

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207981Orig1s000**

**CHEMISTRY REVIEW(S)**

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## Facility Status View for

Displays information for the facilities that are associated to  
 NDA 207981 Original 1. It also shows the Overall  
 Time run: 9/21/2015 9:34:14 AM

### Overall Manufacturing Inspection Recommendations for NDA 207981 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Status
NDA 207981-Orig1-New - Form 3674/NDA(3)	TAIHO ONCOLOGY INC	Approve	Complete

### OPF Facility Recommendations for Facilities on NDA 207981 Original 1

Project Name	FEI	DUNS	Facility Name
NDA 207981-Orig1-New - Form 3674/NDA(3)	3010872322	692199778	TAIHO PHARMACEUTICAL CORPORATION LTD
NDA 207981-Orig1-New - Form 3674/NDA(3)			(b) (4)
NDA 207981-Orig1-New - Form 3674/NDA(3)			
NDA 207981-Orig1-New - Form 3674/NDA(3)			
NDA 207981-Orig1-New - Form 3674/NDA(3)			
NDA 207981-Orig1-New - Form 3674/NDA(3)			
NDA 207981-Orig1-New - Form 3674/NDA(3)			
NDA 207981-Orig1-New - Form 3674/NDA(3)	3002646390	695734327	TAIHO PHARMACEUTICAL CO LTD
NDA 207981-Orig1-New - Form 3674/NDA(3)	3002646390	695734327	TAIHO PHARMACEUTICAL CO LTD
NDA 207981-Orig1-New - Form 3674/NDA(3)			(b) (4)
NDA 207981-Orig1-New - Form 3674/NDA(3)			

Data refreshed on: 09/21/15 12:15:30 AM



First Approval for Metastatic Colorectal Cancer Indication

Recommendation: Approval

NDA 207981  
Review # 1  
19-Aug-15

<b>Drug Name/Dosage Form</b>	Tablet, Film-Coated
<b>Strength</b>	Trifluridine (FTD) and Tipiracil (TPI) (15 mg/6.14mg) and 20 mg/8.20 mg)
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Taiho Oncology, Inc.
<b>US agent, if applicable</b>	Julie Boisvert

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original Submission (0000)	12/19/14
Quality Amendment (0006)	1/16/15
Quality Amendment (0010)	2/13/15
Labeling/Package Insert (0012)	2/19/15
Labeling/Container Closure (0023)	5/20/15
Quality/Response to IR (0027)	6/3/15
Labeling/Package Insert (0031)	7/13/15
Quality/Response to IR (0032)	7/24/15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund	Branch II/NDAPI (ONDP)
Drug Product	Rajiv Agarwal	Branch II/NDP I (ONDP)
Process	Quamrul Majumder	Branch II/Div I/OPF
Microbiology	Quamrul Majumder	Branch II/Div I/OPF
Facility	Marisa Heayn	OMPT/CDER/OPQ/OPF/DIA/IA BIII
Biopharmaceutics	Salaheldin Hamed	OMPT/CDER/OPQ/ONDP/DB/B BIII
Project/Business Process Manager	Rabiya Laiq	OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI
Application Technical Lead	Olen Stephens	Branch II/NDP I (ONDP)
Laboratory (OTR)	Mike Trehy	OMPT/CDER/OPQ/OTR/DPA/P ABII
ORA Lead	Sharon Thoma	OGROP/ORA/OO/OMPTO/DMP TPO/MDTP

- Taiho Oncology, Inc. is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for trifluridine/tipiracil film-coated tablets, 15/6.14 mg, and 20/8.19 mg, according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant and/or animal material 21 CFR 25.21(b).  
***Granted.***

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## Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:
2. RELATED/SUPPORTING DOCUMENTS:
  - A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Trifluridine	Adequate	12-AUG-2015	Reviewed by Dr. Erika E. Englund
28368	Type II	Taiho Pharmaceutical Co. Ltd.	Tipiracil HCl	Adequate	03-AUG-2015	Reviewed by Dr. Erika E. Englund
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	9-OCT-2012	Reviewed by Dr. Nina Ni
	Type III			Adequate	12-AUG-2004	Reviewed by Dr. Sarah Pope
	Type III			Adequate	24-APR-2012	Reviewed by Dr. George Lunn
	Type III			Adequate	24-OCT-2012	Reviewed by Dr. Donald N Klein
	Type IV			Adequate	Refer to the DP section of this review	See 2.3.P.1 section of the review.

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents: *IND*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57674	Active (since 28-DEC-1998)
Pre NDA (CMC)	57674	<b>27-NOV-2013</b>
EOP-2 (CMC)	57674	<b>29-NOV-2011</b> DS: Starting material acceptance criteria DP: Bracketing, packaging, manufacturing process etc. were discussed in this meeting
Additional CMC comments and preliminary responses to EOP-2 meeting dated <b>29-NOV-2011</b>	57674	<b>23-NOV-2011</b> DP: Discussion on expiration dating period of 24 months based on 12 month long term and 6 month at accelerated stability

### 3. CONSULTS: None

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

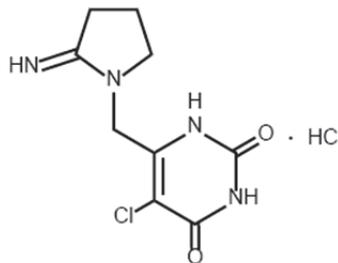
NDA 207981 for Lonsurf (trifluridine and tipiracil) tablets is recommended for approval by the Office of Pharmaceutical Quality. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “approve” recommendation was entered into Panorama 17-Aug-15.

Based on the adequate totality-of-stability data at the 12 months at long term storage condition and 6 months at accelerated storage conditions, 24 months of expiration dating may be granted for this product.

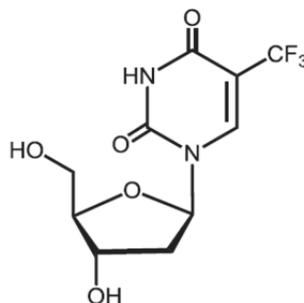
#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

### II. Summary of Quality Assessments

#### A. Drug Substances [Trifluridine and Tipiracil] Quality Summary



Tipiracil HCl,  $C_9H_{11}ClN_4O_2 \cdot HCl$ ; MW = 279.12  
2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-,  
hydrochloride (1:1)



Trifluridine  $C_{10}H_{11}F_3N_2O_5$ ; MW = 296.20  
2'-deoxy-5-(trifluoromethyl)uridine  
thymidine,  $\alpha,\alpha,\alpha$ -trifluoro-

Trifluridine (FTD) has a solubility of (b) (4) and Tipiracil (TPI) has a solubility of (b) (4) in physiological pH range (pH 1-7). While tipiracil hydrochloride is a salt, as per the salt nomenclature policy, the established name only captures the base and not the salt form. FTD and TPI are polymorphic. However, given the high solubility of these compounds there is no clinically meaningful difference in the solubility between the polymorphic forms. For further information regarding the drug substances, refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D.

## B. Drug Product [Trifluridine and Tipiracil] Quality Summary

FTD/TPI Film-Coated Tablets (FCT) (15 mg/6.14 mg) contain 15 mg of trifluridine and 6.14 mg tipiracil. They are white, round, biconvex, immediate-release film-coated tablets imprinted with “15” on one side, and “102” and “15 mg” on the other side, in gray ink.

FTD/TPI Film-Coated Tablets (FCT) (20 mg/8.20 mg) contain 20 mg of trifluridine and 8.20 mg of tipiracil. They are pale red, round, biconvex, immediate-release film-coated tablet imprinted with “20” on one side, and “102” and “20 mg” on the other side in gray ink.

The commercial presentation for FTD/TPI FCT (15 mg and 20 mg) is (b) (4) high density polyethylene (HDPE) bottles with child resistant (b) (4) screw caps (b) (4). The two dosage strength tablets (b) (4) and the formulation is a conventional immediate release formulation, containing only lactose monohydrate (b) (4), pregelatinized starch (b) (4), and stearic acid (b) (4). Each strength is available in 20, 40, and 60 tablet count bottles. The compendial excipients used in the formulation of FTD/TPI FCT (15 mg and 20 mg) comply with requirements of the compendial references listed. All excipients are within the acceptable ranges used in oral products. Non-compendial excipients (b) (4) are composed of compendial constituents and do not impact the safety of this product. There are no novel excipients used in the manufacture of the drug product.

Both drug substances are highly soluble, so due to their low Caco-2 cell membrane permeability, absorption is expected to be determined by the permeability of the two drug substances. Therefore, the solubility was likely to have little impact on the absorption of the drug substances. (b) (4)

controlling the quality of the pre-gelatinized starch (b) (4) will be recommended post approval. Assay, content uniformity, microbial limits and dissolutions are considered Critical Quality Attributes of the finished product. The drug product specification has Microbial Enumeration test per USP <61> and <62 > to assure sterility/microbial limits of the final drug product

The product contains an NME, so method validation packages were sent to the OTR, St. Louis lab (in DARRTS dated 14-APR-2015) per IQP for its evaluation. The methods were verified and found acceptable for quality control and regulatory purposes (refer to the review dated 8-JUL-2015 by Laura Pogue in DARRTS).

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “approve” recommendation was entered into Panorama 17-Aug-15.

Based on the adequate totality-of-stability data at the 12 months at long term storage condition and 6 months at accelerated storage conditions, **24 months of expiration dating may be granted for this product.**

### C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	LONSURF
Non Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Substance	Trifluridine and Tipiracil
Proposed Indication(s) including Intended Patient Population	Metastatic colorectal cancer
Duration of Treatment	Administered orally twice daily for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.
Maximum Daily Dose	Orally twice daily
Alternative Methods of Administration	N/A

### D. Biopharmaceutics Considerations

1. BCS Classification: The applicant did not request BCS Classification at this time.
2. Biowaivers/Biostudies



**QUALITY ASSESSMENT**  
**NDA # 207981**



- Biowaiver Requests: NA
- PK studies: NA
- IVIVC: NA

**E. Novel Approaches: None**

**F. Any Special Product Quality Labeling Recommendations : None**

**G. Process/Facility Quality Summary (see Attachment A)**

**H. Life Cycle Knowledge Information (see Attachment B)**

**Application Technical Lead Comments: Recommended for approval from OPQ.**

Olen Stephens -S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Olen Stephens -S,  
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## Primary Quality Review

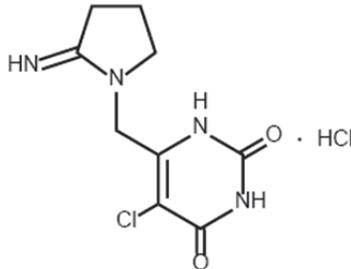
### ASSESSMENT OF THE DRUG SUBSTANCE

#### 2.3.S DRUG SUBSTANCE

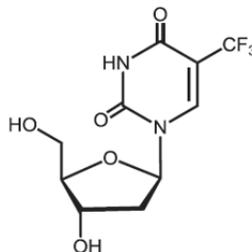
**NOTE: SOME OF THESE SECTIONS MAY BE PART OF A REFERENCED DMF REVIEW (including evaluation of a sterile API). IF SO, PLEASE REFERENCE THE DMF REVIEW(S), AS NEEDED.**

#### 2.3.S.1 General Information

##### Applicant's Response:



Tipiracil HCl,  $C_9H_{11}ClN_4O_2 \cdot HCl$ ; MW = 279.12  
2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-,  
hydrochloride (1:1) (USAN, CAS)



Trifluridine  $C_{10}H_{11}F_3N_2O_5$ ; MW = 296.20  
2'-deoxy-5-(trifluoromethyl)uridine  
thymidine,  $\alpha,\alpha,\alpha$ -trifluoro-

#### Reviewer's Assessment:

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the general information. A summary of the tipiracil and trifluridine information from the NDA is copied above. This is adequate.

