CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s000

CHEMISTRY REVIEW(S)

<table cellspacing=0 width="1100" > <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold,color:#000080,white-space.nowrap" class="TitleCell"> Facility Alerts</td></tr> <tr><td style="text-align.left,font-family Times New Roman;font-size:25px;font-style:normal;font-weight:bold;color:#000080;white-space:nowrap" class="TitleNameCell" tabindex="0"><label></label></td></tr> <tr><td style="font-family:Microsoft Sans Serif,font-size.11px,color:#8055B7," class="SubtitleCell"> This report displays the Alerts associated with facilities on the selected applications</td></tr> <tr><td style="text-align:left;border-style:none;border-bottom.solid 1px #/1/1/1,font-family.Microsoft Sans Serif,font-size 10px,color.#000080," class="SubtitleCell"></td></tr></tbody> </table> <style type="text/css"> td.ResultLinksCell { } </style>
 <FONT SIZE =2><FONT COLOR="#000080"> No active OAI / POAI Alerts are present against the facilities on selected Projects</FONT></FONT>

Facility Status View for NDA 208159 Original 1

Displays information for the facilities that are associated to NDA 208159 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 12/11/2015 7:41:35 AM

Overall Manufacturing Inspection Recommendations for NDA 208159 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3)	WELLSTAT THERAPEUTICS CORP	Approve	Complete	11/6/2015

OPF Facility Recommendations for Facilities on NDA 208159 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3)	(b) (4)				Approve Facility	Complete	(b) (4)
NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3)					Approve Facility	Complete	
NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3)			(b) (4)	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	

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QUALITY ASSESSMENT

(b) (4)

Recommendation: Approval

NDA 208159
Review #1
Review Date 6-Nov-15

Drug Name/Dosage Form	Uridine Triacetate/ (b) (4) / granules
Strength	10g (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Wellstat Therapeutics Corporation
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
	January 16, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern	OMPT/CDER/OPQ/ONDP/DNDAPI/NDBII
Drug Product	Xiao Hong Chen	ONDP Division I/Branch II
Process	Christina Capacci-Daniel	OMPT/CDER/OPQ/OPF/DIA/IABII
Microbiology	Christina Capacci-Daniel	OMPT/CDER/OPQ/OPF/DIA/IABII
Facility	Christina Capacci-Daniel	OMPT/CDER/OPQ/OPF/DIA/IABII
Biopharmaceutics	Ge Bai	OMPT/CDER/OPQ/ONDP/DB/BBIII
Business Process Manager	Rabiya Laiq	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Olen Stephens	ONDP Division I/Branch II
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment	Xiao Hong Chen	ONDP Division I/Branch II

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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[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	Adequate	Dec 29, 2014*	Reviewed by Elise T Luong, Ph.D.
	Type III			Adequate	Nov 10, 2011*	Reviewed by Andrew B. Yu, Ph.D.
	Type II			Closed	N/A**	Closure was requested on Sep 29, 2009, received on Oct 14, 2012
	Type II			Inactive, no updates since 2001	Aug 5, 1997**	Reviewed by Pardhasara Komanduri
	Type II			Closed	N/A**	Closure was requested on Nov 6, 2012, received on Nov 13, 2012

[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)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	39,571	
IND	118931	
NDA	208169	

3. CONSULTS: None

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Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has rendered a final "Acceptable" recommendation for the facilities involved in this application (refer to Panorama 6-Nov-2015).

The claim for the Categorical Exclusion for the Environmental Assessment as per 21 CFR 25.31 (b) is granted. The labels/labeling issues have been resolved as of this review through meetings with the clinical division.

Therefore, from the OPQ perspective, this NDA is recommended for approval. A 24 month shelf life is granted for the drug product when stored in the proposed container configuration and stored at 25°C (77°F), excursions permitted to 15° to 30 °C (59° to 86°F).

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

There will be one post-marketing commitments for this NDA. In the cross referenced NDA 208-169, the process validation batches demonstrated segregation during the (b) (4) filling step such that there is significant variability in dissolution of the products intra-batch and inter-batch. Presumably, this is due to dissolution dependence on the particle size of the granules. Because the indication for NDA 208-159 is lifesaving, orphan designated, (b) (4) and there is no toxic dose known for the product, the risk-benefit analysis for this product dictates that the NDA be approved. Furthermore, for the 5-fluorouracil toxicity indication, dosing and monitoring of the patients is frequently enough such that variability in the drug product is not likely to adversely impact the patient. Post-marketing commitments were established for NDA 208-169 that will address the same product quality concerns for NDA 208-159. The new post-marketing commitment for NDA 208-159 is as follows:

As part of the dissolution method revision, perform retrospective analysis and confirm the dissolution studies submitted to support this manufacturing process, including:

(b) (6)

Study the effect of drug substance particle size distribution and final granule particle size distribution on dissolution to determine the size limits at which dissolution may become retarded. Establish justified drug substance and granule particle size distribution limits based on this understanding.

