

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212801Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL**NDA 212801****Review # 1**

Drug Name/Dosage Form	Osilodrostat, Film-coated tablets
Strength	1 mg, 5 mg, and 10 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	03/07/2019
Proprietary Name/Request for Review	03/26/2019
Quality Response to Information Request	06/20/2019
Quality Information	07/02/2019
Quality Response to Information Request	08/07/2019
Quality Response to Information Request	09/06/2019
Quality Response to Information Request	09/25/2019
Quality Response to Information Request	10/01/2019
Quality Information	10/17/2019
Quality Response to Information Request	10/22/2019
Quality Response to Information Request	11/07/2019
Quality Response to Information Request	11/26/2019
Quality Response to Information Request	12/13/2019
Quality Response to Information Request	12/16/2019
Labeling Response	12/19/2019
Quality Response to Information Request	12/20/2019

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Dhanalakshmi Kasi	Danae Christodoulou
Process/Facility	Ying Zhang	
Bio Pharmaceuticals	Kalpana Paudel	Haritha Mandula
Regulatory Business Process Manager	Leeza Rahimi	
Application Technical Lead	Dhanalakshmi Kasi	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: None

B. Other Documents: None

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The final OPQ recommendation is for Approval.

II. Summary of Quality Assessments

NDA 212801 is a 505(b)(1) application covering the new molecular entity osilodrostat phosphate. The drug product is an inhibitor of 11 β -hydroxylase (CYP11B1), the enzyme that catalyzes the final step in the synthesis of cortisol in the adrenal cortex. It is developed for the treatment of adult patients with Cushing's disease. The drug product is supplied as 1 mg, 5 mg, and 10 mg film-coated tablets and it is an immediate release dosage form for oral administration.

Drug Substance:

The drug substance used in the manufacture of the drug product is osilodrostat phosphate. Osilodrostat phosphate is a white to practically white powder. Osilodrostat phosphate has one chiral center and is used as a single isomer (R-enantiomer). The drug substance is crystalline, anhydrous, non-hygroscopic and has been designated as (b) (4). The synthetic scheme and manufacturing process are adequately detailed in the application. The Applicant has provided adequate data in support of the structure elucidation and characterization of the drug substance. The drug substance specification is adequate to ensure the quality of osilodrostat phosphate. The stability data indicated that the (b) (4) is compatible with the drug substance and suitable for its use as a primary packaging material. The stability data supports the proposed (b) (4)-month retest period for osilodrostat phosphate.

During the review cycle, (b) (4)

(b) (4)

Drug Product:

The commercial formulation of 1 mg, 5 mg and 10 mg film-coated tablets is identical to the formulation used in clinical trials. The composition of osilodrostat 1 mg film-coated tablets contains a (b) (4)

and differ only in tablet weight. The excipients used in the tablet core are microcrystalline cellulose, mannitol, magnesium stearate, croscarmellose sodium and colloidal silica. The film coating comprises of hydroxypropylmethyl

cellulose, titanium (b) (4), iron oxide yellow, iron oxide red, iron oxide black, polyethylene glycol 4000 and talc as excipients. The drug product release and stability specifications include all critical quality parameters and it is adequate. Batch data provided for representative clinical and stability batches for 1 mg, 5 mg and 10 mg strengths and the test results are within the specified limits. Stability data provided for 24 months at long term storage conditions support the shelf life of 36 months.

FDA issued

(b) (4)

(b) (4)

Process and Facility:

The drug substance (b) (4) are manufactured at (b) (4) (b) (4) and the drug product is manufactured at Novartis Pharma Stein AG. Both the facilities have satisfactory cGMP history and approved based on the profile.

