CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208169Orig1s000

CHEMISTRY REVIEW(S)

NDA 208169
Review #1, Addendum
Review Date: Sept. 4, 2015

Drug Name/Dosage Form	Xuriden (uridine triacetate) oral granules
Strength	2g and (b) (4) packets (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Wellstat Therapeutics Corporation
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/IABII

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ASSESSMENT OF THE FACILITIES

This is an addendum to the **Overall Quality Assessment** for NDA 208169 that was filed in the Panorama review platform on **June 24, 2015**. This addendum provides an updated and final assessment of the Drug Product Manufacturing facility (see: ***Question #31, Overall Quality Assessment***) as well as a final Overall Facility Review Assessment. The Drug Substance facilities evaluation (see: ***Question #30, Overall Quality Assessment***) was documented in the June 24, 2015 review and since it was complete, is not reproduced here.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

31. 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	Initial Risks Identified	Current status	Final Recommendation
(b) (4)		**POW** - DP manufacturing, (b) (4) packaging & labeling, (b) (4)	(b) (4)		**Acceptable based on inspectional results, PMC, and RAI follow-up**

Reviewer's Assessment:

Initial facility Risk Assessment for the site involved in drug product manufacturing:

(b) (4)

Conclusions

(b) (4)

[redacted]

Post Marketing Commitment:

a) Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.

b) Determine the particle size distribution of the final drug product and, using the updated dissolution method, evaluate the impact of the particle size distribution on dissolution. The studies should also include an evaluation of batches submitted in the application (e.g., W017891, W017893, W017895, W012785, and W021129). Based on findings from these studies, update the final drug product particle size specification and the in-process controls.

(b) (4)

[redacted]

The RAI and the exact language sent to the firm can be found in CMS Case [redacted]

Because these deficiencies are not significant enough to withhold the application, the [redacted] inspection will be classified initial VAI and acceptable for this submission. The compliance evaluation will not be closed until the firm adequately responds to the RAI items.

Based on the discussions described herein, the PMC, and RAI items, **this facility is acceptable for NDA 208169.**

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Acceptable

This overall assessment is based on information provided in the application, inspectional history, data collected during pre-approval inspections, and discussion with the clinical team about the criticality of observed quality attributes. Given the low risk to patients, variability in the drug product will be corrected via the agreed upon Post-Marketing Commitments with the Application and five RAI items sent to [redacted] (b) (4) At this time, there are no significant, outstanding manufacturing risks that prevent approval of this application; therefore, the manufacturing facilities for [redacted] (b) (4) are found to be acceptable.

1) **The Following PMC were agreed to by the Applicant on Sept 1, 2015:**

   a) Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.
   b) **Determine the particle size distribution of the final drug product and, using the updated dissolution method, evaluate the impact of the particle size distribution on dissolution. The studies should also include an evaluation of batches submitted in the application (e.g., W017891, W017893, W017895, W012785, and W021129). Based on findings from these studies, update the final drug product particle size specification and the in-process controls.**

   Final Protocol Submission: September 2015
   Study Completion: February 2016
   Final Report Submission: March 2016

2) **A five item Request for Additional Information was sent to [redacted] (b) (4) The response due date is Sept 25, 3015.**

3) **A post-approval inspection of [redacted] (b) (4) to cover drug substance manufacturing for [redacted] (b) (4) is recommended.** See the IQA

review dated June 24, 2015 for more details.

Christina A. Capacci-daniel -S

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Christina Capacci-Daniel, PhD
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Supervisor Comments and Concurrence:

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Concur, Mahesh Ramanadham, PharmD – 9/4/15
Acting Branch Chief, OPF/DIA/IABII

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
API manufacturing; (b) (4)	(b) (4)	(b) (4)	(b) (4)	**Acceptable based on inspectional history** Post-approval coverage recommended
(b) (4)	Limited (b) (4)			**Acceptable based on inspectional history**
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
(b) (4) manufacturing, (b) (4), packaging & labeling, (b) (4)	(b) (4) (b) (4)	(b) (4)	(b) (4)	**Acceptable based on inspectional results, PMC, and RAI follow-up**

Recommendation:

This 505(b)(1) **NME** application is ***not*** deemed ready for **Approval** at this time in its present form, per 314.125(b)(6),(13).

NDA 208169
Review # 1
Review Date 06/22/2015

Drug Name/Dosage Form	Xuriden (uridine triacetate) oral granules
Strength	2g and (b) (4) packets (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Wellstat Therapeutics Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	01/08/2015
Amendment	01/21/2015
Amendment	01/23/2015
Amendment	02/12/2015
Amendment	04/03/2015
Amendment	04/10/2015
Amendment	04/22/2015
Amendment	04/28/2015
Amendment	05/04/2015
Amendment	05/11/2015
Amendment	05/22/2015
Amendment	05/29/2015
Amendment	06/01/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern	ONDP/DNDAPI/Branch II
Drug Product	Hamid R. Shafiei	ONDP/DIV II/Branch V
Process	Jean Tang	OPF/DPAII/BranchV
Microbiology	Jean Tang	OPF/DPAII/BranchV
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/IABII
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Drug Product Performance	Arzu Selen	OTR/IO
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Laboratory (OTR)	Michael E. Hadwiger	OTR
ORA Lead		
Environmental Assessment (EA)	Raanan A. Bloom	ONDP/IO

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Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505 (b)(2)**

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	Nov 10, 2011*	Adequate, Andrew B. Yu, Ph.D.
	Type III			N/A	Dec 29, 2014*	Adequate, Elise T Luong, Ph.D.
	Type II			(b) (4)	Aug 5, 1997**	Pardhasara Komanduri
	Type II					(b) (4)
	Type II					

[1] 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)
*All submission since the review date are LOAs, annual reports, or additional stability reports as appropriate.

