹ 25 responses were mitigated to acceptable and 3 responses were mitigated to incorrect

Table 3 below shows the results for Primary Endpoint 2 ‘Take 2 tablets’ among the adults. Based on the prespecified analysis, Primary Endpoint 2 nearly met the 90% performance threshold, with comprehension PE 91.7% and 95% CI (88.9, 93.8). This pre-specified analysis used a single follow-up question and no cross-scoring from other questions.

Social Science Reviewer Comment: *This endpoint fell just short of the 90% performance threshold. The most common incorrect answer for this endpoint was ‘6 tablets in 24 hours’, which was mentioned by 23.3% of the adult subjects. It is possible that the location of these dosing directions is part of the reason behind the confusion; with subjects stopping reading at the most prominent dosing direction instead of continuing to read down the label. A labeling change is suggested in the recommendations section to address this issue.*

Table 3. Comprehension Results: Primary Endpoint 2 (Take 2 tablets)

	n* (%)	Wilson Score 95% CI
Pre-specified primary analysis ^{1,2}	441 (91.7%)	(88.9,93.8)

Source: Reviewer Table, derived from Table 10 of the pivotal LCS report

CI=confidence interval

* The sample size for the analysis population is 481. One low literacy subject among the adults did not respond to this question

¹ The sponsor did not pre-specify any acceptable responses

² 1 response was mitigated to acceptable and 1 response was mitigated to incorrect

4.3.2 Secondary Endpoints

Table 4 below shows the results for Secondary Endpoint 1 ‘Severe liver damage may occur if you take with other drugs containing acetaminophen’ among the adults. Based on the prespecified analysis, Secondary Endpoint 1 met the 80% performance threshold, with comprehension PE 84.8% and 95% CI (81.3, 87.8). This prespecified analysis used two follow-up questions and cross scoring from Q4. In a sensitivity analysis with a single follow-up question, no cross-scoring from other questions, and no mitigation, comprehension for Secondary Endpoint 1 was not met (76.3% PE, 72.3% LB). For the LB to meet the 80% threshold under this sensitivity analysis, 33 (29%) out of the 114 incorrect answers would need to be mitigated to acceptable.

Social Science Reviewer Comment: Overall, the coding for this endpoint is acceptable. The Social Science Reviewer examined responses for Question 6 to determine if proper coding was utilized. Cross-scoring was applied appropriately with subjects mentioning at some point in Question 4 or Question 6 an understanding that acetaminophen products cause harm to the liver when taken together. Responses to the additional follow-up question provided minimal information regarding rationale. Based on examining the responses provided in the transcripts, the Social Science reviewer noted a pattern of mentions of the allergy alert as the reason why 2 acetaminophen products could not be taken together. In particular, it was noted that the number of mentions of ‘allergic’/‘allergy’ was 87 for Question 4 and 88 for Question 6. For the incorrect responses to Question 6, 29% of subjects mentioned ‘allergic’/‘allergy’; and, among the incorrect responses, 32% of low literacy adults mentioned ‘allergic’/‘allergy’. It appears as though there was confusion between the acetaminophen allergy alert and the acetaminophen liver warning. Both of these warnings are contained within the “Warnings” section of the DFL, but the allergy alert appears first. It is possible that the placement order of these warnings is part of the reason behind the confusion; with subjects stopping reading at the allergy alert instead of continuing to read down the label. A labeling suggestion to address this issue is in the recommendations section. See comment under Section 4.4 for more details on this endpoint.

Table 4. Comprehension Results: Secondary Endpoint 1 (Severe liver damage may occur if you take with other drugs containing acetaminophen)

	n* (%)	Wilson Score 95% CI
Pre-specified primary analysis ^{1,2}	408 (84.8%)	(81.3,87.8)
Analysis without cross-scoring from Q4 ¹	385 (80.0%)	(76.2,83.4)
Analysis with a single follow-up question and no cross-scoring from Q4 and no mitigation ¹	367 (76.3%)	(72.3, 79.9)

Source: Reviewer Table, derived from Table 11 of the pivotal LCS report and Table 6 of Information Request Response 4 dated 15 April 2019

CI=confidence interval

*The sample size for the analysis population is 481. One low literacy subject among the adults did not respond to this question

¹The sponsor did not pre-specify any acceptable responses

² 15 responses were mitigated to acceptable and 0 responses were mitigated to incorrect

Table 1Table 5 below shows the results for Secondary Endpoint 2 ‘May cause severe stomach bleeding. The chance is higher if you take other drugs containing prescription or nonprescription NSAIDs’ among the adults. Based on the prespecified analysis, Secondary Endpoint 2 met the 80% performance threshold, with comprehension PE 92.1% and 95% CI (89.3, 94.2). This prespecified analysis did not use any cross scoring from other questions but used multiple follow-up questions. However, a sensitivity analysis showed that even when a single follow-up question was used, comprehension for Secondary Endpoint 2 was met (89.0% PE, 85.9% LB).

Social Science Reviewer Comment: *The results for this endpoint were acceptable.*

Table 5. Comprehension Results: Secondary Endpoint 2 (May cause severe stomach bleeding. The chance is higher if you take other drugs containing prescription or nonprescription NSAIDs)

	n* (%)	Wilson Score 95% CI
Pre-Specified primary analysis ¹	443 (92.1%)	(89.3,94.2)
Analysis with a single follow-up question and no mitigation	428 (89.0%)	(85.9, 91.5)

Source: Reviewer Table, derived from Table 12 of the pivotal LCS report and Table 8 of Information Request Response 4 dated 15 April 2019

CI=confidence interval

* The sample size for the analysis population is 481. One low literacy subject among the adults did not respond to this question

¹ 15 responses were mitigated to acceptable and 5 responses were mitigated to incorrect

4.3.3 Other Endpoints

- **Take (a dose) every 8 hours**

Out of 480, 393 adult subjects (81.9%) classified as correct, acceptable, or mitigated to acceptable with 95% Wilson CI (78.2, 85.1).

Social Science Reviewer Comment: *The most common incorrect answer to this question was ‘6 tablets in 24 hours’, which was mentioned by 24.8% of the adult subjects. It is possible that the location of these dosing directions is part of the reason behind the confusion; with subjects stopping reading at the most prominent dosing direction instead of continuing to read down the label. A labeling change is suggested in the recommendations section to help address this issue.*

- **Take no more than 6 tablets in 24 hours**

Out of 480, 461 adult subjects (96.0%) classified as correct, acceptable, or mitigated to acceptable, with 95% Wilson CI (93.9, 97.5).

Social Science Reviewer Comment: *Results for this endpoint were acceptable.*

- **Adult consumers’ understanding of the term “Dual Action”**

Out of 479, 409 adult subjects (85.4%) gave a response evaluated as fully correct (indicating the product contains 2 ingredients or similar) in articulating the meaning of “Dual Action” in the product name.

Social Science Reviewer Comment: *Results for this question were acceptable. The most common incorrect answer for this endpoint was “(b) (4)”, which was mentioned by 20.9% of adult subjects.*

- **Adult consumers’ understanding of the active ingredients in common OTC pain reliever medicines**

After asking all the LCS questions for Advil Dual Action with Acetaminophen, respondents were asked to identify those OTC products that contain acetaminophen and those that contain an NSAID. Approximately half were provided a list of several pain relievers and the other half were shown package front images of the same products in the same alphabetical order. “Failure to recognize” error rates for acetaminophen from the images of the representative acetaminophen- containing products were generally low (3.8%-5.4%) and much higher when only provided a list of products. “Failure to recognize” error rates for NSAIDs from the images of the representative NSAID- containing products were generally low (2.9 – 8.8%), though higher for Aleve (10.5%) and Bayer (21.8%) and much higher when only provided a list of products.

- **Adult consumers’ understanding if they have used a product in the past containing acetaminophen**

194 out of 350 (55.4%) subjects who reported they had previously taken a non-prescription pain reliever containing acetaminophen responded that they had taken Tylenol, which correctly identified an OTC pain reliever containing acetaminophen. However, based on the limited verbatim responses collected with no follow up probes, it is difficult to determine the total

number of consumers who appropriately identified acetaminophen- containing products they had previously taken; as Excedrin (13), Midol (2), Dayquil/Nyquil (6), Generic brands (44), and Cold/flu medication (6) all have variants that contain acetaminophen, as well as the Advil with acetaminophen variant identified in the label tested in this study (7). These responses provide up to an additional 78 consumers who may have correctly identified acetaminophen products they had previously taken in addition to the Tylenol responses for a total of up to 272 (77.7%). Approximately 10% didn't know, remember, were not sure of, or did not name an OTC medicine or named a prescription medicine.

Social Science Reviewer Comment: *Due to the lack of follow-up probes used for these questions it is difficult to do much analysis. Many subjects listed acetaminophen in products that don't actually contain acetaminophen. This could indicate that they would be cautious about combining ingredients, but most likely points to an overall lack of knowledge of active ingredients in general. The high comprehension rate for the primary endpoint 'Do not use with any other drug containing acetaminophen.' helps alleviate concern.*

- Adolescent Medication Decision-Making

All adolescent subjects were asked questions to help characterize how they select and use OTC medicines. Of the 80 total adolescent subjects, 97.5% reported that they had ever taken an OTC medicine (Question 1). Among all adolescent subjects who had taken an OTC medicine, 51.3% reported that they used them a few times per month and 37.2% had taken them a few times per year (Question 1a). Almost all adolescents in the study (97.4%) reported that their parent or guardian purchases the OTC medicines they take (Question 1b) and 82.1% reported that their parent or guardian usually decides which ones they will take (Question 1c). Similarly, 79.5% said their parent or guardian decides how much OTC medicine they will take (Question 1d). When asked how often they, themselves, read the written information on the package or bottle, the largest proportion said sometimes (23.1%) followed by every time (21.8%), rarely (21.8%) and most times (20.5%) (Question 1e).