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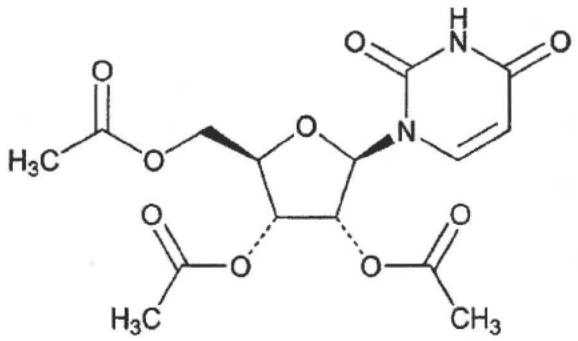
II. Summary of Quality Assessments

The proposed drug product, Vistogard™ (uridine triacetate) oral granules, is intended to treat patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration.

The granule dosage form provides dosing flexibility. (b) (4) the applicant has suggested that mixing of the granules with soft foods such as applesauce, vanilla pudding, and yogurt as dosing vehicles will further facilitate the oral administration of the drug product. (b) (4) The information provided in the application supports the use of all proposed dosing vehicles.

Vistogard™ (uridine triacetate) oral granules are to be marketed in 10g packets (b) (4). The CMC information for NDA 208-159 is cross referenced to NDA 208-169 for Xuriden™ by the same applicant. Xuriden™ is the same product except the same product except for a smaller (b) (4) fill (2 g instead of 10 g). All post-approval risk mitigation steps apply to both products.

A. Drug Substance [Uridine Triacetate] Quality Summary



Uridine triacetate, *[(2R,3R,4R,5R)-3,4-Diacetyloxy-5-(2,4-dioxopyrimidin-1-yl)-oxolan-2- yl]methyl acetate,* is a white to off-white (b) (4) This drug substance has a melting point of 128.1°C (b) (4) It has (b) (4) known polymorphs identified as (b) (4) has been found to be the most stable form produced under typical processing conditions. (b) (4) has been regarded as metastable forms. This drug substance can also be produced as the (b) (4)

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(b) (4)

[redacted]

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

B. Drug Product [Established Name] Quality Summary

The drug product, Vistogard™ (uridine triacetate) oral granules, is indicated to treat patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration.

During the pharmaceutical development, (b) (4) granules formulations were examined. It was determined that oral granules with maximum drug substance load can provide the flexibility in dosing that is required. Another consideration for pursuing oral granules as the final drug product was that this type of dosage form enables mixing the drug product with soft foods and further facilitates dosing of patients.

Vistogard™ is white to off white granules packaged as 10g uridine triacetate in (b) (4) (packet). This drug product contains 95.08% uridine triacetate as the active ingredient and (b) (4)% Opardy (b) (4) Clear (b) (4) % natural orange juice flavor (b) (4) as the excipients. The total amount of excipients used in this drug product is less than (b) (4) uridine triacetate and flavoring of the granules. All excipients are appropriately tested and released for use in the manufacture of Vistogard™.

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The drug product release specification includes testing and acceptance criteria for appearance (white to off-white granules), identity (by HPLC; RT for the standard and sample within (b) (4)%), related substances (total known and unknown related impurities (b) (4)% with individual unknown impurities NMT (b) (4)% and excluding impurities (b) (4)% with individual unknown impurities NMT (b) (4)% and excluding (b) (4) uniformity of dosage unit (USP <905>), dissolution (Q = (b) (4) at (b) (4) minutes, Q = (b) (4) at (b) (4) minutes, and report results for other time-points), (b) (4) content (NMT (b) (4)% by volumetric Karl Fischer), Bioburden (TAMC: NMT (b) (4) CFU/g, TYMC: NMT (b) (4) CFU/g, and E- coli: Negative in (b) (4)), and particle size distribution (report mean and %RSD values (n (b) (4)) for x10, x50 and x90).

The proposed dissolution method is considered somewhat inadequate, but it has been accepted as an interim method while the applicant has agreed to develop and validate a new dissolution method (see the Biopharm section below). The proposed drug product specification is deemed adequate to assure identity, strength, purity, and quality of the drug product for this patient population.

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 developmental batch of drug product 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 for the drug product when packaged in the proposed packaging configuration and stored at controlled room temperature, 25°C (77°F) with excursions permitted to 15° to 30 °C (59° to 86°F).

C. Manufacturing Process

Uridine triacetate oral granules are manufactured using (b) (4) process. This product contains >95% drug substance and <5% excipients. The excipients used in this drug product are (b) (4).

The manufacturing process for the uridine triacetate oral granules is well controlled through a series of appropriate in-process testing and process controls. 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. The applicant has expressed that the granule (b) (4)

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(b) (4) Therefore, classification as immediate release is considered satisfactory.

To make the dissolution testing of the granules (b) (4) method is accepted only on an interim basis for the approval of this application provided that applicant develops a more suitable dissolution method post approval . In a Telcon with the applicant on May 22, 2015, the applicant agreed to postapproval commitments that a more suitable dissolution method will be developed and validated within 6 months after the approval of the cross referenced application (208-169) with updated dissolution acceptance criteria. The agency recommended that the interim dissolution acceptance criteria to NLT (b) (4)% in 15 minute and Q = (b) (4) in 45 minutes. The applicant submitted and amendment on June 1, 2015 and accepted the postapproval commitment required by the Agency. The amendment also includes an updated drug product specification that includes the tightened interim dissolution acceptance criteria.

