CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213082Orig1s000

OTHER REVIEW(S)

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:	September 23, 2020
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 213082 and NDA 203214/S-026
Product Name and Strength:	Xeljanz (tofacitinib) (tofacitinib) oral solution , 1 mg/ml Xeljanz (tofacitinib) oral tablets, 5 mg
Applicant/Sponsor Name:	Pfizer
OSE RCM #:	2020-600-1, 2020-786-1, and 2020-1733-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 23, 2020 for Xeljanz (tofacitinib). The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels and carton labeling for Xeljanz (tofacitinib) (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 all of our recommendations and we have no additional recommendations at this time.

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] McMillan T. Label and Labeling Review for Xeljanz (tofacitinib) (NDA 213082 and NDA 203214/S-026). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 19. RCM No.: 2020-600 , 2020-786, and 2020-1733.

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/

TERESA S MCMILLAN
09/23/2020 03:47:42 PM

IDALIA E RYCHLIK
09/24/2020 11:35:22 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **Sep 23, 2020**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch V

Through: **Wendy Wilson, Ph.D.**
Director, Division II/Branch V

To: **Labeling Review #1 of NDA 213082**

Subject: **Final labeling/labels**

The Labeling review #1 has noted the following pending issues:

For Container/Carton Labels:

Include an equivalence statement that each 1 mL of oral solution contains 1 mg of tofacitinib (equivalent to 1.62 mg tofacitinib citrate)

And because of this deficiency in the Labeling/labels Review #1, this NDA was not recommended for approval from the labeling perspective.

The above request has been implemented in the revised labeling/labels. The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

CRAIG M BERTHA
09/23/2020 12:19:49 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020293
NDA Number:	NDA 203214 S-026, NDA 213082
Applicant:	Pfizer, Inc.
Established Name/Trade Name:	Tofacitinib (Xeljanz)
Indication:	Treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
Deliverable:	Advice Letter/Advice to Division
Review Division:	Division of Rheumatology and Transplant Medicine
Clinical Reviewer:	Juwaria Waheed
Clinical Team Leader (TL):	Anil Rajpal
Review Division Project Manager:	Elaine Sit
COA Reviewer/Acting TL:	Onyeka Illoh, OD, MPH
COA Acting Director:	Elektra Papadopoulos, MD, MPH
Date Consult Request Received:	July 6, 2020
Date Submission Received:	March 26, 2020
Date COA Review Completed:	September 1, 2020

Please check all that apply: ☒Rare Disease/Orphan Designation
☒Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 203214 supplement 026. The Applicant completed the phase 3 study A3921104, a randomized, withdrawal, double-blind, placebo-controlled study of subjects from 2 to <18 years of age with juvenile idiopathic arthritis (JIA). The proposed indication is for the treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older.

The Applicant administered the Childhood Health Assessment Questionnaire (CHAQ) caregiver-reported version to both caregivers and patients aged ≥ 14 years in Study A3921104 (b) (4) (b) (4) (b) (4). The Division of Rheumatology and Transplant Medicine (DRTM) seeks input from the Division of Clinical Outcome Assessment (DCOA) on the adequacy of the CHAQ Disability Index (b) (4)

This review concludes the following:

1. There is insufficient evidence to demonstrate that the CHAQ Disability Index caregiver-reported version is fit-for-purpose (b) (4) (b) (4)

instructions, items, and response options are appropriate and understandable to patients and caregivers as intended.

a. We note that the CHAQ Disability Index includes a "Not Applicable" response option that is intended to be used for functional activities that are not expected to be developmentally appropriate for young children, but it is unclear whether caregivers are able to accurately discern which functional activities are developmentally appropriate (i.e., at which age a child should be expected to be able to perform a given functional activity).

b. The CHAQ Disability Index includes 8 domains (functional areas) each including 2 or more items, and all items include a "not applicable" response option. Each functional area only requires one item to be scored (i.e., all the remaining items could be marked as "not applicable") in order to produce a domain score. If a caregiver determines that none of the items for a domain are relevant, the patients would not receive a score for that domain, and it would be missing.

c. It is unclear whether each functional area truly includes items that are relevant to patients across the entire age range of 2 to < 18 years.

d. Additionally, there appears to be overlap between the activities assessed by certain functional areas (e.g., "dressing and grooming" and "hygiene").

e. We also note that patients aged ≥ 14 years in Study A3921104 completed the caregiver-reported version of the CHAQ, instead of the self-reported version which was not included in the study. The interpretability of data obtained from use of a caregiver format for self-report is unclear.

2. It is unclear whether the demonstrated change in CHAQ Disability Index score is clinically meaningful. Anchor-based analyses are our preferred method for determining clinically meaningful change thresholds for COA scores, but the Applicant did not include anchor scales in Study A3921104, so anchor-based analyses were not conducted. The Applicant cites published literature [1] that describes minimal clinically important differences (MCIDs) in CHAQ Disability Index scores of -0.188 for improvement and +0.125 for deterioration (on a scale of 0-3, where "0" indicates no difficulty performing functional activities and "3" indicates inability to conduct functional activities), but the authors of the publication noted that these differences were small and concluded that "the CHAQ in its current form may be too insensitive to determine important short term changes in health and disease for a given patient."