**2.3.S.2      Manufacture*****S.2.2 Description of the Manufacturing Process and Controls***

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches? (Note: add applicant's response and reviewers assessment box after this question)
2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

**Applicant's Response:****Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the manufacturing process. Both DMFs are adequate to support NDA 207-981.

***Control of Critical Steps and Intermediates***

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?
4. Are intermediates controlled adequately to assure the structure and impurity profile of the final drug substance?

**Applicant's Response:****Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the manufacturing process. Both DMFs are adequate to support NDA 207-981.

***Process Validation and/or Evaluation***

5. Is the proposed process validated adequately?

***Manufacturing Process Development***

6. What process development and scale up information supports the commercial process and proposed control strategy?

**Applicant's Response:**

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the manufacturing process. Both DMFs are adequate to support NDA 207-981.

**2.3.S.3 Characterization**

7. Do all the characterization data unequivocally support the proposed structure?  
8. Are the potential impurities (e.g. related substances, degradants, inorganic impurities, residual solvents, reagents, and genotoxic impurities) well characterized and controlled in the drug substance?

**Applicant's Response:**

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the characterization of the drug substances. Both DMFs are adequate to support NDA 207-981

**2.3.S.4 Control of Drug Substance**

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?  
10. Are all the analytical procedures appropriately described and validated for their intended use?

**Applicant's Response:**

Table 3.2.S.4.1-1: Specifications for TPI

Quality attribute	Test Method	Acceptance Criteria
Description	Visual	White crystals or a crystalline powder
Identification IR	Infrared spectrophotometry USP <197K>	The spectrum of the sample exhibits absorption bands only at the same wavenumber as that of the reference standard.
Identification HPLC	Assay (in-house method by HPLC)	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the assay.
Identification (b) (4)	Qualitative tests for (b) (4) (in-house method)	Responds to qualitative tests (b) (4) (b) (4)
Identification XRD	X-ray powder diffraction USP <941>	The diffraction pattern conforms to that of the reference standard.
Heavy metals	USP <231> (b) (4)	NMT (b) (4)
Related substances	Related substances (in-house method by HPLC)	(b) (4) NMT (b) (4) Each unspecified related substances: NMT (b) (4) Total related substances: NMT (b) (4)
Residual solvents	Residual solvents (in-house method by GC)	(b) (4)
(b) (4)	(b) (4)	NMT (b) (4)
Residue on ignition	USP <281>; (b) (4)	NMT (b) (4)
Assay	Assay (in-house method by HPLC)	98.0%–102.0% (b) (4)

**Table 3.2.S.4.1-1 FTD Specification**

Test item	Test method	Acceptance criterion
Description	Visual	White to off-white powder.
Identification (1) Infrared absorption	USP<197K>	Spectra from FTD and FTD reference standard exhibit similar intensities of absorptions at the same wavenumbers.
Identification (2) Retention time by HPLC	HPLC (in house method)	The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
Specific rotation	USP<781S> Test solution: 30 mg/mL, in water (25°C)	between (b) (4)
Heavy metals	USP<231> (b) (4)	Not more than (b) (4)
Related substances	HPLC (in house method)	(b) (4) Not more than (b) (4) (b) (4) Not more than (b) (4) (b) (4); Not more than (b) (4) Each unspecified related substance: Not more than (b) (4) Total related substances: Not more than (b) (4)
Residual solvents (b) (4)	GC (in house method)	(b) (4)
Residual solvents (b) (4)	GC (in house method)	
(b) (4)		
Residue on ignition	USP<281>	Not more than (b) (4)
Assay	HPLC (in house method)	Not less than 98.0% and not more than 102.0% (b) (4)
Microbial enumeration	USP<61>	Total aerobic microbial count: (b) (4) CFU/g Total combined yeasts/molds count: (b) (4) CFU/g

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the manufacturing process. Both sets of specifications are copied above. The specifications for TPI do not include a test for microbiological attributes testing. This was considered adequate because there is a test for microbial enumeration in the drug product specifications. Both DMFs are adequate to support NDA 207-981.

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

**Applicant's Response:**



**QUALITY ASSESSMENT**  
**NDA # 207981**



**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the drug substances. Both DMFs are adequate to support NDA 207-981.

**2.3.S.5 Reference Standards or Materials**

12. Are the drug substance reference standards satisfactory?

**Applicant's Response:**

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the drug substances. Both DMFs are adequate to support NDA 207-981

**2.3.S.6 Container Closure System**

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

**Applicant's Response:**

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the drug substances. Both DMFs are adequate to support NDA 207-981.

**2.3.S.7 Stability**

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:**

Refer to the Quality Reviews of trifluridine (DMF (b) (4)) dated 12-AUG-2015 and tipiracil (DMF 28368) dated 03-AUG-2015 by Erika E. Englund, Ph.D. for a full discussion of the drug substances. Both DMFs are adequate to support NDA 207-981.

**OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE****Reviewer's Assessment and Signature:**

Both DMF (b) (4) and DMF 28368 are currently adequate to support NDA 207-981. The retest dates for trifluridine (DMF (b) (4)) and tipiracil (DMF 28368) are covered in the respective DMF reviews and are adequate to support this NDA. This NDA is recommended for approval from a CMC API perspective.

**Erika E. Englund, Ph.D.**

Erika E.

Englund -S

Digitally signed by Erika E.  
Englund -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
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**Supervisor Comments and Concurrence:****Donna F. Christner, Ph.D.**

Donna F. Christner -S

Digitally signed by Donna F. Christner -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
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Date: 2015.08.20 05:11:03 -04'00'

**ASSESSMENT OF THE DRUG PRODUCT****2.3.P****DRUG PRODUCT**

**2.3.P.1 Description and Composition of the Drug Product**

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Trifluridine (FTD)/Tipiracil (TPI) Film-Coated Tablets (FCT) (15 mg/6.14 mg) contain 15 mg of trifluridine and 6.14 mg tipiracil. They are white, round, biconvex, immediate-release film-coated tablets imprinted with “15” on one side, and “102” and “15 mg” on the other side, in gray ink.

Trifluridine (FTD)/Tipiracil (TPI) Film-Coated Tablets (FCT) (20 mg/8.20 mg) contain 20 mg of trifluridine and 8.20 mg of tipiracil. They are pale red, round, biconvex, immediate-release film-coated tablet imprinted with “20” on one side, and “102” and “20 mg” on the other side in gray ink.

The commercial presentation for FTD/TPI FCT (15 mg and 20 mg) is (b) (4) (b) (4) high density polyethylene (HDPE) bottles with a child resistant (b) (4) screw caps with aluminum foil induction inner seals.

The commercial tablet counts per HDPE bottle are 20, 40, and 60 of each product strengths (15 mg and 20 mg) of FTD/TPI FCT. The same container closure is used for all different counts tablets of both strengths. (b) (4)

*Note: Trifluridine has been used in two other FDA approved products under applications, NDA 18229 (Ophthalmic solution, 1980) and ANDA 74311 (Ophthalmic solution/drops, 1995).*

**Composition of the drug product**

Component	Quality standard	Function	Quantity (mg)/tablet	
			FTD/TPI FCT 15 mg	FTD/TPI FCT 20 mg
<b>Tablet core</b>				
Trifluridine (FTD)	In-house	Active ingredient	15.000	20.000
Tipiracil hydrochloride (TPI)	In-house	Active ingredient	7.065	9.420
Lactose monohydrate	NF	(b) (4)		
Pregelatinized starch	NF			
Stearic acid	NF			
	(b) (4)			
Hypromellose	USP			
Polyethylene glycol	NF			
Titanium dioxide	USP			
Ferric oxide	NF			
	(b) (4)			
Magnesium stearate	NF			
	(b) (4)			
(b) (4)				

NF = National Formulary; USP = United States Pharmacopeia

### Composition of the tablet printing ink

Component	Quality standard	Component ratio (%)
Shellac	NF	(b) (4)
Ferric oxide <sup>a)</sup>	NF	
Ferric oxide <sup>b)</sup>	NF	
Titanium dioxide	USP	
FD&C Blue No.2 – Lakes	21 CFR 82.51	
Carmauba wax	NF	
Talc	USP	
(b) (4)		

<sup>a)</sup> The color is red

<sup>b)</sup> The color is yellow

(b) (4)

NF = National Formulary; USP = United States Pharmacopeia; CFR = Code of Federal Regulations

### Reviewer's Assessment:

The trifluridine (FTD)/tipiracil (TPI) film-coated tablets (FCT) are fixed dose combination products that contain the drug substances trifluridine (FTD) and tipiracil hydrochloride (TPI) in a molar ratio 1:0.5.

Two following two tablet strengths of FTD/TPI, as immediate-release film-coated tablets have been developed for commercialization.

- FTD/TPI FCT (15 mg/6.14 mg) contains 15 mg of FTD and 6.14 mg of TPI (as base).
- FTD/TPI FCT (20 mg/8.20 mg) contains 20 mg of FTD and 8.20 mg of TPI (as base).

*While the second API is tipiracil hydrochloride, as per the salt nomenclature policy, the established name should only capture the base and not the salt form. Therefore, while it is correct to say that the tablet strengths are in a 1:0.5 molar ratio as far as the API, the strength for the tipiracil should be expressed as the amount of the base and not the salt. The composition table correctly captures the amount/weight of the APIs included in the formulation. However, the strength of the tablet should be captured as FTD/TPI, 15 mg /6.14 mg and 20 mg/8.20 mg. Throughout the review, the strength is sometimes captured as both drug substances and sometimes as only the strength of the FTD. While the combined strength is correct, the truncated strength designation is used to facilitate flow of the review document and is not the correct or preferred regulatory terminology.*

*The compendial excipients used in the formulation of FTD/TPI FCT (15 mg and 20 mg) comply with requirements of the compendial references listed. Methods for these excipients are representative of Pharmacopoeial General Chapters, and thus, method and validation are not provided.*

*All excipients are within the acceptable ranges used in oral products. The proposed inactive ingredient levels do not affect the safety of the proposed drug product, and the requirements outlined in 21 CFR 314.50(d)(1)(ii). FTD/TPI FCT (20 mg/8.20 mg) are red, which is due to the Ferric oxide, NF in the coating material.*

(b) (4)

*There are no novel excipients used in the manufacture of the drug product.*

***Adequate***

### 2.3.P.2      Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

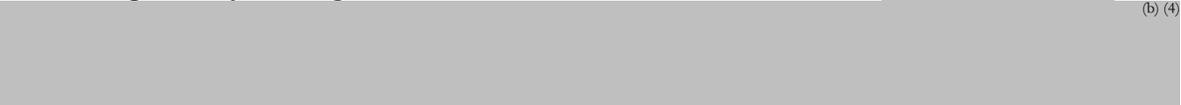
**A summary:** The to-be-marketed formulation is identical to the Late Clinical Trial Material (CTM) formulation with the exception of the imprinting on each side of the tablet.

