CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208082Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approve

NDA 208082

Review 2

Drug Name/Dosage Form	SD-809 Austedo (deutetrabenazine)
Strength	6 mg, 9 mg, 12 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals, Inc.
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	Branch1/DNDAPI/ONDP
Drug Product	Martha Heimann	Branch 1/DNDP 1/ONDP
Process	N/A	
Microbiology	N/A	
Facility	Wayne Seifert	Branch1/DIA/OPF
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP

Submissions Reviewed

SUBMISSION	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD #: 21	April 14, 2016	Drug Substance
SD #: 23	May 09, 2016	Drug Substance, Drug Product
SD #: 26	October 3, 2016	Drug Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Refer to Overall Quality Assessment, Review No. 1, dated April 26, 2016.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112975	Development of deutetrabenazine for Huntington's disease.
IND		(b) (4)
NDA	21894	Approved NDA for Xenazine® (tetrabenazine) tablets currently held by Valeant Pharmaceuticals. Reference drug for 505(b)(2) submission.
NDA		(b) (4)

2. CONSULTS:

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

Executive Summary

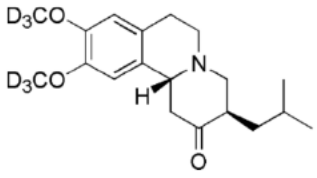
I. Recommendations and Conclusion on Approvability

From a quality perspective, approval of NDA 208082 is recommended. The applicant has adequately addressed the outstanding deficiencies from the original review.

II. Summary of Quality Assessments

A. Product Overview

Deutetrabenazine (TBZ-d_6) (**1**) is a new chemical entity indicated for treatment of chorea associated with Huntington's disease (HD). Chemically, deutetrabenazine is an analog of an approved drug, tetrabenazine (TBZ) (**2**) in which the hydrogen atoms at the 9- and 10-methoxy (-OCH_3) substituents of tetrabenazine are replaced by deuterium. Both deutetrabenazine and tetrabenazine are racemic mixtures. The absolute stereochemistry of the 3*R*,11b*R* enantiomers is shown in the figures below.



1: Deutetrabenazine

(b) (4)

Deutetrabenazine tablets are round, (b) (4)-coated tablets containing 6 mg, 9 mg, or 12 mg deutetrabenazine. Deutetrabenazine tablets contain excipients, and have physical characteristics, such as dissolution profile, that are characteristic of extended-release products. However, the applicant is not seeking an extended-release claim and did not submit data to support such a claim.

Proprietary Name of the Drug Product	Austedo is proposed
Non Proprietary Name of the Drug Product	Deutetrabenazine Tablets
Non Proprietary Name of the Drug Substance	Deutetrabenazine
Proposed Indication(s) including Intended Patient Population	Treatment of chorea associated with Huntington's disease
Duration of Treatment	Chronic
Maximum Daily Dose	48 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

The OPQ review team identified one major deficiency related to control of the bulk drug substance, and two minor deficiencies. The applicant addressed the deficiencies in the resubmission. There are no other CMC changes.

Drug Substance

The drug substance specification submitted in the original NDA -did not include a test for (b) (4), a known genotoxic substance used in manufacture of deutetrabenazine. The applicant submitted a validated GC method for determination of (b) (4) in the drug substance.

Drug Product

The applicant submitted a revised post-approval stability protocol that includes placing the first three commercial batches on long-term and accelerated stability studies, and withdrawing and/or discussing any out of specification batches with the Agency. The applicant also revised the claim for categorical exclusion from environmental assessment to include a statement that to Teva's knowledge, no extraordinary circumstances exist.

Facilities

All facilities proposed for manufacture and testing of deutetrabenazine and Austedo (deutetrabenazine) tablets are currently acceptable.

C. Novel Approaches

The applicant did not employ any novel approaches.

D. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

E. Life Cycle Knowledge Information/Final Risk Assessment

See Attachment 1.

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1.14 Labeling

Immediate Container Label

Reviewer's Assessment: The proposed container label is acceptable, from a CMC perspective, with one minor change. The proposed Patient Information insert includes an instruction to (b) (4) However, container labels and Section 16 of the PI (How Supplied/Storage and Handling) do not contain corresponding language. The draft PI has been revised to include the statement "Protect from light and moisture." The applicant has agreed to add the same statement to the container labels once labeling recommendations from OSE/DMEPA are available.

Carton Labeling

Not applicable.

Primary Drug Product/Labeling Reviewer: Martha R. Heimann, Ph.D.

Secondary Reviewer Name): Wendy I. Wilson-Lee, Ph.D.

Martha Heimann

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
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ATTACHMENT 1

Final Risk Assessment for NDA 208082
Deutetrabenazine Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: excipient reactions, (b) (4)	L	(b) (4)	Acceptable	
Content uniformity 6 mg tablet	Low dose, particle size/shape, segregation, (b) (4)	M	Use of (b) (4) process with adequate understanding of process variables from (b) (4).	Acceptable	
Content uniformity 9 mg, 12 mg tablets		L		Acceptable	
Physical (solid state) stability	Formulation, process parameters, (b) (4)	M	(b) (4)	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, (b) (4)	L	Microbial evaluation of stability samples did not show evidence of microbial growth.	Acceptable	
Alcohol dose dumping	Formulation, solubility of (b) (4) excipient and/or API	L	(b) (4), (b) (4) In vitro dissolutions studies demonstrate that alcohol does not affect drug release.	Acceptable	
Dissolution	Particle size, (b) (4) (b) (4), size, shape, (b) (4) coat, formulation, process parameters	M	Dissolution method is discriminating with respect to (b) (4) (b) (4) (b) (4) do not have a large impact on the dissolution profile of the SD-809 tablets, the current dissolution method is capable of identifying trends in these variables.	Acceptable	

*Risk ranking applies to product attribute/CQA

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

Martha Heimann

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: May 24, 2016

From: Martha R. Heimann, Ph.D., CMC Lead, OPQ/ONDP and ATL for NDA 208082

To: NDA 208082

Subject: Manufacturing Facility Status and Complete Response (CR) Recommendation for NDA 208082, Austedo (deutetrabenazine) Tablets

This memorandum is an addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 208082 dated April 20, 2016. At the time the original review was completed, the review team determined that outstanding quality issues would preclude approval. However, the overall facility recommendation was still pending.