3. In summary, there is limited information to support content validity of the CHAQ Disability Index from the perspective of patients with JIA and their caregivers. Additionally, the treatment effect appears modest, and the Applicant did not provide

[1] H I Brunner, M S Klein-Gitelman, M J Miller, A Barron, N Baldwin, M Trombley, A L Johnson, A Kress, D J Lovell, E H Giannini. *Minimal clinically important differences of the childhood health assessment questionnaire*. J Rheumatol. 2005 Jan;32(1):150-61.

evidence to support a clinically meaningful within-patient change in the CHAQ Disability Index score. (b) (4) (b) (4).

4. For future clinical trials in patients with JIA, we recommend that sponsors provide evidence from interviews with patients and/or caregivers to support content validity of COAs (b) (4), including evidence that assessments are age-appropriate for the patient population being studied in the clinical trial. This evidence is especially important when the clinical trial includes a wide age range of patients (e.g., very young children through adolescents), as concepts that are relevant to one age group (e.g., very young children) may be different, or may manifest differently, than in other age groups (e.g., adolescents).[2,3] We also recommend that sponsors evaluate measurement properties and include anchor scales in their clinical trials to facilitate determination of clinically meaningful changes in COA scores from the patient and/or caregiver perspective. Sponsors should refer to the FDA Guidance for Industry: (b) (4) (b) (4)

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:

- This NDA supplement was previously reviewed by DCOA under IND 117400.

Previous COA Reviews:

- C2019040_IND 117400_CHAQ_JIA_DPARP (DARRTS ID: 4461929)
- C2019146_IND 117400_CHAQ_JIA_DPARP (DARRTS ID: 4461932)

Disease Background:

- JIA is an umbrella term describing a heterogeneous group of conditions characterized by chronic arthritis with onset before the age of 16 years, persisting for at least 6 weeks, and having no other identifiable cause. Polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6-month period.

Investigational Product:

- Xeljanz (tofacitinib) is a selective Janus kinase (JAK) inhibitor. It was first approved by the FDA in November 2012 for the treatment of adult subjects with active moderate to severe RA who have had an inadequate response or intolerance to methotrexate.

[2] E J Papadopoulos, D L Patrick, M S Tassinari, A E Mulberg, C Epps, A R Pariser, L B Burke. Chapter 42: *Clinical Outcome Assessments for Clinical Trials in Children*. In: *Pediatric Drug Development: Concepts and Applications*, Second Edition. 2013.
[3] L S Matza, D L Patrick, A W Riley, J J Alexander, L Rajmil, A M Pleil, M Bullinger. (b) (4) (b) (4)

Materials reviewed:

- Applicant's patient-reported outcome (PRO) evidence dossier for the CHAQ
- Clinical Trial Report for Study A3921104
- Study A3921104 clinical protocol and amendments
- Summary of Clinical Efficacy
- U.S. Food and Drug Administration. Guidance for Industry: (b) (4) (b) (4)
- G Singh, B H Athreya, J F Fries, D P Goldsmith. *Measurement of health status in children with juvenile rheumatoid arthritis*. Arthritis Rheum. 1994 Dec;37(12):1761-9. doi: 10.1002/art.1780371209.
- H Dempster, M Porepa, N Young, B M Feldman. *The clinical meaning of functional outcome scores in children with juvenile arthritis*. Arthritis Rheum. 2001 Aug;44(8):1768-74. doi: 10.1002/1529-0131(200108)44:8<1768::AID-ART312>3.0.CO;2-Q.
- M Nørgaard, M Thastum, T Herlin. *The relevance of using the Childhood Health Assessment Questionnaire (CHAQ) in revised versions for the assessment of juvenile idiopathic arthritis*. Scand J Rheumatol. 2013;42(6):457-64. doi: 10.3109/03009742.2013.768701. Epub 2013 Mar 21.
- J Pouchot, E Ecosse, J Coste, F Guillemin, French Quality of Life Study Group; Paediatric Rheumatology International Trials Organisation. *Validity of the childhood health assessment questionnaire is independent of age in juvenile idiopathic arthritis*. Arthritis Rheum. 2004 Aug 15;51(4):519-26. doi: 10.1002/art.20529.
- N Ruperto, A Ravelli, A Pistorio, C Malattia, S Cavuto, L Gado-West, A Tortorelli, J M Landgraf, G Singh, A Martini, Paediatric Rheumatology International Trials Organisation. *Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology*. Clin Exp Rheumatol. Jul-Aug 2001;19(4 Suppl 23):S1-9.
- L S Matza, D L Patrick, A W Riley, J J Alexander, L Rajmil, A M Pleil, M Bullinger. (b) (4)
- A Tennant, S Kearns, F Turner, S Wyatt, R Haigh, M A Chamberlain. *Measuring the function of children with juvenile arthritis*. Rheumatology (Oxford). 2001 Nov;40(11):1274-8. doi: 10.1093/rheumatology/40.11.1274.
- H I Brunner, M S Klein-Gitelman, M J Miller, A Barron, N Baldwin, M Trombley, A L Johnson, A Kress, D J Lovell, E H Giannini. *Minimal clinically important differences of the childhood health assessment questionnaire*. J Rheumatol. 2005 Jan;32(1):150-61.