E. Facilities

The facility involved in the testing of the drug substance, uridine triacetate, and (b) (4) and the drug substance manufacturing site, (b) (4) have been recommended as acceptable based on the inspectional history. A post-approval inspection of (b) (4) to cover drug substance manufacturing is recommended.

The facility involved in the manufacture, packaging, and release testing of the drug product, (b) (4) has been determined to be "acceptable" based on inspectional results, a pending PMC, and requests of additional information. The overall assessment of the facilities, therefore, is acceptable.

F. Environmental Assessment

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

C. Summary of Drug Product Intended Use

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Proprietary Name of the Drug Product	Vistogard oral granules
Non Proprietary Name of the Drug Product	Uridine triacetate oral granules
Non Proprietary Name of the Drug Substance	Uridine triacetate
Proposed Indication(s) including Intended Patient Population	[redacted] (b) (4) (b) (4)
Duration of Treatment	10 grams every 6 hours for 20 doses (120 hours)
Maximum Daily Dose	None
Alternative Methods of Administration	Via nasogastric tube or gastrostomy tube when necessary

D. Biopharmaceutics Considerations

1. BCS Classification: Not classified

2. Biowaivers/Biostudies: None
   - Biowaiver Requests
   - PK studies
   - IVIVC

E. Novel Approaches: NA

F. Any Special Product Quality Labeling Recommendations: NA

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

H. Life Cycle Knowledge Information (see Attachment B

I. OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: OPQ recommends this NDA for approval and granting a 24 month shelf life.

Olen Stephens - S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.11.06 12:37:33 -05'00'

Olen Stephens, Ph.D.
6-Nov-15

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ANDA 208169 are found to be acceptable.

A post-approval inspection of (b) (4) to cover drug substance manufacturing for ANDA 208159 is recommended.

Christina Capacci-Daniel, PhD – Nov 4, 2015
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Supervisor Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D., 11/4/2015
Branch Chief, OPQ/OPF/DIA

ASSESSMENT OF THE BIOPHARMACUETICS

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

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

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

The uridine triacetate drug product consist of white to off-white granules ((b) (4) uridine triacetate drug substance) (b) (4) with orange juice flavor. The uridine triacetate API exhibits a solubility of 7.7 mg/mL across different pH values. The proposed dose is (b) (4) mg/kg/day. (b) (4) The proposed dose is high relative to the drug substance solubility; therefore, the drug substance can be classified as low solubility.

The drug product is packaged in (b) (4) 10 g uridine triacetate drug substance. The formulation contains 95% w/w API, (b) (4)% Opadry®, (b) (4)% natural orange juice flavor. The manufacturing process is comprised (b) (4)

DISSOLUTION METHOD

The Applicant initially proposed the dissolution method listed in Table 1, which was the same dissolution method for NDA 208169 (XURIDEN®). In the proposed dissolution

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method, 550 mg of granules are weighed and transferred to size 00 hard gelatin capsules. The proposed dissolution method was found not adequate during the review of NDA 208169. Refer to biopharmaceutics review for NDA 208169 (XURIDEN®) for details.

The dissolution method and the recommended acceptance criteria (Table 2) were accepted on an interim basis for release and stability testing of NDA 208169. A Post-Marketing Commitment (PMC # 2392-2) was agreed to with the Applicant. The PMC aimed at (1) developing a new dissolution method that has discriminatory capability and is representative of the proposed product, and (2) setting the final dissolution acceptance criteria based on dissolution profiles of a minimum of 5 commercial batches. Once the new dissolution method and acceptance criteria are approved, they can be used for both drug products (NDA 208159 and NDA 208169)

Since, NDA 208159 has exactly the same drug product (only the indication is different) as NDA 208169 and the Applicant proposed exactly the same dissolution method, the review decision on dissolution method and acceptance criteria for NDA 208159 is the same. The current proposed method (Table 1) and the FDA recommended dissolution acceptance criteria (Table 2) are acceptable on an interim basis. The Applicant needs to execute PMC # 2392-2 to develop a new dissolution method and set dissolution acceptance criteria based on data.

Table 1. Proposed Dissolution Method and Acceptance Criterion

Apparatus	USP I (10 mesh baskets)
Speed	100 rpm
Sample Preparation	550 mg of granules in size 00 white hard gelatin capsules
Medium	0.05 M citrate buffer, pH 4.0 (900 mL)
Sampling Times	15, 20, 30, 45, 60, 90, and 120 minutes
Acceptance Criteria	Q = (b)(4)% at 15 minutes and Q = (b)(4)% at (b)(4) minutes
Detection	HPLC/UV, λ=260 nm

Table 2. FDA Recommended Interim Dissolution Acceptance Criteria

Interim Acceptance Criteria	Q = (b)(4)% at 15 minutes and Q =(b)(4)% at 45 minutes

The Applicant submitted the dissolution method development protocol on 09/15/2015 in accordance with the PMC timeline. In this protocol, the Applicant provided background information, the study plan and preliminary data (e.g. Figure 1). Based on the PMC protocol, the Applicant is conducting dissolution method development with (b)(4) . These are significantly different from the current method. However, in the protocol the Applicant did not provide justification for this selection. In addition, the Applicant did not specify how (b)(4) of the drug product in the dissolution vessels.