During development it is noted that both drug substances are highly soluble according to the Biopharmaceutics Classification System (BCS). Due to their low Caco-2 cell membrane permeability, absorption is expected to be determined by the permeability of the two drug substances. Therefore, the solubility was likely to have little impact on the absorption of the drug substances. Trifluridine (FTD) and tipiracil hydrochloride (TPI)

are polymorphic. However, given the high solubility of these compounds there is no difference in the solubility between the polymorphic forms. Therefore, polymorphic form(s) was likely to have little impact on the content uniformity and dissolution of the drug substances. (b) (4)



The compatibility of drug substances with each other was assessed. (b) (4)



(b) (4) Related substances were present initially and didn't increase upon storage when compared with the control. Moreover, there were no new degradation products detected. Therefore, it was concluded that there are no compatibility issues between the two drug substances.



**Reviewer's Assessment:**

For the Phase 3 clinical study, the tablet shape of the 20 mg strength was changed (b) (4). With the aim of discriminating between the FTD 15 mg strength tablets and the FTD 20 mg strength tablets, red ferric oxide was included as a color in the FTD 20 mg strength tablets. In addition, (b) (4) magnesium stearate was added (b) (4). All these changes were Level (b) (4) changes per SUPAC Guidance.

(b) (4)

Assay, content uniformity, microbial limits and dissolutions are considered critical Quality Attributes of the finished product.

For assay, (b) (4) of label claim is the target for each active substance, however, a tighter acceptance criterion is proposed and it is acceptable. FTD/TPI FCT are tested for content uniformity as per USP <905> requirements. All batches complied with the requirement at release. At release and selected intervals during stability, the product is tested for total aerobic microbial count, total combined yeasts and molds and *E. coli* content. Acceptance criteria of (b) (4) cfu/g for total aerobic microbial count, (b) (4) cfu/g for total combined yeasts and molds and a absence of *E. coli* have been established based on generally accepted compendial recommendations for tablets. The Microbial Enumeration release testing results for all batches met the proposed acceptance criteria. The stability data generated show that all test results have met the proposed acceptance criteria for Microbial Enumeration throughout stability testing. TPI and FTD are highly soluble compounds. The dissolution test employs paddles at 50 rpm, with 900 mL of 0.1 N hydrochloric acid as the medium at  $37 \pm 0.5^\circ\text{C}$ . All batches met the proposed acceptance criteria for USP <711> dissolution at release. There is no trend in dissolution results during stability testing, therefore, the target (Q-value is (b) (4) % dissolved at 15 minutes for FTD and TPI) is justified.

*The container closure system was selected*

(b) (4)

(b) (4)

*The pharmaceutical development followed a comprehensive manufacturing science paradigm to demonstrate that a quality product could be manufactured. Provided information is adequate.*

### 2.3.P.4 Control of Excipients

18. Is the quality of all excipients adequately controlled with satisfactory specifications?

**List of Excipients, their functions and compendial references of the excipients:**

Excipient	Function	Quality Standard
Lactose monohydrate	(b) (4)	NF
Pregelatinized starch	(b) (4)	NF
Stearic acid	(b) (4)	NF
Titanium dioxide	(b) (4)	USP
Hypromellose	(b) (4)	USP
Polyethylene glycol	(b) (4)	NF
Ferric oxide	(b) (4)	NF
Magnesium stearate	(b) (4)	NF
(b) (4)	(b) (4)	USP
(b) (4)	(b) (4)	USP
(b) (4)	(b) (4)	NF

NF = National Formulary; USP = United States Pharmacopoeia

**Reviewer's Assessment:**

*The compendial excipients used in the formulation of FTD/TPI FCT (15 mg and 20 mg) comply with requirements of the compendial references listed. Methods for these excipients are representative of Pharmacopoeial General Chapters, and thus, method and validation are not provided, and it is adequate.*

(b) (4)

*The excipient selection was based on excipient compatibilities and therefore adequate.*

**2.3.P.5 Control of Drug Product**

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

**Specifications for FTD/TPI FCT (15 and 20 mg) tablet: Amended on 3-JUN-2015**

Quality Attribute	Test method	Acceptance criteria
Description	Visual	FTD/TPI FCT (15 mg): white, round, biconvex film-coated tablets with '15' printed on one side, and '102' and '15 mg' printed on the other side, in gray ink.
		FTD/TPI FCT (20 mg): pale red, round, biconvex film-coated tablets with '20' printed on one side, and '102' and '20 mg' printed on the other side, in gray ink.
Identification: (Retention time and UV)	HPLC (in house method)	The retention times of two main peaks obtained from the sample solution are the same as those from the standard solution in the assay.
	UV (in house method)	For the peaks at the same retention times, both the absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.
Elemental Impurities	USP <233>	(b) (4) NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT
Related Substances	HPLC (in house method)	Individual specified related substances: (b) (4) NMT (b) (4) NMT (b) (4) (b) (4) NMT (b) (4)
		Each Individual unspecified related substances: NMT (b) (4)
		Total related substances: NMT (b) (4)
Uniformity of Dosage Units – Content Uniformity	USP <905>	Complies with USP <905>  (b) (4)
Dissolution	USP <711>	Q-value is (b) (4) at 15 minutes for FTD, and TPI
Microbial Enumeration	USP <61> and <62>	Acceptance criteria for total aerobic microbial count and total combined yeasts and molds count (b) (4) CFU/g and (b) (4) CFU/g, respectively. Absence of Escherichia coli (b) (4)

Quality Attribute	Test method	Acceptance criteria
Assay	HPLC (in house method)	(b) (4) of label claim for FTD, and TPI

**Batch Analyses:** Drug product release testing results are provided for batches (11J0015A, 12J0015A; 15 mg and 12K7020A and 11K7020B; 20 mg) used in clinical trials (protocol numbers are included in the tables) and stability studies. Batches T1513001, T1513002, and T1513001 (15 mg/6.14 mg) and batches T2013001, T2013002, and T2013003 (20 mg/8.20 mg) are the primary stability batches. The data generated on the stability batches of the clinical batches and on the primary stability batches were similar (refer to the evaluation for discussion).

**Impurities and degradation products:** The impurities and/or degradation products present in the drug product arising from FTD and TPI drug substances are discussed in their DMF reviews. Information on these impurities, mechanism of their formation is presented in the DMFs (b) (4) and 28368.

None the degradation products reported in the drug product specifications arise from the drug product manufacturing process. All impurities are generated from the drug substance manufacturing processes from starting materials. The following tables provide the chemical structure, and the origin of the impurities.

**Impurities arising from FTD Drug substance**

(b) (4)

**Impurities arising from TPI drug substance**

(b) (4)

**Batch Analyses (15 mg tablet)**

Lot Number	Batch size (# of Tablets)	Manufacturing and Testing Site	Manufacturing Date	Lot Number of Drug Substance FTD/TPI	Use of Batch	Specifications applied
T1513001	(b) (4)	Kitajima Plant of Taiho Pharmaceutical Co., Ltd.	Sep 2013	129028/3E93	Process validation Stability study <sup>a)</sup>	Proposed Commercial Specifications
T1513002			Sep 2013	129028/3F76R	Process validation Stability study <sup>a)</sup>	
T1513003			Sep 2013	129028/3F76R	Process validation Stability study <sup>b)</sup>	
12J0015A	(b) (4)	Investigational product plant of Taiho Pharmaceutical Co., Ltd.	Oct 2012	11Y027/110425	Stability study <sup>c)</sup> Clinical studies (TPU-TAS-102-103, 104, and 301)	CTM Specifications for Phase3
11K7015A			Nov 2011	119026/110606	Clinical studies (TPU-TAS-102-102, 103)	
11J0015A			Oct 2011	117025/110425	Stability study <sup>d)</sup> Clinical study (TPU-TAS-102-301)	

- a): Long-term stability, accelerated stability  
b): Long-term stability, accelerated stability, in-use stability study  
c): Bulk stability, Thermal cycle study  
d): Stress stability

Lot Number	Batch size (# of Tablets)	Manufacturing and Testing Site	Manufacturing Date	Lot Number of Drug Substance FTD/TPI	Use of Batch	Specifications applied
11J0015B	(b) (4)	Investigational product plant of Taiho Pharmaceutical Co., Ltd.	Oct 2011	117025/110516	Clinical study (TPU-TAS-102-301)	CTM Specifications for Phase3
S10E7915			May 2010	056020/7C0108	Clinical study (TPU-TAS-102-101) <sup>e)</sup> Clinical study (J004-10040040) <sup>f)</sup>	CTM Specifications for Early development 2
S08J9915			Oct 2008	058021/6E0108	Clinical study (J003-10040030)	CTM Specifications for Early development 1

- e): Lot number after packaging (S10E7915F)  
f): Lot number after packaging (S10E7915R)

**Batch Analyses (20 mg tablet)**

Lot Number	Batch size (# of Tablets)	Manufacturing and Testing Site	Manufacturing Date	Lot Number of Drug Substance FTD/TPI	Use of Batch	Specifications applied
T2013001	(b) (4)	Kitajima Plant of Taiho Pharmaceutical Co., Ltd.	Sep 2013	129028,12Y029 /3E93	Process validation Stability study <sup>a)</sup>	Proposed Commercial Specifications
T2013002			Sep 2013	12Y029 /3F76R, 3F78R	Process validation Stability study <sup>a)</sup>	
T2013003			Sep 2013	12Y029/3F78R	Process validation Stability study <sup>b)</sup>	
12K7020A	(b) (4)	Investigational product plant of Taiho Pharmaceutical Co., Ltd.	Nov 2012	11Y027/110606	Stability study <sup>c)</sup> Clinical studies (TPU-TAS-102-104 and 301)	CTM Specifications for Phase 3
11K7120A			Nov 2011	117025/110516	Clinical study (TPU-TAS-102-301)	
11K7120B			Nov 2011	119026/110606	Clinical studies (TPU-TAS-102-102, 103 and 301)	
11K7020B			Nov 2011	117025/110425	Stability study <sup>d)</sup> Clinical study (TPU-TAS-102-301)	

a): Long-term stability, accelerated stability  
b): Long-term stability, accelerated stability, in-use stability study  
c): Bulk stability, (b) (4) cycle study  
d): Stress stability

Lot Number	Batch size (# of Tablets)	Manufacturing and Testing Site	Manufacturing Date	Lot Number of Drug Substance FTD/TPI	Use of Batch	Specifications applied
S10E7920	(b) (4)	Investigational product plant of Taiho Pharmaceutical Co., Ltd.	May 2010	056020/7C0108	Clinical study (TPU-TAS-102-101) <sup>e)</sup> Clinical study (J004-10040040) <sup>f)</sup>	CTM Specifications for Early development 2
S08J9920			Oct 2005	058021/6E0108	Clinical study (J003-10040030)	

e): Lot number after packaging (S10E7920F)  
f): Lot number after packaging (S10E7920R)