(b) (4)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA		(b) (4)

3. **CONSULTS: N/A**

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This applicant has ***not*** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has ***not*** made a final "Acceptable" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The labels/labeling issues have ***not*** been completely resolved as of this review.

Therefore, from the ONDP perspective, this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(1)(6) & (13), until the above issues are satisfactorily resolved (see the List of Deficiencies on p. 116).

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

N/A

II. Summary of Quality Assessments

The proposed drug product, Xuriden™ (uridine triacetate) oral granules is intended for uridine replacement [redacted] (b) (4) of hereditary orotic aciduria.

Granules dosage form provides dosing flexibility and enables the dosing of pediatric patients for whom the dosage is adjusted based patient's weight.

Although granules are coated [redacted] the applicant has suggested that mixing of the granules with soft foods such as applesauce, [redacted] pudding, and yogurt as dosing vehicles will further facilitate the oral administration of the drug product to pediatric patients. The applicant has also suggested that the granules can be mixed with milk, infant formula, or [redacted] as dosing vehicles [redacted]. The information provided in the application supports the use of all proposed dosing vehicles.

Performance and appropriateness of uridine triacetate granules for dosing of young pediatric patients have been reviewed by Dr. Arzu Selen (Associate Director OPQ/OTR/IO). Dr. Selen has raised concerns about the drug product and whether this drug product can be successfully administered to pediatric patients under 12 years of age. Her concerns have been discussed with the clinical team and will be further discussed with the applicant during late-cycle communication and may be delineated as a post-approval commitment.

Xuriden™ (uridine triacetate) oral granules [redacted] the applicant intends to market this product in [redacted] 2g packets after the approval of this application. The information and postapproval commitments provided in this application adequately support the future marketing of 2g packets.

A. Drug Substance, Uradine Triacetate Quality Summary

Uridine triacetate,

[redacted]

is white to off-white solid [redacted].

[redacted]

(b) (4)

In conclusion, the drug substance, uridine triacetate is manufactured using a well-established well-characterized starting material, (b) (4) and the manufacturing process is controlled through appropriate strategies that allow for production of API with consistent quality batch to batch. This API is tested and released according to an API specification that clearly assures the identity, strength, purity and quality of this new molecular entity. The stability results provided from the batches of API produced to date support the proposed (b) (4) retest date for this drug substance.

B. Drug Product, Uradine Triacetate Oral Granules Quality Summary

The drug product, Xuriden™ (uridine triacetate) oral granules is indicated for uridine replacement (b) (4) with hereditary orotic aciduria.

During the pharmaceutical development, (b) (4)
(b) (4)

Xuriden™ is white to off white granules packaged (b) (4) uridine triacetate in (b) (4) sachet (packet). (b) (4) applicant intends to manufacture and market 2g sachets after the approval of this application. Adequate information and post-marketing commitments are provided to allow for marketing of 2g sachets.

This drug product contains 95 (b) (4) % uridine triacetate as the active ingredient and (b) (4) Opardy (b) (4) Clear (b) (4) natural orange juice flavor S.D. #80618 (b) (4) as the excipients. The total amount of excipients used in this drug product is (b) (4) and are used only as (b) (4)
(b) (4)
All excipients are appropriately tested Xuriden™.

The drug product release specification includes testing and acceptance criteria for appearance (b) (4)

(b) (4)

The proposed dissolution method (b) (4) the applicant has agreed to develop and validate a new dissolution method (see the Biopharm section below). Therefore, the proposed drug product specification is deemed adequate to assure identity, strength, purity, and quality of the drug product.

The applicant provided 6-month accelerated and 12-month long term stability results from three registration batches and 31-month long-term stability results from a (b) (4) in support of the proposed 24-month expiration dating period. Based on the review of the stability data, the proposed expiration period of 24 months is granted.

C. Manufacturing Process

(b) (4)

(b) (4)

Based on the information submitted in the application, it is concluded that the proposed commercial manufacturing process and process controls are satisfactory and will provide the ability to manufacture this drug product with consistent quality for commercialization.

D. Biopharmaceutics

Unridine triacetate oral granules have been classified by the applicant as an immediate release drug product. (b) (4)

(b) (4)

(b) (4)

[redacted] In a Telcon with the applicant on May 22, [redacted] he agency recommended that the interim dissolution acceptance criteria to NLT [redacted] in 15 minute and Q = [redacted] in 45 minutes. The applicant submitted and amendment on June 1, 2015 and accepted the postapproval commitment required by the Agency. The amendment also include an updated drug product specification that includes the tightened interim dissolution acceptance criteria.

E. Facilities

[redacted]

F. Environmental Assessment

The applicant claimed for the exclusion from the Environmental Assessment which is granted.

G. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xuriden oral granules
Non Proprietary Name of the Drug Substance	Uridine triacetate
Proposed Indication(s) including Intended Patient Population	Uridine replacement [redacted] with hereditary orotic aciduria
Duration of Treatment	Life-time
Maximum Daily Dose	Dosage depends on patient's weight
Alternative Methods of Administration	N/A

[redacted]

Hamid Shafiei, Ph.D.
Application Technical Lead
ONDP, Branch V, Division II

Hamid Shafiei -S

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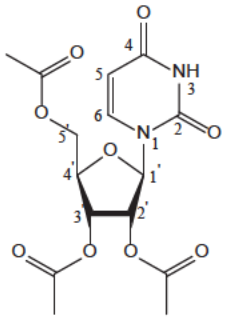
Primary Quality Review

Assessment of the Drug Substance

2.3.S Drug Substance [Uridine Triacetate]

2.3.S.1 General Information

General information on the drug substance Uridine Triacetate (nomenclature, molecular formula and molecular weight, and chemical structure) is summarized in Table S.1-1.

