

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211651Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: Approval**

**NDA 211651  
Review #1**

Drug Name/Dosage Form	Talazoparib capsules
Strength	0.25 mg and 1 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	04/06/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0007	05/30/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0011	06/15/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0016	07/09/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0019	07/20/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0021	08/01/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0023	08/09/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0030	08/28/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0031	09/14/2018	API/DP/Process/Facility/Biopharm
Quality Amendment 0038	10/03/2018	DP/Biopharm

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Mohd Shahjahan Kabir	CDER/OPQ/ONDP/DNDAP1
Drug Product	Xing Wang	CDER/OPQ/ONDP/DNDP1
Process	Kumar Janoria	CDER/OPQ/OPF/DPA1
Facility	Kumar Janoria	CDER/OPQ/OPF/DPA1
Biopharmaceutics	Qi Zhang	CDER/OPQ/ONDP/DB

Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	Xing Wang	CDER/OPQ/ONDP

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

<b>DMF #</b>	<b>Type</b>	<b>Holder</b>	<b>Item Referenced</b>	<b>Status</b>	<b>Date Review Completed</b>	<b>Comments</b>
(b) (4)	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.
	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.
	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.
	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.
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	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.
	Type III		(b) (4)	Adequate	Sept. 5, 2018	DMF not reviewed since sufficient information is in the NDA.

**B. Other Documents:** *IND, RLD, or sister applications*  
N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108708	Initial IND for talazoparib for the treatment of patients with locally advanced and solid tumors was submitted on December 10, 201.

**2. CONSULTS**  
N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

## Executive Summary

### I. Recommendations and Conclusion on Approvability

The NDA 21651, Talazoparib Capsules, is recommended for Approval from the product quality perspective. The product quality team reviewed complete CMC information in the NDA including the manufacturing facilities, and they are deemed acceptable. There are no outstanding product quality issues for the NDA.

### II. Summary of Quality Assessments

#### A. Product Overview

Talazoparib is a small molecule poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitor. Talazoparib is a potent inhibitor of PARP1 and PARP2, which play important roles in DNA repair. PARP inhibitors exert cytotoxic effects by 2 mechanisms: inhibition of PARP catalytic activity and PARP trapping. This NDA seeks approval for talazoparib for the treatment of adult patients with germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. The recommended dose of talazoparib is 1 mg taken orally once daily. Initial IND 108708 for talazoparib for the treatment of patients with locally advanced and solid tumors was submitted on December 10, 2010. During the course of drug development, there have been EOP-2 meeting (4/12/2013), CMC Type C meetings (1/8/2014,) discussing drug substance manufacturing process changes, impurities controls (10/31/2017) and dissolution method (2/27/2015, 3/17/2017), and preNDA meetings (7/7/2017 and 2/5/2018). The IND was not granted breakthrough therapy designation.

<p><b>Proposed Indication(s) including Intended Patient Population</b></p>	<p>TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (<i>gBRCAm</i>) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.</p>
<p><b>Duration of Treatment</b></p>	<p>Until disease progression or unacceptable toxicity occurs</p>
<p><b>Maximum Daily Dose</b></p>	<ul style="list-style-type: none"> <li>• The recommended dose of TALZENNA is 1 mg taken as a single oral daily dose with or without food.</li> <li>• Patients should be treated until disease progression or unacceptable toxicity occurs.</li> <li>• For adverse reactions, consider dosing interruption or dose reduction.</li> <li>• For patients with moderate renal impairment (CrCL 30 - 59 mL/min), the recommended dose of TALZENNA is 0.75 mg once daily.</li> </ul>

Alternative Methods of Administration	N/A
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## B. Quality Assessment Overview

### Drug Substance

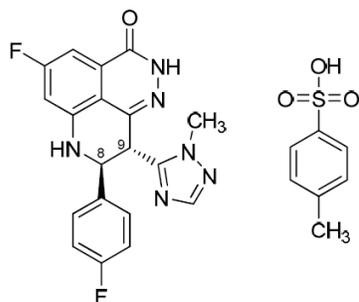
International Nonproprietary Name (rINN): Talazoparib