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Figure 1: Uridine Triacetate Dissolution Profile in (b) (4) mL

(b) (4)

% Dissolution

Figure 1. Uridine Triacetate Dissolution Profile in (b) (4) mL (Submitted 09/15/2015)

There were two formulations used during the clinical development of the drug product. The first formulation contained (b) (4)% w/w API, (b) (4)% Opadry®, (b) (4) % natural orange juice flavor. The first formulation was manufactured using (b) (4) process. The first formulation was used in two studies: study PN401.07.001 to determine the relative bioavailability of the (b) (4) granules to the unformulated API and study PN401.07.002 to determine the effect of food on bioavailability. The second formulation was manufactured using (b) (4) process. The second formulation contained 95% API, (b) (4)% Opadry®, (b) (4) % natural orange juice flavor. The second formulation (Lot W017891) was used in the pivotal clinical study and is the to-be-marketed formulation.

There is no bridge required between the to-be-marketed formulation and the efficacy study formulation. However, a bridge is needed between the to-be-marketed formulation and the food effect study formulation. The Applicant was asked to comment on the applicability of the food effect study results obtained with the first formulation to the second, to-be-marketed formulation as part of the NDA 208169 XURIDEN® review (74-day Letter on 23-MAR-2015).
The Applicant provided the following arguments:

(a) (b) (4) API while maintaining the immediate release nature of the product; the amount of API in

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both formulations is >90% w/w. Therefore, the (b) (4) level change at this low percentage is not expected to have an effect with regard to food.

(b) The food effect study formulation (b) (4) and the pivotal clinical study formulation (b) (4) had very similar dissolution profiles (see Figure 3 of this review for comparison of dissolution profiles).

(c) (b) (4) does not have an effect on PK based on the relative bioavailability study results comparing (b) (4) granules and (b) (4) API.

Reviewer's Assessment: *The applicability of the food effect study results obtained with the first formulation to the second (to-be-marketed formulation) falls under the purview of Clinical Pharmacology. From a biopharmaceutics perspective, a dedicated BE study may not be required for bridging the findings of the food effect study for the following reasons:*

(i) There was no observed food effect on the bioavailability of the first formulation and, thus, it is not expected that the second formulation, (b) (4) would exhibit changes due to food intake. In addition, there was no effect of food on bioavailablity when the drug product was administered as 500 mg tablets (Study PN401/10.PKL.01).

(ii) The clinical trial was conducted without regards of food.

(iii) The changes in (b) (4) levels did not result in changes in dissolution profiles (see Figure 5 of this review), which indicates that it is highly likely that both formulations will have similar performance in vivo.

PK Study PN401.07.001 showed that the (b) (4) levels tested have no effect on the extent of exposure of the drug product.

EXTENDED RELEASE DESIGNATION

The proposed to-be-marketed formulation contains (b) (4) The study is a randomized, single-dose, 2-way crossover study. The primary objective of the study was to compare the relative BA of uridine after single oral dose (6 g of API) of either unformulated uridine triacetate drug substance or formulated orange flavored uridine triacetate granules given under fasted conditions. The drug substance PSD (Lot 23130207A.0.01) is D_{10} = (b) (4), D_{50} = (b) (4), and D_{90} = (b) (4). The drug product (Lot 0605015) was manufactured using the same drug substance lot.

A total of 20 healthy male (N=12) and female (N=8) subjects ranging from 19 to 55 years of age (mean = 30.6) were enrolled in the study. Subjects were randomly assigned to receive one of two regimens: uridine triacetate drug substance 6 gram strength (Reference) or uridine triacetate granules 6 gram strength (Test). Both treatments were sprinkled on approximately ½ cup of Mott's® original applesauce and immediately administered to the subject followed by 500 mL of bottled water. Blood samples were taken at predose (t = 0), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, and 24 hours post-dose (Figure 2 and Figure 3). The PK parameters are summarized in Table 3.

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Table 3. PK Parameters of Uridine in Plasma

Pharmacokinetic Parameter	Uridine Triacetate Drug Substance (Reference) (Mean ± SD)	Uridine Triacetate Sprinkles (Test) (Mean ± SD)
C_{max} (μM)	131.14 ± 23.08	106.64 ± 23.12
T_{max} (hr) *	2.00 (0.998, 3.00)	2.50 (1.49, 5.00)
k_{el} (1/hr)	0.340 ± 0.0660	0.337 ± 0.0851
$t_{1/2}$ (hr)	2.13 ± 0.508	2.22 ± 0.732
$AUC_{(0-t)}$ (μM*hr)	710.38 ± 86.118	634.93 ± 97.598
$AUC_{(0-\infty)}$ (μM*hr)	742.43 ± 85.337	670.06 ± 105.62

* T_{max} is presented as median (minimum, maximum)
All subjects had baseline uridine set to the LLOQ (10.24 μM), thus $AUC_{(0-t)} = AUC_{(0-\infty)}$