**Analysis of the DATA:**

**Batch Analysis Data for FTD/TPI FCT (15 mg) used for Phase III clinical trial and Process Validation/Primary Stability Study:**

**Related substance Specifications:**

- **Individual specified NMT** (b) (4) %
- **Individual unspecified NMT** (b) (4) %
- **Total NMT** (b) (4) % (Clinical): 12J0015A, 11K7015A, 11J0015A, 11J0015B
- **Total NMT** (b) (4) (Commercial): T1513001, T1513002, T1513003

Related substances	12J0015A	11K7015A	11J0015A	11J0015B	T1513001	T1513002	T1513003
(b) (4)							



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**Batch Analysis Data for FTD/TPI FCT (20 mg) used for Phase III  
clinical trial and Process Validation/Primary Stability Study:**

**Related substance Specifications:**

- **Individual specified NMT** (b) (4) %
- **Individual unspecified NMT** (b) (4) %
- **Total NMT** (b) (4) % (Clinical): 11K7120A, 11K7120B, 12K7020A, 11K7020B
- **Total NMT** (b) (4) (Commercial): T2013001, T2013002, T2013003

Related substances	11K7120A	11K7120B	12K7020A	11K7020B	T2013001	T2013002	T2013003
(b) (4)							

**Reviewer's Assessment:**

*Note: Batches used in phase III clinical trials were not the primary stability batches to establish the expiration dating period of the drug product.*

*A summary is provided above to show only the differences and similarity in the related substance profile.*

*The drug product is tested for Description, Identification, Assay, Related substances, Uniformity of dosage unit, dissolution and Microbial limits. Based on the product characteristics, these tests are reasonable for this immediate release tablet formulation and Uniformity of dosage unit and dissolution may be considered critical quality attributes. FTD/TPI FCT are tested for content uniformity as per USP <905> requirements. All batches complied with the requirement at release. The specification for dissolution is being reviewed by Quality Biopharmaceutics staff and the evaluation is pending*

*The identity, quality and purity of each batch of FTD/TPI FCT are assessed and confirmed according to the proposed specification. Each test was selected to monitor a specific characteristic of the drug product and the justifications for the proposed specification are discussed in this section. The proposed acceptance criteria for each test are based on analytical data at release and the available stability data. Evaluation of the available 12 months of primary stability data from studies conducted under ICH conditions on batches manufactured at commercial scale provides increased assurance that appropriate test and acceptance criteria for FTD/TPI FCT have been chosen. Reference is made to the batch analyses data, long-term stability data and accelerated stability data. The tables presented above in this section provide information and analytical results for batches of FTD/TPI FCT (15 mg and 20 mg), including clinical, development, and manufacturing process validation batches (stability). Analytical data for each batch are presented in accordance to the test, method, and acceptance criteria in place at the time of release of that batch.*

*The maximum daily dose of each drug substance in FTD/TPI FCT is (TPI: 75.36 mg and FTD: 160 mg) and this accounts for (b) (4) % of the identification threshold limits according to the guideline Impurities in New Drug Products (ICH Q3B(R2)). The acceptance criterion for each related substance (b) (4) and total is (b) (4) %, respectively. The amount of total impurities reported is higher than what was reported for clinical batches (Total: (b) (4) %) but is acceptable based on ICH Q3B(R2). The maximum levels for impurities seen to date, in commercial batches, at release or at stability are well below the specification limit (b) (4)*

*(b) (4)*

(b) (4)

(b) (4)

*I: Common Permitted Concentration Limits of Elements across Drug Product Components for Drug Products with Daily Intakes of NMT (b) (4) in ICH Q3D Guideline (Current Step 4 version).*

*At release and selected intervals during stability, the product is tested for total aerobic microbial count, total combined yeasts and molds and E. coli content. Acceptance criteria of (b) (4) cfu/g for total aerobic microbial count, (b) (4) cfu/g for total combined yeasts and molds and absence of E. coli have been established based on compendial recommendations for tablets. The Microbial Enumeration release testing results for all batches met the proposed acceptance criteria. The stability data generated show that all test results have met the proposed acceptance criteria for Microbial Enumeration throughout stability testing.*

*The specification is based on the ICH Q6A Guidance: "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" and are adequate.*

20. Are all the analytical procedures appropriately described and validated for their intended use?

Analytical method is developed to assay and quantitate the related products by the applicant. The methods and their validations to quantitate drug substance (assay for content uniformity and during dissolution testing) and the impurities/degradation products are presented here:

Validation of a stability-indicating, reverse-phase, high-pressure liquid chromatography (HPLC) method, is provided for the determination of the area and weight percent purity of the drug substances in tablet, known impurities (by weight percent) and unknown impurities (by area percent). The validation assessed system suitability, specificity, linearity, limits of detection and quantitation, accuracy, repeatability, intermediate precision, solution stability, robustness, and range of the method.

**HPLC method to Assay/Related substances in tablets:**

Parameters	HPLC
<b>Specification</b>	(b) (4)
<b>HPLC column</b>	
<b>Detection</b>	
<b>Injection volume</b>	
<b>Column temperature</b>	
<b>Flow rate</b>	
<b>Stop time</b>	
<b>Mobile Phase</b>	
<b>Gradient</b>	
<b>RRF/RRT</b>	

<p><b>Sample Chromatograph</b></p>	<p>(b) (4)</p>
<p><b>System suitability</b></p>	
<p><b>Stability</b></p>	<p>Stable at 5°C for at least 60 hours Stable at room temperature for at least 24 hours</p>
<p><b>Validation</b></p>	<p><b>Assay and related substance Validation(10EA50):</b></p> <p>Related substance:</p> <p>The test results of analytical validation of the assay and related substances test method for 15 and 20 mg tablets are summarized in the submission and tested for specificity, LOD, LOQ, linearity, accuracy, precision, range and stability.</p> <p>All of the validation characteristics for the assay method were acceptable and this test method was adequately accurate, precise, reproducible, and linear. Therefore, this test method was concluded to be suitable for purpose.</p>

**Reviewer's Assessment:**

*The validation of non-compendial analytical procedures is performed in accordance with ICH guidance Q2(R1) "Validation of Analytical Procedures: Text and Methodology" and Q6A "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances".*

*For assurance of the quality performance of the chromatographic system, necessary parameters of the recommended system suitability are measured through specificity, linearity of the method, and precision robustness and they are deemed adequate.*

*The method has been validated as a stability indicating method and is considered suitable for its intended use. The analytical procedures and their validation were found to be adequate*

*Since the product contains an NME, method validation packages was sent to the OTR, St. Louis lab (in DARRTS dated 14-APR-2015) per IQP for its evaluation. The methods were verified and found acceptable for quality control and regulatory purposes (refer to the review dated 8-JUL-2015 by Laura Pogue in DARRTS). Adequate*

21. Is the proposed control strategy for the drug product manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

**Reviewer's Assessment:**

*Part of the drug product control strategy includes establishment of specifications and appropriate acceptance criteria. The applicant has provided data on both developmental and production-scale batches. The only change in the acceptance criteria is for the amount of total impurities, increasing from NMT (b) (4) % to NMT (b) (4) %. At the dose level, the identification threshold as per ICH Q3B(R2) for individual impurities would be set at (b) (4) %, which the applicant has followed with each related substance (b) (4) (b) (4)). The total impurities are also set in accordance with the ICH Q3B(R2) guidelines. The maximum levels for impurities seen to date at release or at stability are well below the specification limit (b) (4) and comparable to what was found in the clinical batches. Therefore, from the drug product manufacturing perspective, the control strategy is acceptable and any residual risk is mitigated by appropriately set specifications.*

*The control strategy (manufacturing parameters) for the drug Product manufactured at commercial stage will be reviewed by the Drug Product Process reviewer.*

**2.3.P.7 Container Closure System**

22. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen, moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?

The commercial presentation for FTD/TPI tablets (15 mg and 20 mg) is (b) (4) white high density polyethylene (HDPE) bottles with a child resistant (b) (4) (b) (4) screw caps with aluminum foil induction inner seals. The commercial tablet counts per HDPE bottle are 20, 40, and 60 of each product strength (15 mg and 20 mg) of FTD/TPI FCT. The same container closure is used for all different counts tablets of both strengths.

(b) (4)  
(b) (4) The suitability of the container closure systems and its components has been demonstrated by the assessment of the container closure system provided in the submission.

**Specifications for Bottle:**

Packaging Component	Testing Frequency	Test	Analytical Procedure	Attribute	Acceptance Criterion
(b) (4) White HDPE (b) (4)	Each Receipt	Description	Visual examination	Style	Round
(b) (4)				Neck Finish	(b) (4)
(b) (4)				Color	White
	The first receipt of the product, and annually thereafter	Identification by IR spectroscopy	(b) (4)	Material	HDPE (b) (4)
	Each Receipt	Dimensions	Manual measurement		

**Reviewer's Assessment:**

*Based on compatibility study results (refer to the Pharmaceutical Development section of this review), FTD/TPI FCT (15 mg and 20 mg)* (b) (4)

(b) (4)

*selected packaging form is HDPE bottles, child-resistant (b) (4) caps with an induction inner* (b) (4)

(b) (4)  
(b) (4) The highest amount of the total related substance did not increase beyond (b) (4) % (acceptance Criterion: (b) (4) %). The product contact surfaces of the container closure components comply with US FDA requirements for indirect food additives as described in 21 CFR 177. As part of the characterization and qualification of the container closure system proposed, the (b) (4) containers comply with the USP <661>. The materials used in the container closure systems conform to the 21 CFR, for Indirect Food Additives. The vendors provide conformance letters. The container closure systems have been tested according to USP <671> and these tests include MVTR data.

(b) (4)  
Additionally, ICH photostability studies on exposed tablets, as discussed in the stability section demonstrated that the FTD/TPI film-coated tablets are not sensitive to light and therefore no special light protection is needed.

Based on this evaluation, it is determined that the container closure will provide adequate protection to the drug product for the duration of the granted expiration dating period.

### 2.3.P.6 Reference Standards or Materials

23. Are the proposed drug product reference standards acceptable?

The Certificates of Analysis for the Reference Standards for each drug substance, FTD, and TPI used for the analysis of FTD/TPI FCT, are provided in (b) (4) (b) (4) drug master file (DMF (b) (4)), and the Taiho Pharmaceutical Co., Ltd. drug master file (DMF 28368). The reference standards used in the analysis of FTD/TPI tablets are the same as those used for the analysis of FTD and TPI drug substance.

#### **Reviewer's Assessment:**

The applicant obtains the reference standard of the drug substance and related substances from the manufacturers of the drug substance. The CoAs are provided in the cross referenced DMFs and they are adequate (refer to the CMC reviews of the DMFs (b) (4) and 28368 by Dr. Erika Englund dated 12-AUG-2015 and 3-AUG-2015, respectively).

### 2.3.P.8 Stability

24. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?

Based on the available stability data for FTD/TPI FCT (15 and 20 mg) packaged in HDPE bottles, the applicant proposed a 24 months of expiration dating period with the following label statement: “Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].”