USAN: Talazoparib Tosylate

IUPAC: (8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-*de*]phthalazin-3-one 4-ethylbenzenesulfonate (1:1)

CAS Registry Number: Tosylate salt: 1373431-65-2; Free base: 1207456-01-6

### Chemical Structure:



Molecular Formula: C<sub>26</sub>H<sub>15</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S (tosylate salt); C<sub>19</sub>H<sub>14</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub> (free base)

Molecular Weight: 552.56 (tosylate salt); 380.35 (free base)

Talazoparib is an inhibitor of mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. Talazoparib tosylate drug substance tosylate drug substance is a white to yellow solid. It has limited solubility in aqueous solutions, and the solubility increases as the pH increases. It is freely soluble in DMS, DMA and DMF. The partition coefficient (log P) was determined using talazoparib free base to be 1.6. Talazoparib tosylate is non-hygroscopic and requires no special protection from humidity during handling, shipping, or storage. It has a sharp melting endotherm with an onset of 326°C. Talazoparib tosylate exists as a single crystal form and no other polymorphs have been observed through extensive screening studies during development including conditions covering the solvent compositions used in the final isolation process. (b) (4)

(b) (4). Talazoparib contains two chiral centers. The particle size is controlled by the specification of D[v, 0.9] NMT (b) (4) μm to achieve desired dissolution rate and content uniformity of the drug product.

Talazoparib tosylate drug substance is manufactured (b) (4)

(b) (4) It is synthesized in a 6-step chemical synthesis. Talazoparib Tosylate is manufactured by 6-step chemical synthesis. Data from 11 commercial batches including

three registration batches using the proposed commercial process (b) (4) and two development batches are provided. Sufficient detail is provided to describe process knowledge, risk management, process understanding, and improvement to support the manufacturing process controls including impurity control strategy and the regulatory specifications, along with the details of impurity genealogy as well as their respective controls in each step of the manufacturing process. (b) (4)

(b) (4) Based on the stability data, the applicant proposed (b) (4) months retest date for the Talazoparib tosylate drug substance stored at room temperature.

### Drug Product

Talazoparib capsules are for oral administration. Talazoparib 0.25 mg capsules are provided as (b) (4) hypromellose (HPMC) capsules with an ivory cap (printed with "Pfizer" in black) and a white body (printed with "TLZ 0.25" in black). Talazoparib 1 mg capsules are provided as (b) (4) hypromellose (HPMC) capsules with a light red cap (printed with "Pfizer" in black) and a white body (printed with "TLZ 1" in black). Talazoparib contains (b) (4) the inactive ingredients silicified microcrystalline cellulose (sMCC) (b) (4). The white/ ivory and white/light red opaque capsule shells contain hypromellose (HPMC), yellow iron oxide, red iron oxide and titanium dioxide; and the printing ink contains shellac, black iron oxide, potassium hydroxide, ammonium hydroxide, and propylene glycol. The commercial package configuration will be (b) (4) 30, (b) (4) capsules in (b) (4) high-density polyethylene (HDPE) bottles (b) (4). (b) (4).

The drug product specifications consist of appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, water content, and microbial limits. The dissolution specification is evaluated by biopharmaceutics reviewer, Dr. Qi Zhang. Microbial test is reviewed by Dr. Kumar Janoria. Based on the primary and supportive stability data, a shelf life of 24 months, as proposed by the applicant may be granted to 0.25 mg and 1 mg Talazoparib capsules packaged in HDPE bottles (b) (4) (b) (4) when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).

After the drug product reviewer, Dr. Xing Wang, signed off his review in Panorama, Biopharmaceutics reviewer, Dr. Qi Zhang, requested the applicant to submit dissolution data at 30 minutes. Based on the 30 minutes dissolution data, Dr. Zhang recommended the applicant to change the dissolution specification from NLT (b) (4)% (Q) at 30 minutes to NLT (b) (4)% (Q) at 30 minutes. The applicant accepted the FDA's recommended dissolution specification. It is noted that stability data for the three primary stability batches were provided, and all conformed to the revised dissolution specification (NLT (b) (4)% (Q) at 30 minutes).