2 FIT-FOR-PURPOSE SUMMARY

The Applicant did not submit evidence to support content validity of the CHAQ Disability Index from the perspective of patients with JIA and their caregivers. Therefore, there is insufficient evidence to demonstrate that the CHAQ Disability Index is fit-for-purpose for the context of use of this clinical development program.[5]

(b) (4)

3 CONTEXT OF USE

3.1 Clinical Trial Population

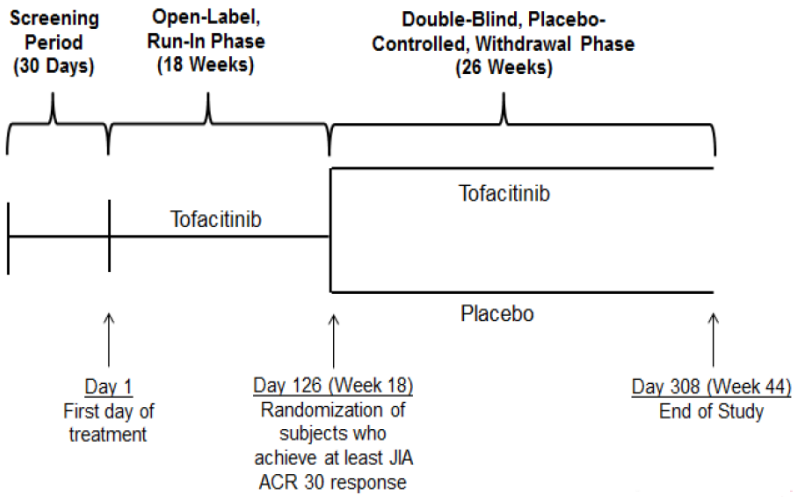
The patient population of Study A3921104 were 173 patients aged 2 to < 18 years with JIA, randomized 1:1 to treatment (n = 88) and placebo (n = 85). Approximately 62% of patients were aged 12 to < 18, 26% were aged 6 to < 12, and 12% were aged 2 to < 6.

A complete list of the inclusion and exclusion criteria is summarized in the clinical trial protocol for Study A3921104.

3.2 Clinical Trial Design

Study A3921104 was a randomized withdrawal, double-blind, placebo-controlled study of subjects from 2 to <18 years of age with JIA. A schematic of the study is described in Figure 1.

Figure 1. Study Schematic



Refer to the clinical trial protocol for more details on the clinical trial design.

[5] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. BEST (Biomarkers, Endpoints and Other Tools) Resource. Available from: https://www ncbi nlm nih.gov/books/NBK338448/

3.3 Endpoint Position, Definition, and Assessment Schedule

Primary Endpoint:

- Occurrence of disease flare (according to the Pediatric Rheumatology Collaborative Study Group (PRCSG) / Paediatriac Rheumatology International Trials Organisation (PRINTO) Disease Flare criteria) at Week 44/End of Study (Week 26 of the double-blind phase).

  Assessment schedule: Screening; Day 1; Weeks 2, 4, 8, 12, 18, 20, 24, 28, 32, 36, 40, 44 (end of study) or early termination.

Key Secondary Endpoints (strictly controlled for Type I error):

- Achieving JIA American College of Rheumatology (ACR) 30-50-70 response at Week 44/End of Study (Week 26 of the double-blind phase).

  Assessment schedule: Screening; Day 1; Weeks 2, 4, 8, 12, 18, 20, 24, 28, 32, 36, 40, 44 (end of study) or early termination.

- Change from double-blind baseline in CHAQ disability index at Week 44/End of Study (Week 26 of the double-blind phase).