The commercial tablet counts per bottle are 20, 40, and 60 for each strengths of FTD/TPI FCT. The same container closure is used for all different tablet counts of both strengths. Therefore, a bracketing design is applied to the long-term and accelerated stability studies in accordance with ICH Q1D. This bracketing design was used to bracket the intermediate (40-count) bottle fill size between 20- and 60-count fill sizes. The Agency agreed to the proposed bracketing design for the Long-term stability study and accelerated stability study (*Pre-NDA Meeting dated 27-NOV-2013*).

Stability data are currently available up to 12 months at ICH long-term stability (25°C / 60%RH) and up to 6 months at accelerated stability (40°C / 75%RH).

Data from bulk tablet stability studies (b) (4) (b) (4) bulk shipping study is provided to support the storage and shipment of bulk drug product.

Stability data from photostability, stress and in-use stability data is also provided on FTD/TPI FCT (15 and 20 mg) to evaluate the product in real life scenario.

The following table summarizes the batches used for stability station:

Batch	Strength	Packaging	Conditions	Available stability data (in months)
T1513001S T1513002S T1513003S	15 mg	20 count bottle	25°C/60% RH	0, 3, 6, 9 and 12
T1513001L T1513002L T1513003L	15 mg	60 count bottle	25°C/60% RH	0, 3, 6, 9 and 12
T2013001S T2013002S T2013003S	20 mg	20 count bottle	25°C/60% RH	0, 3, 6, 9 and 12
T2013001L T2013002L T2013003L	20 mg	60 count bottle	25°C/60% RH	0, 3, 6, 9 and 12
T1513001S T1513002S T1513003S	15 mg	20 count bottle	40°C/75% RH	0, 3, and 6

T1513001L T1513002L T1513003L	15 mg	60 count bottle	40°C/75% RH	0, 3, and 6	
T2013001S T2013002S T2013003S	20 mg	20 count bottle	40°C/75% RH	0, 3, and 6	
T2013001L T2013002L T2013003L	20 mg	60 count bottle	40°C/75% RH	0, 3, and 6	
11J0015A	15 mg	(b) (4)			
11J0015A	15 mg				
11J0015A	15 mg				0, 1, and 2
11J0015A	15 mg				0, 1, and 2
11K7020B	20 mg				
11K7020B	20 mg				
11K7020B	20 mg				0, 1, and 2
11K7020B	20 mg				0, 1, and 2
12J0015A	15 mg				0, 3, 6, 9 and 12
12J0015A	15 mg				0, 3, 6, 9 and 12
12K7020A	20 mg				0, 3, 6, 9 and 12
12K7020A	20 mg				0, 3, 6, 9 and 12

		(b) (4)	
T1513002	15 mg		0, 1, 2, and 3
T2013003	20 mg		0, 1, 2, and 3
12J0015A	15 mg		Cycle 0, and 3
12K7020A	20 mg		Cycle 0, and 3

25. Are the post-approval stability protocols and other stability commitments for the drug product adequate?

The following stability commitments are made:

- Taiho Oncology, Inc. also commits to an ongoing stability program, in compliance with Good Manufacturing Practices. Following the initial production requirement described above, Taiho Oncology, Inc. commits to placing one batch of each product strength in the lower bottle fill size (20-count) in HDPE bottles on routine stability annually, according to the protocols. The Agency recommended to select the annual stability batches using the lowest count configuration (20 counts) for each strength (15 mg and 20 mg) of the drug product for the annual stability testing program (Pre-NDA Meeting Briefing Document, November 27, 2013).
- In the event a batch of drug product may fall outside the approved specifications, Taiho Oncology, Inc. commits to 1) discussing a solution with the Health Authority to arrive at a mutually satisfactory resolution to the problem or 2) withdrawing from the market the batch(es) involved.
- Expiry dating extensions may be based on results from studies involving either the primary stability batches or the annual commercial stability batches, and will be reported in accordance with the applicable procedures.

**Post Approval Stability Protocol:**

Long-Term Storage Condition 25°C / 60%RH									
Study Variation	Time (months)	0	3	6	9	12	18	24	36
Initial Production	Description	✓	✓	✓	✓	✓	✓	✓	✓
	Identification (HPLC/UV)	✓	-	-	-	✓	-	✓	✓
	Related substances	✓	✓	✓	✓	✓	✓	✓	✓
	Dissolution	✓	✓	✓	✓	✓	✓	✓	✓
	Microbial enumeration	✓	-	-	-	✓	-	✓	✓
	Assay	✓	✓	✓	✓	✓	✓	✓	✓
	Water	✓	✓	✓	✓	✓	✓	✓	✓
	Hardness	✓	✓	✓	✓	✓	✓	✓	✓
Routine Production	Description	✓	-	-	-	✓	-	✓	✓
	Related substances	✓	-	-	-	✓	-	✓	✓
	Dissolution	✓	-	-	-	✓	-	✓	✓
	Microbial enumeration	✓	-	-	-	✓	-	✓	✓
	Assay	✓	-	-	-	✓	-	✓	✓
	Water	✓	-	-	-	✓	-	✓	✓

Notes:  
 Acceptance Criteria: The acceptance criteria and analytical methods utilized for each test will be the approved regulatory specifications, except the method for water. The method for water is included in the 3.2.P.8.3.1.  
 ✓: Tested  
 -: Not tested

**Reviewer's Assessment:**

*The tests on release and stability specification are not identical; however, the acceptance criteria for the common tests are the same. On stability, the primary stability batches were tested for description, identification, microbial limits, specified organisms, (b) (4) assay, dissolution, (b) (4) and related substances.*

(b) (4)

Data from photostability studies demonstrate that FTD/TPI FCT (15 and 20 mg) are not light sensitive. Stress studies were carried out to assess the effect of severe conditions (e.g. during shipping) on the drug product. The data is summarized below:

FTD/TPI FCT (15 and 20 mg) are stable based on the results of all tests performed when stored for up to 12 months in HDPE bottles at 25°C / 60%RH. There is no trend in description, identification, assay, related substances, (b) (4), dissolution, microbial enumeration (TAMC, TYMC, and E-coli) (b) (4). The tablets are also stable when stored for 6 months in HDPE bottles under accelerated condition (40°C / 75%RH). (b) (4)

The results from the low strength tablets (15 mg) and the high strength tablets (20 mg) were comparable.

A bracketing design is applied to the long-term and accelerated stability studies in accordance with ICH Q1D. The 40-count fill size is supported by stability data from tablets packaged in **20-count** (b) (4) and **60-count** (b) (4) HDPE bottles with the same closure. Results from the low fill (20 tablets / bottle) and high fill (60 tablets / bottle) were comparable and support the stability of the medium fill (40 tablets / bottle) by virtue of a bracketing stability design. These results provide reassurance over the suitability of the proposed container closure system.

*If the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug product will remain well within the acceptance criteria for that attribute during the proposed expiration dating period of 24 months. In these circumstances, a statistical analysis is normally considered unnecessary. Extrapolation of the expiration dating period (24 months) beyond the period covered by long-term data (12 months) is proposed by the applicant. Per ICH Q1E, the proposed expiration can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. Based on the adequate totality-of-stability data at the 12 months at long term storage condition and 6 months at accelerated storage conditions, it may be concluded that **the proposed 24 months of expiration dating may be granted for this product.***

*Per ICH 1A (R2), and 21 CFR 211.166, the applicant provided both stability commitments and stability protocol which are reasonable.*

**Deficiency (4-MAY-2015):**

Propose acceptance criteria [REDACTED] (b) (4) at both release and stability. Amend both the release and stability specifications in the NDA to include the acceptance criteria [REDACTED] (b) (4).

**Response (3-JUN-2015):**

[REDACTED] (b) (4)

Based on these data, Taiho proposes an acceptance criterion [REDACTED] (b) (4) at release and stability. The proposed specification for FTD/TPI FCT is provided.

**Evaluation:** *The applicant accepts the recommendation and amends the specification [REDACTED] (b) (4)*

[REDACTED] (b) (4)



QUALITY ASSESSMENT  
NDA # 207981



(b) (4)

(b) (4) Taiho believes that it is not necessary to set an acceptance criterion for (b) (4) FTD/TPI film coated tablets.

*Evaluation:* Based on the provided information, it is determined that it is not necessary to set an acceptance criterion for (b) (4) FTD/TPI film coated tablets. In accordance with the principles outlined in the ICH Q6A guidance, (b) (4)

(b) (4) It is acceptable to this reviewer. The applicant accepts the recommendation to add the acceptance criterion (b) (4) in the drug product specification. Adequate.

**R.2 Comparability Protocols**

26. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

**Reviewer’s Assessment:**

Not applicable

**OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT**

**Reviewer’s Assessment and Signature:**

Original CMC information, amendments and responses to the CMC deficiencies related to the drug product in the NDA have been reviewed and found “Adequate”.

Revisions to the proposed PI labeling (Highlight, Description and How Supplied sections) have been conveyed to the OND PM and will be finalized during team review of the labeling.

Rajiv Agarwal -S  
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**Rajiv Agarwal**

**Supervisor Comments and Concurrence:**

The control strategy for the drug product, batch, and stability data submitted under NDA 207981 as reviewed Dr. Agarwal support approval. A 24 month shelf life may be granted pursuant overall “approval” recommendation by the CMC team.

Olen Stephens -S  
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**Olen Stephens**

## ASSESSMENT OF THE PROCESS

### 2.3.P DRUG PRODUCT

#### 2.3.P.3.2 *Batch Formula*

1. Does the provided batch formula reflect the proposed composition and that of the registration batches?

**The batch formulae of Trifluridine/Tipiracil Hydrochloride (FTD/TPI) Film-Coated Tablets (FCT) (15/7.065 mg and 20/9.420 mg) for commercial scale:**



The commercial batch formula and registration batch formula used for early critical trials are same except (b) (4)

(b) (4) The changes are minor should not affect critical CPP.

The applicant has provided a comparative dissolution profile and an in-vivo study between Early CTM Formulation (20 mg) (lot: S10E7920) and Late CTM Formulation (20 mg) (lot: 11K7120A) in Fasted Dogs (n=8) to demonstrate that there were no differences in dissolution between the Late CTM formulation and the To-be-marketed formulation. The argument is acceptable.

*Description of the Manufacturing Process and Process Controls*

(b) (4)

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(b) (4)

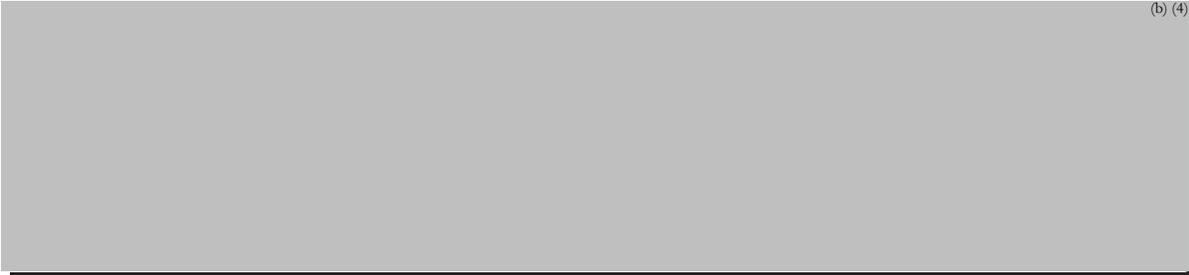
The process validation/evaluation results support that the commercial process results in drug product that meets the CQAs.

**The submission batches** of FTD/TPI FCT (15 mg (lot# 3182, Batch Size: (b) (4) tablets) and 20 mg (lot# 3195A, Batch Size: (b) (4) tablets)) were manufactured at the commercial manufacturing facility in Tokushima (Kitajima Plant) at full commercial size.

(b) (4)

After the review of second IR response, the In-process Controls for both the DP manufacturing and Packaging are deemed acceptable.

The applicant provided translated English and original Japanese copy of the **executed batch record** in module 3. The executed batch record is electronic. The applicant submitted the pages of manufacturing record shown on the computer screens were copied, translated into English, and converted into PDF for the agency.



- Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

**Reviewer’s Assessment: Adequate**

The DP is oral IR tablet. The manufacturing process (b) (4) (b) (4)).

The applicant has provided up to 12 month CRT stability data (b) (4) (b) (4).

The DP specification has Microbial Enumeration test per USP <61> and <62 > to assure sterility/microbial limits of the final drug product as shown below:

**Table 3.2.P.2.5-1: Microbiological Examination of FTD/TPI FCT (15 mg and 20 mg)**

Test Item	Acceptance Criteria	Test Results on All Batches to Date
Microbial limits	Acceptance criteria for total aerobic microbial count and total combined yeasts and molds count are (b) (4) CFU/g and (b) (4) CFU/g, respectively. Absence of <i>Escherichia coli</i> (b) (4)	- Total aerobic microbial count: (b) (4) CFU/g - Total combined yeasts and molds count: (b) (4) CFU/g - <i>Escherichia coli</i> : Absence/g

The specifications comply with USP <1111> for non-aqueous, non-sterile preparations for oral use. Hence acceptable. Testing is performed initially and then yearly.

**R.2 Comparability Protocols**

- Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

**Applicant’s Response:** None.

**OVERALL ASSESSMENT AND SIGNATURES:**  
**PROCESS: Adequate**



**QUALITY ASSESSMENT  
NDA # 207981**



**Reviewer's Assessment and Signature:**

The DP manufacturing process has been reviewed and found adequate.

DP Microbiology has been reviewed and it complies with USP <1111> for non-aqueous, non-sterile preparations for oral use.

*Quamrul Majumder*

Quamrul H.  
Majumder -S

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**Supervisor Comments and Concurrence:** Jennifer A.

*Jennifer Maguire*

Maguire -S

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**ASSESSMENT OF THE FACILITIES**

**2.3.S DRUG SUBSTANCE**

**2.3.S.2 Manufacture**

*Manufacturer(s)*

- Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
		(b) (4)	Acceptable	Warning letter issued within last 5 years, new API	Acceptable
Taiho Pharmaceutical Co., Ltd., Saitama Plant	3002646390	Manufacture, Packaging, QC testing and Release of tipiracil HCl	Acceptable	No previous inspection history	Acceptable

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment: Satisfactory**

This product includes two active pharmaceutical ingredients: tipiracil hydrochloride and trifluridine.

Tipiracil hydrochloride is manufactured via chemical synthesis by Taiho Pharmaceutical Co., Ltd. located at 200-22, Motohara, Kamikawa-machi, Kodama-gun, Saitama, Japan. This facility has no previous FDA inspection history and therefore a pre-approval inspection was requested and performed. The inspection was conducted May 11-15, 2015 and focused on the manufacturing operations for tipiracil hydrochloride. No deficiencies were identified and the facility is considered to be acceptable to perform this operation.

Trifluridine is manufactured via chemical synthesis by (b) (4)  
(U) (+)  
(b) (4)  
(b) (4). The most recent inspection was performed in March 2014 and covered API manufacturing operations. A 483 was not issued and the facility was deemed acceptable. (b) (4)

(b) (4)  
(b) (4) Because this facility has corrected previous cGMP deficiencies and has been routinely inspected for operations similar to those proposed in this submission, a pre-approval inspection was not performed and it is considered to be acceptable for the manufacture of trifluridine API.

**2.3.P DRUG PRODUCT****2.3.P.3 Manufacture*****Manufacturer(s)***

6. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?



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Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
Taiho Pharmaceutical Co., Ltd. Kitajima Plant	3010872322	TAS-102 Tablets: Manufacture, QC testing, Release, and Stability Testing	Acceptable	No previous FDA inspection history, NME, vulnerable patient population	Acceptable
(b) (4)			Acceptable	Lower risk; consistent acceptable cGMP inspection history; NME and patient population elevated risk score for all facilities	Acceptable
			Acceptable	No previous FDA inspection history, NME	Acceptable
			Acceptable	Lower risk; consistent acceptable cGMP inspection history; NME and patient population elevated risk score for all facilities	Acceptable
			Acceptable	Lower risk; consistent acceptable cGMP inspection history; NME and patient population elevated risk score for all facilities	Acceptable

**Reviewer's Assessment: Satisfactory**

The drug product manufacturer is Taiho Pharmaceutical Co. Ltd., Kitajima Plant, located at 1-1 Iuchi, Takabo, in Tokushima, Japan. This facility has no previous FDA inspectional history. The manufacturing process consists of

(b) (4)

(b) (4)

(b) (4)

(b) (4) Because this tablet consists of two fixed dose drug substances, contains a new molecular entity, and has a vulnerable target patient population affected by metastatic colorectal cancer, a pre-approval inspection was requested. The pre-approval inspection was conducted May 18-22, 2015 and no 483 was issued. One general discussion item was identified regarding the firm's

(b) (4)

(b) (4)

(b) (4) No other concerns were identified, and the firm is therefore considered to be acceptable to manufacture Lonsurf tablets.

(b) (4)

(b) (4) The proposed packaging configuration described in this submission consists of (b) (4) HDPE bottles with child resistant (b) (4) caps with aluminum foil induction inner seals. Tablet

counts per bottle may be 20, 40, or 60 for each strength.

(b) (4)

(b) (4)

## OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

### Reviewer's Assessment and Signature:

Marisa Heayn -S

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### Supervisor Comments and Concurrence:

Grace E. McNally -S

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## ASSESSMENT OF THE BIOPHARMACUETICS

7. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Trifluridine (FTD) and Tipiracil Hydrochloride (FTD/TPI) film-coated tablets (FCT) are designed as a combination (15/7.065 mg and 20/9.42 mg) in one immediate release tablet.



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FTD has a solubility of (b) (4) and TPI has a solubility of (b) (4) in physiological pH range (pH 1-7). The two dosage strength tablets (b) (4) and the formulation is a conventional immediate release formulation; containing only lactose monohydrate (b) (4), pregelatinized starch (b) (4), and stearic acid (b) (4). The manufacturing process includes (b) (4). The Applicant developed an early formulation (Early CTM) during Phase I, which was then changed in late formulation in Phase I, which was used for the clinical development of the product and commercial production.

**DISSOLUTION METHOD**

The proposed method is summarized in table BP 1:

**Table BP1:** Proposed Dissolution Method and Acceptance Criterion.

Apparatus	Speed	Volume	Medium	Detection	Acceptance Criterion
USP II	50 rpm	900 mL	0.1 N HCl	HPLC/UV $\lambda=210$ nm	$Q = (b) (4) \%$ at 15 min

The Applicant proposed the use of apparatus II with paddles for dissolution testing because it is considered a standard apparatus. The Applicant provided data to justify the selection of the method parameters as follows:



(b) (4)

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## ACCEPTANCE CRITERION

The Applicant proposes  $Q = \frac{(b) (4)}{(4)}\%$  at 15 minutes as acceptance criterion for both FTD and TPI. The proposal is based on the high solubility of both active ingredients;  $(b) (4)$  ingredients are almost completely dissolved by 10 minutes.

8. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

*Initially, the Applicant developed an Early Clinical Trial Material formulation (Early CTM) with the aim of optimizing the manufacturing process. The Early CTM was used in the Japanese Phases 1 and 2 clinical studies and the US food-effect study. Subsequently, the tablet  $(b) (4)$  (20 mg) of the Early CTM formulation was changed  $(b) (4)$   $(b) (4)$   $(b) (4)$  to develop the Late Clinical Trial Material formulation (Late CTM) that was used in the Phase III study. Finally, the Late CTM formulation was imprinted with a unique identification to provide the To-be-marketed formulation (Table 1).  $(b) (4)$*

$(b) (4)$

**Reviewer's Assessment: RECOMMENDED FOR APPROVAL**

The biopharmaceutics review was focused on the evaluation and acceptability of the following:

- Adequacy of the proposed dissolution method
- Adequacy of the proposed dissolution acceptance criteria
- Confirmation that no formulation bridging is needed

***Dissolution Method Parameters:***

(b) (4)

(b) (4) The proposed dissolution method was found **ACCEPTABLE**.

***Dissolution Method Discriminating Ability:***

The Applicant investigated the effect of varying critical material attributes (particle size distribution) and critical manufacturing steps (b) (4)

(b) (4) on dissolution. (b) (4)

(b) (4)

(b) (4) Therefore, the discriminating ability of the method is **ACCEPTABLE**.

***Acceptance Criteria:***



**QUALITY ASSESSMENT  
NDA # 207981**



The acceptance criteria (Q = <sup>(b)(4)</sup>% at 15 minutes) proposed by the Applicant are found to be ACCEPTABLE based on the fast and complete dissolution of the drug product by 10 minutes.

**BIOPHARMACEUTICS INFORMATION REQUESTS**

*The developmental parameters of the dissolution method have not been adequately justified. Provide experimental data to support the selection of the dissolution medium, pH, and agitation/rotation speed. In addition, comment on whether or not sink conditions are maintained for the duration of dissolution testing.*

*The developmental parameters of the dissolution method have not been adequately justified. Provide experimental data to support the selection of the dissolution medium, pH, and agitation/rotation speed. In addition, comment on whether or not sink conditions are maintained for the duration of dissolution testing.*

The Applicant provided sufficient data in response to the information request and the provided data was incorporated in the biopharmaceutics summary included above.

**OVERALL ASSESSMENT AND SIGNATURES:  
BIOPHARMACEUTICS**

**Reviewer's Assessment and Signature:**

The dissolution method and acceptance criteria listed in the table below are acceptable and NDA 207981 (LONSURF®) is **RECOMMENDED FOR APPROVAL**.

Apparatus	Speed	Volume	Medium	Detection	Acceptance Criterion
USP II	50 rpm	900 mL	0.1 N HCl	HPLC/UV λ=210 nm	Q = <sup>(b)(4)</sup> % at 15 min

Salaheldin S. Hamed -A  
(Affiliate)

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**Supervisor Comments and Concurrence:**

Okponabofa  
Eradi -S

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**ASSESSMENT OF MICROBIOLOGY**



**QUALITY ASSESSMENT**  
**NDA # 207981**



9. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:** The microbiology assessment was completed by the process reviewer above.

**2.3.P.6 Reference Standards or Materials**

10. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Point to consider**

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:** The microbiology assessment was completed by the process reviewer above.

**A APPENDICES**

**A.2 Adventitious Agents Safety Evaluation**

11. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of (b) (4) contamination (b) (4)?

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:** NA

12. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug



**QUALITY ASSESSMENT**  
**NDA # 207981**



substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:** NA

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:**

The microbiology assessment was completed by the process reviewer above.

**Supervisor Comments and Concurrence:** NA

## I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

### Labeling & Package Insert

#### 1. Package Insert



Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: Lonsurf Established Name: (trifluridine and tipiracil)	Established name is modified per MAPP 5021.1 and salt nomenclature guidance
Dosage form, route of administration	Dosage: Tablet Route: Oral	Modified per labelling tool.
Controlled drug substance symbol (if applicable)	Not Applicable	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths		Established name is modified per MAPP 5021.1 and salt nomenclature guidance

**Conclusion:** The changes/edits are made to this section per labelling tool and will be conveyed to the applicant by the OND.

**(b) “Full Prescribing Information” Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

**3 DOSAGE FORMS AND STRENGTHS**

The Lonsurf (b) (4) 15 mg trifluridine/6.14 (b) (4) mg tipiracil (b) (4) is a white, biconvex, round, film-coated tablet, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.

The Lonsurf (b) (4) 20 mg trifluridine /8.19 (b) (4) mg tipiracil (b) (4) is a pale red, biconvex, round, film-coated tablet, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Tablet	Adequate
Strengths: in metric system	Lonsurf tablet 15 mg/6.14 mg (trifluridine/tipiracil)  Lonsurf tablet 20 mg/8.20 mg (trifluridine /tipiracil)	Established name is modified per MAPP 5021.1 and salt nomenclature guidance
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The Lonsurf tablet 15 mg/6.14 mg (trifluridine/tipiracil) is a white, biconvex, round, film-coated tablet, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.  The Lonsurf tablet 20 mg/8.20 mg (trifluridine /tipiracil) is a pale red, biconvex, round, film-coated tablet, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.	Established name is modified per MAPP 5021.1 and salt nomenclature guidance

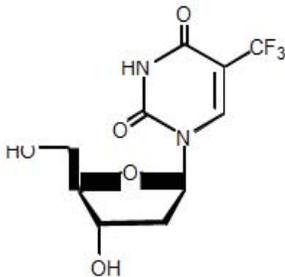
**Conclusion:** The changes/edits are made to this section per labelling tool and will be conveyed to the applicant by the OND.

**#11: Description (21CFR 201.57(c)(12))****11 DESCRIPTION**

Lonsurf (b) (4) contain trifluridine and tipiracil hydrochloride (b) (4)  
(b) (4) a molar ratio of 1:0.5.

**Trifluridine**

Trifluridine is described chemically as 2'-deoxy-5-(trifluoromethyl)uridine, and has the following structural formula:

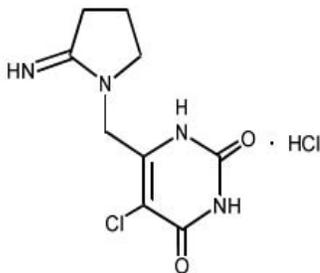


Trifluridine has a molecular formula C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> and a molecular weight of 296.20.

Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

**Tipiracil hydrochloride**

Tipiracil hydrochloride is a thymidine phosphorylase inhibitor described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1), and has the following structural formula:



Tipiracil hydrochloride has a molecular formula  $C_9H_{11}ClN_4O_2 \cdot HCl$  and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

Lonsurf <sup>(b) (4)</sup> Tablet (15 mg trifluridine/6.14 <sup>(b) (4)</sup> mg tipiracil <sup>(b) (4)</sup>)

Each film-coated tablet of Lonsurf, for oral use, contains 15 mg of trifluridine and 6.14 <sup>(b) (4)</sup> mg of tipiracil <sup>(b) (4)</sup> equivalent to 7.065 <sup>(b) (4)</sup> 6.14 mg of tipiracil hydrochloride as active ingredients, and the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, and magnesium stearate.

Lonsurf <sup>(b) (4)</sup> Tablet (20 mg trifluridine/ 8.19 <sup>(b) (4)</sup> mg tipiracil <sup>(b) (4)</sup>)

Each film-coated tablet of Lonsurf, for oral use, contains 20 mg of trifluridine and 8.19 <sup>(b) (4)</sup> mg of tipiracil <sup>(b) (4)</sup> equivalent to 9.420 <sup>(b) (4)</sup> mg of tipiracil hydrochloride as active ingredients, and the following inactive ingredients: lactose monohydrate, pregelatinized starch,

stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate.

Both film-coated tablets (Lonsurf 15 mg/6.14 mg and 20 mg/8.19 mg) are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	<u>Lonsurf Tablet (15 mg trifluridine/6.14 mg tipiracil)</u> <u>Lonsurf Tablet (20 mg trifluridine/8.20mg tipiracil)</u>	Established name is modified per MAPP 5021.1 and salt nomenclature guidance
Dosage form and route of administration	Tablet, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	The statement has been modified and captured.	Established name is modified per MAPP 5021.1 and salt nomenclature guidance
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Added	Added
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

**Conclusion:** The changes/edits are made to this section per labelling tool and will be conveyed to the applicant by the OND.

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

Lonsurf 15 mg/6.14 mg tablets are supplied as white, biconvex, round, film-coated tablet imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-10<sup>(b) (4)</sup>-1
- 40 counts: NDC 64842-10<sup>(b) (4)</sup>-2
- 60 counts: NDC 64842-10<sup>(b) (4)</sup>-3

Lonsurf 20 mg/8.19 mg tablets are supplied as pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-10<sup>(b) (4)</sup>-1
- 40 counts: NDC 64842-10<sup>(b) (4)</sup>-2
- 60 counts: NDC 64842-10<sup>(b) (4)</sup>-3

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	The strengths have been modified and captured.	Established name is modified per MAPP 5021.1 and salt nomenclature guidance
Available units (e.g., bottles of 100 tablets)	Provided	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided	Adequate
Storage conditions	Provided	Adequate

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Not provided	Not adequate

**Conclusion:** The changes/edits are made in this section and will be conveyed to the applicant by the OND.

**2. Labels** (Note: This review captures the flavor of one strength of bottle label and one tablet count carton label. Other strength and carton labels will follow the same advice)

**1) Immediate Container Label**

DRAFT LABELING



Reviewer's Assessment:



**QUALITY ASSESSMENT**  
**NDA # 207981**



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name of TPI has been modified and captured. Font size and prominence are acceptable.	Established name (TPI) needs to be amended
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The strengths have been modified and captured. Equivalency statement is included for Tipiracil	Need to be amended
Net contents (21 CFR 201.51(a))	Yes	Adequate
Lot number per 21 CFR 201.18	Yes	Adequate
Expiration date per 21 CFR 201.17	Yes	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Yes	Adequate
Storage (not required)	Yes	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Adequate
Name of manufacturer/distributor	Yes	Adequate
Others		

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion:** The deficiencies are identified, discussed with the DMEPA and P/T and communicated. The applicant accepts the proposal via amendment dated 28-MAY-2015 and revised the labels as advised. **Adequate**

**2) Cartons**



**QUALITY ASSESSMENT**  
**NDA # 207981**



(b) (4)



QUALITY ASSESSMENT  
NDA # 207981



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name of TPI has been modified and captured. Font size and prominence are acceptable.	Established name (TPI) needs to be amended
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The strengths have been modified and captured. Equivalency statement is included for Tipitacil	Needs to be amended
Net contents (21 CFR 201.51(a))	Yes	Adequate
Lot number per 21 CFR 201.18	Yes (Space is provided)	Adequate
Expiration date per 21 CFR 201.17	Yes (Space is provided)	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][ 201.10(a), 21CFR201.100(b)(5)(iii)]	Yes	Adequate
Sterility Information (if applicable)	N/A	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Yes	Adequate
Storage Conditions	Yes	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Adequate
Name of manufacturer/distributor	Yes	Adequate
“See package insert for dosage information” (21 CFR 201.55)	Yes	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	N/A	N/A
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	N/A	N/A

**Conclusion:** The deficiencies are identified, discussed with the DMEPA and P/T and communicated. The applicant accepts the proposal via amendment dated 28-MAY-2015 and revised the labels as advised. **Adequate**

## **II. List of Deficiencies**

- A. Drug Substance: awaiting response from Type II DMF
- B. Drug Product: None Pending
- C. Process/Facility
- D. Biopharmaceutics
- E. Microbiology
- F. Label/Labeling



**QUALITY ASSESSMENT  
NDA # 207981**



**III. Attachments**

A. Facility

B. Lifecycle Knowledge Management

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**



**QUALITY ASSESSMENT**  
**NDA # 207981**



<b>Assay, Stability</b>	<ul style="list-style-type: none"> <li>• Impurity formation (b) (4)</li> </ul>	L	Factors identified in CQA will not affect the assay or stability	Acceptable	(b) (4)
					Changes in formulation or process should be assessed according to relevant SUPAC
<b>Physical stability (solid state)</b>		L	Factors identified in CQA will not affect the physical stability	Acceptable	No comment
<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>	M	Adequate weight variation assay	Acceptable	(b) (4)
					Changes in formulation or process should be assessed according to relevant SUPAC
<b>Microbial limits</b>	<ul style="list-style-type: none"> <li>• Equipment, process environment</li> </ul>	L	Assessed during development	Acceptable	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
<b>Dissolution –</b>	<ul style="list-style-type: none"> <li>• API particle size</li> </ul>	L	Assessed	Acceptable	Changes in formulation or



**QUALITY ASSESSMENT**  
**NDA # 207981**



<b>BCS Class I &amp; III</b>	<p>(b) (4)</p> <ul style="list-style-type: none"><li>• Formulation</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipments<ul style="list-style-type: none"><li>• Site</li><li>• Size shape</li></ul></li></ul> <p>(b) (4)</p>		during development		process should be assessed according to relevant SUPAC Guidances for Post-Approval changes***
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\*Risk ranking applies to product attribute/CQA

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



(b) (4)

#### **IV. Administrative**

##### **A. Reviewer's Signature**

##### **B. Endorsement Block**

Reviewer Name/Date: [*Same date as draft review*]

Secondary Reviewer Name/Date:

Project Manager Name/Date:

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Michael Trehy**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** NAME, Methods Validation Requestor,

**CMC Reviewers:**

Erika E. Englund (drug substance)

Rajiv Agarwal (drug product)

E-mail Address: erika.englund@fda.hhs.gov, [rajiv.agarwal@fda.hhs.gov](mailto:rajiv.agarwal@fda.hhs.gov)

Phone: 301-796-2957 (Erika E. Englund); 301-796-1322 (Rajiv Agarwal);

NAME, Methods Validation Requestor:

**Branch Chiefs:**

Donna Christer, Ph.D. (DS)

Olen Stephens, PhD (DP)

Office of Pharmaceutical Quality (OPQ)

E-mail Address: donna.christner@fda.hhs.gov, [Olen.Stephens@fda.hhs.gov](mailto:Olen.Stephens@fda.hhs.gov)