### Process

The proposed Talazoparib drug products are immediate release capsules of 0.25 mg and 1 mg strengths. The 0.25 mg and 1 mg capsules both have (b) (4) fill weights and differ in the (b) (4). The capsules are manufactured by (b) (4) (b) (4). The commercial batch size is expressed as (b) (4) for each strength. Firm has discussed each unit operation in detail and appropriate control strategies were identified. Applicant conducted adequate studies to determine the critical process parameters and established the range accordingly. (b) (4) (b) (4) DS screening step was found non-critical to capsule content uniformity. Particle size is critical to content uniformity (CU) and dissolution. Applicant justified the one-point particle size specification ( $D[v, 0.9]$  NMT (b) (4)  $\mu\text{m}$ ) by the results for CU and dissolution performance and specification (Refer to Biopharm review regarding the discriminating power for particle size). These studies were discussed in the development reports and assessment is provided above in the control of particle size section. Based on such studies firm proposed  $D[v, 0.9]$  NMT (b) (4)  $\mu\text{m}$ .

(b) (4) Sponsor has provided the blend uniformity (BU) and CU data from few clinical batches and all three registration batches. Data indicate that the RSDs were less than 5% and good correlation between BU and CU for the registration batches. For some clinical batches the data was not as tight as registration. Applicant is proposing not to conduct any further (b) (4) testing due to potential exposure risk but is committed to performing stratified CU testing until sufficient batch data is accumulated to demonstrate that the process has limited variability. BU and CU data from registration batches along with continued SCU testing mitigates the risk of not testing (b) (4) during commercial manufacturing. This approach is deemed acceptable. Applicant has provided sampling plan for SCU (b) (4) (b) (4); and also provided the acceptance criteria for the test which is based on Parametric Two One-Sided Tolerance Interval (PTOSTI) and discussed that such is tighter than USP<905> test requirements. This is found acceptable. The applicant was advised not to remove this (b) (4) control (b) (4) test (b) (4) (b) (4). The applicant acknowledged that the removal of this (b) (4) test (SCU) should be submitted in accordance with the regulations at 21CFR314.70 and the guidance documents "Changes to an Approved NDA or ANDA (and the accompanying Q and A document)".

### Facility

Following a review of the application and past inspectional documents, there are no outstanding manufacturing or facility risks that prevent approval of this application. PAI inspection for (b) (4) (b) (4) site was requested for this application. The manufacturing and associated facilities listed in 356 h for NDA 211651 are found to be acceptable.

### Drug Substance Facility:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			<b>Medium</b>	<b>Acceptable</b> Reason: District Recommendation

**Drug Product Facility:**

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			<b>High</b>	<b>Acceptable</b> : Based on PAI outcome
<b>Pfizer Pharmaceuticals LLC</b> (KM 1.9 Road 689 Vega Baja, PR US 00693)	2623619	DP Labeling, DP Secondary Packaging, DP Release: <b>CHG</b>	<b>Low</b>	<b>Acceptable</b> : Based on file review
(b) (4)			<b>Low</b>	<b>Acceptable</b> : Based on file review
(b) (4)			<b>Low</b>	<b>Acceptable</b> : Based on file review
(b) (4)			<b>NFE</b>	No Further Evaluation
(b) (4)			<b>NFE</b>	No Further Evaluation

A pre-approval inspection for NDA 211651, Talazoparib Capsules 0.25mg and 1mg (sponsored by Pfizer) was performed August 06 – 10, 2018. The following systems were

covered during the inspection: Quality, Production, Facilities & Equipment, Materials Management, and Laboratory systems. At the conclusion of the inspection, a FDA-483, Inspectional Observations, with 5-item was issued. Based on the pre-approval inspection evaluation and the firm's response to the 5-item 483 (refer to (b) (4)), this firm appears to be capable of performing the proposed manufacturing operations and is acceptable for NDA 211651.