Social Science Reviewer Comment: *Adolescents reported heavy reliance on or consultation from their parent or caregiver regarding selection and use of OTC medications. This helps to alleviate concern over adolescents generally scoring lower than the adult population on comprehension endpoints. It is noted that the physical presence of their parent or caregiver in the room with the adolescent could have influenced adolescent responses to these questions.*

4.4 Subgroup Analyses

Table 6 shows the comprehension results by literacy, in adults. Across all primary and secondary endpoints, comprehension scores were lower (~7-25 percentage points) for the low literacy group. Comprehension of Secondary Endpoint 1 was particularly low for the low literacy group, with PE 67.4% and 95% CI (59.2,74.6).

Social Science Reviewer Comment: *It is typical and expected to have roughly a 10 point difference in comprehension scores between normal literacy and low literacy subjects. However, the 25 point difference for Secondary Endpoint 1 was concerning and prompted the Social Science reviewer to examine responses to Questions 6 and 4 and look for any hidden themes within the data. Low literacy subject responses to this question showed a general understanding*

that two acetaminophen products should not be used together, but they struggled to locate the reason behind it on the labeling (e.g. they referenced a different area of the label as their rationale). Comprehension of the warning not to use two acetaminophen products together alleviates concern that low literacy subjects do not understand exactly what could happen if the products are used together. It is possible that altering the placement of the liver damage warning will help to increase comprehension in the low literacy population. A labeling suggestion to address this issue is in the recommendations section.

Table 6. Low vs Normal Literacy Comprehension (pre-specified primary analysis)

	Normal Literacy* % (95% CI)	Low Literacy* % (95% CI)
Primary Endpoint 1: Do not use with any other drug containing acetaminophen.	97.7% (95.5,98.8)	89.9% (83.7,93.9)
Primary Endpoint 2: Take 2 tablets (per dose)	94.2% (91.2,96.2)	85.5% (78.7,90.4)
Secondary Endpoint 1: Severe liver damage may occur [..]	91.8% (88.5,94.3)	67.4% (59.2,74.6)
Secondary Endpoint 2: May cause severe stomach bleeding [...]	94.5% (91.5,96.4)	86.2% (79.5,91.0)

Source: Reviewer Table, derived from Table 9-12 of the pivotal LCS

*The analysis sample size is 343 for normal literates and 138 for low literates

Table 7 shows the comprehension results for adolescents versus adults. Across all primary and secondary endpoints, comprehension scores were lower (~2-10 percentage points) for the adolescents.

Table 7. Adult vs Adolescent Comprehension (pre-specified primary analysis)

Endpoint	Adults* % (95% CI)	Adolescents* % (95% CI)
Primary Endpoint 1: Do not use with any other drug containing acetaminophen.	95.4% (93.2,97.0)	91.4% (83.2,95.8)
Primary Endpoint 2: Take 2 tablets (per dose)	91.7% (88.9,93.8)	84.0% (74.5,90.4)
Secondary Endpoint 1: Severe liver damage may occur [..]	84.8% (81.3,87.8)	75.3% (64.9,83.4)
Secondary Endpoint 2: May cause severe stomach bleeding [...]	92.1% (89.3,94.2)	90.1% (81.7,94.9)

Source: Reviewer Table, derived from Table 9-12 of the pivotal LCS report

*The analysis sample size is 481 for adults and 81 for adolescents

5. Summary and Conclusions

5.1 Summary of Issues

Biostatistics

There were no major statistical issues found in the LCS study. The primary and secondary analyses methods (i.e. comparing the lower bound of the two-sided exact 95% CI to a pre-specified performance threshold) were valid, and the statistical analyses followed the pre-specified statistical analysis plan. The statistical reviewer was able to reproduce most results for disposition, demographics, and primary and secondary endpoints using the submitted data. Below, we summarize several issues that we identified in our review.

- Some key endpoints (Primary Endpoint 1 ‘Do not use with any other drug containing acetaminophen’ and Secondary Endpoint 1 ‘Severe liver damage may occur if you take with other drugs containing acetaminophen’) only met the performance threshold in the prespecified primary analysis, that used more than one follow-up question and cross-scoring from another question. For the validity of the scoring algorithms used in the prespecified primary analysis, we defer to the Social Scientist.
- For Primary Endpoint 2 ‘Take 2 tablets’, the observed comprehension rate was 91.7% with 95% CI (88.9%, 93.8%). Thus, the LB of the 95% CI was slightly lower than the performance threshold of 90%.
- For Secondary Endpoint 1 ‘Severe liver damage may occur if you take with other drugs containing acetaminophen’, the observed comprehension rate was only 67.4% in the low literacy group.

Social Science

There were two main areas of confusion found in the LCS study. The most concerning is the lack of comprehension, particularly in the low literacy population, about what happens if two or more acetaminophen products are taken together. Subjects struggled to locate the appropriate warning

language on the label and often confused the liver damage warning with the allergy alert warning. This could be due in part to the placement order of labeled warnings and a labeling change could help to improve comprehension.

The other area of concern is confusion between “take no more than 6 tablets in 24 hours,” “take a dose every 8 hours,” and “take 2 tablets per dose.” Subjects noticed the instruction to “take no more than 6 tablets in 24 hours” more often than the directions to take 2 tablets per dose and to take a dose every 8 hours. Comprehension to not take more than 6 tablets in 24 hours somewhat alleviates concern over the slightly lower comprehension rates on the other two endpoints. This also could be due to placement on the label and a label change could help improve comprehension.

5.2 Conclusions and Recommendations

Biostatistics

From a Biostatistics perspective, this application is approvable based on the sponsor’s demonstrating subject’s comprehension of the LCS primary and secondary communication objectives according to the pre-specified analysis. Overall, we do not have any major concern with the statistical methods used in this pivotal LCS study and defer to Social Science for the validity of the scoring algorithms used in the prespecified primary analysis.

Social Science

From a Social Science perspective this application is approvable with the following changes to the label to boost comprehension of the liver damage warning and the proper dose and dosing interval:

- 1) Move the acetaminophen liver damage warning above the allergy alert so that it is the first item under the heading “Warnings.”
- 2) Adjust the dosing directions on the DFL such that they are easier to see instead of getting lost in the text. For some reason subjects are focusing in on the “no more than 6 tablets in 24 hours” section of the directions instead of information about the dose and dosing interval. The addition of a chart in the directions section may help consumers focus on the directions regarding how many tablets to take and how often to take them.

6. Appendix

Table 8. Subject Disposition Status

	All Subjects (N=661)
Subjects who started screening	661 (100.0%)
Subjects who met exclusion criteria ^[1] ^[2]	40 (6.1%)
Refused to provide explicit consent to collect health and demographic information during screening	1 (0.2%)
Refused to provide age	2 (0.3%)
Was less than 12 years old	0 (0.0%)
Was 12-17 years of age and not accompanied to the research site by a parent or legal guardian (or did not sign the parental permission form)	4 (0.6%)
Unable to speak or understand English	0 (0.0%)
Worked (or someone in household worked) for a pharmaceutical or consumer healthcare company	15 (2.3%)
Worked (or someone in household worked) as a healthcare professional (HCP) or as part of a health care practice	15 (2.3%)
Could not see well enough to read information on the label (subject needed contact lenses or glasses to read but did not have them at the time of the visit)	11 (1.7%)
Participated in a clinical trial or market research study for healthcare products in the past 12 months	4 (0.6%)
Subjects who met inclusion criteria	621 (93.9%)
Interview completed	562 (85.0%)
Qualified, but quota group was full	37 (5.6%)
Qualified, but elected to leave before receiving Privacy Notice	8 (1.2%)
Qualified, but refused to sign confidentiality statement or Permission-to-Audio-Record form	4 (0.6%)
Qualified, but did not start comprehension questions	8 (1.2%)
Comprehension questions started but not completed ^[3]	1 (0.2%)
Comprehension questions completed, but survey responses missing (not transcribed) due to malfunction of audio recording	1 (0.2%)
Survey Population ^[3]	563 (85.2%)

Data Source: [Table 14.1](#)

N= number of subjects

[1] Responses are not mutually exclusive. Sum of percentages may be greater than 100%.

[2] Subject 1025-00027 gave explicit consent to collect health and demographic information but all other screening data are missing and cannot be classified in any of the following categories.

[3] Survey population is defined as the number of subjects who met the inclusion criteria and answered at least one comprehension question (which includes "Interview Completed" and "Comprehension questions started but not completed").