The manufacturing process of osilodrostat film-coated tablets involves

(b) (4)

(b) (4)

Biopharmaceutics:

The in vitro dissolution studies were conducted by the Applicant to bridge the two formulations: hard gelatin capsule and film-coated tablet at pH 1, pH 4.5 and pH 6.8. The dissolution of tablets and capsules are rapid and similar in all conditions for all strengths. The applicant did not request biowaiver. (b) (4)

The NDA is adequate from biopharmaceutics perspective. (b) (4)

A. Special Product Quality Labeling Recommendations: None

Final Risk Assessment:

Drug Product (Osilodrostat, 1 mg, 5 mg, and 10 mg Film-coated tablets)

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation
Identity of osilodrostat	Method of manufacture, suitability of analytical methods	Low	(b) (4)	Low. Acceptable
Assay of osilodrostat	Method of manufacture, suitability of analytical methods	Low		Low. Acceptable
Impurities	Suitability of analytical methods	Medium		Low. Acceptable
Content uniformity	Formulation, method of manufacture	Medium		Low. Acceptable
(b) (4) content	API, container and closure	Medium		Low. Acceptable

B. Life Cycle Knowledge Information:

Provide post-action, stability data for at least one batch of commercial drug product packaged in the proposed commercial container and closures under long term and accelerated storage conditions for three months.

C. RBPM communication to the applicant: None

Application Technical Lead Name and Date: Dhanalakshmi Kasi, Ph.D., 01/02/19



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Kasi

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Labeling Review:**Carton**

(b) (4)

Reviewers Evaluation: Revised carton and container label is attached.

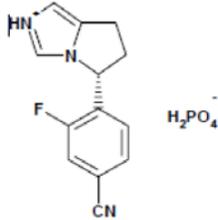
Package Insert Information:

DOSAGE FORMS AND STRENGTHS

(b) (4)

DESCRIPTION

TRADENAME (osilodrostat) is a cortisol synthesis inhibitor.



The chemical name of osilodrostat is 4-[(5R)-6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitriledihydrogen phosphate.

Molecular formula of osilodrostat salt (phosphate) form on anhydrous basis is: (C₁₃H₁₁FN₃) (H₂PO₄).^{(b) (4)} Relative molecular mass of osilodrostat phosphate salt form is 325.24 g/mol.

TRADENAME for oral administration contains 1 mg, 5 mg, or 10 mg of osilodrostat^{(b) (4)} and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, mannitol, microcrystalline cellulose, and magnesium stearate. The film coat is composed of hypromellose, titanium dioxide, ferric oxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Store at room temperature between 68°F to 77°F (20°C to 25°C).

Comment to the Sponsor:

TRADENAME for oral administration contains 1 mg, 5 mg, or 10 mg of osilodrostat equivalent to 1.4 mg, 7^{(b) (4)} and 14.3 mg of osilodrostat phosphate respectively.



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Kasi

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BIOPHARMACEUTICS

Product Background:

NDA: NDA-212801-ORIG-1

Drug Product Name / Strength: Osilodrostat Tablets/1mg, 5mg, 10mg

Route of Administration: Oral

Applicant Name: Novartis Pharmaceuticals Corporation

Review Recommendation: ADEQUATE

Review Summary:

The proposed drug product, Osilodrostat Tablets/1mg, 5mg, 10mg is indicated for the treatment of patients with Cushing’s disease. Osilodrostat is an orally-administered inhibitor of 11 beta-hydroxylase (CYP11B1). Given the mechanism of action to inhibit cortisol synthesis at the adrenal glands, osilodrostat has therapeutic potential in all forms of endogenous Cushing syndrome (i.e., pituitary Cushing’s disease, adrenal Cushing’s syndrome and ectopic ACTH syndrome). Osilodrostat is a new molecular entity and is not yet approved or marketed in any country.

Dissolution Method and Acceptance Criteria: ADEQUATE

Osilodrostat 1 mg, 5 mg and 10 mg film-coated tablets are an immediate release oral dosage form. Dissolution Apparatus I (Basket) was selected during method development (b) (4)

(b) (4) The following dissolution method and acceptance criterion are approved.