### Biopharmaceutics

The Biopharmaceutics review focused on 1) the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and 2) bridging throughout product development.

- 1) **Dissolution Method and Acceptance Criterion:** The proposed commercial dissolution method [*USP apparatus II (Paddle) at 75 rpm; 500 mL of 0.01 N HCl with 0.2% SDS at 37°C*] and the revised acceptance criterion of NLT (b) (4) % (Q) at 30 minutes for batch release and stability testing, are acceptable. The revised acceptance criteria are based on the FDA's recommendation to provide discriminating power for API particle size.
- 2) **Bridging Throughout Product Development:** The formulation of the drug product used in the Phase 3 clinical study is reported to be the same as that of the proposed commercial drug product, except (b) (4). The provided complete dissolution data support the (b) (4) change between the clinical and the primary stability batches. The manufacturing site of the drug product batches used in the clinical and registration-stability studies is the proposed commercial site.

A BCS designation request has not been submitted to FDA. Per the Applicant, talazoparib has low solubility and moderate permeability. Talazoparib tosylate has pH independent solubility, and exhibits low solubility with a range of 17 to 38 µg/mL across the physiological pH range at 37°C. However, solubility is sufficient to provide sink conditions for the maximum dose of 1 mg.

### C. Special Product Quality Labeling Recommendations (NDA only)

N/A

### D. Final Risk Assessment (see Attachment)

#### **Application Technical Lead Name and Date:**

Xiao Hong Chen, Ph.D.

9-October-2018



Xiao  
Chen

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**QUALITY ASSESSMENT**  
**Chapter VII-Biopharmaceutics**



**NDA:** 211651

**Submission Type:** 505 (b) (1) NME

**Drug Product Name/Strength:** Talzenna® (talazoparib) Capsules, 0.25 mg, and 1 mg

**Applicant Name:** Pfizer, Inc.

**Route of Administration:** Oral

**Dosage Form:** Immediate Release Capsules

**Intended for Use:** For the treatment of adult patients with germline BRCA-mutated HER2 negative locally advanced or metastatic breast cancer

**REVIEW SUMMARY**

The proposed drug product is a hard hypromellose (HPMC) capsule containing the active ingredient, talazoparib tosylate, and inactive ingredient, silicified microcrystalline cellulose (b) (4)

(b) (4) The recommended dose of Talzenna is 1 mg taken orally once daily, with or without food. The 0.25 mg capsule is available for dose reduction. The clinical studies conducted to support the approval of this NDA are: Phase 3 pivotal study (673-301), Phase 2 study (673-201), and Phase 1 study (PRP-001).

The Biopharmaceutics review focused on **1)** the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and **2)** bridging throughout product development.

**1) Dissolution Method and Acceptance Criterion:** The proposed commercial dissolution method [*USP apparatus II (Paddle) at 75 rpm; 500 mL of 0.01 N HCl with 0.2% SDS at 37°C*] and the revised acceptance criterion of NLT (b) (4)% (Q) at 30 minutes for batch release and stability testing, are acceptable.

**2) Bridging Throughout Product Development:** The formulation of the drug product used in the Phase 3 clinical study is reported to be the same as that of the proposed commercial drug product, except for (b) (4). The provided complete dissolution data support the (b) (4) change between the clinical and the primary stability batches. The manufacturing site of the drug product batches used in the clinical and registration-stability studies is the proposed commercial site.

**BIOPHARMACEUTICS REVIEW RECOMMENDATION: Adequate**

**SIGNATURES**

**Primary Biopharmaceutics Reviewer Name and Date:**

Qi Zhang, PhD  
Division of Biopharmaceutics  
Office of New Drug Products, OPQ

**10/5/2018**

**Secondary Biopharmaceutics Reviewer Name and Date:**

Banu Zolnik, PhD  
Division of Biopharmaceutics  
Office of New Drug Products, OPQ