Table S.1-1.	**Uridine Triacetate Drug Substance General Information**
USAN / INN Name:	Uridine triacetate
Proprietary Name:	Xuriden™ (conditional)
Company Code:	PN401
CAS Registry # :	4105-38-8
Chemical Name(s):	
(IUPAC)	[(2*R*,3*R*,4*R*,5*R*)-3 (b) (4) -(2,4-dioxopyrimidin-1-yl)-oxolan-2-yl]methyl acetate
(Chemical Abstracts)	1-(2',3',5'-tri-*O*-acetyl-ß-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione
(Common Names)	Uridine 2',3',5'-triacetate Triacetyluridine 2',3',5'-Triacetyluridine
Molecular Formula:	$C_{15}H_{18}N_2O_9$
Molecular Weight:	370.31 g/mole
Structure: *(numbering as per the Chemical Abstract Service)*	

The drug substance uridine triacetate, (b) (4) is a white to off-white solid. (b) (4) As indicated in Table S.1-2, (b) (4) (b) (4) (b) (4)

Table S.1-2. Solubility Estimates of Uridine Triacetate at 20 °C

Solvent	*Solubility range (mg/mL)*	*USP Solubility Category*
acetone	105-210	Freely Soluble
acetonitrile	> 200.7	Freely Soluble
anisole	< 22.8	Sparingly Soluble
benzyl alcohol	~ 21.8	Sparingly Soluble
t-butanol	< 19.8	Sparingly Soluble
butyl acetate	< 23.5	Sparingly Soluble
chlorobenzene	< 23.0	Sparingly Soluble
chloroform	74.3-111.5	Soluble to Freely Soluble
cumene	< 26.0	Sparingly Soluble
cyclohexane	< 22.9	Sparingly Soluble
dichloromethane	106.5-213.0	Freely Soluble
diethyl ether	< 23.3	Sparingly Soluble
diisopropyl ether	< 25.8	Sparingly Soluble
dimethoxyethane	45.2-56.5	Soluble
Dimethylacetamide (DMA)	145.3-218.0	Freely Soluble
Dimethylsulfoxide (DMSO)	154.7-232.0	Freely Soluble
dioxane	90.8-113.5	Soluble to Freely Soluble
ethanol	< 23.4	Sparingly Soluble
ethyl acetate	~ 22.5	Sparingly Soluble
formamide	53.8-71.7	Soluble
heptane	< 22.3	Sparingly Soluble
hexafluoro *iso*-propanol	153.3-230.0	Freely Soluble
methanol	33.8-36.7	Soluble
methyl ethyl ketone (MEK)	26.4-29.8	Sparingly Soluble
methyl *i*-butyl ketone	< 21.9	Sparingly Soluble
methyl *t*-butyl ether (MTBE)	< 22.3	Sparingly Soluble
N-methyl pyrrolidine	> 231.0	Freely Soluble
methyl-THF	~ 22.4	Sparingly Soluble
nitromethane	158.0-237.0	Freely Soluble
pentan-1-ol	< 23.6	Sparingly Soluble
1,2-propanediol	< 19.2	Sparingly Soluble
nitromethane	158.0-237.0	Freely Soluble
pentan-1-ol	< 23.6	Sparingly Soluble
1,2-propanediol	< 19.2	Sparingly Soluble
2-propanol	<23.6	Sparingly Soluble
sulfolane	~21.0	Sparingly Soluble
Tetrahydrofuran (THF)	83.7-125.5	Soluble to Freely Soluble
toluene	< 23.8	Sparingly Soluble
trifluoroethanol	153.3-230.0	Freely Soluble
xylene	< 24.8	Sparingly Soluble
ethanol:water (3.6 % v/v)	< 24.5	Sparingly Soluble
2-propanol:water	< 22.4	Sparingly Soluble
MEK:water (9.1% v/v)	~ 23.5	Sparingly Soluble
MTBE:water (2.2 % v/v)	< 25.8	Sparingly Soluble
Water, 25 °C	12[a]	Sparingly Soluble
Water, 25 °C, pH = 7	7.7[a]	Slightly Soluble
Water, 25 °C	24.5[b]	Sparingly Soluble
Water, 25 °C	~ 4[c]	Slightly Soluble

USP Solubility Classification	Part of Solvent required for 1 Part of Solute	Conversion to mg Solute to mL Solvent
Very Soluble	Less than 1	More than 1000
Freely Soluble	From 1 to 10	From 1000 to 100
Soluble	From 10 to 30	From 100 to 33.33
Sparingly Soluble	From 30 to 100	From 33.33 to 10
Slightly Soluble	From 100 to 1,000	From 10 to 1
Very Slightly Soluble	From 1,000 to 10,000	From 1 to 0 1
Practically Insoluble or Insoluble	Greater than or equal to 10,000	Less than or equal to 0 1

(b) (4)

Table S.1-3. Main Physicochemical Properties of Uridine Triacetate Drug Substance

Property	*Description*
Appearance:	Uridine triacetate is a white to off-white solid.
Melting Point:	(b) (4)
pKa:	
pH:	
Specific Rotation:	
Solid-State Characterization:	
Polymorphs:	
Aqueous Solubility	(b) (4)

[a] Uridine triacetate is a neutral molecule with no ionizable functional groups; therefore, as shown below, neither the solubility nor the partition coefficient between octanol and water are affected by changes in pH.

Reviewer's Assessment: Adequate information on the main physicochemical properties of Uridine Triacetate Drug Substance has been provided by the Applicant (Applicant's Sections 3.2.S.1.3 General Properties and 3.2.S.3.1 Elucidation of the Structure and Other Characteristics).