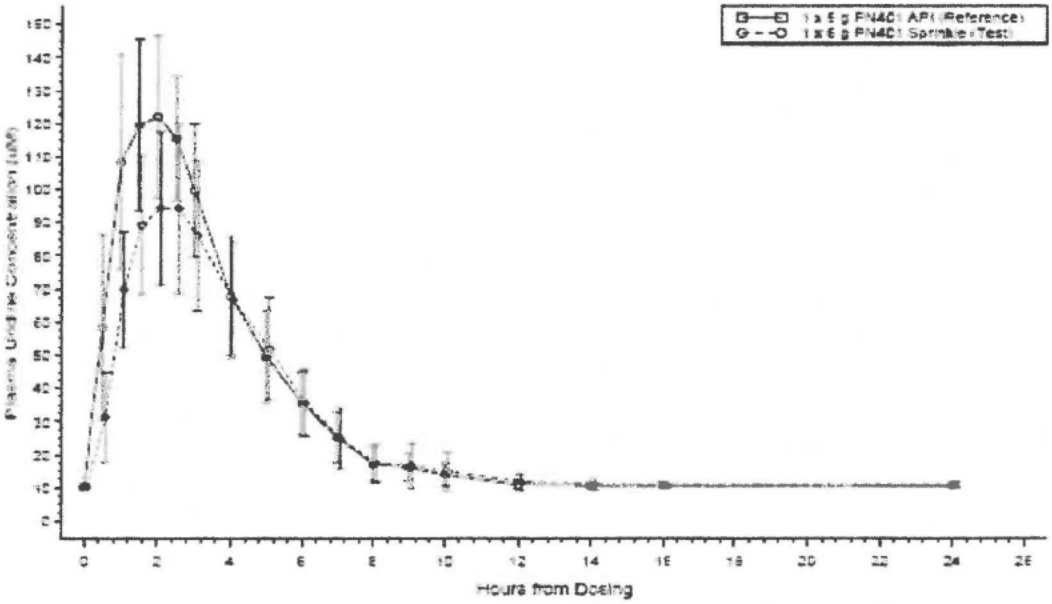

Figure 2. Mean (SD) plasma uridine concentrations versus time for API and granules on a linear scale.

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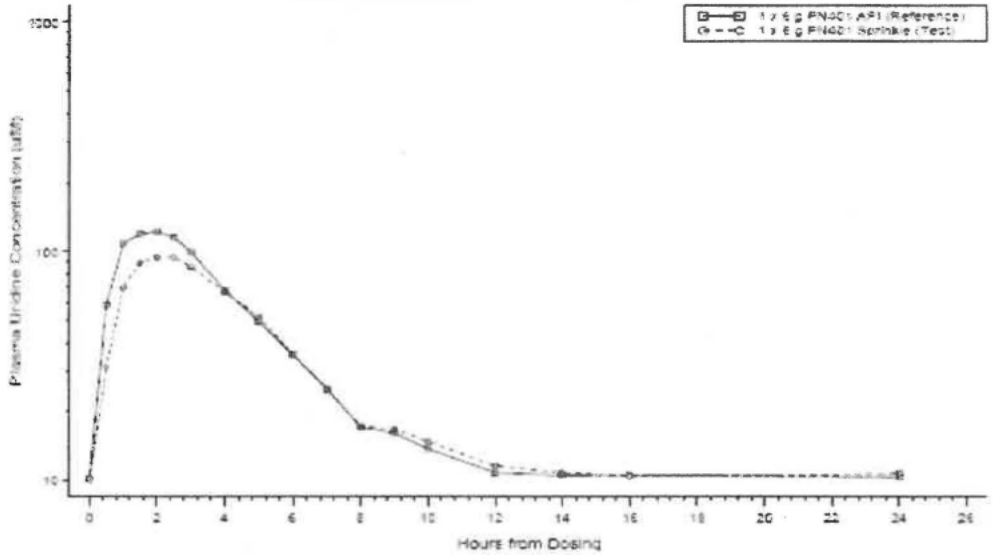

Figure 3. Mean plasma uridine concentrations versus time for API and granules on a log scale.

ANOVA was conducted on a linear mixed-effects model with treatment, period, sequence as fixed effects and patients within a sequence as random effects. The geometric mean ratio along with 90% CI for each PK parameter are summarized in Table 4.

Table 4. Statistical Analysis Resutls of the PK Parameters

Parameter	Geometric -- LS Means --		Confidence Intervals	
	Uridine Triacetate Sprinkles (Test)	Uridine Triacetate Drug Substance (Reference)	(90% Confidence)	Mean Ratio
C_{max}	104.0	129.4	75.83 – 85.23	80.39
$AUC_{(0-t)}$	628.8	705.5	87.18 – 91.12	89.13
$AUC_{(0-inf)}$	663.4	737.9	88.06 – 91.79	89.91

All subjects had a baseline uridine set to the LLOQ (10.24 µM), thus $AUC_{(0-t)} = AUC_{(0-24)}$.
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS means) are calculated by exponentiating the LS MEANS from the ANOVA.
Mean Ratio = 100*(test/reference)

Reviewer's Assessment:

The provided data suggest that the (b) (4) *granules exhibit lower C_{max} and delayed T_{max} relative to the unformulated API. However, there is not sufficient evidence to suggest* (b) (4) *product. Specifically, the data suggest that no significant change in the rate of absorption occurs* (b) (4) *which would result in a prolonged concentration-time profile and reduced dosing frequency.*

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OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

Because NDA 208159 is for the same drug product as NDA 208169 and the proposed dissolution method and acceptance criteria are also the same, the decisions made under NDA 20169 in terms of the biopharmaceutics information are also applicable to NDA 208159. The following dissolution method and acceptance criteria are acceptable only on an interim basis for release and stability testing.