Source: Table 5 of the Pivotal LCS Report

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMANDA H PIKE-MCCRUDDEN
09/17/2019 08:40:12 AM

ELANDE N BARO
09/17/2019 09:07:19 AM

YONG MA
09/17/2019 10:08:12 AM

MATTHEW J SOUKUP
09/17/2019 01:07:43 PM

JODY E GREEN
10/05/2019 04:45:07 PM

Draft Labeling Review for Advil® Dual Action with Acetaminophen Tablets (ibuprofen 125 mg/acetaminophen 250 mg)

SUBMISSION DATES: January 31, 2019

NDA: 211733/Original NDA

ACTIVE INGREDIENTS: Ibuprofen 125 mg/Acetaminophen 250 mg

DOSAGE FORM: Tablets, (b) (4) in capsule shape as 'caplets', (b) (4)

SPONSOR: Pfizer Inc.
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Madison, NJ 07940

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TEAM LEADER: Kevin Lorick, PhD, RAC, DNDP/ODE IV

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PROJECT MANAGER: Kristen Haslam, BSN, RN, DNDP/ODE IV

I. BACKGROUND

Pfizer Inc. submitted, on January 31, 2019, new drug application (NDA) 211733, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the over-the-counter (OTC) treatment of pain (b) (4) using ibuprofen (125 mg)/acetaminophen (250 mg) oral tablets. Sponsor proposed a dosing regimen of two fixed-dose combination (FDC) tablets every 8 hours, for a total daily dose of 750 mg of ibuprofen and 1500 mg of acetaminophen.

Labeling for this product was developed over several years, with a focus on developing a label that informs the consumer that this product contains two active ingredients, ibuprofen and acetaminophen, and that they should not take this product with other acetaminophen or nonsteroidal anti-inflammatory drug (NSAID) products, because of known problems of consumers accidentally using multiple acetaminophen or NSAID-containing products at the same time. Sponsor developed a principal display panel (PDP) and drug facts label (DFL) with

implicit messaging to not use this drug product with any other drug containing acetaminophen and that consumers should take 2 tablets per dose (see REVIEWER'S COMMENTS II(A)(i) for a discussion of each element). The viability of the proposed labeling, including elements discussed in REVIEWER'S COMMENTS II(A)(i)(e) (i.e. the fifth panel), was demonstrated in pilot and pivotal labeling comprehension studies. These visual cues and warnings outside of the DFL are necessary to provide adequate instructions for use and adequate warnings against misuse.

Sponsor developed a proprietary name, *Advil Dual Action with Acetaminophen*, aimed at informing the consumer that this product contains two active ingredients, ibuprofen and acetaminophen. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name to be acceptable. In their review, DMEPA determined that "Advil" implies the product contains ibuprofen, and the modifiers "Dual Action with Acetaminophen" indicate the product contains acetaminophen, satisfying 21 CFR 201.6(b).

The proposed labeling was reviewed under the premise that the product 1.) will receive a complete response letter, as early discussions with the review team revealed significant concerns that appear to preclude approving this application in its current form, 2.) is being considered for (b) (4) pain relief (b) (4) indications and 3.) would not include any additional instruction to use the medication in a fasting state. Significant labeling changes would be required if the second or third premises were altered. For instance, if the product is only considered for pain relief indications (b) (4) significant labeling changes will be needed to provide adequate instructions for use (b) (4) acetaminophen and ibuprofen, exclusively for pain relief.

The reviewed labeling includes draft labeling submitted January 31, 2019. The Agency reserved labeling revision requests for labeling negotiations since the labeling recommendations at the end of this review can be quickly implemented.

Submitted Labeling	Date Submitted
50 x 2-ct Packet dispenser	January 31, 2019
2-ct Packet, front label	January 31, 2019
2-ct Packet, back label	January 31, 2019
4-ct Carton (2 x 2-ct packets) without drug facts label (DFL)	January 31, 2019
Peel-back DFL for 4-ct carton	January 31, 2019
8-ct Loose vial	January 31, 2019
8-ct Loose vial (alternate style)	January 31, 2019
8-ct Loose vial shelf tray	January 31, 2019
8-ct Packed vial	January 31, 2019
8-ct Packed vial (alternate style)	January 31, 2019
8-ct Pack vial large backer card	January 31, 2019
8-ct Pack vial small backer card, without DFL	January 31, 2019

Submitted Labeling Continued	Date Submitted
Peel-back DFL for 8-ct pack vial small backer card	January 31, 2019
18-ct Outer carton without complete DFL	January 31, 2019
18-ct Immediate container (bottle)	January 31, 2019
24-ct (18+6-ct) Outer carton with incomplete DFL	January 31, 2019
24-ct (18+6-ct) Immediate container (bottle)	January 31, 2019
36-ct Outer carton with incomplete DFL	January 31, 2019
36-ct Immediate container (bottle)	January 31, 2019
Peel-back DFL for 18-ct, 24-ct (18+6-ct), and 36-count outer carton	January 31, 2019
Duplicate peel-back DFL for 24-ct (18+6-ct) outer carton	January 31, 2019
72-ct Outer carton with incomplete DFL	January 31, 2019
72-ct Immediate container (bottle)	January 31, 2019
90-ct (72+18-ct) Outer carton with incomplete DFL	January 31, 2019
90-ct (72+18-ct) Immediate container (bottle)	January 31, 2019
Peel-back DFL for 72-ct and 90-ct (72+18-ct) outer carton	January 31, 2019
144-ct Outer carton	January 31, 2019
144-ct Immediate container (bottle)	January 31, 2019
144-ct Immediate container (stand-alone bottle) with “Easy Open” cap	January 31, 2019
162-ct (144+18-ct) Outer carton	January 31, 2019
162-ct (144+18-ct) Immediate container (bottle)	January 31, 2019
162-ct (144+18-ct) Immediate container (stand-alone bottle) with “Easy Open” cap	January 31, 2019
180-ct Immediate container (stand-alone bottle)	January 31, 2019
216-ct Outer carton	January 31, 2019
216-ct Immediate container (bottle)	January 31, 2019
216-ct Immediate container (stand-alone bottle)	January 31, 2019
240-ct Outer carton	January 31, 2019
240-ct Immediate container (bottle)	January 31, 2019
240-ct Immediate container (stand-alone bottle)	January 31, 2019
288-ct Immediate container (stand-alone bottle)	January 31, 2019
Instantly redeemable coupon (IRC) sticker \$1.00 off any Advil Dual Action 18-ct or larger	January 31, 2019
IRC sticker \$2.00 off any Advil Dual Action 36-ct or larger	January 31, 2019
IRC sticker \$2.00 off any Advil Dual Action 72-ct or larger	January 31, 2019
IRC sticker \$3.00 off any Advil Dual Action 72-ct or larger	January 31, 2019
IRC sticker \$2.00 off any Advil Dual Action EZ Open 144-ct or larger	January 31, 2019
18-ct IRC (peel-off PDP) \$1.00 off	January 31, 2019
36-ct IRC (peel-off PDP) \$1.00 off	January 31, 2019
72-ct IRC (peel-off PDP) \$1.00 off	January 31, 2019
144-ct IRC (peel-off PDP) \$1.00 off	January 31, 2019

II. REVIEWER'S COMMENTS

A. Outer Carton Label for Immediate Containers

Sponsor proposed secondary container labeling for 18-ct, 24-ct (18+6-ct), 36-ct, 72-ct, 90-ct (72+18-ct), 144-ct, 162-ct (144+18-ct), 216-ct, and 240-ct outer cartons (bottles), for 8-ct card backers (vials), for outer cartons housing two 2-ct packets/pouches, and for a 50 x 2-ct pouch dispenser.

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

The principal display panel (PDP) is consistent across the secondary containers for bottles, pouches, and vials. Its elements, which are mostly compliant with 21 CFR 201.60, 21 CFR 201.61, 21 CFR 201.62, 21 CFR 201.326, and 21 CFR 299.4 are described below.

The background of the PDP is dark blue with a light blue grid that matches the style of Sponsor's product line for Advil (ibuprofen, 200 mg) Tablets. To the right of the grid are two tubes, one red and the other blue, that have a circular arche (see image below). The background distinctly contrasts with the proprietary name, statement of identity, and net quantity. The PDP also contains a red flag in the upper left corner with the word "NEW" in white color type and a graphic image of two cream-color tablets marked with "Advil II" on the right side. This graphic image of the two tablets was added to help reinforce the dosing regimen of two tablets every eight hours.



Comment: This labeling is acceptable. However, Sponsor should consider using a background color that appreciably differs from Advil Tablets. For instance, Sponsor used significantly different background colors to distinguish between Advil, Advil Migraine, and Advil Multi-Symptom Cold & Flu (see below). Using a different background color with the same graphics and brand name would indicate that this drug product is different from Advil Tablets, but still contains ibuprofen. Moreover, it would reduce the risk of confusing Advil Dual Action with Acetaminophen for Advil Tablets.



a. **Proprietary Name**

The proprietary name, Advil Dual Action with Acetaminophen, infers that this drug product contains two active ingredients, ibuprofen and acetaminophen. It was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), which found it to be acceptable. In their review, DMEPA determined that “Advil” implies the product contains ibuprofen and the modifiers “Dual Action with Acetaminophen” indicate the product contains acetaminophen, satisfying 21 CFR 201.6(b) (see the May 02, 2019 review by DMEPA).

Advil Dual Action with Acetaminophen is displayed in two different fonts and color and in four different type sizes. “Advil” is displayed most prominently on the PDP in yellow print that matches the style used for the Advil brand. Its letter height appears almost twice as large as “Dual Action,” which is in white type outlined in light blue with a shadow effect. Immediately below is “with Acetaminophen,” which is displayed in two print sizes. The letter height for “Acetaminophen” appears to be about 2/3 the height of “Dual Action” and the letter height for “with” is about a quarter the of “Dual Action.”