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?***

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: The commercial manufacturing process is adequately described. Its adequacy to ensure consistent manufacturing of acceptable drug substance batches is fully supported by the release and stability data.

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?***

   N.A. *[There are no online/in line technologies proposed for routine commercial production.]*

Reviewer's Assessment: Not Applicable.

Control of Critical Steps and Intermediates

(b) (4)

[redacted]

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(b) (4)

[redacted]

Xavier J. Ysern -S

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OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
Sufficient and adequate information on the drug substance has been provided by the Applicant. The quality of the described drug substance is deemed acceptable to support its use in the manufacture of the proposed drug product.

Supervisor Comments and Concurrence:

I concur with Dr. Xavier Ysern's assessment of the adequacy of the drug substance.

Donna F. Christner, Ph.D.
Branch Chief (Acting)
DNDP/DNDAPI/Branch II

Donna F. Christner -S

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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?*

To be marketed composition of the drug product, Xuriden™ (uridine triacetate) oral granules is provided in Table 1.This drug product has been developed for uridine replacement therapy in pediatric patients with hereditary orotic aciduria. To provide dosing flexibility and to facilitate dosing of pediatric patients for whom the dosage is adjusted based patient's weight, this drug product was formulated as coated oral granules and is offered in (b) (4). The granules coating (b) (4) (b) (4) the applicant intends to offer this drug product in a (b) (4) 2g sachet packaging configuration, after approval of this application. (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment:

- All excipients used in this drug product [redacted]
- Two non-compendial excipients are used in the formulation /composition of this drug product. Opadry® [redacted] Clear and Natural Orange Juice flavor, S.D. #80618.
- Opadry® [redacted] Clear is supplied [redacted] of Hypromellose (HPMC) [redacted] Macrogol [redacted] The components used in the composition of this excipient are compendial [redacted] This excipient is accepted based on the certificate of analysis from the manufacturer. Detailed information regarding the manufacture, release, and stability of this excipient is provided in [redacted] has been reviewed by Elise T. Luong on 12/26/2014 and found to be adequate.
- Natural Orange Juice Flavor S.D. #80618 [redacted] Therefore, from the CMC perspective the use of Natural Orange Juice Flavor S.D. #80618 [redacted] excipient is acceptable.

Conclusion:
The excipients [redacted] used in the formulation of drug product are well established excipients and are considered safe from the CMC perspective. Therefore, the proposed drug product composition is deemed **satisfactory**.

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?*

- Uridine triacetate granules were developed for [redacted] indications including treatment of pediatric patients with hereditary orotic aciduria and as an antidote to 5-fluorouracil overexposure in cancer patients. [redacted]

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accelerated and long-term stability from 3 registration batches of the drug product.

Reviewer's Assessment:

- The proposed final drug product composition / formulation as well as the compatibility of excipient with the API and the compatibility of the packaging material with the final drug product were demonstrated by the applicant's pharmaceutical development work and have been further confirmed by results from supporting accelerated and long-term stability studies. Based information provided in this section of this NDA, it can be concluded that the intended drug product (b) (4) and the targeted flexibility to adjust dosage for the treatment pediatric patient and infants have been appropriately addressed by the selected drug product formulation and dosage form.
- (b) (4)

Conclusion:
The proposed formulation is **satisfactory**.

2.3.P.4 Control of Excipients

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

- (b) (4)

- The total amount of excipients used in this drug product (b) (4)
- All excipients used in this drug product (b) (4)
- There are (b) (4) excipients; Opadry (b) (4) Clear and Natural Orange Juice flavor, S.D. #80618 are listed in product composition table as non-compendial excipients. The components used in the manufacture of Opadry (b) (4) Clear are all compendial and this excipient is used in other solid dosage drug products currently marketed. The information regarding the manufacture Opadry® (b) (4) Clear (b) (4). DMF (b) (4) has been reviewed by Elise T. Luong on 12/26/2014 and found to be adequate. (b) (4)

(b) (4)

- The excipient, Natural Orange Juice flavor, S.D. #80618 (b) (4) he amount of this excipient used in the formulation of this drug product is (b) (4) (b) (4)

[redacted] Natural Orange Juice flavor, S.D. #80618 is provided in Table 3.

Table 3: Wellstat testing and acceptance specification for Natural Orange Juice flavor, S.D. #80618

[redacted]

- All compendial excipients are tested and accepted according the compendial requirements. Opadry® [redacted] Clear [redacted] This DMF has been reviewed and found to be adequate. Natural Orange Juice flavor, S.D. #80618 is tested and accepted using compendial procedures.

Reviewer's Assessment:

- The amount excipients [redacted]

[redacted]

(b) (4)

Conclusion:
Based on the information provided, it is concluded that the proposed excipients are compatible with the drug substance and are adequately tested and accepted before use. Therefore, the proposed excipients are deemed **appropriate**.

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*

The specification for the testing and release of the drug product, uridine triacetate oral granules are provided in Table 4. The specification includes testing and acceptance criteria for appearance, identification, assay, related substances (impurities), uniformity of dosage unit, dissolution, moisture content, bioburden, and particle size.

(b) (4)

Table 4: Specification for testing and release of the drug product, uridine triacetate granules – continued

(b) (4)

[redacted]

Reviewer's Assessment:

- The proposed acceptance criteria in the specification for the release testing of the drug product, uridine triacetate granules, are set based on the results from pharmaceutical and manufacturing process development as well as the results from release and stability testing of batches of drug product manufactured to date. The acceptance criteria in the specification are also consistent with ICH Q3B guidelines. (b) (4) (b) (4) [redacted] ill be reviewed and qualified by the Pharm/Tox reviewer, Dr. Sruthi King. The dissolution rate and classification of the drug product as an immediate release will be assessed and determined by CMC Biopharm reviewer, Dr. Salaheldin Hamed. (b) (4) will also be reviewed and assessed by CMC Microbiology reviewer, Dr. Jean Tang.
- In summary, solely from the CMC drug product review perspective, the proposed specification for release testing of the drug product is considered adequate to assure, identity, strength, purity, and quality of the drug product, uridine triacetate granules.