Apparatus	USP I (10 mesh baskets)
Speed	100 rpm
Sample Preparation	550 mg of granules in size 00 white hard gelatin capsules
Medium	0.05 M citrate buffer, pH 4.0 (900 mL)
Sampling Times	15, 20, 30, 45, 60, 90, and 120 minutes
Acceptance Criteria	NLT (b)(4)% at 15 minutes and Q = (b)(4)% at 45 minutes

The Applicant needs to execute Post-Marketing Commitment (PMC #2392-2) to develop a new dissolution method and set dissolution acceptance criteria based on dissolution data from at least five commercial scale batches. Once the new dissolution method and dissolution criteria are approved, they can be applied to both NDA 208159 and NDA 208169.

On 09/15/2015, the Applicant submitted dissolution method development protocol which contains background information, timeline, study plans and preliminary data. Based on the incomplete information provided in this protocol, the Applicant need to justify on the proposed types of dissolution medium and dissolution apparatus. In addition, the Applicant needs to specify how to prevent (b)(4) *of the drug product in the dissolution vessels for the new dissolution method.*

(b)(4)

(b)(4) *Specifically, the data suggest that no significant change in the rate of absorption occurs* (b)(4) *which would result in a prolong concentration-time profile and reduced dosing frequency.*

From a biopharmaceutics perspective, the overall data provided (dissolution, in vivo PK, drug product composition, etc.) suggest that a dedicated BE study may not be required for bridging the findings of the food effect study conducted with an earlier formulation.

The following IR comments were conveyed to the Applicant as part of the PMC issued under NDA 208169:

1. We acknowledge the information provided on 09/15/2015 as part of dissolution

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method development protocol. We notice that you did not provide justification for the selection of (b) (4) dissolution medium and USP (b) (4). In addition, you should provide detailed information on the approach(es) taken to prevent (b) (4) of the drug product in the dissolution vessels.

2. We remind you that the selection of the final dissolution method should include information/data on the discriminating ability of the method toward the identified critical material attributes and process parameters. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent. Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

Ge (Larry) Bai, Ph.D
Biopharmaceutics Reviewer
ONDP/OPQ

Salaheldin S. Hamed, Ph.D.
Biopharmaceutics Reviewer
ONDP/OPQ

Supervisor Comments and Concurrence:
Sandra Suarez-Sharp, Ph.D.
Acting Biopharmaceutics Lead,
ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response: The release specifications include testing for Total Aerobic Microbial Count [TAMC], Total Combined Yeasts and Molds [TYMC], and *Escherichia coli.*

Test	Acceptance Criterion	Analytical Procedure Reference
Microbial Purity	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g Escherichia coli: Negative in (b) (4)	QCM564/03 Section 3.2.P.5.2.5

See the ***Manufacturing Process Review***, especially Question #29, for additional controls on the (b) (4) granules.

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Reviewer's Assessment: Adequate

(b) (4)

2.3.P.6 Reference Standards or Materials

36. 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: (b) (4) oral dosage form.

Reviewer's Assessment: Not Applicable

Drug product (b) (4)

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

37. 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: No components are derived from animal or biological origin.

Reviewer's Assessment: Not Applicable

38. 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

Reference ID: 3863656

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: No components are derived from animal or biological origin.

Reviewer's Assessment: Not Applicable

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

There are no microbiological concerns that prevent approval of this application.

Christina Capacci-Daniel, PhD – Nov. 3, 2015
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Supervisor Comments and Concurrence:

I concur, the microbiology assessment overall recommendation is acceptable.

Celia N. Cruz, Ph.D. – 11/03/2015
Acting Branch Chief, OPF/DPAII/BV

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

Labeling & Package Insert

1. Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VISTOGARD™ (uridine triacetate) oral granules

Reference ID: 3863656

Initial U.S. Approval: [2015]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Vistogard™ (uridine triacetate) oral granules	Proprietary name and established name is provided. Satisfactory
Dosage form, route of administration	oral granules	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Oral granules: 10 gram packet	Satisfactory

Conclusion: The information provided in this section is found to be satisfactory.

(b) "Full Prescribing Information" Section

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

Oral granules: 10 grams of orange-flavored oral granules (95% w/w) in (b) (4) packets

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral granules	Satisfactory
Strengths: in metric system	10 grams in (b) (4) packet	The term should be changed to "single-dose"
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	N/A	N/A

Conclusion: Satisfactory

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

VISTOGARD (b) (4) oral granules (b) (4) contain (b) (4) uridine triacetate. (b) (4) the chemical (b) (4) (2',3',5'-tri-O-acetyl-ß-Dribofuranosyl)-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 (b) (4) 10 gram packet of VISTOGARD orange-flavored oral granules (95% w/w) contains 10 grams of uridine triacetate and the following inactive ingredients: ethylcellulose (0.309 grams), Opadry Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.077 grams), and natural orange juice flavor (0.131 grams).