**10/5/2018**

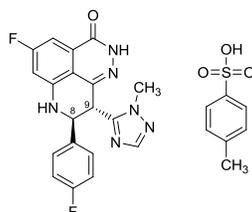
**BIOPHARMACEUTICS ASSESSMENT**

**LIST of SUBMISSIONS BEING REVIEWED**

eCTD # (SND#)	Received date	Document
0000 (1)	04/06/2018	Original submission
0021 (22)	08/01/2018	Response to information request dated 7/24/2018
0038 (37)	10/03/2018	Response to T-con information request dated 9/27/2018

**DRUG SUBSTANCE**

Talazoparib tosylate is a white to yellow colored powder. The chemical formula of talazoparib tosylate is C<sub>26</sub>H<sub>22</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S and the relative molecular mass is 552.56 Daltons. The chemical structure of talazoparib tosylate is shown below:



**Particle Size:** The proposed acceptance criterion for the drug substance particle size is D [v, 0.9] NMT <sup>(b) (4)</sup> μm. The drug substance batches used to manufacture the clinical drug product batches (Sec. 3.2.P.5.4) have d<sub>90</sub> values between <sup>(b) (4)</sup> (Sec. 3.2.S.4.4).

**Solid State Form:** Talazoparib tosylate exists as a single crystal form <sup>(b) (4)</sup> and it has been used in clinical supplies and registration stability batches. No other polymorphs have been observed per the Applicant.

**DRUG PRODUCT**

The qualitative and quantitative compositions of the proposed commercial formulations and the formulations used in clinical development are presented in below (**Table 1**).

**Table 1 (Table 2.3.P.2-4) Summary of Formulations of Talazoparib Capsules**

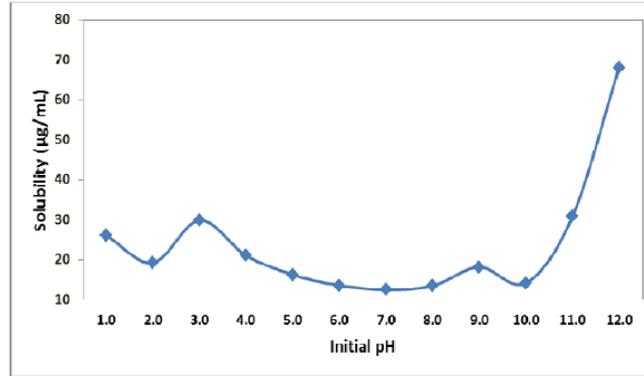
	Phase 1 capsules	Phase 1 capsules	Phase 1 capsules	Phase 1 capsules	Phase 2 & 3 capsules	Phase 1, 2 & 3 capsules	Phase 2 & 3 capsules	Phase 1, 2, 3 capsules & commercial	Phase 2, 3 capsules & commercial
Formula Identifier	DP Gen 1.0	DP Gen 1.0	DP Gen 1.0	DP Gen 1.0	DP Gen 2.0	DP Gen 2.0	DP Gen 3.1	DP Gen 3.1	DP Gen 3.1
Strength	25 μg	50 μg	0.25 mg	1.00 mg	0.10 mg	0.25 mg	0.10 mg	0.25 mg	1.00 mg
Dosage form	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule
Talazoparib tosylate <sup>a</sup>	<sup>(b) (4)</sup>							0.363 mg	1.453 mg
Silicified Microcrystalline Cellulose <sup>(b) (4)</sup>	<sup>(b) (4)</sup>							<sup>(b) (4)</sup>	
Silicified Microcrystalline Cellulose <sup>(b) (4)</sup>	<sup>(b) (4)</sup>							<sup>(b) (4)</sup>	
Silicified Microcrystalline Cellulose <sup>(b) (4)</sup>	<sup>(b) (4)</sup>							<sup>(b) (4)</sup>	
Capsule shell	HPMC	HPMC	HPMC	HPMC	HPMC	HPMC	HPMC	HPMC	HPMC
Capsule size #	<sup>(b) (4)</sup>								
Total	<sup>(b) (4)</sup>								
	a. The quantity of active listed is based on a 100% assay value.								
	<sup>(b) (4)</sup>								

**BCS DESIGNATION**

A BCS designation request has not been submitted to FDA. Per the Applicant, talazoparib has low solubility and moderate permeability.