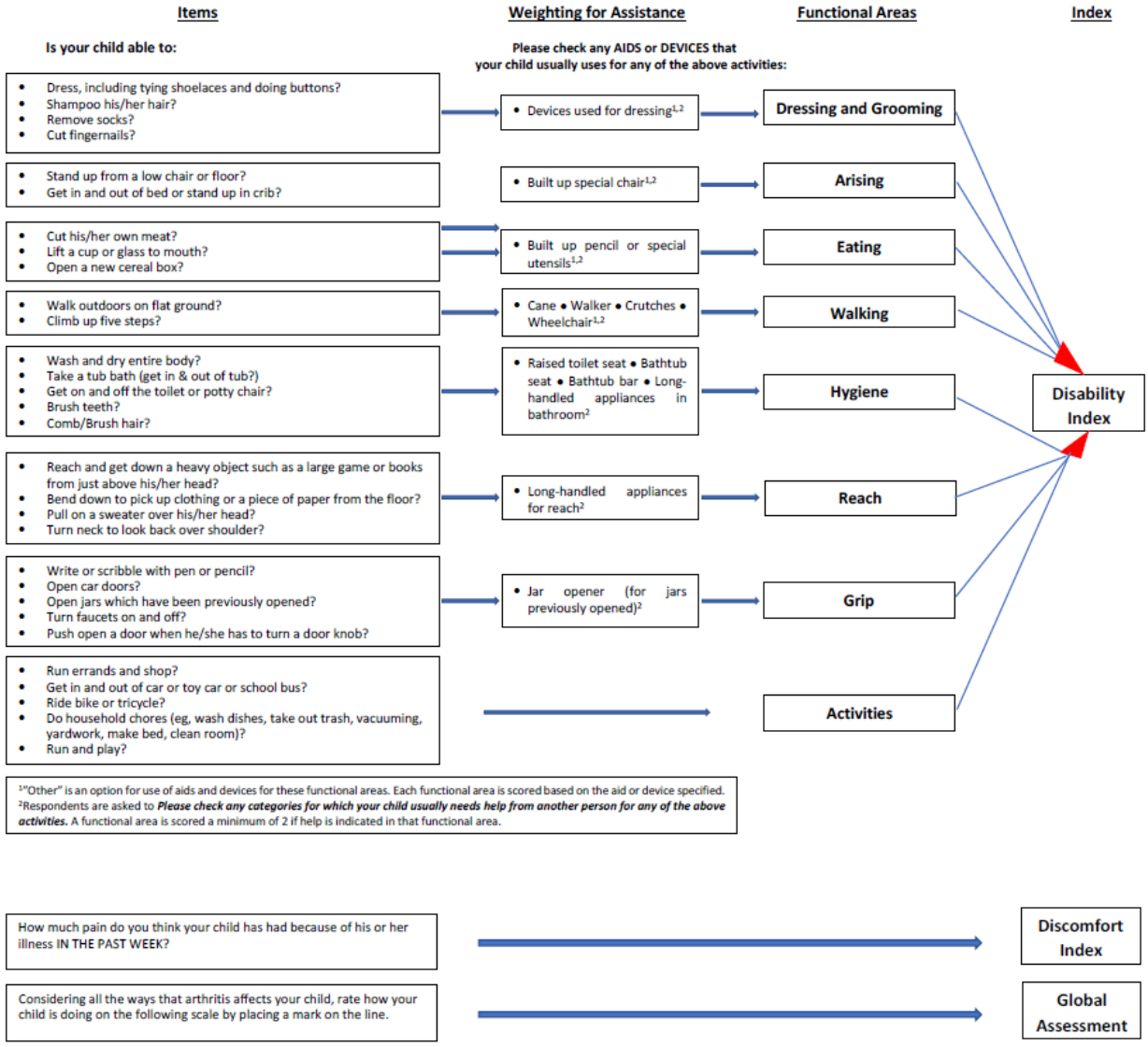
  Assessment schedule: Screening; Day 1; Weeks 2, 4, 8, 12, 18, 20, 24, 28, 32, 36, 40, 44 (end of study) or early termination.

(b) (4)

(b) (4)

4 CONCEPTUAL FRAMEWORK

The Applicant's evidence dossier contains the following conceptual framework for the CHAQ:



5 CLINICAL OUTCOME ASSESSMENT

Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ is a self- or caregiver-reported instrument that assesses functional status in children with JIA, which is measured using a Disability index, a Discomfort index (pain) and a global assessment of arthritis (overall well-being).

The CHAQ Disability Index (see **Appendix A**) is a 30-item assessment of the child's functional abilities across 8 functional areas:

- Dressing & Grooming (4 items)
- Arising (2 items)
- Eating (3 items)

- Walking (2 items)
- Hygiene (5 items)
- Reach (4 items)
- Grip (5 items)
- Activities (5 items)

The recall period is "over the past week" and the response options are as follows (emphasis verbatim):

- Without ANY Difficulty
- With SOME Difficulty
- With MUCH Difficulty
- UNABLE To Do
- Not Applicable

In Study A3921104, the CHAQ caregiver-reported version was completed by either the caregivers or the pediatric patients if aged ≥ 14 years at open-label baseline and able to do so correctly and consistently for the duration of the study. The self-report version of the CHAQ was not included in the study.

Reviewer's comments: The Applicant cites Tennant et al. (2001)[6] as to why the age of 14 years was chosen as the cut-off point for obtaining caregiver report versus patient self-report. Patients without cognitive impairment are generally able to validly and reliably self-report by age 12 or younger, depending on the complexity of the concepts being assessed.[3]

Furthermore, patients aged ≥ 14 years were given the caregiver-reported version of the CHAQ to self-complete. This means that these patients were given questions with instructions such as "is your child able to…" and expected to ignore the instructions and self-report on their own functioning instead. It is inappropriate to administer a caregiver-reported instrument to a patient without any testing (and modification, as needed) to ensure that the instrument is appropriate for use as a patient self-reported assessment.