Reference ID: 3863656

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Vistogard™ (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 (b) (4) 10 gram packet of VISTOGARD orange flavored oral granules contains 10 grams of uridine triacetate	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each (b) (4) 10 gram packet of VISTOGARD orange flavored oral granules contains the following inactive ingredients: ethylcellulose (0.309 grams), Opadry Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.077 grams), and natural orange juice flavor (0.131 grams).	Satisfactory
Statement of being sterile (if applicable)	N/A	N/A
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: $C_{15}H_{18}N_2O_9$	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: Some edits have been made in this section while the review is ongoing. The edits were discussed at the NDA labeling meeting.

Reference ID: 3863656

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

VISTOGARD orange-flavored oral granules (95% w/w) are available in [redacted] (b) (4) packets containing 10 grams of uridine triacetate.

NDC Number	Package Configuration
69468-151-20	Course of therapy package: 1 carton containing 20 [redacted] (b) (4) packets of VISTOGARD
69468-151-04	24-Hour Pack: 1 carton containing 4 [redacted] (b) (4) packets of VISTOGARD

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	[redacted] (b) (4) packets containing 10 grams of uridine triacetate	Satisfactory
Available units (e.g., bottles of 100 tablets)	available in [redacted] (b) (4) packets containing 10 grams of uridine triacetate in cartons of 4 and 20 packets each	The correct term is "single-dose"
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 69468-151-20 NDC 69468-151-04	Satisfactory
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
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: Satisfactory

2. Labels

1) Immediate Container Label

Reference ID: 3863656

(b) (4)

[redacted]

Reviewer's Assessment:

Reference ID: 3863656

QUALITY ASSESSMENT
NDA # 208159

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 (b) (4) (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). Each (b) (4) packet contains 10 g of uridine triacetate	Satisfactory
Net contents (21 CFR 201.51(a))	Each (b) (4) packet contains 10 g of uridine triacetate. 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 not 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 (b) (4) (packet) label but provided on the carton label.	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	It is displayed on the (b) (4)(packet) label.	Satisfactory
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. "Rx only" and Barcode should be displayed on the immediate container.

Reference ID: 3863656

2) Cartons

(b) (4)

[redacted]

Reference ID: 3863656

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 (b) (4) (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). Each (b) (4) packet contains 10 g of uridine triacetate	Satisfactory
Net contents (21 CFR 201.51(a))	Each carton contains 20 packets. Each (b) (4) packet contains 10 g of uridine triacetate. Or Each carton contains 4 packets. Each (b) (4) packet contains 10 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)]	N/A. The drug product is for oral administratin.	**N/A**
Sterility Information (if applicable)	N/A	**N/A**
"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"	Appropriately displayed.	Satisfactory

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(optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Route of administration is provided as oral.	Satisfactory

Conclusion: Satisfactory.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Review of the proposed package insert (PI) and container carton labels are ongoing while this review is being finalized. Overall, the proposed PI and container carton labels appear to be acceptable with some edits and comments to be communicated to the applicant.

Xiao Hong Chen, 27-Oct-2015

Secondary Review Comments and Concurrence: I concur with the primary reviewer

Olen Stephens, 30-Oct-15

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Wellstat is claiming a categorical exclusion under 21 CFR 25.31 (b). Using the calculation for estimating the concentration (EIC) of an active moiety into the aquatic environment from the FDA Guidance on Environmental Assessment and inputting the yearly direct use of [redacted] (b) (4) 5-fluorouracil indication, the EIC is estimated to be [redacted] (b) (4) ppb, which is well below the 1 ppb limit in the FDA guidance and to the applicant's knowledge no extraordinary circumstances exist.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL ANALYSIS

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**.

Xiao Hong Chen, 27-Oct-2015

Secondary Review Comments and Concurrence: I concur with the primary reviewer

Olen Stephens, 30-Oct-15

II. List of Deficiencies To Be Communicated: None

Reference ID: 3863656

III. Attachments

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	INITIAL RISK RANKING	RISK MITIGATION	FINAL RISK RANKING	LIFECYCLE CONSIDERATIONS
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	LOW		MEDIUM	PMC issued to evaluate and control segregation, dissolution dependence on PSD
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	MEDIUM		LOW	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	LOW	Validation batches were observed to have high variability in dissolution and possible segregation	MEDIUM	PMC issued to evaluate and control segregation, dissolution dependence on PSD
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	LOW		LOW	
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	MEDIUM	Patient population is closely monitored during treatment and there is no detectable toxic dose	MEDIUM	PMC issued to improve dissolution method discriminating ability for PSD
Disintegration (ODT)	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	LOW		LOW	
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	MEDIUM	Product is administered mixed with foods (b) (4) (b) (4)	LOW	

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NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3) - Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Request More Access

Task Summary | Task Details | Issues | Task Email Form | Updates | Application History | **Inspection Management Form**

Inspection Management Form

Inspection Management Form

NDA 208159-Orig1-User Fee - Form 3674 - New/Coversheet - NDA(3)