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
I (Basket)	100	Phosphate buffer, pH 6.8/37°C ± 0.5°C	<u>1 mg:</u> 500ml <u>5mg, 10 mg:</u> 900 ml	<u>1 mg:</u> Q = $\frac{(b)}{(4)}\%$ in 20 minutes <u>5 mg and 10 mg:</u> Q = $\frac{(b)}{(4)}\%$ in 15 minutes

Bridging of clinical formulations: ADEQUATE

The Applicant has conducted in vitro dissolution studies to bridge the two formulations (CSF: hard gelatin capsule and FMI: film-coated tablet) at pH 1 (0.1 N HCl), pH 4.5 (50 mM sodium acetate buffer) and pH 6.8 (50 mM potassium phosphate buffer). The dissolution of tablets and capsules are rapid and similar in all conditions for all strengths.

Biowaiver: Not requested

BCS Package: Not reviewed in this cycle

(b) (4) _____ (b) (4)
(b) (4) _____ (b) (5), _____ (b) (4)
completed at this time. _____ (b) (5)

(b) (5) The NDA is adequate from biopharmaceutics perspective. (b) (4)

From Biopharmaceutics perspective, NDA 212801 is adequate and recommended for approval.

(b) (5)

BCS Designation

Reviewer's Assessment: BCS package was not reviewed in this cycle.

The Applicant stated that Osilodrostat _____ (b) (4)

_____ The following information was provided.

Solubility:

Per the Applicant, osilodrostat phosphate is highly soluble (> 50 mg/mL) in water and selected buffer solutions in the physiological pH range from 1 to 6.8.

Solubility of Osilodrostat phosphate

Solvent / Buffer solution	Solubility (mg/mL) at 25 °C
Buffer pH = 1	> 50
Buffer pH = 3	> 50
Buffer pH = 5	> 50
Buffer pH = 6.8	> 50
Water	> 50
Ethanol	5.8
Acetone	1.5
Propylene glycol	1.5
Methanol	14.2
Acetonitrile	0.2
Heptane	0.3
Ethyl acetate	0.4
Methylene chloride	0.9
Tetrahydrofuran	0.3

Permeability:

Per the Applicant, the passive permeability of osilodrostat was estimated to be greater than 155×10^{-5} cm/min using human Caco-2-cell monolayers ([\\cdsesub1\evsprod\nda212801\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\dmpk-r0600901\dmpk-r0600901--pre-clinical-study-report.pdf](https://cdsesub1.evsprod.nda212801.0000.m5.53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\dmpk-r0600901\dmpk-r0600901--pre-clinical-study-report.pdf)).

Osilodrostat phosphate physicochemical parameters

Parameters	Results
pH	4.45 in 1% solution in water
Melting point	214°C (DSC)
Dissociation constant (pKa)	6.9
Partition coefficient	cLogP 1.61
PAMPA permeability	log Pe, pH 4.0: -4.85 log Pe, pH 6.8: -4.7
Permeability	High, greater than 155×10^{-5} cm/min ^[1]
Polymorphism	Osilodrostat phosphate is crystalline and designated as (b) (4)

[1] In vitro osilodrostat exhibited high permeability in Caco-2 cell monolayers [DMPK R0600901]. Osilodrostat uptake into human hepatocytes in vitro, most likely, by a passive permeation process without modulation by a solute-carrier system [DMPK R1200572]
cLogP: partition coefficient
DSC: Differential Scanning Calorimeter
Source: [Module 3.2.S.1.3-General properties]; [Module 3.2.S.3.1-Elucidation of structure and other characteristics]

Absorption:

The Applicant stated that following a single oral administration of 50 mg osilodrostat containing 100 µCi of 14C in N=5 healthy male volunteers (Study CLCI699C2101), the majority of the radioactivity dose was eliminated in the urine with only a minor amount eliminated in the feces (1.6%). This evidence supports a high oral absorption of osilodrostat in humans (b) (4).

(b) (4)

(b) (4) As a result, osilodrostat absorption in the GI tract is not expected to limit the bioavailability of the compound.