6 SCORING ALGORITHM

Each item in the CHAQ Disability Index is rated on a four-point (0-3) scale, where higher scores indicate more severe functional impairment:

- Without ANY Difficulty = 0
- With SOME Difficulty = 1
- With MUCH Difficulty = 2
- UNABLE To Do = 3
- Not Applicable = not scored

The CHAQ Disability Index is an average of functional area scores; the scores for the functional areas are summed together, then that score is divided by the number of categories answered. A CHAQ Disability Index total score was calculated if responses for at least 6 out of the 8

[6] A Tennant, S Kearns, F Turner, S Wyatt, R Haigh, M A Chamberlain. *Measuring the function of children with juvenile arthritis*. Rheumatology (Oxford). 2001 Nov;40(11):1274-8. DOI: 10.1093/rheumatology/40.11.1274.

functional areas were available (i.e., if less than 6 functional areas were scored, then no total score was calculated). The CHAQ Disability Index total score ranges from 0 to 3, where "0" indicates no difficulty performing functional activities and "3" indicates inability to perform functional activities.

The item with the highest score determines the score for the entire functional area. In other words, a response is given for each item, but only the highest score within each functional area is used to calculate the overall CHAQ Disability Index score. To use the "Eating" functional area as an example, if a patient were to receive a score of 1 for ability to "cut his/her own meat" and "lift a cup or glass to mouth" but receive a score of 3 for "open a new cereal box," then the score for the "Eating" functional area would be a 3. If any aids or devices are reported, or if it is reported that the child usually needs help from another person, then the minimum score for the corresponding functional area(s) is 2.

The instrument developers state that, "in each functional area, there is at least 1 question (activity) that is relevant to a child of any age group." Therefore, even though "Not Applicable" is a response option for items that may not be developmentally appropriate for a young child, a score can be generated for any given functional area provided that at least one item (e.g., the item that is "relevant to a child of any age group") can be scored.

Reviewer's comment: The response option of "Not Applicable" is intended to be used for items that are not developmentally appropriate for a young child, but it is unclear whether caregivers can be expected to accurately gauge which activities are supposed to be developmentally appropriate for a child. See Section 7 of this review (Content Validity) regarding the need for cognitive testing of the instrument in JIA patients and their caregivers.

7 CONTENT VALIDITY

The Applicant did not collect evidence of content validity from JIA patients and their caregivers. Rather, the Applicant's evidence dossier cites the original publication of the CHAQ by Singh et al. (1994),[7] in which the authors describe administering the CHAQ to 7 rheumatologists, 8 health personnel (nurses, social workers, occupational and physical therapists), 2 developmental pediatricians, and 3 child psychologists to assess face validity. Singh et al. also administered the CHAQ to parents of 22 healthy children to "establish that it did not incorrectly attribute disability in children without disability."

Reviewer's comments: Singh et al. provide information regarding face validity of the CHAQ Disability Index from the clinician perspective. However, the Applicant did not submit evidence to demonstrate that JIA patients and their caregivers provided input on the relevance and comprehensiveness of items in the CHAQ Disability Index, as well as on the clarity and appropriateness of the instrument's contents (i.e., instructions, items wording, recall period, and response options). One issue that should specifically have been evaluated in cognitive interviews, as mentioned in the reviewer's comments for Section 6 of this review (Scoring

[7] G Singh, B H Athreya, J F Fries, D P Goldsmith. *Measurement of health status in children with juvenile rheumatoid arthritis.* Arthritis Rheum. 1994 Dec;37(12):1761-9. DOI: 10.1002/art.1780371209

Algorithm), is whether caregivers can be expected to know when to use the response option of "Not Applicable" appropriately.

For an instrument completed by JIA patients and/or their caregivers, content validity should include input from both JIA patients and their caregivers.

8 OTHER MEASUREMENT PROPERTIES

The Applicant's PRO evidence dossier cites several literatures regarding the reliability (internal consistency only), construct validity, and ability to detect change of the CHAQ Disability Index in JIA patients only. [6, 8, 9, 10, 11, 12, 13]

Reviewer's comments: ***The Applicant did not provide any information regarding the measurement properties and performance of the CHAQ Disability Index in Study A3921104. However, even if these analyses were to be conducted on Study A3921104 data, they still would not replace or rectify the absence of information to establish content validity from the patient and caregiver perspective. Furthermore, the Applicant did not include the appropriate instrument version in the adolescent study population.***

9 INTERPRETATION OF SCORES

The Applicant did not conduct anchor-based analyses on Study A3921104 data to derive a threshold(s) for what constitutes a meaningful change in the CHAQ Disability Index score for the target population. Instead, the Applicant's evidence dossier cites Dempster et al. (2001)[14] and Brunner et al. (2005)[1] with regards to the interpretation of the CHAQ Disability Index change scores. Dempster et al. published minimal clinically important change thresholds of -0.13 for improvement and +0.75 for deterioration based on hypothetical scenarios, while Brunner et al. published minimal clinically important difference (MCID) thresholds of -0.188 for improvement and +0.125 for deterioration based on actual assessments completed by patients with juvenile rheumatoid arthritis and their caregivers during routine clinic visits.