(b) (4) [redacted] Approve Facility

Approve Facility

Approve Facility

Overall Manufacturing Inspection Recommendation

Approve
Withhold

Assigned To

OPF Reviewer

Christina Capacci-Daniel

IM - OPF Reviewer

Edit Assignment

This was done on
Nov 6, 2015

Status
Complete

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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	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	• Impurity formation due to excipient reactions or unspecified reactions • (b) (4) degradation (b) (4) • Organic solvents • Polymorphic conversion (b) (4)	Mod stable drug 3)	2	Release (1)	6
					Stability (3)	18
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Polymorphic conversion • (b) (4)	(b) (4)(3)	BCS (b) (3)	4	36
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Low dose • Particle size/shape • Segregation • Flow property	(b) (4) % (2)	2	4	16
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Moisture • Equipment, process environment	1	2	Release with spec (3)	6
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	• API particle size • (b) (4) • (b) (4) • Disintegration • Size shape • (b) (4) • (b) (4)	4	2	4	32
Disintegration (ODT)	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	• Does not perform (disintegrate) as intended	3	2	3	18
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	• Fail to mask • Taste/ Smell Masking (ODT)	3	3	5	45

C. FILING CONSIDERATIONS					
	o Mycoplasma 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				

208169-208159-cmc-differences-23-jan-2(

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, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.08.10 20:20:10 -04'00'

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C. FILING CONSIDERATIONS					
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? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☒	☐	☐	
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.	☐	☒	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	
REGIONAL INFORMATION AND APPENDICES					
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?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ 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: o LAL instead of rabbit pyrogen				NA

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C. FILING CONSIDERATIONS					
	❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o 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 o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o 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) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o 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 ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☒	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ Is the schedule feasible to conduct an inspection within the review cycle?				
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	All DMFs referenced with LOAs are **CLOSED.** Manufacturing information is included in the application.
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o 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) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o 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	☒	☐	☐	

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49.	New product design[1]	☐	☒	
50.	Other	☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☐	☒	☐	Applicant will be asked to provide categorical exclusion request.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	Note that the QOS is not written in a QbR format, but that is not a requirement for the NDA submission.
	FACILITY INFORMATION				
3.	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: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided?	☐	☐	☒	

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					for related substances in uridine triacetate drug product appear appropriate. Include a test for Particle Size Distribution, tests for degradation products (each specified identified degradation product, each specified unidentified degradation product, any unspecified degradation product, and total degradation products). Dissolution method based on 2-point specification: **2-point specification would be acceptable, but time points should be selected based on data – applicant instructed to collect data on the clinical and registration batches at 15, 20, 30, 45, and 60 minutes.**
22.	SPOTS (Special Products On-line Tracking System)		☒	☐	Source of (b) (4)
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☒	☐	Change in (b) (4) is not acceptable without a post-approval supplement; labeling for new configuration may be reviewed in original NDA.
25.	Other		☐	☒	
	Quality Considerations				
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☒	☐	Consistent with Eur. Ph. 2.6.12 and 2.6.13 instead of USP
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	(b) (4) OPADRY, and orange juice flavoring
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	None found in initial triage of NDA
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	

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Regulatory Considerations				
20.	USAN Name Assigned	☒	☐	(b) (4)™ has been proposed as the proprietary name
21.	End of Phase II/Pre-NDA Agreements	☒	☐	Refer to 5-Dec-14 CMC-only pNDA WRO: Starting material (b) (4) **Yes, (b) (4) is acceptable, provided it conforms to the predefined acceptance criteria.** (b) (4) **We remind you however, that the elemental impurity limits should be based on the maximum recommended dose and conform to permitted daily exposure (PDE) recommendations defined by ICH.** From the 21-Aug-13 EOP2 meeting: -Designation (b) (4) as the regulatory starting material and to Wellstat's receipt specifications: **In addition to your proposed specification for (b) (4) as a regulatory starting material, consider providing the following additional information:** (b) (4) **• Use of any other possible method for impurities that can't be identified by your proposed HPLC method.** **Alternately, you may consider providing the CMC information for (b) (4) DMF with Letter of Authorization (LOA) as appropriate. Final evaluation of (b) (4) CMC information will be made during NDA review.** Drug Product specifications: **Justifications for the proposed specifications**

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B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☒	☐	(b) (4)
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☒	☐	The (b) (4) packaging configuration allows for dosing (b) (4)
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product	☐	☒	
19.	Other_____	☒	☐	Orphan designation for four indications across two clinical divisions.

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Application #: 208159	**Submission Type: 505(b)(1)**	**Established/Proper Name: Uridine Triacetate**
Applicant: Wellstat Therapeutics Corporation	**Letter Date: 16-Jan-2015**	**Dosage Form: Oral Granules**
Chemical Type:	**Stamp Date: 16-Jan-2015**	**Strength: 10g** (b) (4)

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?	X		

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	(b) (4)(uridine triacetate) is indicated (b) (4) [redacted] The NDA is not cross referenced to NDA 208169 for uridine replacement therapy in pediatric patients with hereditary orotic aciduria, but it was submitted by the same applicant. Note that this NDA is (b) (4) [redacted] to NDA 208-169, submitted for an orphan indication in the Gastroenterology and Inborn Errors Clinical Division. There are minor differences in the two NDA's that have been elucidated by the applicant (see attached PDF). The two review teams will share DS, Process, Facilities, Micro, and Biopharm Reviewers, but two separate Reviews will be written.