Reviewer's comments:

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (5)

(b) (4)

[Redacted]

(b) (5)

Dissolution: Please see below.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: Adequate

Osilodrostat 1 mg, 5 mg and 10 mg film-coated tablets are an immediate release oral dosage form. The following dissolution method and specifications are proposed:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
I (Basket)	100	Phosphate buffer, pH 6.8/37°C ± 0.5°C		<p><u>1 mg:</u> Q = (b) (4)% in 20 minutes</p> <p><u>5 mg and 10 mg:</u> Q = (b) (4)% in 15 minutes</p>

Dissolution method development

(b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

Discriminating ability of the dissolution method

The Applicant conducted dissolution study with the proposed QC method to assess the discriminatory ability of the batches

- with different manufacturing process
- with different level of excipients
- stored in different packaging during stability
- with different hardness / manufactured with (b) (4)

The details are provided in the document <\\cdsesub1\evsprod\nda212801\0000\m3\32-body-data\32p-drug-prod\lci699-film-coated-tablets\32p2-pharm-dev\pharmaceutical-development-dp.pdf>.

The dissolution method showed some sensitivity to the above factors specially for 1 mg strength. However, all the profiles met the proposed acceptance criterion. This is acceptable as Osilodrostat is highly soluble, highly permeable and rapidly dissolving. Owing to the listed factors, the discriminating ability may not be feasible.

Acceptance Criteria

The proposed acceptance criteria are as follows:

1 mg

Q= (b) (4)% in (b) (4) minutes

5 mg and 10 mg

Q= (b) (4)% in 15 minutes

Per the Applicant, the 1 mg strength is manufactured by (b) (4)

(b) (4)

(b) (4)

(b) (4)

A detailed discussion on the choice of the dissolution method, dissolution profile data and justification for the assigned Q-value is provided in section [3.2.P.2.2, Section 2.3.2.2].

In response to an IR (See IR3.2) to revise the acceptance criterion for 1 mg to $Q = \frac{(b)}{(4)}\%$ in (b) (4) minutes, the Applicant provided additional data and proposed an acceptance criterion $Q = \frac{(b)}{(4)}\%$ in 20 minutes. The Applicant's justification is acceptable.

Dissolution profiles

The Applicant has provided in vitro dissolution profiles of the film-coated tablets used in clinical studies in the link (<\\cdsesub1\evsprod\nda212801\0000\m3\32-body-data\32p-drug-prod\lci699-film-coated-tablets\32p2-pharm-dev\pharmaceutical-development-dp-app1.pdf>).

Bridging of Formulations

Reviewer's Assessment: Adequate

Bridging of formulations used in clinical studies

Initially 0.25 mg, 0.5 mg, 1 mg, 5 mg and 50 mg hard gelatin capsules (clinical service form, CSF) were developed which were used in first Phase 1 and Phase 2 clinical studies. The hard gelatin capsules were later replaced by 1 mg, 5 mg, 10 mg and 20 mg film-coated tablets (final market image, FMI). The film-coated tablets were used in late Phase 1, Phase 2 and the pivotal Phase 3 clinical trial supporting the clinical development in Cushing's disease. From the four dosage strengths used in clinical trials, three (1 mg, 5 mg and 10 mg) will be marketed. Details on formulation development studies are provided in Module [3.2.P.2.2, Section 2.1.2.1].

The composition of Osilodrostat 0.25 mg, 0.5 mg, 1 mg, 5 mg and 50 mg hard gelatin capsules is presented below in Table 1.

Table 1: Composition of Osilodrostat 0.25 mg, 0.5 mg, 1 mg, 5 mg and 50 mg hard gelatin capsules

(b) (4)



The composition of film-coated tablets is provided below.