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[8] Pouchot J, Ecosse E, Coste J, Guillemin F, Group FQoLS, Organisation PRIT. Validity of the childhood health assessment questionnaire is independent of age in juvenile idiopathic arthritis. Arthritis Care & Research. 2004;51(4):519-526. DOI: 10.1002/art.20529

[9] Groen W, Ünal E, Nørgaard M, et al. Comparing different revisions of the Childhood Health Assessment Questionnaire to reduce the ceiling effect and improve score distribution: Data from a multi-center European cohort study of children with JIA. Pediatric Rheumatology. 2010;8(1):16. doi: 10.1186/1546-0096-8-16

[10] Brown GT, Wright FV, Lang BA, et al. Clinical responsiveness of self-report functional assessment measures for children with juvenile idiopathic arthritis undergoing intraarticular corticosteroid injections. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2005;53(6):897-904. DOI: 10.1002/art.21599

[11] Moretti C, Viola S, Pistorio A, et al. Relative responsiveness of condition specific and generic health status measures in juvenile idiopathic arthritis. Annals of the rheumatic diseases. 2005;64(2):257-261. doi: 10.1136/ard.2003.016519

[12] Magni-Manzoni S, Cugno C, Pistorio A, Garay S, Tsitsami E, Gasparini C. Responsiveness of clinical measures to flare of disease activity in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2005;23(3):421-425. Access here

[13] Peters S, Ota S, Bolous E, Reich E, Chait S, Feldman BM. The responsiveness of the modified childhood health assessment questionnaire. The Journal of rheumatology. 2016;43(10):1904-1908. DOI: 10.3899/jrheum.151139

[14] H Dempster, M Porepa, N Young, B M Feldman. *The clinical meaning of functional outcome scores in children with juvenile arthritis*. Arthritis Rheum. 2001;44(8):1768-74. doi: 10.1002/1529-0131(200108)44:8<1768::AID-ART312>3.0.CO;2-Q

The Applicant proposed an improvement score threshold of -0.188 based on the work by Brunner et al.

***Reviewer's comments*: The Applicant did not include anchors in Study A3921104. Anchor-based analyses are the preferred method for determining clinically meaningful within-patient change thresholds.**

The MCID discussed by Brunner et al (-0.188 for improvement and +0.125 for deterioration) is very small. This led Brunner et al to question the CHAQ's ability to detect change, stating, "our results do not support some earlier studies' finding that the CHAQ is a very responsive measure in [juvenile rheumatoid arthritis]. The small MCID of the CHAQ in our study supports reports that the measure has, at most, moderate responsiveness to short term changes in [juvenile rheumatoid arthritis]" and, "based on the small MCID for changes actually experienced by children with arthritis, the CHAQ in its current form may be too insensitive to determine important short term changes in health and disease for a given patient."

Hence, there is insufficient evidence to interpret the clinical meaningfulness of the CHAQ Disability Index score change.

D. APPENDICES

Appendix A: Childhood Health Assessment Questionnaire (CHAQ)

Appendix A: Childhood Health Assessment Questionnaire (CHAQ)

Protocol ID: A3921145 CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) - Page 1 of 2

☐ (1) NOT DONE Language administered: ☒ (44) English for USA

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. In the following questions, please check the one response which best describes your child's usual activities (averaged over an entire day) OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not Applicable
DRESSING & GROOMING					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to:					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to:					
- Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift up a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to:					
- Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

***Please check any AIDS OR DEVICES that your child usually uses for any of the above activities:**

☐ Cane
☐ Walker
☐ Crutches
☐ Wheelchair
☐ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
☐ Built up pencil or special utensils
☐ Special or built up chair
☐ Other (Specify: _____)

***Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

☐ Dressing and Grooming
☐ Arising
☐ Eating
☐ Walking

Protocol ID: **A3921145**

CENTER | SUBJECT ID

DATE OF VISIT: dd - MMM - yyyy

Visit: _____

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) - Page 2 of 2

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

***Please check any AIDS OR DEVICES that your child usually uses for any of the above activities:**

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom

***Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 26, 2020

To: Elaine Sit, Pharm.D., Regulatory Health Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for XELJANZ (tofacitinib)

NDA: 203214 / Supplement 026
213082

In response to DRTM consult request dated April 16, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for XELJANZ® (tofacitinib) tablets, for oral use, XELJANZ® XR (tofacitinib) extended-release tablets, for oral use, and XELJANZ® (tofacitinib) oral solution (Xeljanz). This supplement (S026) provides for the addition of polyarticular juvenile idiopathic arthritis indication to the PI. It also provides for the review of a New Drug Application (NDA 213082) for XELJANZ® (tofacitinib) Oral Solution.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRTM (Elaine Sit) on August 12, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on August 26, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 26, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 25, 2020
To:	Elaine Sit, PharmD Regulatory Health Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route:	XELJANZ (tofacitinib) tablets, for oral use XELJANZ XR (tofacitinib) extended-release tablets, for oral use XELJANZ (tofacitinib) Oral Solution
Application Type/Number and Supplement Number:	NDA 203214 S-026 NDA 213082
Applicant:	Pfizer Inc.

1 INTRODUCTION

On March 26, 2020 Pfizer Inc. submitted for the Agency's review a New Drug Application (NDA 213082) for XELJANZ (tofacitinib) Oral Solution. Simultaneously, the Applicant submitted for the Agency's review a supplemental NDA (NDA 203214 S-026) to support XELJANZ (tofacitinib) tablets, for oral use for the proposed indication to treat Polyarticular Juvenile Idiopathic Arthritis (pJIA) in patients 2 years of age and older and to fulfill the following post marketing requirements (PMRs):

- A multiple-dose pharmacokinetic trial in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA).
- A randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tofacitinib in children from 2 to less than 18 years of age with pJIA.