301-796-1431 (Donna Christner); 301-796-3901 (Olen Stephens)

Fax.: (301)- 796-9745

**Through:** NAME, CMC Lead or Branch Chief (as appropriate):

Olen Stephens, PhD (Branch Chief and ATL)

Phone: (301)-796-3901

**And Youbang Liu**

ONDQA Methods Validation Project Manager

Phone: (301)-796-1926

**SUBJECT:** Methods Validation Request

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Application Number:	NDA 207981(DMF 28368 (for NME) and DMF (b) (4) (for non-NME))
Name of Product:	Lonsurf
Applicant:	Taiho
Applicant's Contact Person:	Julie Boisvert
Address:	202 Carnegie Center, Suite 100 Princeton, NJ
Telephone: (650) 467-8564	email: boisvert@taihopui.com

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Date NDA Received by CDER: **12/19/2014**

Date of Amendment(s) containing the MVP:

DATE of Request: **04/10/2015**

Requested Completion Date: **09/10/2015**

PDUFA User Fee Goal Date: **12/18/2015**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

**Format of Methods Validation Package (MVP)**

Paper  Electronic  Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

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MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 207981
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
List of samples (tablets 15 and 20 mg, DS, and impurities) to test the drug product	Varies based on the samples	3.2 R (Table 3.2.R.2.1)		
⇒ ITEM 2: <b>Contents of Attached Methods Validation Package</b>				Volume/Page Number(s)
Assay and related substances for Tipiracil (DMF 28368)				3.2.S.4.1
Assay and Related substance in the DP (15 and 20 mg)				3.2.P.5 (Table 3.2.5.2-1)
Other: Note: DS means drug substance, DP means drug product				
⇒ ITEM 3: <b>REQUESTED DETERMINATIONS</b> Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
N/A	Related Substances for Tipiracil (in DMF 28368)	3.2.S.4.1	0	DS impurities
N/A	Assay for Tipiracil (in DMF 28368)	3.2.S.4.1	0	Assay
N/A	Assay for FTD/TPI (15 and 20 mg)	3.2.P.5.2	0	Assay
N/A	Related Substances for FTD/TPI (15 and 20 mg)	3.2.P.5.2	0	Related substances
Additional Comments: <b>This NDA is assigned a standard review timeline. The CMC review of this NDA is not dependent on the result of the analytical method validation request.</b>				

## Methods Validation Request Criteria

MV Request Category	Description
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
<b>7</b>	Methods that are subject to a “for cause” reason

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJIV AGARWAL  
04/13/2015

OLEN M STEPHENS  
04/13/2015

YOUBANG LIU  
04/13/2015

**Application #: 207981      Submission Type: 505 (b)(1)**

**Established/Proper Name:**  
Trifluridine and Tipiracil  
Hydrochloride tablets

TAS-102/Lonsurf

**Applicant: Taiho  
Oncology, Inc.**

**Letter Date: 12/19/2014**

**Dosage Form: Tablet, Film-  
Coated**

**Chemical Type:**

**Stamp Date: 12/19/2014**

**Strength: 15/7.065 mg and  
20/9.420mg**

<b>A. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA

3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?	X	<ol style="list-style-type: none"> <li>1. Provide batch analysis for the drug substance batches used in the manufacture of supporting drug product batches.</li> <li>2. In the risk evaluation, you mention that Drug Substance (solubility in a range of pH values), amount of (b) (4) and packaging are low risk factors with regard to dissolution. The amount of (b) (4), (b) (4), on the other hand, are medium risk factors. Provide data to support the risk evaluation conclusions.</li> <li>3. The developmental parameters of the dissolution method have not been adequately justified. Provide experimental data to support the selection of the dissolution medium, pH, and agitation/rotation speed. In addition, comment on whether or not sink conditions are maintained for the duration of dissolution testing.</li> <li>4. The discriminating ability of the proposed dissolution method is not demonstrated Please submit experimental data to support the discriminating power of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target product and variant formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (b) (4)</li> </ol>
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B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
<b>Product Type</b>				
1.	New Molecular Entity <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product _____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	This is a combination product trifluridine and tipiracil hydrochloride
19.	Other _____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>- Applicant claims BCS Class III for both drug substances. This claim is used to justify the (b) (4)</p> <p>solubility and permeability, this is not a consideration for product design or manufacturing.</p> <p>- The formulations are dose proportional with the exception of the film coat coloring.</p> <p>- The drug product specifications include testing (b) (4)</p> <p>The drug substance reviewer should evaluate the DMF's to determine the source of these potential heavy metal impurities and determine if it is also controlled (b) (4) to the drug product.</p> <p>- The drug substances are covered by two new DMFs, 28368 (tipiracil hydrochloride) and (b) (4) (trifluridine)</p> <p>- Additional DMFs are referenced (b) (4)</p> <p>The applicant claims conformance to 21 CFR requirements for packaging components – the drug product reviewer will need to determine if the container closure DMFs need to be reviewed or if the information in the NDA is sufficient.</p> <p>- Note that the applicant has included bulk stability, in-use stability, (b) (4) and shipping stability data to support their plan to package the bulk tablets at a different site than the tablet manufacturing site.</p>

Regulatory Considerations					
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Trifluridine and Tipiracil are both approved.	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>- The tipiracil hydrochloride (TPI) drug substance has <sup>(b) (4)</sup> designated starting materials: <sup>(b) (4)</sup></p> <p><sup>(b) (4)</sup> Reference is made to IND #57,674, Meeting Minutes issued by FDA for EOP2 CMC Type B Meeting held on November 29, 2011; Serial No. 0217, Pre-NDA Briefing Package submitted on October 31, 2013, and Meeting Preliminary Comments received from FDA on November 27, 2013.</p> <p>- The FDA agreed to allow different drug substance specifications due to different supply chains for the same drug substance. Reference is made to IND #57,674, Meeting Minutes issued by FDA for EOP2 CMC Type B Meeting held on November 29, 2011.</p> <p>- 12 month stability updates on the drug product will be submitted within 30 days of NDA submission. Refer to pNDA comments 27-Nov-2013</p> <p>- Since all strength and count configurations of the drug product use the same container, the 20-count configuration (worst case) will be placed on annual stability studies for testing. (pNDA minutes 27-Nov-13).</p> <p>- In the EOP2 CMC Type B Meeting held on November 29, 2011, the biopharmaceutics team stated they would prefer a dissolution medium of 0.1 N HCl, which is what the applicant currently uses.</p>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None were noted in the NDA, however, the drug substance and drug product reviewer should determine the how alternate suppliers of the drug substances will be incorporated into the supply chain.	
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Quality Considerations					
26.	Drug Substance Coverage	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
35.	Non-compendial Analytical	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Assay, related substances
36.	Procedures and/or	Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

37.	specifications	Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
38.	Unique analytical methodology <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin		<input checked="" type="checkbox"/>	<input type="checkbox"/>	BSE/TSE compliance statements provided.
40.	Novel Excipients		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days		<input type="checkbox"/>	<input checked="" type="checkbox"/>	Shipping studies and bulk hold times are used to support the plan to manufacture the tablets <sup>(b) (4)</sup> and package in the US. However, these are not hold times as we typically define them.
43.	Genotoxic Impurities or Structural Alerts		<input checked="" type="checkbox"/>	<input type="checkbox"/>	However, the drug substances damage DNA as their primary mode of action.
44.	Continuous Manufacturing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (TVIVC, dissolution models for real time release).		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other		<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>FACILITY INFORMATION</b>					

**C. FILING CONSIDERATIONS**

3.	<p>Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Name of facility,</li> <li><input type="checkbox"/> Full address of facility including street, city, state, country</li> <li><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</li> <li><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</li> <li><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</li> <li><input type="checkbox"/> DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Is a manufacturing schedule provided?</li> <li><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

**DRUG SUBSTANCE INFORMATION**

5.	<p>For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture <ul style="list-style-type: none"> <li><input type="checkbox"/> Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li><input type="checkbox"/> Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li><input type="checkbox"/> Includes complete description of product lots and their uses during development – BLA only</li> </ul> </li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <li><input type="checkbox"/> Includes data to demonstrate comparability of product to be marketed to that used in</li> </ul> </li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Note that the drug substances are covered by DMF's primarily. These are new DMFs that have not been reviewed.</p>

**C. FILING CONSIDERATIONS**

- the clinical trials (when significant changes in manufacturing processes or facilities have occurred)
  - Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only
- reference standards or materials
- container closure system
- stability
  - Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment

**DRUG PRODUCT INFORMATION**

7. Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?
- Description and Composition of the Drug Product
  - Pharmaceutical Development
    - Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots
    - Includes complete description of product lots and their uses during development
  - Manufacture
    - If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?
  - Control of Excipients
  - Control of Drug Product
    - Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)
    - Includes data to demonstrate process consistency (i.e. data on process validation lots)
    - Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)
    - Analytical validation package for release test procedures, including dissolution
  - Reference Standards or Materials
  - Container Closure System
    - Include data outlined in container closure guidance document

### C. FILING CONSIDERATIONS

	<input type="checkbox"/> Stability <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION				
<b>BIOPHARMACEUTICS</b>					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> <li>• Does the application contain the complete BA/BE data?</li> <li>• Are the PK files in the correct format?</li> <li>• Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>REGIONAL INFORMATION AND APPENDICES</b>					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <li><input type="checkbox"/> facilities and equipment               <ul style="list-style-type: none"> <li>○ manufacturing flow; adjacent areas</li> <li>○ other products in facility</li> <li>○ equipment dedication, preparation, sterilization and storage</li> <li>○ procedures and design features to prevent contamination and cross-contamination</li> </ul> </li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**C. FILING CONSIDERATIONS**

	<input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <li>○ avoidance and control procedures</li> <li>○ cell line qualification</li> <li>○ other materials of biological origin</li> <li>○ viral testing of unprocessed bulk</li> <li>○ viral clearance studies</li> <li>○ testing at appropriate stages of production</li> </ul> <input type="checkbox"/> novel excipients				
17.	<p>Are the following information available for Biotech Products:</p> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <li>○ LAL instead of rabbit pyrogen</li> <li>○ Mycoplasma</li> </ul> <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>			X	

**OFFICE OF PHARMACEUTICAL QUALITY  
FILING REVIEW**

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	<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>	(b) (4)	Highly stable drug (1)	2	Release (1)	2
					Stability (3)	6
Physical stability (solid state)	<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>	(b) (4)	(b) (4)	BCS I/III (2)	4	24
Content uniformity	<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>	<ul style="list-style-type: none"> <li>• Low dose</li> <li>• Particle size/shape</li> <li>• Segregation</li> <li>• Flow property</li> </ul>	(b) (4)	3	4	36
Microbial limits	<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>	<ul style="list-style-type: none"> <li>• Equipment, process environment</li> </ul>	1	2	Release with spec (3)	6

**OFFICE OF PHARMACEUTICAL QUALITY  
FILING REVIEW**

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
<p>Dissolution – BCS Class I &amp; III</p>	<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>	<ul style="list-style-type: none"> <li>• API particle size</li> <li>• Size shape</li> </ul>	<p align="center">3</p>	<p align="center">2</p>	<p align="center">2</p>	<p align="center">12</p>

(b) (4)