- **Solubility:** Talazoparib tosylate has pH independent solubility, and exhibits low solubility with a range of 17 to 38 µg/mL across the physiological pH range at 37°C (Figure 1 and Table 2). However, solubility is sufficient to provide sink conditions for the maximum dose of 1 mg.

**Figure 1 (3.2.P.2.2-2): Talazoparib Tosylate Aqueous Solubility at Different pH Levels**



Source: Module 3 Section 3.2.P.2.2 Figure 3.2.P.2.2-2.  
The solubility of talazoparib tosylate in water and aqueous solutions of various pH values were investigated. Talazoparib tosylate drug substance was added in excess of its solubility. The solutions were agitated for 5 days at 24°C, filtered, and analyzed by LC.

**Table 2 (3.2.P.2.2-18): Solubility of Talazoparib Tosylate Across Physiological pH Range**

Medium	Solubility (µg/mL) <sup>a</sup>	Sink Ratio <sup>b</sup>
pH 1.2 (0.1N HCl)	38	19
pH 1.2 (SGF <sup>c</sup> )	29	15
pH 2.0 (0.01N HCl)	27	14
pH 3.0 (50 mM sodium phosphate)	25	13
pH 4.0 (50 mM sodium phosphate)	23	12
pH 4.5 (50 mM sodium acetate)	17	9
pH 6.8 (50 mM sodium phosphate)	17	9

a: Solubility is calculated as the talazoparib free base concentration in solution  
b: Sink ratio is calculated as the equilibrium solubility (mg/mL) divided by the concentration of the highest strength (1 mg) in 500 mL of medium.  
c: SGF, simulated gastric fluid without enzyme (0.1N HCl with 0.2% (w/v) sodium chloride)

- **Permeability:** Talazoparib permeability was determined to be moderate, based on a Caco-2 cell assay and the human mass balance study (MDV3800-03).

The apparent permeability (P<sub>app</sub>) values were moderate, with the absorptive (apical to basolateral) permeability of 2.49 × 10<sup>-6</sup> cm/sec and secretory (basolateral to apical) permeability of 43.4 × 10<sup>-6</sup> cm/sec. Talazoparib absolute bioavailability was estimated to be at least 54.6% from the recovered unchanged talazoparib in urine with a fraction absorbed of at least 68.7% (total radioactivity recovered in urine) following a single 1 mg oral dose of <sup>14</sup>C talazoparib.

**DISSOLUTION**

***Proposed Dissolution Method and Acceptance Criterion:***

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II (Paddle, with sinkers)	75	0.01 N HCl with 0.2% (w/w) SDS	500 mL/37°C	<p><u>Originally proposed:</u> NLT (b) (4) % (Q) at (b) (4) minutes</p> <p><u>Revised:</u> NLT (b) (4) % (Q) at 30 minutes</p>