Table 2: Composition of 1 mg, 5 mg, 10 mg and 20 mg film-coated tablets

Ingredient	Amount per 1 mg film-coated tablet	Amount per 5 mg film-coated tablet	Amount per 10 mg film-coated tablet	Amount per 20 mg film-coated tablet
Tablet core				
Osilodrostat phosphate ¹	1.4 (b) (4)	7. (b) (4)	14.3 (b) (4)	28.6 (b) (4)
Microcrystalline cellulose, (b) (4)				
Mannitol				
Croscarmellose sodium				
Magnesium stearate				
Colloidal silicon dioxide, (b) (4)				
Total core tablet weight				
Film-coat (b) (4)				

Osilodrostat 1 mg film coated tablets are manufactured

(b) (4)
(b) (4)

(b) (4)

The Applicant has conducted in vitro dissolution studies to bridge the two formulations (CSF: hard gelatin capsule and FMI: film-coated tablet). In line with biowaiver requirements, dissolution comparisons were performed at pH 1 (0.1 N HCl), pH 4.5 (50 mM sodium acetate buffer) and pH 6.8 (50 mM potassium phosphate buffer) using USP apparatus 1 (basket) at 100 rpm. To cover the strengths used during Phase 3 pivotal study, dissolution profiles of 1 mg, 5 mg, 10 mg and 20 mg film-coated tablets have been compared with 1 mg, 5 mg, 2 x 5 mg and 4 x 5 mg hard gelatin capsules, respectively. The dissolution of tablets and capsules were rapid and similar in all conditions for capsules and film-coated tablets for all strengths. Details on this comparative dissolution study including the dissolution profiles are provided in M.3.2.P.2. (<\\cdsesub1\evsprod\nda212801\0000\m3\32-body-data\32p-drug-prod\lci699-film-coated-tablets\32p2-pharm-dev\pharmaceutical-development-dp-app1.pdf>).

The Applicant also mentioned that clinical pharmacokinetic results supported no clinically meaningful difference between capsules and tablets formulations of osilodrostat (Section 3.2; <\\cdsesub1\evsprod\nda212801\0000\m2\27-clin-sum\summary-biopharm-cd.pdf>). Healthy volunteer studies [Study A2101], [Study C2103] and [Study C2104] were used for comparing pharmacokinetics of capsule and tablet formulations at 30 mg. Per an email communication on April 15, 2019, Clin. Pharm. reviewer mentioned that according to the sponsor’s summary, the to-be-marketed formulation (tablet) was used in the pivotal Phase 3 study (table below). Thus, they may not need the pivotal BE study for a bridging. They used the tablet in a few clin. Pharm. studies, and thus they can have labeling for PK of to-be-marketed.

Phase	Study	Objective	Dosing
Phase I	A2101	SAD/MAD	3, 10, 30, 100, 200 mg capsule
	C2101	ADME (mass balance)	50 mg capsule+radiolabeled
	C2102	DDI using cocktail	50 mg capsule
	C2108	DDI with OC	30 mg tablet BID for 12 days
	A2102	Caucasian vs. Japanese	Day 1: 0.5, 1, 2 mg capsule Day 2-14: 0.25, 0.5 , 1 mg BID
	C2103	HI	30 mg tablet
	C2104	RI	30 mg tablet
	C1101	Food effect	30 mg tablet
	C2105	TQT	10, 150 mg capsule
Phase II	C2201	Proof-of-concept	2 mg capsule BID, adjusted to 50 mg BID (n=12)
	C1201	Proof-of-concept	2 mg tablet BID to 30 mg BID in Japanese (n=9)
Phase III	C2301	Pivotal: 8-Week, placebo- controlled, randomized withdrawal study after 24 weeks open label osilodrostat	2 mg tablet BID to 30 mg BID (n=137)