Comment: This labeling is acceptable. The proprietary name is prominent and conspicuous on the PDP. DMEPA found it to be acceptable and that it satisfied § 201.6(b) (see the May 02, 2019 review by DMEPA).

b. **Statement of Identity**

The proposed statement of identity (SOI) is comprised of an incomplete established name, the word “(NSAID)”, and the pharmacological categories, and the SOI is immediately beneath the proprietary name.

The established name, Acetaminophen 250 mg and Ibuprofen 125 mg, is incomplete because it is missing the dosage form, “tablets.” The established name should be “**Acetaminophen** 250 mg and Ibuprofen 125 mg Tablets.” This established name must include the active ingredients, strength, and dosage form. For instance, each approved label for ibuprofen drug products lists the strength such as “Ibuprofen Tablets, 200 mg” for Advil Tablets drug products. It was suggested that the strength interrupts the SOI and therefore should be moved outside of the SOI. However, this suggestion is inconsistent with decades of approved labeling and would reduce the prominence of a key element that consumers rely on to identify their medication.

The terms “Acetaminophen” and “(NSAID)” are in bold type. The type size of “(NSAID)” is at least one-quarter the size of the most prominent matter (i.e. Advil) and is at least as large as the size of the “Drug Facts” title, per 21 CFR 201.326(a).

The pharmacological categories, pain reliever (b) (4) are appropriate for the proposed indications (if approved). These categories are consistent with the current monograph indications for acetaminophen and approved indications for ibuprofen. The SOI is in white-color print that distinctly contrasts with the dark blue background.

Comment: The statement of identity (SOI) should include the dosage form, “tablets,” after “Ibuprofen 125 (NSAID)” so that it reads “**Acetaminophen** 250 mg and Ibuprofen

125 mg (NSAID) Tablets Pain Reliever (b) (4) Otherwise, the SOI meets the requirements found in § 201.61, § 201.326, and § 299.4.

c. **Net Quantity**

The net quantity numerical count is displayed in the lower right corner in white-color type outlined in blue. Beneath the numerical count is the term “Caplets,” which is defined as capsule-shaped tablets. Moreover, the net quantity appears in conspicuous boldface print.

Comment: This labeling is acceptable. The net quantity is evident per § 201.62.

d. **New Flag**

There is a red flag in the upper left corner with the word “New” in white print.

Comment: This labeling is acceptable. Remind Sponsor to remove the flag six months after the product is introduced.

e. **Fifth Panel**

A five-panel carton was used to emphasize that the drug product contains two active ingredients and not to use this drug product with any other drug containing acetaminophen.

Front Side



The front side of the fifth panel matches the style of the PDP and extends the background grid from the top panel. The fifth panel contains a red banner with the statement “CONTAINS 2 MEDICINES.” This statement, in yellow and white color type, is the panel’s most prominent printed material. Below the banner is the statement, “Acetaminophen+Ibuprofen,” in a smaller, but still prominent type size.

Comment: This labeling is acceptable and necessary to inform the consumer not use this drug product with any other drug containing acetaminophen.

Back Side



The back side of the fifth panel contains a portion of the drug facts label (DFL) and two additional statements. Both statements are above the DFL. The first statement is a warning, “Do not use with other medicines containing ACETAMINOPHEN; can cause liver damage,” in red color print contained in a bright yellow box. Below this warning is the statement, “READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION,” in white print against a dark blue background.

Comment: This labeling is acceptable and necessary to inform the consumer not use this drug product with any other drug containing acetaminophen.

f. **Tamper Evident Statement**

The tamper evident statement, “Do Not Use if seal under bottle cap imprinted with “SEALED for YOUR PROTECTION” is broken or missing,” is displayed on a side panel. For the 18, 24, 36, 72, and 90 count sizes, it is displayed on the side panel directly below a copy of the statement of identity, in white type against a dark blue background. For the 144 and 162 count sizes, it is displayed on the side panel directly below the DFL, in white type against a dark blue background. For the 216 and 240 count sizes, it is displayed directly above the UPC, in blue print against a white background.

Comment: This labeling is acceptable per 21 CFR 211.132(c). The tamper evident statement is prominently displayed and identifies the tamper evident feature.

g. **Expiration Dating and Lot Number**



A placeholder for the expiration date and lot number is indicated in the annotated labeling for each outer carton and backer card (see examples above). However, the format for the expiration date is not defined on the container and carton labeling.

Comment: Sponsor designated an area for expiration dating and lot numbers, per 21 CFR 201.17 and 21 CFR 211.37 (expiration dating) and 21 CFR 201.18 (control numbers). However, the format for the expiration date is not defined. Request that Sponsor identify the format they intend to use for the expiration dating to minimize confusion and reduce the risk for deteriorated drug medication errors.

h. **Place of Business of Distributor**

The place of business of distributor statement, Pfizer, Madison, NJ 07940 USA, is contained on the side panel.

Comment: This labeling is acceptable per 21 CFR 201.1.

i. **Promotional Banner**

The 24 (18+6), 90 (72+18), and 162 (144+18) count sizes utilize bonus labeling. The bonus labeling includes a yellow vertical promotional banner positioned on the left side of the principal display panel and declares the number of so-called “free” tablets (e.g., “33% MORE FREE/6 Free Caplets”) in red print.

Comment: This labeling is acceptable and consistent with approved bonus labeling.

j. **Large Backer Card for Packed Vials**



(b) (4)

rd for the pack vials contains the statement, “Pocket Pack,” and the same elements described above for outer cartons: Proprietary Name (see comment **a**), Statement of Identity (see comment **b**), Net Quantity (see comment **c**), New Flag (see comment **d**), Tamper Evident Statement (see comment **f**), the statements contained on the fifth panel (see comment **e**), and Place of Business of Distributor (see comment **h**).

Comment: This labeling is acceptable. It matches the style and content of the outer carton labeling. Like the outer carton labeling, this labeling does not define the format for the expiration date. Request that Sponsor identify the format they intend to use for the expiration dating to minimize confusion and reduce the risk for deteriorated drug medication errors.

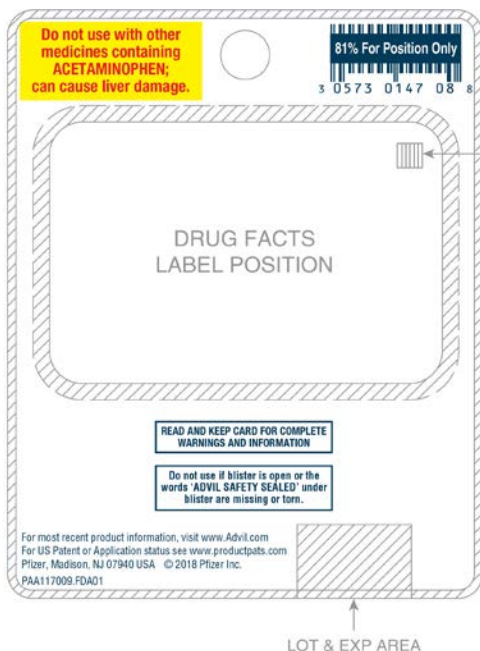
k. **Small Backer Card for Packed Vials**



(b) (4)

The front side of the small backer card for the pack vials contains a principal display panel nearly identical to the principal display panel found on the proposed outer carton labeling, except it also incorporates the red banner from the fifth panel with the statement “CONTAINS 2 MEDICINES” and the statement, “Pocket Pack.”

Comment: This labeling is acceptable. It matches the style and content of the outer carton labeling above.



The back side of the small backer card contains:

- o The tamper evident statement (see comment **f** above for full discussion),
- o The place of business of distributor (see comment **h** above for full discussion)
- o A peel-out DFL (see section **II(A)(ii)** Outer Carton Drug Facts Label)
- o The statements above the DFL located on the fifth panel of the outer cartons for bottles (see comment **e** for full discussion). The first statement is a warning, “Do not use with other medicines containing ACETAMINOPHEN; can cause liver damage,” in red color print outlined in a bright yellow box. The second statement is below the peel back DFL, “READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.”

Comment: This labeling is acceptable. It matches the style and content of the outer cartons for the bottle containers. Like the outer carton labeling above, placeholders for the expiration date and lot number are indicated in the annotated labeling. However, the format for the expiration date is not defined on the container label and carton labeling. Request that Sponsor identify the format they intend to use for the expiration dating to minimize confusion and reduce the risk for deteriorated drug medication errors.

ii. Outer Carton Drug Facts Label

The outer carton Drug Facts Label (DFL) is displayed differently depending on count size, but each DFL has identical content. The 4-count carton (2 x 2-ct pouches) and the small backer card display the DFL entirely on peel-back/piggyback labeling. The cartons for the 18, 24, 36, 72, and 90 count sizes contain a partial DFL on the back panel that is continued on the bottom panel, which contains a peel-back label. The 18, 24, and 36 count size share a peel-back DFL, while the 72 and 90 count sizes share a larger sized peel-back DFL. The cartons for the 144, 162, 216, and 240 count sizes, the pouch dispenser, and the large backer card display the DFL without utilizing a peel-back label.

a. Drug Facts Title

The Drug Facts title, "***Drug Facts***," appears at the top of the DFL in italicized, boldface 9-point type. "***Drug Facts (continued)***" appears in italicized, boldface 8-point type at the top of each subsequent panel.

Comment: This labeling is acceptable per § 201.66.

b. Active Ingredient/Purposes

"***Active ingredient (in each caplet)***" ***Purposes***" appears as the first headings in italicized, boldface 8-point print.