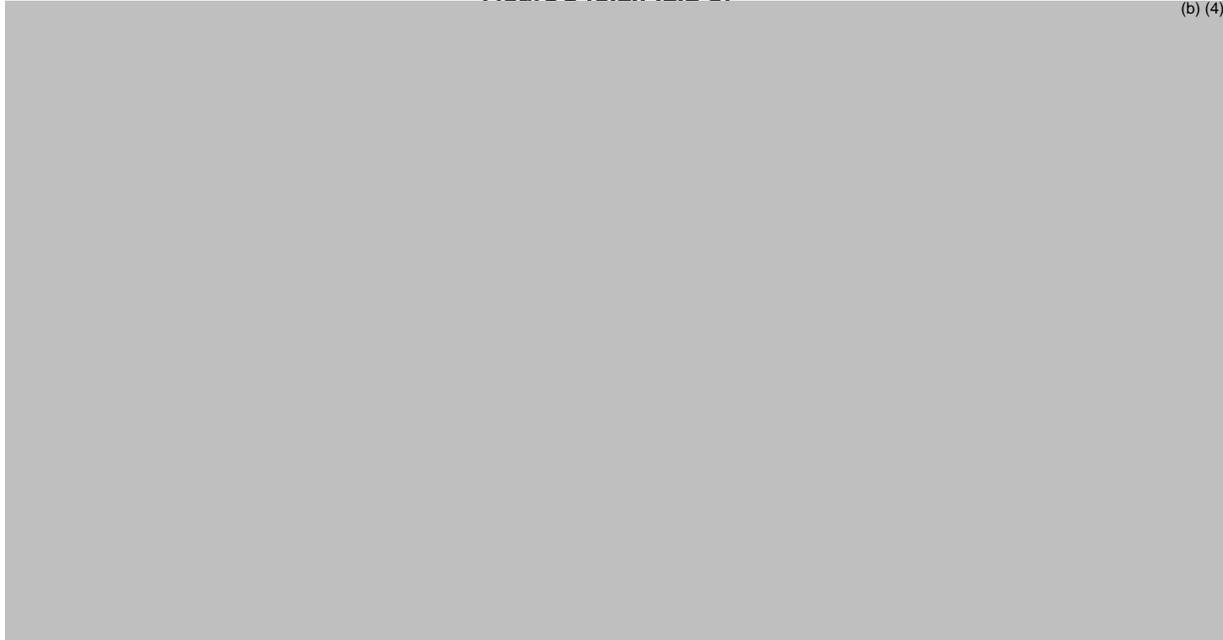
***Dissolution Method Development:***

(b) (4)

(b) (4)

Figure 8 (3.2.P.2.2-5)

(b) (4)



**Reviewer's Assessment: ADEQUATE**

The formulation of the drug product used in the Phase 3 clinical study is reported to be the same as that of the proposed commercial drug product, except for the (b) (4). The provided complete dissolution data support the (b) (4) change between the clinical and the primary stability batches. The manufacturing site of the drug product batches used in the clinical and registration-stability studies is the proposed commercial site.

**BIOWAIVER REQUEST**

A biowaiver is not requested nor required for this NDA. The Applicant conducted the clinical studies for both strengths, 0.25 mg and 1 mg (Phase 2 study 673- 201 and Phase 3 study 673-301).

**CONCLUSION and RECOMMENDATION**

From the Biopharmaceutics perspective, NDA 211651, for Talzenna® (talazoparib) Capsules, 0.25 mg, 1 mg, is **ADEQUATE** and recommended for **APPROVAL**.

## BIOPHARMACEUTICS INFORMATION REQUEST (IR)

## IRs dated 7/24/2018:

1. Explain the observed the dissolution profiles differences between 1 mg and 0.25 mg (b) (4) (b) (4) as shown in Figure 3.2.P.2.2-5) in the proposed dissolution method.
2. Batch information for Figures 3.2.P.2.2.8 to 3.2.P.2.2.24 are missing in the Selection of the Dissolution Test Method Section. Clearly specify batch numbers/batch use/age of drug product batch at time of dissolution testing for figure described in the report.
3. It is noted that you only provided mean dissolution data collected at 30 and 45 minutes for 0.25 mg and 1 mg capsules in Table 3.2.P.5.6-9 and Table 3.2.P.5.6-10. To support the adequacy of the proposed dissolution acceptance criterion, provide complete dissolution profile data (n=12, individual, mean, RSD, and profiles at each sampling time points e.g. 10, 15, 20, 30, 45, and 60 minutes) for all the clinical and registration batches at lot release for both strengths. Submit the updated tables accordingly.
4. Provide complete dissolution profile data (n=12, individual, mean, RSD, and profiles) associated with the Figure 3.2.P.2.2-1, and include result of the statistical similarity test (e.g. f2 test) for the dissolution profiles to support the discriminating ability of the proposed dissolution method for API particle size.
5. Submit all the requested complete dissolution profile data in “.xlsx” format.