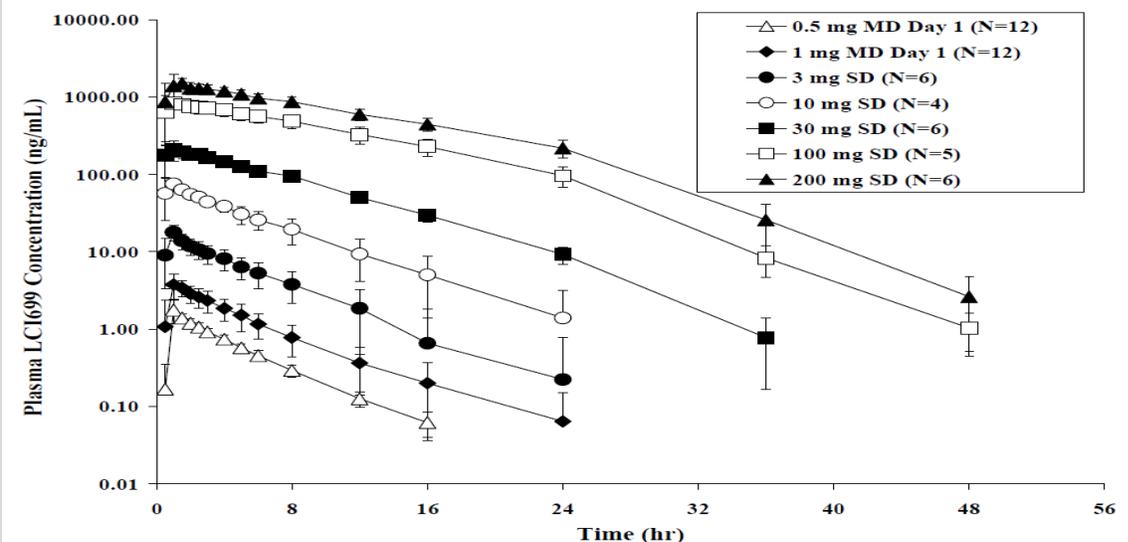
The Applicant also noted that the intended commercial formulation of 1 mg, 5 mg and 10 mg film-coated tablets is identical to the formulation used in late Phase 1, Phase 2 and the pivotal Phase 3 clinical trial, i.e. same qualitative and quantitative composition, same appearance etc. The Applicant has provided comparative dissolution data to confirm comparability of clinical / registration stability batches (film-coated tablets) and confirmatory production batches (film-coated tablets), both manufactured at the proposed commercial site Novartis Pharma Stein AG, Stein (see Module 3.2.P.2.2, Section 2.3.2.2.4; [\\cdsesub1\evsprod\nda212801\0000\m3\32-body-data\32p-drug-prod\lci699-film-coated-tablets\32p2-pharm-dev\pharmaceutical-development-dp.pdf](#)). The confirmatory production batches are representative of commercial process with regard to manufacturing process and batch size. Both batches show similar ^{(b) (4)} dissolution (more than ^{(b) (4)} % of the drug is dissolved within 15 minutes) in the proposed dissolution medium (phosphate buffer pH 6.8, basket, 100 rpm).

Biowaiver Request

Reviewer's Assessment: The Applicant has not requested biowaiver for any strengths.

The Applicant has conducted ascending dose study (Study A2101), following administration of 0.5 mg to 200 mg single oral ascending doses to healthy volunteers under fasting conditions. The PK profiles are shown below.

Figure 2-1 Mean (SD) plasma concentration-time profile of osilodrostat single oral ascending doses in healthy subjects (Study A210)



In study A2101, dose proportionality was evaluated based on a power model, $Y = a * \text{Dose}^b$, where Y is C_{max} or AUC. Since the value for exponent b deviated significantly from unity (greater than 1) based on analysis of data from the single dosing and multiple dosing cohorts, it was suggested that the increases in the osilodrostat exposure were over dose proportional over the dose range investigated. The Applicant states that given the individual dose-titration scheme implemented in patient studies, dose can be adjusted based on efficacy, safety and tolerability, thus this slight over dose-proportionality is of no clinical concern. Clinical

Pharmacology team will review this data. For additional details, please refer to clinical pharmacology review.

Appendix 1

List of Deficiencies:

(b) (4)



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