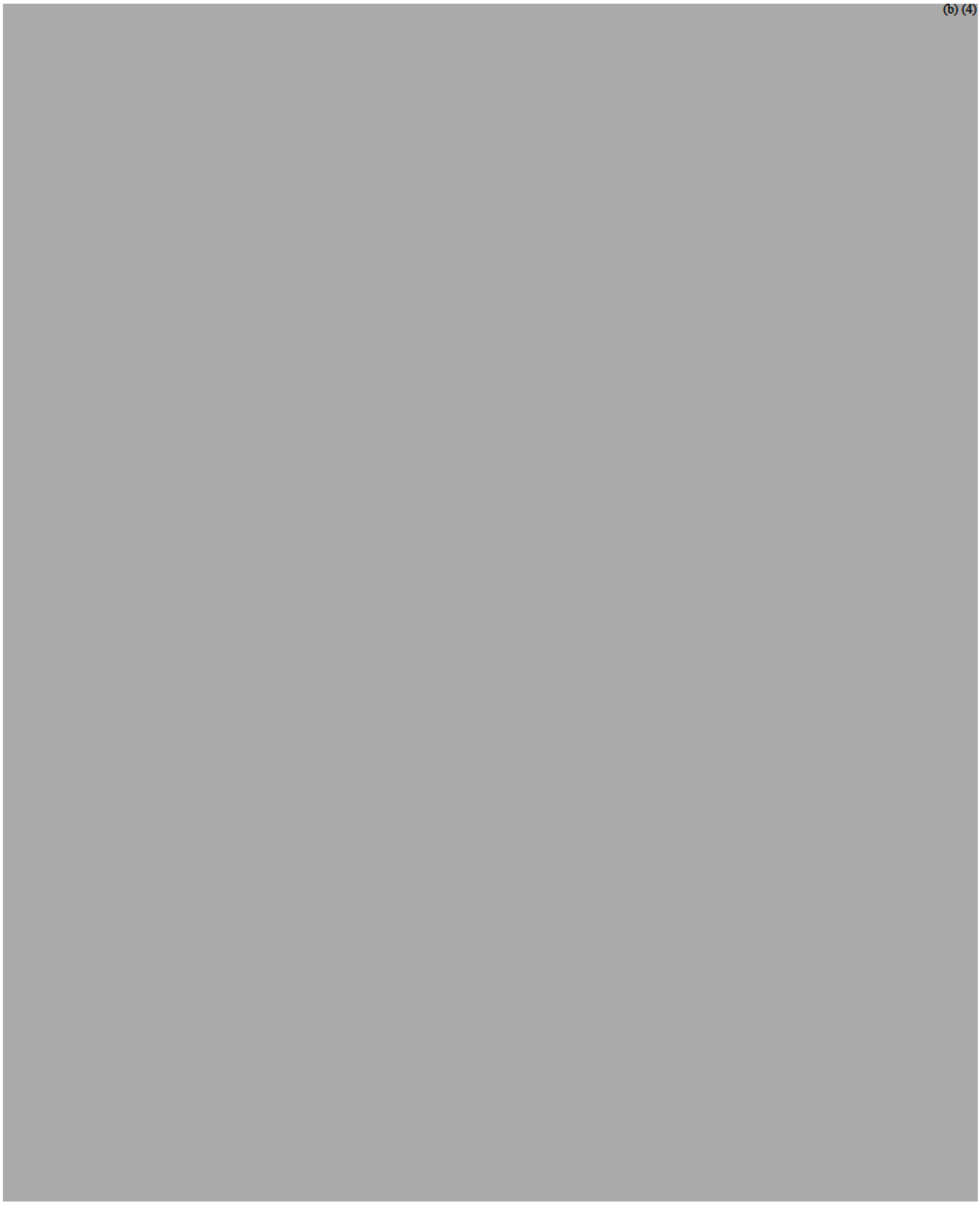
Conclusion:
Based on the ONDP assessment, the proposed drug product specification is **satisfactory**.

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

(b) (4)

(b) (4)

(b) (4)



Reviewer's Assessment:

- The method for the identification and determination of assay and related substances has been demonstrated to be a stability indicating method with adequate selectivity and specificity. This analytical method has also been proven

(b) (4)

- Other methods that are also considered important for the determination of the quality of drug product are methods for determination of uniformity of the dosage unit, determination (b) (4) dissolution, and bioburden.
- The adequacy of proposed methods for the determination of the dissolution and bioburden are reviewed and determined by the CMC Biopharm Dr. Salaheldin Hamed and CMC Microbiology reviewers, Dr. Jean Tang, respectively.
- The method for the determinatio (b) (4)
- (b) (4)

(b) (4)

Conclusion:

Based on the ONDP assessment, it is determined that the proposed analytical methods are **adequate** for determination of identity, strength, purity, and quality of the drug product.

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?*

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

Reviewer's Assessment:

Refer to the response to question 28.

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?*

- Xuriden (uridine triacetate) oral granule [redacted] The applicant intends to manufacture and commercialize this drug product in a [redacted] 2g sachet after approval of this application. The applicant has declared that the packaging materials that will be used for packaging of the 2g sachets [redacted].
- The proposed secondary packaging for the uridine triacetate granules is cartons that hold [redacted] thirty 2g sachets.
- [redacted]
- The applicant has also expressed that the drug product is a solid dosage form [redacted] extractable is not required.
- The specifications, certificate of analyses, and statement of compliance from the manufacturers of packaging components are provided but for brevity is not copied into this review document.