XELJANZ (tofacitinib) tablets, for oral use and XELJANZ XR (tofacitinib) extended-release tablets, for oral use were approved on February 23, 2016 and are Janus kinase (JAK) inhibitors indicated for the treatment of:

- Rheumatoid Arthritis: for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. (b) (4) (b) (4)
- Psoriatic Arthritis: for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.
- Ulcerative Colitis: for the treatment of adult patients with moderately to severely active UC.

This review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on April 16, 2020, for DMPP and OPDP to review the Applicant's Medication Guide (MG) and Instructions for Use (IFU) for XELJANZ (tofacitinib) tablets, for oral use, XELJANZ XR (tofacitinib) extended-release tablets, for oral use and XELJANZ (tofacitinib) Oral Solution.

2 MATERIAL REVIEWED

- Draft XELJANZ (tofacitinib) tablets, for oral use, XELJANZ XR (tofacitinib) extended-release tablets, for oral use and XELJANZ (tofacitinib) Oral Solution MG and IFU received on March 26, 2020 and received by DMPP and OPDP on August 12, 2020.
- Draft XELJANZ (tofacitinib) tablets, for oral use, XELJANZ XR (tofacitinib) extended-release tablets, for oral use and XELJANZ (tofacitinib) Oral Solution Prescribing Information (PI) received on March 26, 2020, revised by the Review

Division throughout the review cycle, and received by DMPP and OPDP on August 12, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Arial font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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LABEL, LABELING AND USE-RELATED RISK ANALYSIS 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:	August 19, 2020
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 213082 and NDA 203214/S-026
Product Name and Strength:	Xeljanz (tofacitinib) oral solution, 1 mg/mL Xeljanz (tofacitinib) oral tablets, 5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer
FDA Received Date:	March 26, 2020 and July 22, 2020
OSE RCM #:	2020-600 , 2020-786, and 2020-1733
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF REVIEW

Pfizer submitted a New Drug Application (NDA 213082) for Xeljanz (tofacitinib) Oral Solution that proposes a new dosage form of an oral solution and indication of Polyarticular Course Juvenile Idiopathic Arthritis. Pfizer also submitted a supplement for NDA 203214/S-026, Xeljanz (tofacitinib) Oral Immediate Release Tablets that proposes the indication of Polyarticular Course Juvenile Idiopathic Arthritis.

Subsequently, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed packaging, label and labeling, and Use-Related Risk Analysis (URRA) for areas that may lead to medication errors.

2 BACKGROUND/REGULATORY HISTORY (IF APPLICABLE)

Xeljanz (tofacitinib) immediate-release tablets and Xeljanz XR (tofacitinib) extended-release tablets were approved on November 6, 2012 and February 23, 2016, respectively. Pfizer submitted the proposed new dosage form of an oral solution and proposed indication of Polyarticular Course Juvenile Idiopathic Arthritis for review under NDA 213082 on March 26, 2020 and the proposed indication of Polyarticular Course Juvenile Idiopathic Arthritis under NDA 203214/S-026 under March 26, 2020.

3 MATERIALS 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 none relevant to this review
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other-Use-Related Risk Analysis	E
Labels and Labeling	F

N/A=not applicable for this review

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

4 USE-RELATED RISK ANALYSIS (URRA)

The sponsor submitted a URRA, which identified and evaluated the tasks involved in the use of the proposed product, the errors that users might commit, the tasks they might fail to perform,

and the potential negative consequences of use errors. The sponsor also provided information regarding known use-related problems with similar marketed products.

We reviewed the URRA for the proposed product and agree that the tasks evaluated are comprehensive and appropriate for the proposed product. We also reviewed the URRA to ensure that all potential use errors and risks involved in using the proposed product, including known use issues with currently marketed products, have been considered and adequately mitigated. In addition, we did not identify any new, differing, or unique risks for the proposed product as compared to other approved HDPE bottles packaged with one press-in bottle adapter and one 5 mL oral dosing syringe intended for use by healthcare professionals, patients, and laypersons.

5 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted label, labeling, and URRA, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Rheumatology and Transplant Medicine (DRTM)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The immediate release oral solution and the extended release tablets are not interchangeable and this information is not available within the PI.	Per the clinical team, no studies were performed to determine interchangeability.	Consider adding a statement that the immediate release oral solution and the extended release tablets are not interchangeable. Also consider adding 'immediate release' and extended release' where appropriate throughout the Prescribing Information to minimize risk of confusion between formulations.

Table 3: Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling (all)			
1.	The expiration date format is not defined.	Lack of a defined expiration date may contribute to deteriorated drug medication errors.	As currently presented, the format for the expiration date is not defined. 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.
2.	The terminology used to describe the recommended dosage are not consistently presented.	Lack of consistency of dosage terminology may contribute to dosing errors.	For consistency with the Prescribing Information (PI) consider revising (b) (4) (b) (4)

			(b) (4) to the following: Recommended dosage: See Prescribing Information
USE-RELATED RISK ANALYSIS (URRA)			
1.	We determined that you do not need to submit the results of the Human Factors (HF) validation study as part of the NDA. However, because the proposed product is a combination product, please note that the device constituent should comply with the Quality System regulation, 21 CFR Part 820. In particular, Section 30, Design Controls, includes requirements relevant to human factors. Additionally, if further changes are made to the user interface or device constituent part subsequent to this advice, please submit your updated URRA and your determination for HF data requirement for your product.		

6 CONCLUSION

Our evaluation of the proposed label, labeling, and Use-Relate Risk Analysis identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Pfizer so that recommendations are implemented prior to approval of this NDA and Supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xeljanz that Pfizer submitted on March 26, 2020.

Table 4. Relevant Product Information for Xeljanz

Product Name	Xeljanz (NDA 203214)	Xeljanz XR (NDA 208246)	Xeljanz (NDA 213082)
Initial Approval Date	November 6, 2012	February 23, 2016	N/A – proposed
Intended Pronunciation	zell-jans		
Active Ingredient	tofacitinib		
Indication	• Rheumatoid Arthritis • Psoriatic Arthritis • Ulcerative Colitis • Polyarticular Course Juvenile Idiopathic Arthritis*		
Route of Administration	oral		
Dosage Form	immediate-release tablets	extended-release tablets	oral solution
Strength	5 mg, 10 mg	11 mg, 22 mg	1 mg/mL*
Dose and Frequency	*Rheumatoid Arthritis* • XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. • Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. *Psoriatic Arthritis (in combination with nonbiologic DMARDs)* • XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily • Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. *Ulcerative Colitis* • Induction: XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily for 8 weeks; evaluate patients and transition to		

<table>
<tr><th>Product Name</th><th>Xeljanz
(NDA 203214)</th><th>Xeljanz XR
(NDA 208246)</th><th>Xeljanz
(NDA 213082)</th></tr>
<tr><td></td><td colspan="3">maintenance therapy depending on therapeutic response. If needed, continue XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily for a maximum of 16 weeks. Discontinue XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily after 16 weeks if adequate therapeutic response is not achieved.
• Maintenance: XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. For patients with loss of response during maintenance treatment, XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response.
• Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment: see full prescribing information.

Polyarticular Course Juvenile Idiopathic Arthritis*
• XELJANZ/XELJANZ Oral Solution 5 mg twice daily or weight-based equivalent twice daily
• Recommended Tofacitinib Dosing for Pediatric Subjects with pJIA
<table>
<tr><th>Body Weight (kg)</th><th>Dosage Regimen</th></tr>
<tr><td>10 to <20</td><td>3.2 mg (3.2 mL oral solution) BID</td></tr>
<tr><td>20 to <40</td><td>4 mg (4 mL oral solution) BID</td></tr>
<tr><td>≥40</td><td>5 mg (one 5 mg tablet or 5 mL oral solution*) BID</td></tr>
</table>
Abbreviations: BID = twice daily.
*Patients treated with 5 mL XELJANZ Oral Solution may be switched to a XELJANZ 5 mg tablet.
Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment: see full prescribing information.</td></tr>
<tr><td>How Supplied</td><td>Immediate-release 5 mg: White, round, immediate-release</td><td>Extended-release 11 mg: Pink, oval, extended-release</td><td>Clear, colorless solution:</td></tr>
</table>

Product Name	Xeljanz (NDA 203214)	Xeljanz XR (NDA 208246)	Xeljanz (NDA 213082)
	film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side: Bottle sizes 28 and 60 count *Immediate-release 10 mg:* Blue, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 10" on the other side: Bottle sizes 28, 60, 180 count	film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet: Bottles sizes 14, 30 count *Extended-release 22 mg:* Beige, oval, extended-release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 22" printed on one side of the tablet: Bottle size 30	Bottle fill volume-240 mL It is packaged in HDPE bottles as follows: Each bottle is packaged with one press-in bottle adapter and one 5 mL oral dosing syringe with 3.2 mL, 4 mL, and 5 mL gradations. The press-in bottle adapter and oral dosing syringe are not made with natural rubber latex
Storage	20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature	20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP Controlled Room Temperature]. Store in the original bottle and carton to protect from light. Use contents of bottle within 60 days of opening. Discard remaining oral solution after 60 days.

*new proposed indication and strength

APPENDIX B. PREVIOUS DMEPA REVIEWS N/A

APPENDIX C. ISMP NEWSLETTERS-N/A

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) N/A

APPENDIX E. OTHER-Use-Related Risk Analysis (URRA) submitted on July 22, 2020

- Use-Related Risk Analysis (Image not shown)

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APPENDIX F. LABELS AND LABELING

F.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 Xeljanz labels and labeling submitted by Pfizer on March 26, 2020.

- Container label
- Carton labeling
- Instructions for Use (Image not shown)- \\CDSESUB1\evsprod\nda203214\1185\m1\us\spl\xeljanz.xml
- Prescribing Information (Image not shown) - \\CDSESUB1\evsprod\nda203214\1185\m1\us\spl\xeljanz.xml

F.2 Label and Labeling Images

Container Label-Sample and Trade

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

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