Per the Overall Manufacturing Inspection Recommendation (Wayne Seifert, May 24, 2016), all manufacturing facilities are considered acceptable. Thus, there are no facility related deficiencies for the CR letter. Due to the unresolved deficiencies detailed in the April 20, 2016, OPQ still recommends a CR action for NDA 208082.

Martha R. Heimann -S

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NDA 208082 OPQ Review Addendum

Submission Overall Manufacturing Facility Status

Overall Status	Completion Date	Project Name
Approve	5/24/2016	NDA-208082-ORIG-1

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile Code	Association	Alert
Approve Facility	5/24/2016	NDA-208082-ORIG-1					(b) (4)	PENDING	None
Approve Facility	5/24/2016	NDA-208082-ORIG-1						PENDING	None
Cancelled	10/21/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	10/21/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	10/21/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	10/21/2015	NDA-208082-ORIG-1						PENDING	None
No Further Evaluation	10/21/2015	NDA-208082-ORIG-1						PENDING	None
Approve Facility	10/15/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	10/15/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	7/13/2015	NDA-208082-ORIG-1						PENDING	None
Approve Facility	6/29/2015	NDA-208082-ORIG-1						PENDING	None
No Further Evaluation	6/29/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	6/29/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	6/27/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	6/27/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	6/17/2015	NDA-208082-ORIG-1						PENDING	None
Cancelled	6/17/2015	NDA-208082-ORIG-1						PENDING	None

Recommendation: Complete Response

NDA 208082

Review 1

April 18, 2016

Drug Name/Dosage Form	SD-809 Austedo (deutetrabenazine)
Strength	6 mg, 9 mg, 12 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals, Inc.
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	Branch1/DNDAPI/ONDP
Drug Product	Sherita McLamore-Hines	Branch 1/DNDP 1/ONDP
Process	Masih Jaigirdar	Branch 1/DPAI/OPF
Microbiology	Masih Jaigirdar	Branch 1/DPAI/OPF
Facility	Don Obenhuber	Branch1/DIA/OPF
Biopharmaceutics	Jing Li	Branch 1/DB/ONDP
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP

Submissions Reviewed

SUBMISSION	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	5/29/2015	All
Response to IR	9/4/2015	Biopharmaceutics
Response to IR	10/12/2015	Biopharmaceutics
Response to IR	11/2/2015	Process
Stability Update	11/4/2015	Drug Product
Response to FDA mid-cycle teleconference	11/19/2015	Drug Substance, Biopharmaceutics
Response to IR	1/15/2016	Drug Substance
Response to IR	2/22/2016	Drug Substance

Submissions Not Reviewed

The 4/14/2016 amendment contains a partial response to the 2/17/2016 information request regarding controls for (b) (4) in the drug substance. The applicant submitted a revised specification and analytical procedure. However, per the applicant's cover letter the supporting method validation report is not complete. The amendment also contains a response to the 4/12/2016 request for revisions to the drug product post-approval stability commitment.

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Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEWED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	
	Type IV			N/A [1]	N/A [1]	

[1] Adequate information provided in application

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112975	Development of deutetrabenazine
NDA	21894	Approved NDA for Xenazine® (tetrabenazine) tablets currently held by Valeant Pharmaceuticals. Reference drug for 505(b)(2) submission.

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a quality perspective, NDA 208082 is not recommended for approval in its current form. The applicant must adequately address the following deficiencies prior to approval of the application.

Drug Substance

The primary review deficiency is the lack of adequate controls for deutetrabenazine drug substance. The drug substance specification submitted in the original NDA does not include a control for a potential genotoxic impurity, (b) (4) which is used in the manufacture of deutetrabenazine. In the 22-Feb-2016 amendment, the applicant committed to adding a test and acceptance criterion of not more than (b) (4) (ppm) (b) (4), and amending the NDA with this test, acceptance criteria, and method validation information on or before 22-Mar-2016. The 14-Apr-2016 amendment contains a revised specification and the proposed analytical procedure, but the applicant indicated the supporting method validation report is not available yet. The proposed acceptance criterion for (b) (4) is lower than the threshold for toxicological concern (TTC) based on the maximum recommended dose of deutetrabenazine. However, in the absence of the method validation report, the adequacy of the test cannot be evaluated and review of the 14-Apr-2016 amendment is deferred to the next review cycle.

Drug Product

The standard post-approval stability commitment for new applications includes placing the first three commercial batches on stability under long-term (25°C/60% R. H.) and accelerated (40°C/75% R. H.) conditions unless the primary stability batches submitted in the NDA were manufactured at full commercial scale. The stability batches submitted in the NDA were not manufactured at commercial scale; therefore, the applicant was asked to revise the post-approval to include the first three commercial batches. The applicant responded in the 14-Apr-2016 amendment. As review of that amendment is deferred, the response will be evaluated in the next review cycle.

Environmental Assessment/Categorical Exclusion

The applicant has claimed a categorical exclusion under 21 CFR §25.31(b). Approval of the NDA would increase the use of the active moiety, but the estimated concentration of deutetrabenazine at the point of entry into the aquatic environment is below 1 part per billion (ppb). However, the applicant did not confirm that there are no extraordinary

circumstances (information to indicate that approval of the NDA would adversely affect the environment), which is required to support the claim for categorical exclusion.

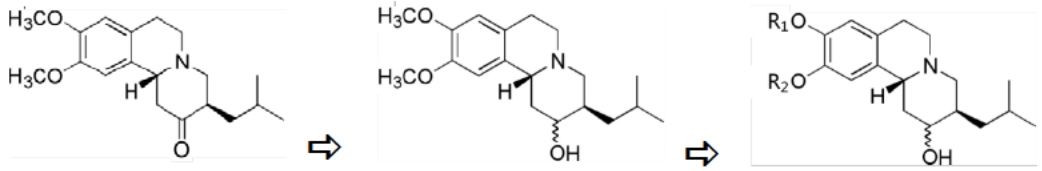
In addition to the deficiencies cited above, the overall manufacturing facility recommendation is still pending. The overall recommendation will be entered into Panorama once completed. An "Acceptable" facility recommendation will *not* affect the final OPQ recommendation. However, a "Withhold" recommendation would require inclusion of standard language inspections in the action letter.