Reviewer's Assessment:

[redacted]

(b) (4) The use of the proposed container closure for packaging of the drug product, uridine triacetate granules is also supported by the results from the long-term and accelerated stability studies.

Conclusion:
The proposed container closure is deemed **satisfactory**.

2.3.P.6 Reference Standards or Materials

23. *Are the proposed drug product reference standards acceptable?*

(b) (4)

Reviewer's Assessment:

The information regarding the batch of drug substance proposed as the reference standard for identification, assay testing of the drug product, uridine triacetate granules has been reviewed by Dr. Javier Ysern during the review of the drug substance section of this application. The proposed reference standard has been found to be adequate. Uridine reference standard was obtained from the USP (b) (4) . The retention time markers were also reviewed by the drug substance reviewer and were found to be fit for their intended purpose.

Conclusion:
The proposed reference standards are deemed **satisfactory**.

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?*

(b) (4)

(b) (4)

(b) (4)

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Reviewer's Assessment:

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Conclusion:

The stability data **adequately support the proposed 24-month expiration dating period** for the drug product packaged in the proposed packaging configuration and stored at 25°C (77°F), "excursions permitted to 15° to 30 °C (59° to 86°F)".

R.2 Comparability Protocols

25. *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?*

- After the approval of this application, the applicant intends to produce and market the drug product in smaller 2g sachets. The applicant has declared that the drug product composition and packaging materials used in the manufacture of 2g sachets (b) (4)

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment:

(b) (4)

[redacted]

Conclusion:

The comparability protocol is deemed **adequate.**

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The drug product, Xuriden™ (uridine triacetate) oral granules has been developed as uridine replacement therapy for pediatric patients with hereditary orotic aciduria. The granules contain >95% uridine triacetate as the active ingredient and (b) (4) excipients. The applicant has provided adequate information to justify the use of each excipient in the drug product composition.

(b) (4)

[redacted]

(b) (4)

[redacted]

pudding, yogurt, applesauce, milk, and infant formula for dosing of infants and young pediatric patients. The applicant has provided supporting stability data and related information that clearly justify the use of the recommended soft foods as dosing vehicles.

The drug product is white to off-white granules (b) (4) . The applicant intends (b) (4) market a smaller 2g drug product sachet after the approval of this application. The information provided in the comparability protocol adequately demonstrate that the drug product to be offered as 2g sachets (b) (4)
The applicant has also provided a certificate of analysis and 6-month accelerated and long-term stability results from testing of a single batch of drug product manufactured as 2g sachets as additional supporting information.

The proposed release and stability specifications are adequate to assure, identity, strength, purity, and quality of the drug product.

The applicant has provided (b) (4) in support of the proposed expiration dating period of 24 months. Based on the review of the stability data, the expiration dating period of 24 months is granted.

In conclusion, the applicant of this new drug application has provided sufficient information to assure identity, strength, purity, and quality of the drug product Xuriden (uridine triacetate) oral granules offered in 2g (b) (4) sachets.

Therefore, from the drug product perspective, this new drug application is recommended for APPROVAL with 24-month of expiration dating period.

Hamid Shafiei, Ph.D.
Branch V/DNDP II

Hamid Shafiei -S

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Supervisor Comments and Concurrence:
Xuriden (uridine triacetate) oral granules, 2g in a sachet is proposed as uridine replacement therapy for pediatric patients with hereditary orotic aciduria. These patients cannot produce uridine due to lack of uridine monophosphate synthetase, thereby blocking conversion of orotic acid into uridine monophosphate. The drug product is formulated as granules (b) (4) The drug product can be safely mixed with soft foods for pediatric patients.

I concur with Dr. Hamid Shafiei's assessment on the adequacy of the proposed drug product and his overall recommendation for approval of this application for the treatment of the subject patients from his drug product perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V/DNDP II/ONDP

Moojhong Rhee -S

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Batch Formula

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

The following table is the representative batch formula of the one of the stability registration batch (lot#: W017891).

(b) (4)

(b) (4)

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(b) (4)

Reviewer's Assessment: Adequate

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

Reviewer's Assessment: Adequate

This drug product is a solid oral dosage form. The microbial limits test is performed in both release and stability studies followed USP and EU methods. The specification meets the requirements of both EP 5.1.4 and USP <1111> for nonaqueous preparations for oral use. There have been no issues passing these criteria on release or during stability studies. It is considered to be adequate for the microbial control.

R.2 Comparability Protocols

29. 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?

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ASSESSMENT OF MICROBIOLOGY

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

Refer to Q29

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

Reviewer's Assessment: Adequate

Refer to Q.29

2.3.P.6 Reference Standards or Materials

34. 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?

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

Reviewer's Assessment: N/A for the solid dosage form

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

1. 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 virus or prion contamination (causative agent of TSE)?

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

Reviewer's Assessment: N/A for the solid dosage form

2. 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 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: N/A for the solid dosage form

Refer to Manufacturing Process Review Section.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Refer to Manufacturing Process Review Section.

Supervisor Comments and Concurrence:

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

36. Is the applicant's claim for categorical exclusion acceptable?

Applicant's Response: NA

Reviewer's Assessment:

The applicant has submitted a claim for categorical exclusion for Xuriden (uridine triacetate). Uridine is one of the five standard nucleosides which make up nucleic acids. The applicant has cited the exclusion listed at 21 CFR 25.31(b) and provides a statement of" no extraordinary circumstances." (b) (4) In response to the new draft guidance, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (FDA 2015), the drug substances were reviewed for any signals of estrogenic, androgenic, or thyroid activity. No signals were found. No "extraordinary circumstances" are indicated for this application. The cited categorical exclusion (21 CFR 25.31(b)) is appropriate for the application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The cited categorical exclusion (21 CFR 25.31(b)) is appropriate for this application. No "extraordinary circumstances" are indicated. The claim for categorical exclusion is acceptable.