"***Acetaminophen 250 mg.....Pain reliever***" appears as the first active ingredient and purpose. It appears in 6-point print that is highlighted in yellow. The active ingredient, acetaminophen, matches the USP compendium. It is followed by the strength, 250 mg, per 21 CFR 201.66(c)(2). The active ingredient is separated from the purpose using a leader. The appropriate pharmacological category, per (b) (4) pain reliever (b) (4) is also found in the statement of identity.

"***Ibuprofen 125 mg (NSAID).....Pain reliever***" appears as the second active ingredient and purpose in 6-point print. The active ingredient, ibuprofen, matches the USP compendium. It is followed by the strength, 125 mg, per § 201.66(c)(2), and the term "(NSAID)*" per 21 CFR 201.326(a)(2)(ii). The term "(NSAID)" is defined below the active ingredient by, "*nonsteroidal anti-inflammatory drug," per § 201.326(a)(2)(ii). The active ingredient is separated from the purpose by a leader. The appropriate pharmacological category, pain reliever (b) (4) is also found in the statement of identity, per § (b) (4).

Comment: It is inappropriate for me to comment on the acceptability of the proposed purposes without a formal comment from the DNDP clinical team. The other labeling elements are acceptable pending the two minor changes below:

Per § 201.66(c)(2), ***Active ingredient (in each caplet)*** should be ***Active ingredients (in each caplet)*** since there are more than one active ingredient in each tablet.

Per § 201.326(a)(2)(ii), the term "(NSAID)*" should be "(NSAID*)."

c. Uses

The heading, ***Uses***, appears below the active ingredient/purpose section in italicized 8-point boldface print. The indications are listed below ***Uses***.

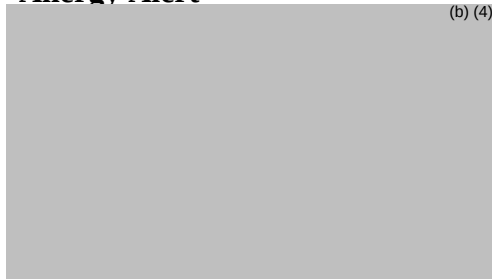
Comment: This labeling includes up-to-date ibuprofen and acetaminophen labeling. However, it is inappropriate for me to comment on the acceptability of the proposed uses without a formal comment from the DNDP clinical team.

d. Warnings

The heading, **Warnings**, appears below the **Uses** section in italicized 8-point boldface print. It contains twelve subheadings, all in 6-point boldface print: Allergy alert (twice), Acetaminophen liver damage warning, NSAID stomach bleeding warning, Heart attack and stroke warning, Do not use, Ask a doctor before use if, Ask a doctor or pharmacist before use if you are, When using this product, Stop use and ask a doctor if, If pregnant or breast-feeding, and Keep out of reach of children.

i. Allergy Alert

(b) (4)



The Warnings section contains two allergy alerts. The first allergy alert follows the August 1, 2013 FDA Drug Safety Communication that informed the public that acetaminophen has been associated with a risk of rare but serious skin reactions.

Comment: This labeling is acceptable. It follows the August 1, 2013 CBE supplemental labeling request letter and the January 2017 guidance for industry *Recommended Warning for Over-the-Counter Acetaminophen Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions*.

The second alert contains the updated allergy alert labeling that was specified in the June 14, 2005 CBE supplemental labeling request letter.

Comment: This labeling is acceptable. It follows the June 14, 2005 CBE supplemental labeling request letter.

ii. Liver damage warning

(b) (4)



The proposed “Acetaminophen liver damage warning” appears immediately below the allergy alert for ibuprofen. This proposed liver damage warning differs, both in content and location, from the liver warning required by 21 CFR 201.326(a)(1)(iii)(A). The proposed warning includes “acetaminophen” in the warning subheading and rearranges the order of the bullets so that, “[bullet] with other drugs containing acetaminophen,” is the first bullet. Both changes emphasize that this product contains acetaminophen and the consumer should not use this drug product with other medicines that contain acetaminophen, which was a primary endpoint of the pivotal label comprehension study.

More importantly, per § 201.326(a)(1)(iii)(A), **the liver damage warning must be the first warning** under the **Warnings** heading. In addition to the regulation, an

argument could be made to improve this warning's prominence since it was the least understood part of the drug facts label during the pivotal label comprehension study.

Comment: Changes to the warning subheading and bullet order are acceptable. However, the liver damage warning **must be the first warning** under the **Warnings** heading, per § 201.326(a)(1)(iii)(A). This revision also supports the social scientist's concern and recommendation about the location of the liver damage warning.

iii. Stomach bleeding warning

(b) (4)

The proposed "NSAID stomach bleeding warning" appears immediately below the proposed liver damage warning. The subheading for the proposed warning is highlighted in yellow and includes the term NSAID. Per § 201.326(a)(2)(iii)(A), the subheading should read, "stomach bleeding warning." Both changes emphasize that "Advil Dual Action with Acetaminophen" contains an NSAID and that taking this product with other NSAID products increases the chance of severe stomach bleeding.

Comment: Changes to the warning subheading, which were made to increase the consumer's understanding of the labeling, are acceptable. This warning should follow the ibuprofen allergy alert. This sequence will be achieved when my recommendation to move the liver damage warning is followed.

iv. Heart attack and stroke warning

(b) (4)

On August 18, 2016 the Agency sent a CBE supplement request letter for NSAID class labeling revisions. This request included the addition of a "Heart attack and stroke warning" under the Warnings heading inserted after the Stomach bleeding warning, as well as changes to the "Ask a doctor before use if," "When using this product," and "Stop use and ask a doctor if" warnings.

Comment: This labeling is acceptable. It follows the August 18, 2016 CBE supplement request.

v. Do not use

(b) (4)

The proposed "Do not use" warning is a combination of the required "Do not use" warnings for acetaminophen and ibuprofen. However, "acetaminophen" has been inserted into the second bullet, "if you have ever had an allergic reaction to acetaminophen or any other pain reliever (b) (4) ."

Comment: This labeling is acceptable. Per § 201.66(c)(5)(iii), the “Do not use” warning is followed by the contraindications for use. The first bullet, required by § 201.326(a)(1)(iii)(B), is present.

vi. Ask a doctor before use if

(b) (4)

ore use if” warning is a combination of the warnings required by § 201.326(a)(1)(iii)(C) and § 201.326(a)(2)(iii)(B), for acetaminophen and ibuprofen.

Comment: This labeling is acceptable. This is up-to-date NSAID class labeling.

vii. Ask a doctor or pharmacist before use if you are

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

The proposed “Ask a doctor or pharmacist before use if you are” warning is required for ibuprofen drug products. It is identical to the warnings contained on approved ibuprofen labeling.

The bullet commonly found on acetaminophen drug products, “taking the blood thinning drug warfarin,” is correctly missing from the proposed labeling. Per § 201.326(a)(1)(iii)(D), this bullet is required on acetaminophen drug products except on labeling of combination products that contain acetaminophen and an NSAID.

Comment: This labeling is acceptable. This is up-to-date NSAID class labeling and correctly follows § 201.326.

viii. When using this product

When using this product

- take with food or milk if stomach upset occurs

The proposed “When using this product” warning is identical to the warning contained on approved ibuprofen labeling. The statement, “take with food or milk if stomach upset occurs,” may be inappropriate based on the effect that food has on the absorption (i.e., C_{max} , T_{max} , and AUC) and onset of action of this drug product.

It correctly does not contain the bullet,

(b) (4)

per the August 18, 2016

CBE supplement request.

Comment: This is up-to-date NSAID class labeling and correctly follows the August 18, 2016 CBE supplement request. However, it is inappropriate for me to comment on this warning without formal input from the clinical pharmacology team regarding the effect of food on the adsorption of this drug product.

ix. Stop use and ask a doctor if

(b) (4)

[Redacted]

(b) (4)

The last four bullets are also contained on acetaminophen drug products.

Comment: This labeling is acceptable. It includes up-to-date NSAID class labeling, acetaminophen labeling, and correctly follows the August 18, 2016 CBE supplement request to add “You have symptoms of heart problems or stroke.”

x. If pregnant or breast-feeding

(b) (4)

[Redacted]

The pregnant or breast-feeding warning is compliant with 21 CFR 201.63. It follows the language provided in § 201.63(a) and § 201.63(e).

Comment: This labeling is acceptable. It is up-to-date NSAID class labeling.

xi. Keep out of reach of children

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

The warnings include the “Keep out of reach of children” warning as set forth in 21 CFR 330.1(g).

Comment: This labeling is acceptable. It is compliant with 21 CFR 201.66(c)(5)(x) and § 330.1(g).

e. Directions

(b) (4)

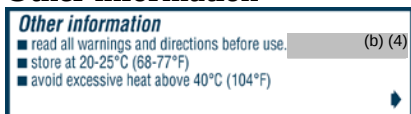
[Redacted]

This section includes four bulleted directions. The first direction, “do not take more than directed,” is in boldface print. The second bullet directs adults and children 12 years and over to take 2 caplets every 8 hours, while symptoms persist. The third bullet provides the maximum daily dosage.

(b) (4)

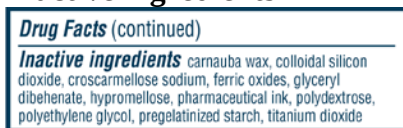
[Redacted]

Comment: It is inappropriate for me to comment on the acceptability of the content for the proposed directions without a formal comment from the DNDP clinical team. However, the visibility of the directions can be improved by using a 2 x 2 table for the bullets, “adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist” and “children under 12 years: ask a doctor.” The visibility of the directions section is especially concerning when considering that it follows a long warnings section.

f. Other information

This section contains another reminder to read and keep the carton. It also provides the storage conditions, which include storage at controlled room temperature and avoidance of excessive heat, as defined by the USP compendium.

Comment: This labeling is acceptable. It includes up-to-date ibuprofen and acetaminophen labeling and follows compendial temperature and storage definitions.

g. Inactive ingredients

This section lists the inactive ingredients in alphabetical order, per 21 CFR 201.66(c)(8), which include Carnauba wax, Colloidal silicon dioxide, Croscarmellose sodium, Ferric oxides, glyceryl dibehenate, Hypromellose (b) (4), Pharmaceutical ink (b) (4), Polydextrose, Polyethylene Glycol, Pregelatinized starch (b) (4), and Titanium oxide.

Comment: This labeling is acceptable and compliant with § 201.66(c)(8).

h. Questions or comments?

This section includes the telephone number of a source to answer questions about the product and the days of the week and times of the day when a person is available to respond to questions, as recommended.

Comment: This labeling is acceptable and compliant with 21 CFR 201.66(c)(9).

B. Immediate Container Label

Immediate container labeling was provided for pouches, vials (loose and packed), and bottles (housed in a carton and stand alone).

i. Immediate Container Label Outside Drug Facts**a. Principal Display Panel**

The text and graphics on the proposed principal display panels (PDPs) are consistent across the proposed product line's bottle and vial immediate containers and are similar to the outer cartons reviewed above in section **II(A)(i)**. Representative examples are displayed above this paragraph. Each PDP contains the proprietary name, statement of identity, net quantity numerical count, a red banner with the statement "CONTAINS 2 MEDICINES," two tubes, one red and the other blue, with a circular arche, and a dark blue background. In addition, the PDP for the stand-alone bottle contains a new flag, a light blue grid that matches the style of Sponsor's product line for Advil (ibuprofen, 200 mg) tablets, a graphic image of two cream-color tablets marked with "Advil II" in black print (This graphic image was added to help reinforce the dosing regimen of two tablets every eight hours).

Comment: This labeling is acceptable. The elements of the PDP are mostly complaint with § 201.60, § 201.61, § 201.62, § 201.326, and § 299.4, and are described below. PDP labeling for bottles (in cartons) and vials do not contain the graphic image of two tablets marked with "Advil II." This graphic image was added to help reinforce the dosing regimen of two tablets every eight hours and was included on the 5-panel carton that Sponsor tested during the pivotal labeling comprehension study. Sponsor should include this graphic image on all immediate container PDP labeling, except for 2-ct pouches.

b. **2-Count Pouches Principal Display Panel**



The 2-ct pouches employs a smaller PDP with simpler graphics. The PDP occupies about a quarter of space on the front pouch in the upper right corner. It contains the proprietary name, statement of identity, and net quantity numerical count. White color print is mostly utilized, except for the word "Advil," to contrast with a dark blue background.

Comment: This labeling is acceptable. The elements of the PDP are compliant with § 201.60, § 201.61, § 201.62, § 201.326, and § 299.4, and are described below.

c. **Proprietary Name**

The proprietary name, Advil Dual Action with Acetaminophen, infers that this drug product contains two active ingredients, ibuprofen and acetaminophen. It was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), which found it to be acceptable (see comment **II(A)(i)(a)** of this review for full description).

Advil Dual Action with Acetaminophen is displayed in two different fonts and color and in four different type sizes. The immediate containers use the same style, coloring, and relative letter height as the outer cartons (see comment **II(A)(i)(a)** of this review for a full description).

Comment: This labeling is acceptable. The proprietary name is prominent and conspicuous on the PDP for the bottle and packed vials.

d. **Statement of Identity**

The proposed statement of identity (SOI) is comprised of an incomplete established name, the word “(NSAID)”, and the pharmacological categories, and the SOI is immediately below the proprietary name.

The established name, Acetaminophen 250 mg and Ibuprofen 125 mg, is incomplete because it is missing the dosage form “tablets.” The established name should be “**Acetaminophen** 250 mg and Ibuprofen 125 mg Tablets.” This established name must include the active ingredients, strength, and dosage form. For instance, approved labeling for ibuprofen drug products lists the strength, such as Ibuprofen Tablets, 200 mg for Advil.

The terms “Acetaminophen” and “(NSAID)” are in bold type. The type size is at least one-quarter the size of the most prominent matter (i.e. Advil) and is at least as large as the size of the “Drug Facts” title, per § 201.326(a) for each type of container. However, it is not at least as large as the size of the “Drug Facts” title, per § 201.326(a)(2)(i) on the loose vial labeling.

The pharmacological categories, pain reliever (b) (4), are appropriate for the approved indications. These categories are consistent with the current monograph indications for acetaminophen and approved indications for ibuprofen. The SOI is in white-color font that distinctly contrasts with the dark blue background.

Comment: The statement of identity should include the dosage form, “tablets,” after Ibuprofen 125 so that it reads, “**Acetaminophen** 250 mg and Ibuprofen 125 mg Tablets Pain Reliever (b) (4)”

While the print size of the term “(NSAID)” in the statement of identity on the loose vial PDP is at least one-quarter the size of the most prominent printed matter, it is not at least as large as the size of the “Drug Facts” title, per § 201.326(a)(2)(i). The type size of the loose vial statement of identity needs to be increased so that “(NSAID)” is at least the size of the “Drug Facts” title. Otherwise, the SOI meets the formatting requirements found in § 201.61, § 201.326, and § 299.4.

e. **Net Quantity**

The net quantity numerical count is displayed in the lower right corner in white-color type outlined in blue. Beneath the numerical count is the term “Caplets,” which is defined as capsule-shaped tablets on the loose vials and stand-alone bottles but not the packed vials and bottles housed in outer cartons. The net quantity appears in conspicuous boldface print.

Comment: This labeling is acceptable. The net quantity is evident per § 201.62.

f. **New Flag**

There is a red flag in the upper left corner of the stand-alone bottle PDP with the word “New” in white print.

Comment: This labeling is acceptable. Remind Sponsor to remove the flag six months after the product is introduced.

g. **Tamper Evident Statement**
Bottles

Do Not Use if seal under bottle cap imprinted with
"SEALED for YOUR PROTECTION" is broken or missing.

Do Not Use if seal under bottle cap imprinted with
"SEALED for YOUR PROTECTION" is broken or missing.

The tamper evident statement, "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing," is located above the warnings labeling in blue print against a white background, outlined in a blue box. For the stand-alone bottles, the warning is located above the drug facts label, in white type against the dark blue background, outlined in a blue box.

Comment: This labeling is acceptable, per § 211.132(c). The tamper evident statement is prominently displayed and identifies the tamper evident feature.

Loose Vials

DO NOT USE IF SEAL AROUND
CAP IS BROKEN OR MISSING.
ADVIL SAFETY SEALED.

The tamper evident statement, "DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED," is located on the peel-back label, below the directions in blue print against a white background, outlined in a blue box.

Comment: This labeling is unacceptable, per § 211.132(c). The tamper evident statement identifies the tamper evident feature but is not prominently displayed. One needs to completely peel back the outer label to detect the tamper evident statement.

Packed Vials

DO NOT USE unless vial was sealed in
unbroken plastic blister on cardboard card.

The tamper evident statement, "DO NOT USE unless vial was sealed in unbroken plastic blister on cardboard card," is located on the peel back label, below the directions in blue print against a white background, outlined in a blue box.

Comment: This labeling is unacceptable, per § 211.132(c). The tamper evident statement identifies the tamper evident feature but is not prominently displayed. One needs to completely peel back the outer label to detect the tamper evident statement.

h. **Expiration Dating and Lot Number**

(b) (4)

A placeholder for the expiration date and lot number is indicated in the annotated labeling for each immediate container (see examples above). However, the format for the expiration date is not defined on the container label and carton labeling.

Comment: Sponsor designated an area for expiration dating and lot numbers, per § 201.17 and § 211.37 (expiration dating) and § 201.18 (control numbers). However, the format for the expiration date is not defined. Request that Sponsor identify the format they intend to use for the expiration dating to minimize confusion and reduce the risk for deteriorated drug medication errors.

i. **Place of Business of Distributor**

The place of business of distributor statement, Pfizer, Madison, NJ 07940 USA, is contained after questions or comments on the proposed bottle labeling and below the tamper evident statement on the proposed vial labeling.

Comment: This labeling is acceptable per § 201.1.

j. **Lift Here Piggyback Label**



18-ct, 24-ct, and 36-ct bottle labeling and all stand-alone bottle labeling utilize peel-back labeling. Sponsor employs, “LIFT HERE for More Drug Facts,” in blue print against a white background to indicate where to peel back.



All vial labeling utilize peel-back labeling. This labeling uses “LIFT HERE for More Drug Facts,” in blue print against a white background or “OPEN HERE TO VIEW MORE PRODUCT INFORMATION” to indicate where to peel back.

Comment: This labeling is acceptable. The “Peel Back” designation is in print that distinctly contrasts with the background. This designation is also consistent with approved labeling for Sponsor’s Advil (ibuprofen) Tablets drug products.

k. **Read and Keep Carton for Complete Warnings and Information (18, 24, 36, 72, 90, 144, 162, 216, and 240 count sizes)**



18-ct, 24-ct, 36-ct, 72-ct, 90-ct, 144-ct, 162-ct, 216-ct, and 240-ct immediate container labeling do not contain drug facts labels, which is consistent with approved labeling for ibuprofen and acetaminophen drug products. The full DFL can be found on the outer carton and the immediate container prominently displays the statement, “READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.” This statement is displayed in blue print, outlined in a blue box against a white background either above the Uses/Warning Labeling (≤ 36 count size) or immediately below the PDP (≥ 72 count sizes).

Comment: This labeling is acceptable. The statement is prominently displayed, both location and print.

l. **Read and Keep Card for Complete Warnings and Information (8-ct packed vial)**

The 8-ct packed vial labeling does not contain a drug facts labels, which is consistent with approved labeling for ibuprofen and acetaminophen drug products. The full DFL can be found on the backer card and the immediate container prominently displays the statement, “READ AND KEEP CARD FOR COMPLETE WARNINGS AND INFORMATION.” This statement is displayed in blue print, outlined in a blue box against a white background immediately below the PDP.

Comment: This labeling is acceptable. The statement is prominently displayed for both location and print.

m. **Uses (18, 24, 36, 72, 90, 144, 162, 216, and 240-ct Bottles; 8-ct Packed Vial; 2-ct Pouches)**

(b) (4)

The labeling restates the **Uses** found in the DFL. This begins a series of sections that includes **Uses, Warnings, Directions, and Questions or comments.**

Comment: This labeling includes up-to-date ibuprofen and acetaminophen labeling. The type size is adequate. It is inappropriate for me to comment on the acceptability of the proposed uses without a formal comment from the DNDP clinical team.

n. **Warnings (18, 24, 36, 72, 90, 144, 162, 216, and 240-ct bottles and 8-ct packed vial)**

(b) (4)

The immediate container labeling contains the required warnings from the CFR and CBE supplement requests. The DFL formatting requirements, however, are not required on the immediate container, leading to the use of 4.5-point type size. Immediate container labeling repeats the following information elements that are discussed above in detail (see **II(A)(ii)(d)Warnings** of this review for full description): Allergy alerts, Acetaminophen liver damage warning, NSAID stomach bleeding warning, Heart attack and stroke warning, Do not use (only for the 18, 24, and 36 count sizes), Ask a doctor before use, Ask a doctor or pharmacist before use if you are, When using this product, and Stop use and ask a doctor if.

Like the DFL labeling, the Liver Damage Warning and the Stomach Bleeding Warning have been modified to include "Acetaminophen" and "NSAID", respectively, and the warnings have been highlighted in yellow. Liver Damage Warning inappropriately follows the allergy alert. Per § 201.326(a)(1)(iii)(A), "This "Liver" warning must be the first warning under the "Warnings" heading."

Curiously, Sponsor broke from approved Advil labeling and did not employ bullets to separate statements on immediate container labeling. Instead, statements are separated using semi-colons. This greatly reduces the legibility of the labeling.

Peel-back labeling for the smaller count sizes (≤ 36 -ct) contain an additional warning, “Do not use.” It’s unclear why this warning was selected to fill in the extra space.

The “Ask a doctor before use” warning contains an additional statement, “If you are pregnant or breast feeding.” This statement is also found on approved labeling for Advil tablets. It’s unclear why this statement is included here, but the labeling does not contain the pregnancy/breast-feeding warning, per § 201.63.

Comment: The warning statements required by § 201.326 are present on the back label. The “Heart attack and stroke warning” is also present.

Two revisions are required:

1. The liver warning must be the first warning, ahead of the allergy alert.
2. Bullets, instead of semi-colons, should be used to separate statements under the liver damage warning, stomach bleeding warning, ask a doctor before use warning. This revision is consistent with approved labeling for ibuprofen and acetaminophen drug products.

o. Directions (18, 24, 36, 72, 90, 144, 162, 216, and 240-ct bottles and 8-ct packed vials)

The immediate containers for the 18, 24, 36, 72, 90, 144, 162, 216, and 240 count sizes repeat the directions from the DFL following the warning sections above. However, the directions on the immediate containers use semi-colons instead of bullets to separate directions.

Comment: This labeling is acceptable. While it’s not required, the use of bullets would greatly improve the legibility of the directions.

p. Questions or Comments? (18, 24, 36, 72, 90, 144, 162, 216, and 240-ct bottles and 8-ct packed vials)

This section follows the “Directions” section and includes the telephone number of a source to answer questions about the product.

Comment: This labeling is acceptable. It is compliant with § 201.66(c)(9).

q. Warnings/Directions/Other Information/Questions or Comment for 2-ct Pouches

(b) (4)



The proposed labeling for 2-ct pouches contain similar warnings to the warnings discussed in comment **II(B)(i)(n)** above. It is not required to contain a full DFL since the pouch dispenser, which contains a full DFL, is considered the outer carton. However, the pouch labeling contains the required warnings from the CFR and CBE supplement requests.

The proposed pouch labeling repeats the entire warnings section of the DFL, except for the Active Ingredient/Purposes section, without following the DFL formatting

requirements (see comments **II(A)(ii)(a)- II(A)(ii)(h)** of this review for a full discussion of the DFL). Instead the sponsor eliminated bullets, barlines, and hairlines and uses 4.5-point print.

Like the DFL labeling, the Liver Damage Warning and the Stomach Bleeding Warning have been modified to include “Acetaminophen” and “NSAID”, respectively, and the warnings have been highlighted in yellow. Liver Damage Warning inappropriately follows the allergy alert. Per § 201.326(a)(1)(iii)(A), “This “Liver” warning must be the first warning under the “Warnings” heading.”

Comment: This labeling is acceptable. The warning statements required § 201.326 are present. The “Heart attack and stroke warning” is also contained by the immediate container’s back label. However, the liver warning must be the first warning, ahead of the allergy alert.

r. **Easy Open ARTHRITIS CAP**



“Easy Open ARTHRITIS CAP” appears in red print in a yellow banner at the top of the PDP for the 144-ct and 162-ct (144-ct + 18-ct) stand-alone bottles. An Arthritis Foundation Ease of Use icon is next to the “Easy Open Arthritis Cap” statement.

Comment: This labeling is acceptable.

This labeling will account for two non-child resistant (CR) packaging (or “non-compliant packaging”), and Sponsor is permitted to marketed only one at a time, per 16 CFR1700. Because a non-child resistant package must not be in the most popular packaging size (e.g., if most consumers buy the 144-ct bottles, the non-CR package cannot be a 144-ct bottle) manufacturers must monitor sales and change packages accordingly. FDA therefore has approved more than one non-CR package labels for use at different times during the year in case a non-CR package count becomes the most popular product size. Sponsor has not provided a right of reference from the Arthritis Foundation to use their service mark. Request Sponsor provide a right of reference from the Arthritis Foundation.

s. **Noncomplying Poison Prevention Packaging Labeling Requirements**

THIS PACKAGE FOR HOUSEHOLDS WITHOUT YOUNG CHILDREN

The statement, “THIS PACKAGE FOR HOUSEHOLDS WITHOUT YOUNG CHILDREN,” conspicuously appears within the borderline of a white rectangle on the PDP, which is parallel to the base on which the package will rest. This statement is displayed in white color print and all capital letters, outlined with a white box, and distinctly contrasts with the blue background.

Comment: This labeling is acceptable per 16 CFR 1700.5.

t. **Additional Acetaminophen Warning (stand-alone bottles, loose vials, and pouches)**

Do not use with other medicines containing ACETAMINOPHEN; can cause liver damage.

Like the outer carton’s fifth panel labeling (see comment **II(A)(i)(e)** of this review), the stand-alone bottles, loose vials, and pouches contain an additional acetaminophen

warning above the drug facts label. The statement, “Do not use with other medicines containing ACETAMINOPHEN; can cause liver damage,” is a warning in red color print outlined in a bright yellow box.

Comment: This labeling is acceptable. It emphasizes not to use this drug product with any other drug containing acetaminophen. The viability of the proposed labeling was demonstrated in pilot and pivotal labeling comprehension studies.

ii. Immediate Container Drug Facts Label

Unlike, the proposed labeling for the 18-ct, 24-ct, 36-ct, 72-ct, 90-ct, 144-ct, 162-ct, 216-ct, and 240-ct immediate containers housed in outer cartons, packed vials, and pouches do not contain a drug facts label (DFL), the stand-alone bottles and loose vials contain DFL labeling. Peel-back labeling is employed to contain the full DFL. DFL content, formatting, and order follows the DFL discussed in comments **II(A)(ii)(a)- II(A)(ii)(h)** of this review.

Comment: This labeling is acceptable. The same recommendations and comments that apply to the outer DFL apply to the immediate container DFL.

C. Coupon Labeling

Sponsor submitted two types of instantly redeemable coupons (IRC): a yellow peel-off sticker and a peel-off sticker that duplicates the PDP.

i. Instantly Redeemable Coupon (IRC) Peel-Off PDP



Sponsor proposed four IRC stickers that duplicate the PDP but with the addition of the IRC value on a yellow flag placed on the left side of the PDP. The coupon contains the statement “SAVE \$1⁰⁰ NOW ON ANY Advil Dual Action xct or larger,” where x is 18, 36, 72, or 144, to denote the terms of the coupon such as the so-called “savings” and the required count size for purchase. The reverse side also contains the expiration date and the terms and conditions. The format, placement, and content of this IRC is nearly identical to the IRC approved in NDA 20180.

Comment: Sponsor submitted renderings of proposed market packages with attached coupons for review to confirm that no regulated information is obscured upon placement of coupons and after each coupon is removed. Sponsor also provided annotation that the peel-off PDP is a full-face coupon and will not leave a visibly obstructive residue. This labeling is acceptable.

ii.

(b) (4)

Sponsor proposed five peel-off IRC stickers presumably to be placed on the 18-ct, 36-ct, 72-ct outer carton and the 144-ct stand-alone bottle. These five IRC stickers contain similar promotional statements, “Save \$X.00 On any Advil Dual Action xct or larger,” in red print against a yellow background. The savings range from \$1.00 to \$3.00 for the 18, 36, 72, and 144 count sizes (see submitted labeling table at the beginning of this review). The coupon has four folds so that only the yellow banner will show. It is unclear where the sticker will be placed and if it will cover or obscure any regulatory information.

Comment: Sponsor submitted renderings of proposed market packages with attached coupons to confirm that no regulated information is obscured upon placement of coupons and after each coupon is removed. This labeling is acceptable.

III. RECOMMENDATIONS

These recommendations are incomplete because it is inappropriate for me to fully comment on the proposed **Purposes**, **Uses**, and **When using this product** sections of the DFL without formal input from the clinical teams assigned to this application (see comments **II(A)(ii)(b)**, **II(A)(ii)(c)**, and **II(A)(ii)(d)(viii)**).

Request the sponsor make the following changes:

1. While the print size of the term “(NSAID)” in the statement of identity on the loose vial PDP is at least one-quarter the size of the most prominent printed matter, it is not at least as large as the size of the “Drug Facts” title, per § 201.326(a)(2)(i). The type size of the loose vial statement of identity needs to be increased so that “(NSAID)” is at least the size of the “Drug Facts” title.
2. As currently presented, the format for the expiration date is not defined on the container label and carton labeling. Per United States Pharmacopoeia (USP) General Chapter <7> Labeling, “the expiration date shall be prominently displayed in high contrast to the background or it shall be sharply embossed, and easily understood (e.g., ‘EXP 6/13,’ ‘Exp. June 13,’ or ‘Expires 6/2013’).” To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.
3. Per § 201.66(c)(2), change the DFL heading “**Active ingredient (in each caplet)**” to “**Active ingredients (in each caplet)**” since there are more than one active ingredient in each tablet.

4. Per § 201.326(a)(2)(ii), change the format of the term “(NSAID)*” in the statement “Ibuprofen 125 mg (NSAID)*.... Pain reliever (b) (4)” under the Active ingredient section of the DFL to “(NSAID*).”
5. Change the statement of identity (SOI) to include the dosage form, “tablets,” after “Ibuprofen 125 (NSAID)” so that it reads “**Acetaminophen** 250 mg and Ibuprofen 125 mg (NSAID) Tablets Pain Reliever (b) (4).”
6. Provide annotated labeling for the 24-count (18-ct + 6-ct) immediate container (bottle).
7. The tamper evident statement located on the vial containers, “DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED,” can only be viewed if the peel back label is completely pulled back. Relocate the tamper evident statement so that it is prominently displayed, per § 211.132(c).
8. Immediate container labeling for bottles and vials without a full DFL separates statements using semi-colons instead of bullets. This format reduces clarity and ease of reading. Use bullets to separate statements under the “liver damage warning,” “stomach bleeding warning,” and “ask a doctor before use” warning. This revision is consistent with approved immediate container labeling for ibuprofen and acetaminophen drug products.
9. Per § 201.326(a)(1)(iii)(A), the liver damage warning, located on the DFL, must be the first warning under the **Warnings** heading. Revise your labeling so that the liver damage warning is the first warning subheading, above the allergy alerts on the DFL and immediate containers labeling that contain warning labeling instead of a full DFL.
10. The visibility of the directions can be improved by using a 2 x 2 table (four cells in total) for the bullets, “adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist” and “children under 12 years: ask a doctor.” The visibility of the directions is concerning because it follows a long warnings section.
11. PDP labeling for bottles (in cartons) and vials does not include the graphic image of two tablets marked with “Advil II.” This graphic image was added to reinforce the dosing regimen of two tablets every eight hours and was included on the 5-panel carton tested in the pivotal labeling comprehension study. This graphic image should be included on all immediate container PDP labeling, except for 2-ct pouches.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review. The labels were compressed in size to meet the uploading data size limitations set by FDA’s Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).

49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT J BAHDE
09/23/2019 01:43:57 PM

KEVIN L LORICK
09/23/2019 02:03:31 PM
I concur with the review and recommendations.

Clinical Inspection Summary

Date	August 8, 2019
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Shila Azodi, MD, Medical Officer DNDP
NDA #	211733
Applicant	Pfizer, Inc.
Drug	Advil Dual Action with Acetaminophen
NME	No
Division Classification	Pain reliever (b) (4)
Proposed Indication	Temporary pain relief (b) (4)
Consultation Request Date	March 2, 2019
Summary Goal Date	August 16, 2019
Action Goal Date	November 22, 2019
PDUFA Date	November 29, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were conducted at two clinical investigator (CI) sites, each of which was the single site for a Phase 3 study. No significant regulatory findings or data integrity issues were noted. The data generated by these sites are acceptable in support of the application.

II. BACKGROUND

Pfizer developed a fixed-dose combination (FDC) consisting of ibuprofen 125 mg and 250 mg of acetaminophen intended for over-the-counter (OTC) use. The proposed product indications are the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4). Each table contains 125 mg of ibuprofen and 250 mg of acetaminophen. The proposed dosing regimen is 2 FDC tablets every 8 hours (for a total daily dose of 750 mg of ibuprofen and 1500 mg of acetaminophen).

Drug: Advil Dual Action with Acetaminophen

Studies– Protocol numbers and titles for all studies that were inspected

1. B5061003, entitled “A Phase 3, Double-Blind, Randomized, Safety and Efficacy Study Comparing a Single Oral Dose of Ibuprofen (IBU) 250 mg/Acetaminophen (APAP) 500 mg (Administered as Two Tablets of IBU/APAP 125 mg/250 mg) to Each Active Drug Monocomponent Alone and to Placebo in the Treatment of Post-Surgical Dental Pain”

Number of subjects: 568 subjects

Number of sites: one

Number of countries where subjects were enrolled: USA only

Dates that study was conducted: September 2015 to June 2016

Efficacy endpoint: SPID[11] 0-8 (sum of pain intensity difference scores) from 0-8 hours (time-weighted Sum of Pain Intensity Difference scores PID[11] based on the 11-point Numerical Pain Severity Rating scale)

2. B5061004, A Phase 3, Double-Blind, Randomized Safety and Efficacy Study Comparing Multiple Administrations of IBU 250 mg/APAP 500 mg (Administered as Two Tablets of IBU/APAP 125 mg/250 mg) to Placebo in the Treatment of Post-Surgical Dental Pain in Adult Subjects”

Number of subjects: 123 subjects

Number of sites: one

Number of countries where subjects were enrolled: USA only

Dates that study was conducted: August 2016 to February 2017

Efficacy endpoint: SPID[11] 0-24 (sum of pain intensity difference scores) from 0-24 hours (time-weighted Sum of Pain Intensity Difference scores PID[11] based on the 11-point Numerical Pain Severity Rating scale)

III. RESULTS (by site):

1. Derek Muse, M.D.
1045 East 3900 South, Salt Lake City, UT 84124

At this site, for Protocol B5061003, a total of 722 people were screened for participation in the study, and 568 subjects were enrolled and received test article; Eight subjects withdrew consent or were terminated from the study. A total of 42 subject records were reviewed. Records reviewed included subject source data and case report forms; communications with the sponsor, monitors, and IRB; financial disclosures; investigational product accountability records; delegation of study personnel; and site staff training. No significant deviations or discrepancies were noted. There was no evidence of under reporting of adverse events or protocol deviations. No Form 483 was issued.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Shawn Searle, M.D.
3838 South 700 East, Salt Lake City, UT 84106

At this site, for Protocol B5061004, a total of 203 people were screened for participation in the study and 80 subjects failed screening. One-hundred twenty-three (123) subjects were enrolled and received test article; eleven (11) persons did not finish the study. A total of 45 subject records were reviewed. Records reviewed included subject source data and case report forms; communications with the sponsor, monitors and IRB; financial disclosures; investigational product accountability records; delegation of study personnel; and site staff training. No significant deviations or discrepancies were noted. There was no evidence of under reporting of adverse events or protocol deviations. No Form 483 was issued.

One discrepancy between source document and derived line listing was noted as follows: Subject ^{(b) (6)} use of rescue medication is reported after 32 hours in the derived endpoint line listings. However, the source documents for rescue medication administration indicate that he received rescue medication after 1.5 hours. In his report, the FDA field investigator noted that the site failed to obtain the pain assessments immediately prior to dosing with the rescue meds. This is a protocol deviation that was accurately reported in the line listings. The ORA field considered that this may have been an explanation for the error in the derived line listing for the endpoint. This discrepancy was reported to the Review division statistical review team on May 21, 2019. The team reviewed the analysis dataset for efficacy and reported that the rescue time for this subject was correctly derived and reported in the dataset as being 1.5 hours.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
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OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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