Qi  
Zhang

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**LABELING**

**I. Package Insert**

**1. Highlights of Prescribing Information**

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TALZENNA™ (talazoparib) capsules
Dosage form, route of administration	Capsules, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: 0.25 mg, 1 mg

**2. Section 2 Dosage and Administration**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

**3. Section 3 Dosage Forms and Strengths**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Capsules
Strengths: in metric system	0.25 mg, 1 mg
Active moiety expression of strength with equivalence statement (if applicable)	None
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<ul style="list-style-type: none"> <li>• 0.25 mg capsule with an ivory cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 0.25” in black)</li> <li>• 1 mg capsule with a light red cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 1” in black)</li> </ul>

**4. Section 11 Description**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Talazoparib
Dosage form and route of administration	capsule
Active moiety expression of strength with equivalence statement (if applicable)	TALZENNA capsules for oral use are available as a 0.25 mg hard hypromellose (HPMC) capsule that contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base or as a 1 mg HPMC capsule that contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Talazoparib is an inhibitor of mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme.
Chemical name, structural formula, molecular weight	The chemical name of talazoparib tosylate is (8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one 4-methylbenzenesulfonate (1:1). The chemical formula of talazoparib tosylate is C <sub>26</sub> H <sub>22</sub> F <sub>2</sub> N <sub>6</sub> O <sub>4</sub> S and the relative molecular mass is 552.56 Daltons.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Talazoparib tosylate is white to yellow solid

**5. Section 16 How Supplied/Storage and Handling**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	0.25 mg, 1 mg
Available units (e.g., bottles of 100 tablets)	0.25 mg: bottles of 30 capsules 1 mg: bottles of 30 capsules
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	0.25 mg: Ivory cap (printed with "Pfizer" in black) and a white body (printed with "TLZ 0.25" in black). NDC: 0069-0296-30  1 mg: Light red cap (printed with "Pfizer" in black) and a white body (printed with "TLZ 1" in black). NDC: 0069-1195-30
Special handling (e.g., protect from light)	None
Storage conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	<p><i>Distributed by</i></p>  <p><b>Pfizer Labs</b> Division of Pfizer Inc, NY, NY 10017</p>

**Reviewer's Assessment of Package Insert: *Adequate***  
*Edits conveyed to DOPI during labeling review meeting. The revision is acceptable.*

**II. Labels:**



(b) (4)





Item	Information provided in the container/carton label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Talzenna™ (talazoparib) capsules
Dosage strength	0.25 mg, 1 mg, with salt content statement
Net contents	30
“Rx only” displayed prominently on the main panel	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes
Lot number and expiration date (21 CFR 201.17)	Yes
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
Name of manufacturer/distributor	Yes
And others, if space is available	N/A

**Reviewer’s Assessment of Labels: Adequate**  
*Revision included salt content statement. Acceptable.*  
*Each capsule contains 0.25 mg of talazoparib (equivalent to 0.363 mg talazoparib tosylate)*  
*Each capsule contains 1 mg of talazoparib (equivalent to 1.453 mg talazoparib tosylate)*

*List of Deficiencies: None*

*Overall Assessment and Recommendation: Approvable from CMC perspective*

**Primary Labeling Reviewer Name and Date:**

***Xing Wang, Ph.D., ONDP/DNDPI/NDPBII***

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**

***Anamitro Banerjee, Ph.D., Branch Chief, ONDP/DNDPI/NDPBII***



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Wang

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### Risk Assessment Table NDA 211651

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
<b>Assay, Stability</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	Controlled for in specifications.	L	None
<b>Physical stability (solid state)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	Only single crystalline form exists, (b) (4) (primary stability batches)	L	None
<b>Content uniformity</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	H	Stratified CU test in place; API particle size control.	L	None
<b>Microbial limits</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	Controlled for in specifications.	L	None
<b>Dissolution – BCS Class II &amp; IV</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Exclude major reformulations</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	Controlled for in specifications. The method is discriminating for particle size (D90 (b) (4) um vs D90 (b) (4) um)	L	None

\*Risk ranking applies to product attribute/CQA

\*\*For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.



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Chen

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