Raanan A. Bloom Ph.D.
Reviewer, ONDP/EA Team

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Date: 2015.06.23 08:35:23 -04'00'

Secondary Review Comments and Concurrence:

I Concur.

Scott Furness, Ph.D.

Ramesh K. Sood -S
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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

a) "Highlights" Section (21CFR 201.57(a))

These highlights do not include all the information needed to use XURIDEN safely and effectively. See full prescribing information for XURIDEN.

XURIDEN™ (uridine triacetate) oral granules
Initial U.S. Approval: (b) (4)

DOSAGE FORMS AND STRENGTHS --
• Oral granules: 2 gram (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Xuriden™ (uridine triacetate) oral granules	Proprietary name and established name is provided. Satisfactory
Dosage form, route of administration	oral granules	Dosage form, route of administration provided. Satisfactory
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Oral granules: 2 gram (b) (4) packets	The dosage forms and strengths are described correctly. Satisfactory

Conclusion: The highlights section of the PI is adequate.

(b) "Full Prescribing Information" Section

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

Oral granules: 2 grams or 10 grams of orange-flavored oral granules (95% w/w) in single-use packets

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral granules	Satisfactory
Strengths: in metric system	2 grams or (b) (4) in single-use packet	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not applicable	Not applicable

Conclusion: The Dosage Forms and Strengths Section of the PI is Adequate

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

XURIDEN (uridine triacetate) oral granules is a uridine replacement (b) (4) Uridine triacetate has the chemical designation (2',3',5' tri O acetyl ß D-ribofuranosyl) 2,4(1H,3H) pyrimidinedione. The molecular weight is 370.3 and it has an empirical formula of $C_{15}H_{18}N_2O_9$.

Each single-use 2 gram packet of XURIDEN orange flavored oral granules (95% w/w) contains 2 grams of uridine triacetate and the following inactive ingredients: ethylcellulose (0.062 grams), Opadry Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.015 grams), and natural orange juice flavor (0.026 grams).

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	XURIDEN (uridine triacetate) oral granules	Proprietary name and established name is described correctly. Satisfactory
Dosage form and route of administration	orange flavored oral granules	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each single-use 2 gram packet of XURIDEN orange flavored oral granules contains 2 grams of uridine triacetate (b) (4)	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each single-use 2 gram packet of XURIDEN orange flavored oral granules contains the following inactive ingredients: ethylcellulose (0.062 grams), Opadry Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.015 grams), and natural orange juice flavor (0.026 grams). (b) (4)	Information for inactive ingredients is provided correctly. Satisfactory
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight	Chemical Name: (2',3',5' tri O acetyl ß D-ribofuranosyl) 2,4(1H,3H) pyrimidinedione. Molecular weight: 370.3 Empirical formula: $C_{15}H_{18}N_2O_9$	Molecular structure is not provided. Unsatisfactory
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not applicable	Not applicable

Conclusion: The information provided in the description section of PI is incomplete. The applicant should add the molecular structure to this section of PI.

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

XURIDEN orange-flavored oral granules (95% w/w) are available in single-use packets containing 2 grams of uridine triacetate in cartons of 30 packets each (NDC 69468-XXXX-30) or [redacted] (b) (4)

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	single-use packets containing 2 grams of uridine triacetate or [redacted] (b) (4)	Satisfactory
Available units (e.g., bottles of 100 tablets)	available in single-use packets containing 2 grams of triacetate in cartons of 30 packets each or [redacted] (b) (4)	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(NDC 69468-XXXX-30) [redacted] (b) (4))	Satisfactory
Special handling (e.g., protect from light, do not freeze)	Not applicable	Not applicable
Storage conditions	Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F)	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured and distributed by Wellstat Therapeutics Corporation Gaithersburg, MD 20878	Satisfactory

Conclusion: The information provided in sections 16 and 17 of the PI is adequate.

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The following strengths are provided on sachets (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). Each single-use packet contains 2 g of uridine triacetate or (b) (4)	Satisfactory
Net contents (21 CFR 201.51(a))	Each single-use packet contains 2 g of uridine triacetate. or (b) (4) . Satisfies 21 CFR 201.51(a).	Satisfactory
Lot number per 21 CFR 201.18	Lot number is displayed. Satisfies 21 CFR 201.18.	Satisfactory
Expiration date per 21 CFR 201.17	Expiration date is displayed. Satisfies 21 CFR 201.17.	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed. Does not satisfy 21 CFR 201.100(b)(1).	Unsatisfactory
Storage (not required)	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not provided on the sachet (packet) label but provided on the carton label.	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	Not displayed on the sachet (packet) label.	Unsatisfactory
Name of manufacturer/distributor	Name of manufacturer/distributor is appropriately displayed.	Satisfactory
Others	An unopened packet must be used for each dose. See package insert for complete information. Keep this and all medication out of the reach of children.	Satisfactory

*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: Immediate container label is inadequate. (b) (4) and Barcode should be displayed on the immediate container.