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

There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

II. Summary of Quality Assessments

Currently, the only drug approved in the US for treatment of chorea associated with Huntington's disease (HD) is Xenazine (tetrabenazine) (**1**), a vesicular monoamine transporter, type 2 (VMAT2) inhibitor. By selectively inhibiting VMAT2 in the central nervous system, tetrabenazine depletes presynaptic monoamines, including dopamine, and decreases chorea in patients with HD. Tetrabenazine is rapidly metabolized *in vivo* to α- and β- isomers of dihydrotetrabenazine (HTBZ) (**2**), which provide systemic exposure for pharmacological activity. However, rapid metabolism of α-HTBZ and β-HTBZ by CYP2D6 to the 9- and 10-O-desmethyl metabolites (**3** and **4**) results in large fluctuations in plasma concentrations and the need for frequent dosing.



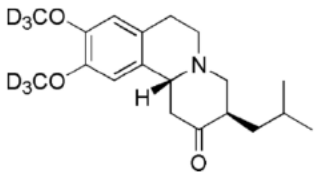
1: HTBZ*

2: α-/β-HTBZ

3: 9-O-desmethyl, $R_1 = H$, $R_2 = H_3C$
4: 10-O-desmethyl, $R_1 = H_3C$, $R_2 = H$

* Tetrabenazine is a racemic mixture. The absolute stereochemistry of the 3*R*,11b*R* enantiomer is shown.

The applicant proposes use of a deuterated analog of tetrabenazine, (d_6)-tetrabenazine or deutetrabenazine (**5**) for treatment of chorea associated with HD.



5: Deutetrabenazine

(b) (4)

A. Drug Substance Quality Summary for Deutetrabenazine

Deutetrabenazine [chemical name: (*RR,SS*)-1,3,4,6,7,11b-hexahydro-9,10-di(methoxy-d_3)-3-(2-methylpropyl)-2*H*-benzo[*a*]quinolizin-2-one] was developed by Auspex Pharmaceuticals (now part of Teva Pharmaceuticals). It is a well characterized small molecule with molecular formula $C_{19}H_{21}D_6NO_3$ and molecular weight 323.46. There are two chiral centers present; however, the drug substance is a racemic mixture. Deutetrabenazine is a moderately lipophilic molecule (Log P 2.88) with pH dependent solubility. It is poorly soluble in water (< 0.05 mg/mL). Solubility increases at lower pH, with maximum solubility (8.2 mg/mL) at pH 3.

The applicant has identified two polymorphic forms of deutetrabenazine, which were characterized. (b) (4) (b) (4)

The applicant has adequately characterized the drug substance by (b) (4) (b) (4) All results from spectroscopic studies and physicochemical analyses are consistent with the proposed structure and route of synthesis.

Deutetrabenazine is manufactured for the applicant by (b) (4) (b) (4)

The applicant has developed and implemented adequate control procedures for starting materials, in-process testing, and (b) (4) to ensure the quality of the finished drug substance. The applicant has also thoroughly characterized potential process impurities.

The drug substance specification includes appropriate tests for critical quality attributes (CQAs) such as appearance, identity, assay, related substances, residual solvents, and elemental impurities. The applicant has provided adequate characterization of related substances and justification for the proposed acceptance criteria. The analytical procedures for these parameters are (b) (4) (b) (4). Non-compendial analytical methods for assay, related substances, and (b) (4) (b) (4) are validated for critical analytical parameters such as linearity, specificity, precision, accuracy, solution stability, and robustness, and are suitable for their intended use. However, the specification submitted in the original NDA does not include a test for (b) (4) a known genotoxic substance used in manufacture of

deutetrabenazine. In response to an information request, the applicant proposed a test method and acceptance criterion for (b) (4) but has not submitted the validation report needed to support suitability of the test method.

(b) (4)

B. Drug Product Quality Summary for Deutetrabenazine Tablets

Deutetrabenazine tablets are round, (b) (4) coated tablets containing 6 mg, 9 mg, or 12 mg deutetrabenazine. The tablet (b) (4) contain mannitol (b) (4), microcrystalline cellulose, povidone (b) (4), polysorbate 80, (b) (4), polyethylene oxide, magnesium stearate, butylated hydroxyanisole, and butylated hydroxytoluene. (b) (4) (b) (4)

The individual strengths are differentiated by (b) (4) coat color and imprint as follows:

6 mg: purple tablets with "SD" over "6" printed on one side
9 mg: blue tablets with "SD" over "9" printed on one side
12 mg beige tablets with "SD" over "12" printed on one side

Deutetrabenazine tablets will be manufacture by (b) (4), (b) (4). The manufacturing process involves (b) (4) (b) (4). The tablets are (b) (4) coated (b) (4) The manufacturer has adequately identified critical process parameters and material attributes that would impact the drug product CQAs.

Deutetrabenazine tablets (b) (4) have physical characteristics, such as dissolution profile, that are characteristic of extended-release products. However, during review of the application, the review team noted that the proposed product labeling does not include an extended-release claim. (b) (4) (b) (4) (b) (4) As the applicant is not seeking an extended-release claim, (b) (4) (b) (4), the product will be labeled simply as "tablets". (b) (4).

The specifications for deutetrabenazine tablets include appropriate tests CQAs such as including appearance, identification by IR and HPLC, assay, dissolution, related substances impurities, content uniformity, and (b) (4) assay. All analytical procedures are adequately described and validated.

Deutetrabenazine tablets are packaged in 60-count, [redacted] HDPE bottles with a [redacted] closure [redacted]. Based on the stability data provided, an expiration dating period of 32 months is acceptable when stored at 25°C.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Austedo is proposed
Non Proprietary Name of the Drug Product	Deutetrabenazine Tablets
Non Proprietary Name of the Drug Substance	Deutetrabenazine
Proposed Indication(s) including Intended Patient Population	Treatment of chorea associated with Huntington's disease
Duration of Treatment	Chronic
Maximum Daily Dose	48 mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: Not established.
   - Drug Product: Not established.

2. Biowaivers/Biostudies
   - Biowaiver Requests. None.
   - PK studies: The PK studies will be reviewed by the Office of Clinical Pharmacology.

The proposed in vitro dissolution method for SD-809 Austedo (deutetrabenazine) Tablet is acceptable. The selection of the apparatus and testing conditions was justified, and the dissolution method was adequately validated. The proposed dissolution acceptance criteria are acceptable and supported by the data on the clinical and the registration batches. The phase 1 formulation and the to-be-marketed formulation were adequately bridged. Therefore, NDA 208082 is recommended for APPROVAL from a Biopharmaceutics perspective.

E. Novel Approaches

The applicant did not employ any novel approaches.

F. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations,

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Martha R. Heimann -S

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ASSESSMENT OF THE BIOPHARMACEUTICS

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

Yes. The in vitro dissolution method is acceptable. The selection of the apparatus and testing conditions was justified. The dissolution method was adequately validated.
The proposed dissolution acceptance criteria are acceptable and supported by the data on the clinical and the registration batches.

The Biopharmaceutics review is focused on the following aspects:

- Solubility of the drug substance
- Drug product formulation
- Dissolution method and method development
- Effect of alcohol on in vitro dissolution
- Dissolution acceptance criterion
- Rationale for absence of extended release claim
- Bridging of different formulations and scales

38.1. Solubility:

The aqueous solubility of the drug substance, deutetrabenazine, is high in acidic conditions, and the solubility is pH dependent, as shown in Figure 38-1.

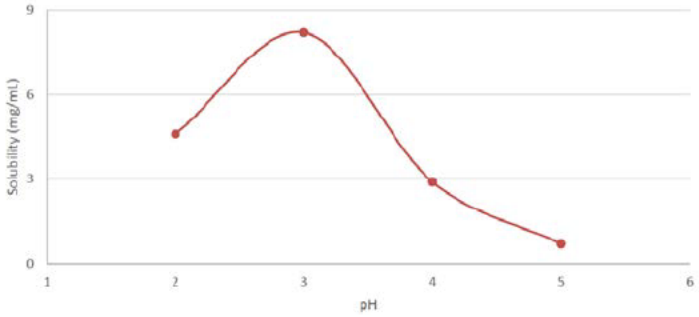

Figure 38-1 Deutetrabenazine solubility profile as a function of pH

38.2. Formulation:

Deutetrabenazine is formulated in 6, 9 and 12 mg tablets for oral administration. The SD-809 Tablets were formulated to provide a [redacted] (b) (4) profile in the low pH region of the digestive tract, the stomach and upper gastrointestinal region, where deutetrabenazine would achieve its maximum potential for solubility.
The composition of the formulation is shown in Table 38-1. [redacted] (b) (4)

[redacted] (b) (4).

(b) (4)

Table 38-1 SD-809 Tablet Composition

Component	Amount per Tablet (mg)			Function	Standard/Grade
Deutetrabenazine	6.00	9.00	12.00	Active ingredient	In-house/GMP
Mannitol (b) (4)				(b) (4)	USP/NF, EP
Microcrystalline Cellulose					NF, EP
Povidone (b) (4)					USP/NF, EP
Polysorbate 80					NF, EP
(b) (4)					(b) (4)
Polyethylene Oxide (b) (4)					NF
Magnesium Stearate					NF, EP
Butylated Hydroxyanisole					NF, EP
Butylated Hydroxytoluene					NF, EP
(b) (4)					(b) (4)
Total					

(b) (4)

38.3. Dissolution Method and Method Development

Table 38-2 shows the conditions employed for the dissolution method.

Table 38-2 Dissolution method for SD-809 Tablets

Apparatus	Apparatus 2 over a disk
Rotation speed	75 rpm
Dissolution media	pH 3.0 acid phthalate buffer
Volume	500 mL
Analytics	HPLC-UV

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:

- SD-809 (deutetrabenazine; d6-tetrabenazine; Austedo™) is a centrally-acting drug indicated for the treatment of chorea in Huntington's disease (HD). The SD-809 tablets are designed to deliver the drug to the upper gastrointestinal. The final commercial SD-809 dosage form is formulated in 6 mg, 9 mg, or 12 mg tablets for oral administration. Daily doses of SD-809 are proposed to be administered with food and range from 6 mg to 48 mg, with daily doses of 12 mg and higher given as two divided doses.
- As the drug product is designed to release the drug in the stomach, an acidic medium of pH 3.0, where the drug substance has good solubility, was chosen for dissolution. The selection of the apparatus and the medium volume were justified. The method was adequately validated.
- The discriminating ability of the dissolution method was demonstrated by utilizing tablets that were intentionally manufactured [redacted] (b) (4) Though process changes [redacted] (b) (4) do not have a large impact on the dissolution profile of the SD-809 tablets, the current dissolution method is capable of identifying trends in these variables.
- No alcohol induced dose dumping was observed.
- Overall the dissolution method has been evaluated and found acceptable.

38.4. Dissolution Acceptance Criteria:

The proposed acceptance criteria are shown in Table 38-3.

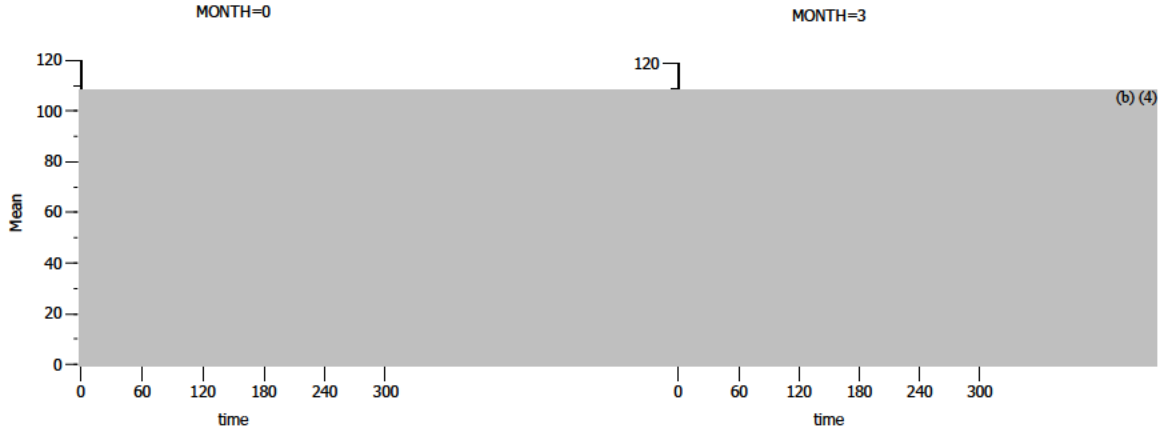
Table 38-3. Proposed dissolution acceptance criteria for SD-809 tablets

Time	Acceptance criterion
1 hour	(b) (4) %
2 hour	(b) (4) %
5 hour	NLT (b) (4) %

In order to evaluate the adequacy of the proposed acceptance criteria, the following IR was communicated to request the raw data for the clinical and registration batches in the 74-day letter dated August 10, 2015.

Provide the complete dissolution profile data (individual, mean, SD, profiles) for the pivotal clinical batch and the primary stability batches in ".xpt" format. Include dissolution data at all the sampling time points in addition to the specification time points.

This Reviewer plotted the mean dissolution profiles for all the clinical (N451173A, N452166B, N451737A, N452168B, N451174A, N452167B) and stability batches at various storage time periods, based on the data provided by the Sponsor on September 4, 2015.



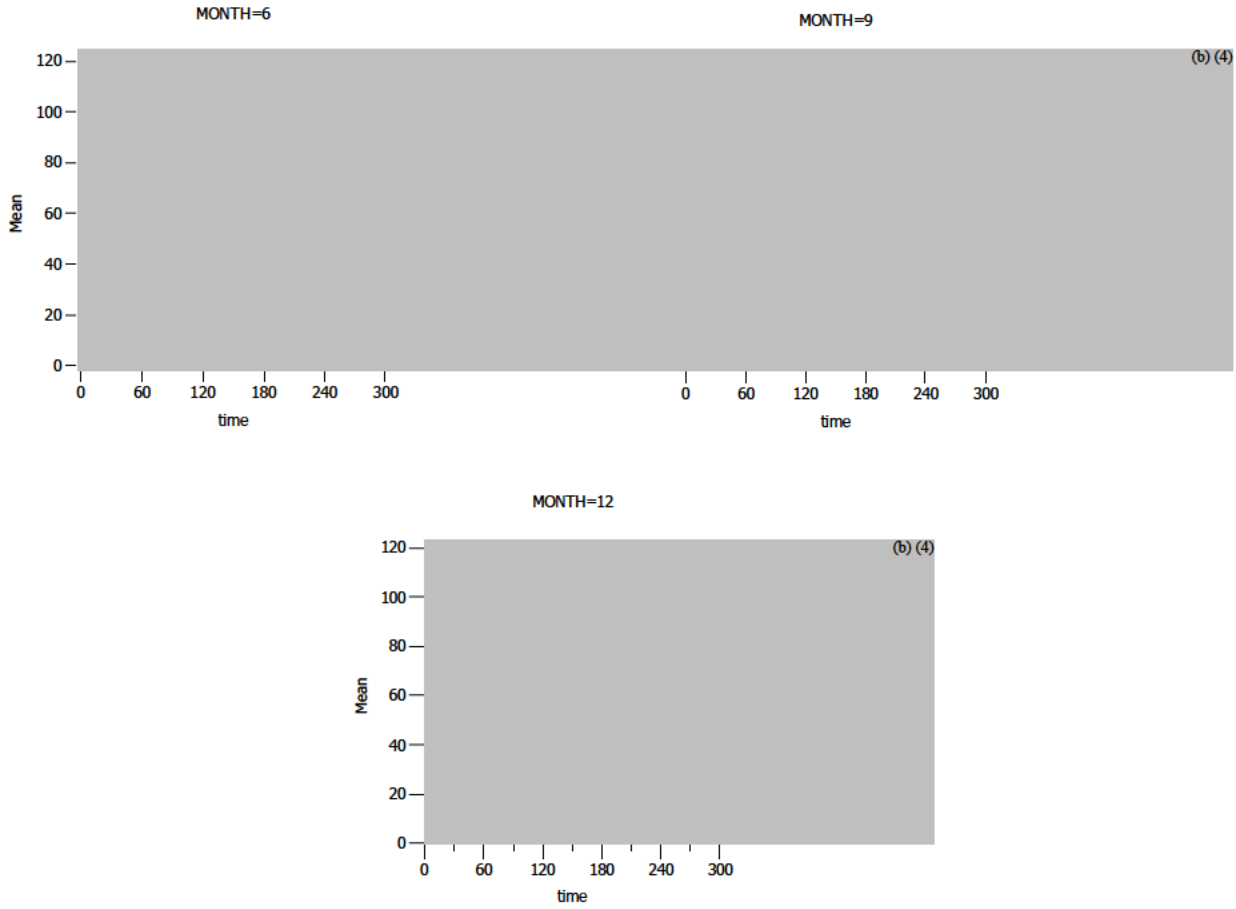


Figure 38-8. The mean dissolution profiles of the clinical and registration batches

The data appear to support the proposed acceptance criterion. However, only the dissolution data at 1, 2, and 5 hours were provided. The data seem to suggest that a tighter limit for the final sampling time (e.g., NLT (b) (4) in 4 hr) may be appropriate. Therefore, the following IR comments were sent to the Sponsor on October 06, 2015.

FDA acknowledges receipt of the dissolution data for the clinical and stability batches which were provided in the file named "disstab.xpt" contained in section 3.2.P.8.3. We have the following additional comments regarding this data file:

- *It is noted that the data were only provided for 3 specification-sampling time points (1, 2, and 5 hr). Provide the dissolution data for the following additional time points if they are available: 0.5, 3, and 4 hr.*
- *Specify in which studies each clinical lot was used (e.g., which clinical trial?).*
- *Submit the complete dissolution data, in ".xpt" format, for the following clinical lots: N452626, N452627, and N452628 (0.5, 1, 2, 3, 4 and 5 hr).*

In their response received on October 12, 2015, the Sponsor stated that the dissolution data at 0.5, 3, and 4 hours were not available and thus not provided. The Applicant also clarified the

confusion caused by the bulk batch numbers and the packaging batch numbers. The data for the clinical batches have been previously provided and used for plots in Figure 38-8 above.

Reviewer's Assessment:

- The proposed acceptance criteria include limits for three time points, and the ranges are within ±10%. All the clinical and registration batches conform to the proposed acceptance criteria. However it appears that an alternative limit for the final time point (Q= (b) (4) in 4 hr) may be applicable to provide tighter quality control.
- Based on the communications with the Applicant, the dissolution data for time points other than the proposed specification time points (0.5, 3, and 4-hr time point) were not provided. Therefore the acceptability of the alternative limit of "Q= (b) (4) in 4 hr" cannot be confirmed/ supported by the data.
- Considering the proposed limit for 5 hr shifted upwards to (b) (4) (instead of (b) (4)), the proposed acceptance criteria are deemed acceptable.

38.5. Absence of Extended release Claim

(b) (4)

In the assessment of the formulation of your proposed product, FDA has identified (b) (4) (b) (4) *excipients;* (b) (4) (b) (4) *. However, you have neither claimed ER characteristics, nor included ER in the proposed name of the drug product. Please clarify why an ER claim was not requested for your proposed drug product.*

In their response received on Dec 22, 2015, the Applicant confirmed that an ER claim will not be requested for this NDA. Per the definition in the United States Pharmacopeia General Chapter <1151>, an "extended-release" product is one "that is deliberately modified to protract the release rate of the API compared to that observed for an immediate-release dosage form." There is no other formulation of deutetrabenazine. The comparative BA studies submitted in the NDA compared the deutetrabenazine to the IR tablets of tetrabenazine, which is a different drug molecule. The results suggested that the differentiated PK profiles compared with the listed drug (Xenazine) were due to the selective deuterium placement in SD-809 instead of drug product formulations.

In addition, the presence of the polyethylene oxide excipient in the SD-809 tablet formulation aids release of deutetrabenazine in the areas of the digestive tract where the drug is maximally soluble. However, this excipient's role does not affect therapeutic efficacy of SD-809 in terms of frequency of dosing or the daily dose requirement.

Therefore, the Applicant does not intend to make extended-release claims for SD-809 and has not otherwise proposed labeling or naming for SD-809 that would indicate that the product should be identified as an extended-release dosage form.

Reviewer's Assessment:

- The NDA for SD-809 (deutetrabenazine; d6-tetrabenazine; Austedo™) was filed as a 505 (b)(2) application, referencing Xenazine® (NDA21894) as the listed drug. However the drug substance deutetrabenazine has different though related chemical structure from that of tetrabenazine and should not be considered as the same entity. (b) (4)

(b) (4) However, the study compared the PK profiles of the proposed drug product of deutetrabenazine tablets versus the tetrabenazine tablets, (b) (4) (b) (4).

- Therefore, the proposed drug product is not considered as an ER product (b) (4) (b) (4)

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

Yes. The bridging of the to-be-marketed formulation to the early-stage formulation is adequate, and the bridging between the different manufacturing scales is adequate as well.

39.1 Bridging for Formulation Change:

Formulation development of the Auspex deutetrabenazine product was initiated with a (b) (4) target dosage strength. As development continued, additional strengths were introduced, including the commercial formulations with 6 mg, 9 mg, and 12 mg deutetrabenazine. In comparison with the phase 1 formulation, the phase 3 formulation (b) (4) (b) (4). The phase 3 formulation is the same as the commercial formulation. The comparison of Phase 1 and Phase 3 formulations is shown in Table 39-1.

Table 39-1 Comparison of Initial Clinical and Phase 3 Commercial Formulations

Component	Phase 1 Study CTP-07[1] (mg/tablet)		Phase 3/Commercial Formulation[2] mg/tablet)		
Deutetrabenazine	7.5	15.0	6.00	9.00	12.00
Mannitol (b) (4)					(b) (4)
Microcrystalline Cellulose					
Povidone (b) (4)					
Polysorbate 80					
(b) (4)					
Polyethylene Oxide (b) (4)					
Magnesium Stearate					
Butylated Hydroxyanisole					
Butylated Hydroxytoluene					
(b) (4)					
Total					

The following comment was conveyed at the mid-cycle communication T-con on November 03, 2015:

It is noted that the 7.5 mg and 15 mg tablets, which were used in pharmacokinetic studies, are (b) (4) *whereas the proposed commercial formulation has a* (b) (4) *coating. In order to bridge these two formulations, provide comparative dissolution data and similarity f2 values for each strength of the* (b) (4) *tablets (7.5, 15 mg) versus each strength of the coated final formulation (6, 9, and 12 mg). Provide the complete dissolution profile data (individual, mean, SD, profiles) at the following sampling time points: 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, and 6 hr.*

In their response received on Dec 22, 2015, the Applicant presented data demonstrating that (b) (4) (b) (4) has no effect on dissolution (see Section 3.2.P.2.3, and the graph below).

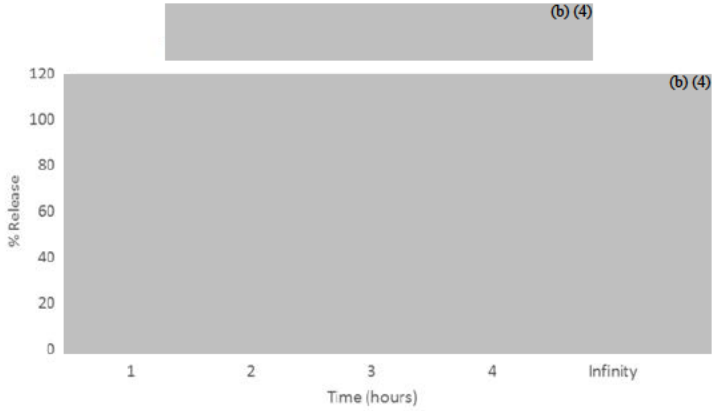


Figure 39-1 Dissolution comparison of the (b) (4) tablets (USP apparatus 2 over a disk, 500 mL of pH 3.0 acid phthalate buffer, 75 rpm)

39.2. Bridging for Scale-up:

The tablet compositions of the Registration and Commercial batches do not differ. Only the scale of production was increased two-fold from the Registration Batches to the intended Commercial Batches. Comparative dissolution testing was conducted on the 12 mg SD-809 Tablets manufactured at both the (b) (4) (clinical/registration process) and the (b) (4) (commercial process) batch scales.

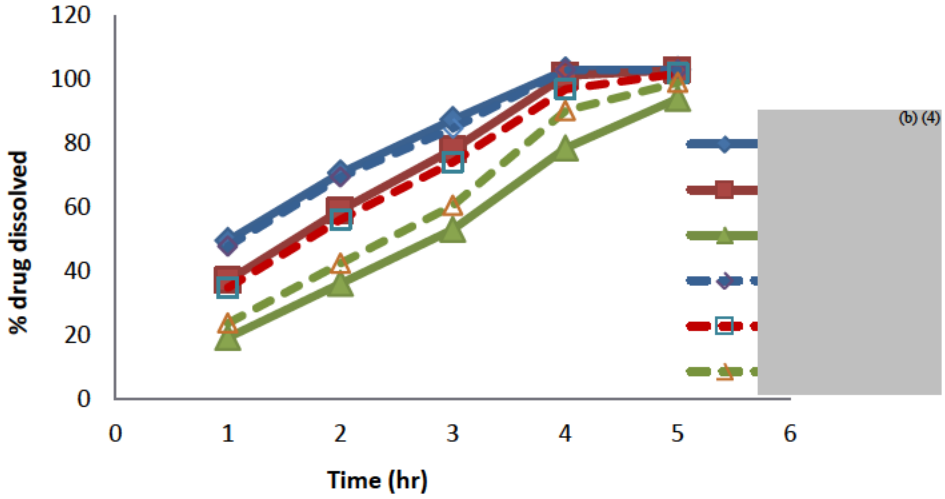


Figure 39-2 Dissolution profiles of the drug product manufactured by two scales

Table 39-2 Summary of f2 values for the drug product manufactured by two scales

	pH = 1.2	pH = 3.0	pH = 4.5
f2	85.0	72.4	56.2

Reviewer's Assessment:

- The differences between the to-be-marketed formulation and the Phase I formulation are (b) (4) in the to-be-marketed formulation. Addition or change (b) (4) usually is not expected to impact the (b) (4) of the drug substance. The (b) (4) coating (b) (4) and the provided dissolution data support the similarity of the in vitro drug release between the (b) (4) formulations. Therefore the Phase 1 formulation was adequately bridged to the to-be-marketed formulation.

- The scale-up in batch size was less than 10-fold, which is a level 1 change per SUPAC-IR, and nothing beyond application/compendial release test is required in terms of dissolution. The Applicant provided the comparative dissolution data and the results demonstrated similarity between the pre-and post-scale-up batches. It is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, NDA 208082 for SD-809 Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg, is recommended for **APPROVAL**.

The approved dissolution method and acceptance criteria are as follows:

Apparatus	Apparatus 2 over a disk
Rotation speed	75 rpm
Dissolution media	pH 3.0 acid phthalate buffer
Volume	500 mL
Acceptance criteria	1 hr (b) (4)% 2 hr % 5 hr NLT (b) (4)%

Jing Li, Ph.D. 1/29/2016
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Li's review and approval recommendation for NDA 208082.

Okpo Eradiri, Ph.D. 2/3/2016
Acting Biopharmaceutics Team Leader
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

Refer to **ASSESSMENT OF THE PROCESS**, **Question 19**.

APPEARS THIS WAY ON ORIGINAL

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

24. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:
The applicant requested categorical exclusion under 21 CFR25.31 (b)…entry into the aquatic environment less than 1ppb) and provided the necessary calculations based on a production scale of (b) (4) to support this claim.

Reviewer's Assessment: Adequate

With an EIC of (b) (4), the applicant's claim for categorical exclusion is acceptable and adequate to support the approval of this application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate

Sherita McLamore-Hines, Ph.D. 4/18/16

Secondary Review Comments and Concurrence: The categorical exclusion is not complete as the applicant did not include the required statement regarding extraordinary circumstances per 21 CFR 25.15(d). After discussion, it was agreed upon by the primary and secondary reviewers as well as the ATL that the following deficiency would be included in the complete response letter:

> Per 21 CFR 25.15(d), revise your claim for categorical exclusion to include a statement that *to the applicant's knowledge, no extraordinary circumstances exist*.

Until this issue is resolved, the environmental assessment is INADEQUATE.

Wendy I. Wilson-Lee, Ph.D. 21-APR-2016
Branch Chief (Acting), DNDP1/ONDP

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 AUSTEDO safely and effectively. See full prescribing information for AUSTEDO.

AUSTEDO (deutetrabenazine) Tablets, for Oral Use
Initial U.S. Approval: [year]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	AUSTEDO (deutetrabenazine)	adequate
Dosage form, route of administration	Tablets, oral	adequate
Controlled drug substance symbol (if applicable)	n/a	adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Dosage form is included but strength is not	Not Adequate

Conclusion: INADEQUATE
The "Highlights" section should be updated to include the strength of the drug product.

(b) "Full Prescribing Information" Section

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

AUSTEDO tablets are available in the following strengths and packages:

The 6 mg (b) (4) tablets are round, (b) (4), purple-coated tablets, with "SD" over "6" printed in black ink on one side.

The 9 mg (b) (4) tablets are round, (b) (4), blue-coated tablets, with "SD" over "9" printed in black ink on one side.

The 12 mg (b) (4) tablets are round, (b) (4) beige-coated tablets, with "SD" over "12" printed in black ink on one side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	tablets	Adequate
Strengths: in metric system	6, 9 and 12 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	complete description included	Adequate

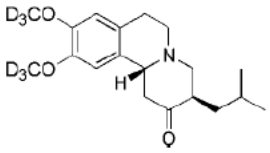
Conclusion: ADEQUATE
The information provided in the Dosage Form and Strength section is adequate to support the approval of this application.

APPEARS THIS WAY ON ORIGINAL

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

AUSTEDO (deutetrabenazine) is a monoamine [(b) (4)] for oral administration. The molecular weight of deutetrabenazine is 323.46; the pKa is 6.31. Deutetrabenazine is a hexahydro-dimethoxybenzoquinolizine derivative and has the following chemical name: (*RR, SS*)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d_3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one.

The [(b) (4)] formula $C_{19}H_{21}D_6NO_3$ is [(b) (4)] the following [(b) (4)]



Deutetrabenazine is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.

[(b) (4)]

AUSTEDO [(b) (4)] tablets contain deutetrabenazine [(b) (4)] and the following inactive ingredients: ammonium hydroxide, black iron oxide, n-butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate 80, polyvinyl alcohol, povidone, propylene glycol, shellac, talc, titanium dioxide, and FD&C blue #2 lake. The 6 mg tablets also contain FD&C red #40 lake. The 12 mg tablets also contain FD&C yellow #6 lake.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Information Provided	ADEQUATE
Dosage form and route of administration	Information Provided	ADEQUATE
Active moiety expression of strength with equivalence statement for salt (if applicable)	Information Provided	ADEQUATE
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		ADEQUATE
Statement of being sterile (if applicable)	n/a	ADEQUATE
Pharmacological/ therapeutic class	Information Provided	ADEQUATE
Chemical name, structural formula, molecular weight	Information Provided	ADEQUATE
If radioactive, statement of important nuclear characteristics.	n/a	ADEQUATE
Other important chemical or physical properties (such as pKa, solubility, or pH)	Information Provided	ADEQUATE

Conclusion: Adequate
The information provided in the Description section is adequate to support the approval of this application.

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

16.1 How Supplied

AUSTEDO tablets are available in the following strengths and packages:

(b) (4) 6 mg (b) (4) round, (b) (4) purple-coated tablets, with "SD" over "6" printed in black ink on one side.

Bottles of 60 tablets: NDC 68546-170-60.

(b) (4) 9 mg (b) (4) round, (b) (4) blue-coated tablets, with "SD" over "9" printed in black ink on one side.

Bottles of 60 tablets: NDC 68546-171-60.

(b) (4) 12 mg (b) (4) round, (b) (4) beige-coated tablets, with "SD" over "12" printed in black ink on one side.

Bottles of 60 tablets: NDC 68546-172-60.

16.2 Storage

Store at 25° C (77° F); excursions permitted to 15-30°C (59-86° F) *[see USP Controlled Room Temperature]*.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Information Provided	ADEQUATE
Available units (e.g., bottles of 100 tablets)	Information Provided	ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Information Provided	ADEQUATE
Special handling (e.g., protect from light, do not freeze)	Information Provided	ADEQUATE
Storage conditions	Information Provided	ADEQUATE

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)	Information Provided	ADEQUATE

Conclusion:
The information provided in the How Supplied is adequate to support approval of this application.

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment: Adequate

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Information included	adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Information included	adequate
Route of administration 21.CFR 201.100(b)(3))	Information included	adequate
Net contents* (21 CFR 201.51(a))	Information included	adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information included	adequate
Lot number per 21 CFR 201.18	Information included	adequate
Expiration date per 21 CFR 201.17	Information included	adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Information included	adequate
Storage (not required)	Information included	adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Information included	adequate
Bar Code per 21 CFR 201.25(c)(2)***	n/a	adequate
Name of manufacturer/distributor (21 CFR 201.1)	Information included	adequate
Others	Information included	n/a

*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.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**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: Adequate

2) **Carton Labeling:** No secondary packaging included

APPEARS THIS WAY ON ORIGINAL

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))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
"See package insert for dosage information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)		

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: ADEQUATE

Sherita McLamore-Hines, Ph.D. 4/18/16

Secondary Review Comments and Concurrence: I concur that the proposed labeling, including the primary container label, are adequate from a product quality perspective.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), DNDP1/ONDP

II. List of Deficiencies To Be Communicated

Drug Substance:
The drug substance specification does not include a test for [redacted] (b) (4). We acknowledge your commitment dated February 22, 2016 to add a test and acceptance criterion of not more than [redacted] (b) (4) (ppm) [redacted] (b) (4) as part of the drug substance specification and amending the NDA with this test, acceptance criterion, and method validation report on or before March 22, 2016. However, the test method was not submitted until April 14, 2016 and validation data was not provided in the amendment.

Drug Product:
In your post-approval stability protocol, you indicate that at least one production batch of the product in the commercial packaging will be placed on long term stability annually. As the registration stability batches were not manufactured at full commercial scale, we request that you update your post-approval stability commitment to include placing the first three commercial batches of each strength of the drug product on long term stability through the proposed shelf life and on accelerated stability for 6 months as per ICH Q1A(R2). The data

should be tabulated and submitted in the annual report with a commitment to withdrawing or discussing any out of specification results in the distributed drug product to the agency.

Process:
Not applicable

Facility:
Pending

Biopharmaceutics:
Not applicable

Microbiology:
Not applicable

Environmental:
Per 21 CFR 25.15(d), revise your claim for categorical exclusion to include a statement that to the applicant's knowledge, no extraordinary circumstances exist.

Label/Labeling:
Not applicable

APPEARS THIS WAY ON ORIGINAL

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	Impurities due to: excipient reactions, (b) (4)	L	(b) (4)	Acceptable	
Content uniformity 6 mg tablet	Low dose, particle size/shape, segregation, (b) (4) (b) (4)	M	Use of (b) (4) process with adequate understanding of process variables from (b) (4).	Acceptable	
Content uniformity 9 mg, 12 mg tablets		L		Acceptable	
Physical (solid state) stability	Formulation, process parameters, (b) (4)	M	(b) (4)	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, (b) (4)	L	(b) (4). Microbial evaluation of stability samples did not show evidence of microbial growth.	Acceptable	
Alcohol dose dumping	Formulation, solubility of (b) (4) (b) (4) excipient and/or API	L	(b) (4) (b) (4) In vitro dissolutions studies demonstrate that alcohol does not affect drug release.	Acceptable	

QUALITY ASSESSMENT

NDA 208082

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Dissolution	Particle size, (b) (4) size, shape, (b) (4) coat, formulation, process parameters	M	Dissolution method is discriminating (b) (4) (b) (4) Though process changes (b) (4) (b) (4) do not have a large impact on the dissolution profile of the SD-809 tablets, the current dissolution method is capable of identifying trends in these variables.	Acceptable	

*Risk ranking applies to product attribute/CQA

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

APPEARS THIS WAY ON ORIGINAL