(b) (4)

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))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2).	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The following strengths are provided on sachets (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). Each single-use packet contains 2 g of uridine triacetate or (b) (4)	Satisfactory
Net contents (21 CFR 201.51(a))	(b) (4) . Or Each carton contains 30 packets. Each single-use packet contains 2 g of uridine triacetate. Satisfies 21 CFR 201.51(a).	Satisfactory
Lot number per 21 CFR 201.18	Appropriately displayed. Satisfies 21 CFR 201.18.	Satisfactory
Expiration date per 21 CFR 201.17	Appropriately displayed. Satisfies 21 CFR 201.17.	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not applicable	Not applicable
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(b)(1)	Approperiately displayed. Satifies 21 CFR 201.100(b)(1).	Satisfactory
Storage Conditions	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Appropriately displayed. Satisfies 21 CFR 201.2.	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	Appropriately displayed. Satisfies 21 CFR 201.25(c)(2).	Satisfactory
Name of manufacturer/distributor	Manufactured for and distributed by: Wellstat Therapeutics Corporation Gaithersburg, MD 20878	Satisfactory

"See package insert for dosage information" (21 CFR 201.55)	Appropriately displayed. Satisfies 21 CFR 201.55.	Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	Appropriately displayed.	Satisfactory
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Route of administration is provided as oral	Satisfactory

Conclusion: Carton labels are satisfactory.

II. List of Deficiencies To Be Communicated

A. Drug Substance: None
B. Drug Product:

1) [redacted] (b) (4)

C. Process/Facility:

1) No final "Acceptable" recommendation from the Office of Compliance has been made for the facilities involved in this application.

D. Biopharmaceutics: None
E. Microbiology : None
F. Label/Labeling

1) Package insert: Provide molecular structure in # 11 "Description" section of package insert.

2) Immediate container (sachet) label: Add [redacted] (b) (4) and Barcode to the sachet labels.

III. Attachments

A. Facility

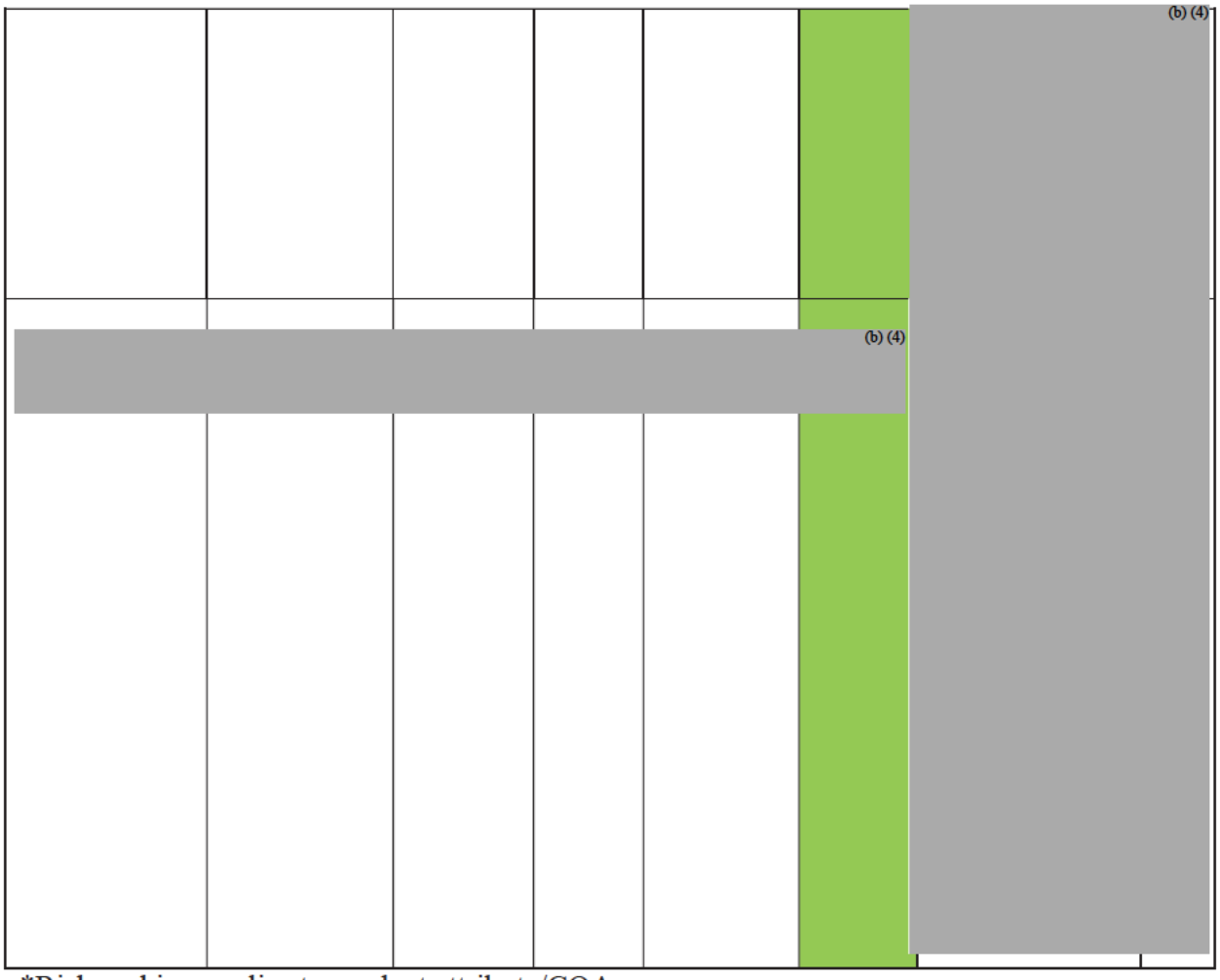
OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
API manufacturing; Release & stability tes ing	[redacted]	[redacted]	(b) (4)	**Acceptable based on inspectional history** Post-approval coverage recommended
(b) (4) testing of the API	[redacted]	[redacted]	(b) (4)	**Acceptable based on inspectional history**
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
Drug product manufacturing, release & stability tes ing, packaging & labeling, API microbiological testing	[redacted]	[redacted]	(b) (4)	***Pending Inspection*** (b) (4)

B. Lifecycle Knowledge Management

a) Drug Substance

(b) (4)

[redacted]



*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

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: