

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204042Orig1s000**

**CHEMISTRY REVIEW(S)**

## **Final Addendum to CMC Reviews**

**From:** Su (Suong) Tran, CMC Lead, ONDQA  
**To:** NDA 204042 (canagliflozin)  
**Subject:** Final ONDQA recommendation for NDA 204042

This addendum is for filing in DARRTS the Compliance/OMPQ/EES overall recommendation dated 28-MAR-2013: ACCEPTABLE.

**Conclusion:** The final ONDQA recommendation for NDA 204042 is APPROVAL with no pending issue.

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/s/  
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SUONG T TRAN  
03/29/2013

**Memorandum to NDA 204042 File**

From: Sheldon Markofsky (Chemistry Reviewer)

Date: February 13, 2013

Subject: Up-dated Drug Substance and Drug Product Specification Tables

Although up-dated specifications for both Canagliflozin (drug substance) and Canagliflozin Tablets have been approved (Chemistry Review 1, dated 2-8-13), the applicant had not provided specification tables for these up-dated specifications. Subsequent to the CMC Review, the applicant provided the following up-dated specification tables.

Specifications for the Drug Substance (2-12-13 amendment)

Parameters	Regulatory Acceptance Criteria	Test Methods
Appearance	White to off-white powder	Visual examination
Identification <sup>a</sup>		
IR	Complies with reference spectrum	Current USP <197K>
Assay	98.0-102.0% (w/w) calculated on anhydrous basis	HPLC-00005-V1
Chromatographic Purity		HPLC-00005-V1
Any Unspecified Impurity	Not more than (b) (4)	
Total impurities	Not more than (b) (4)	
Chromatographic Purity (b) (4)	Not more than (b) (4)	LCMS-008767-V1
Residual Solvents (b) (4)	Not more than (b) (4)	GC-005489-V1
Water Content	(b) (4)	KARL-00002-V1
Particle Size (b) (4)		LD-003457-V1
Residue on Ignition/Sulphated Ash <sup>a</sup>	Not more than (b) (4)	Current USP <281>, 1g
Heavy Metals <sup>a</sup>	Not more than (b) (4)	Current USP <231> method II, 1g

<sup>a</sup> Initial release test only

Specifications for Canagliflozin Tablets (2-8-13 amendment)

Test Parameter	Regulatory Acceptance Criteria	Test Methods
<b>Identification<sup>a</sup></b>		
IR	Complies with reference spectrum	IR-00125-V1 <sup>b</sup>
<b>Appearance</b>		
100-mg	Yellow, capsule-shaped tablet debossed with "CFZ" on one side and "100" on the other side	Visual examination
300-mg	White to off-white, capsule-shaped tablet debossed with "CFZ" on one side and "300" on the other side	Visual examination
Assay	90.0-110.0% of label claim	UPLC-00014-V1 <sup>b</sup> or HPLC-01-V1 <sup>b</sup>
<b>Chromatographic Purity</b>		
Each Unspecified Degradation Product	NMT (b) (4)	UPLC-00014-V1 <sup>b</sup> or HPLC-01-V1 <sup>b</sup>
Total Degradation Products	NMT (b) (4)	UPLC-00014-V1 <sup>b</sup> or HPLC-01-V1 <sup>b</sup>
<b>Chromatographic Purity (b) (4)</b>		
100-mg	NMT (b) (4)	LCMS-008776-V1 <sup>b</sup>
300-mg	NMT (b) (4)	LCMS-008776-V1 <sup>b</sup>
Dissolution	Q: (b) (4) in 20 minutes	DISS-00016-V1 <sup>b</sup>
Uniformity of Dosage Units <sup>a</sup>	Conforms to current USP <905>	Current USP <905> Weight Variation

<sup>a</sup> This test is conducted only at initial release.

<sup>b</sup> (b) (4)

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/s/  
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SHELDON B MARKOFSKY  
02/13/2013

**NDA 204042**

**Invokana**  
**(Canagliflozin) Tablets**

**Janssen Pharmaceuticals, Inc**

**Sheldon Markofsky, Ph.D.**

**Division of Metabolism and Endocrine Products (HFD-510)**

**and**

**Office of New Drug Quality Assessment III Branch VII**

File: 204042c

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I	
S DRUG SUBSTANCE	pp. 11
P DRUG PRODUCT	pp. 80
A APPENDICES (Attachments)	159
R REGIONAL INFORMATION	N/A
II. List Of Deficiencies To Be Communicated	none

# Chemistry Review Data Sheet

1. NDA 204042
2. REVIEW #: 1
3. REVIEW DATE: 05-February- 2013
4. REVIEWER: Sheldon Markofsky, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	31-May-2012
Filing Review Document	02-Aug-2012
Amendment <sup>a</sup>	23-Oct.-2012
Amendment <sup>b</sup>	15-Nov-2012
Amendment <sup>c</sup>	30-Nov-2012
Amendment <sup>d</sup>	21-Dec-2012
Amendment <sup>e</sup>	18-Jan-2013
Amendment <sup>f</sup>	22-Jan-2013
Amendment <sup>g</sup>	30-Jan-2013
IR Letter	19-Nov-2012
IR Letter	12-Dec-2012
IR Letter	11-Jan-2013

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	31-May-2012
Amendment <sup>a</sup>	23-Oct.-2012
Amendment <sup>b</sup>	15-Nov-2012
Amendment <sup>c</sup>	30-Nov-2012
Amendment <sup>d</sup>	21-Dec-2012
Amendment <sup>e</sup>	18-Jan-2013
Amendment <sup>f</sup>	22-Jan-2013
Amendment <sup>g</sup>	30-Jan-2013

- a) The 10-23-12 amendment provides information about a genotoxic impurity.
- b) The 11-15-12 amendment provides carton and container labeling.
- c) The 11-30-12 amendment provides responses to our 11-19-12 Information Requests.
- d) The 12-21-12 amendment provides responses to our 12-12-12 Information Requests.
- e) The 1-18-13 amendment provides robustness information for the validation of some analytical procedures.
- f) The 1-22-13 amendment provides responses to our 1-11-13 Information Requests.
- g) The 1-30-13 amendment provides additional container/closure information.

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Janssen Pharmaceuticals Inc. 1125  
Address: 1125 Trenton-Harbourton Road  
Titusville, New Jersey 08560 7  
Representative: Sukhdev K. Saran. Associate Director, Global  
Regulatory Affairs  
Telephone: (908) 429-1994

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Invokana
- b) Non-Proprietary Name: Canagliflozin tablets
- c) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

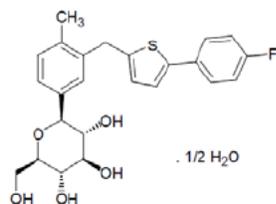
11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 100 and 300 mg  
Canagliflozin (drug substance) is a hemihydrate, but the strength is based on the anhydrous form.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:



Molecular formula: C<sub>24</sub>H<sub>25</sub>FO<sub>5</sub>S•1/2 H<sub>2</sub>O

Molecular weight: 453.53 [444.52 + (0.5 • 18.02)]

**INN:** Canagliflozin

**USAN:** Canagliflozin

Chemical names:

(Chemical Abstracts)

(1S)-1,5-anhydro-1-C-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol

(IUPAC)

(1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol Hemihydrate

CAS Registry Numbers: 928672-86-0 (hemihydrate)

842133-18-0 (anhydrous)

Company Code Numbers: R600348

JNJ-28431754-ZAE

TA-7284

In both the NDA and the Review, the terminology Canagliflozin and Canagliflozin hemihydrate is used interchangeably, unless otherwise noted.

## 17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76479	IND for Canagliflozin

## 18. STATUS:

## ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	8-9-10	
Pharm/Tox	Acceptable	2-1-13	Fred Alavi
Methods Validation	Acceptable	2-4-13	S. B. Markofsky
EA	Acceptable	2-4-13	S. B. Markofsky
Microbiology	N/A		
ONDQA/Biopharm Review	Acceptable	2-1-13 and based on 2-5-13 teleconference	Houda Mahayni

19. ORDER OF REVIEW: N/A (OGD Only)

## The Executive Summary

# The Chemistry Review for NDA 204042

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

The Establishment Inspection work for the relevant manufacturing and testing facilities has not been completed. Thus, the CMC recommendation for approval does not reflect any facility inspection issues.

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

None

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product and Drug Substances

#### 1) Drug Product

The drug product, with the proposed proprietary name Invokana and the established name Canagliflozin, is a sodium-glucose co transporter and is used for the treatment of type 2 diabetes. Canagliflozin immediate-release (film-coated) tablets are proposed to be marketed in 100 mg and 300 mg strengths. The canagliflozin 100 mg capsule-shaped immediate release film-coated tablets are yellow in color with one side debossed with "CFZ" and the other side debossed with "100". The 300 mg capsule-shaped tablets are white with one side debossed with "CFZ" and the other side debossed with "300". Since both strengths are (b) (4)

Although the drug substance is a hemihydrate, the above noted tablet strengths are based on the anhydrous form of canagliflozin. The proposed market packages are shown in the following tables:

100 mg Tablets

Package Type	Count	NDC
		50458-140-
(b) (4)	5	01
	30	30
	90	90
	500	50
	NA	10

300 mg Tablets

Package Type	Count	NDC
		50458-141-
(b) (4)	5	01
	30	30
	90	90
	500	50
	NA	10

Besides canagliflozin, the drug product contains the following inactive ingredients in the core tablets: croscarmellose sodium, hydroxypropyl cellulose, anhydrous lactose, magnesium stearate and microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, Macrogol/PEG, talc and iron oxide yellow E172 (100 mg tablet only). All of the inactive ingredients are compendial.

**2) Drug Substance**

The drug substance, canagliflozin, is manufactured by Janssen Pharmaceutica NV in Belgium, and the relevant CMC issues related to the manufacture of this material are described in the Drug Substance section of the Chemistry Assessment. Canagliflozin is a white to off-white powder, which has been found to exist in (b) (4). The drug substance is (b) (4). Satisfactory stability data was provided to support a retest date of (b) (4) for the drug substance for storage at (b) (4).

From a Chemistry, Manufacturing, and Controls (CMC) point of view, the drug substance is deemed adequate to support this NDA.

## **B. Description of How the Drug Product is Intended to be Used**

The recommended dose of INVOKANA™ is 100 or 300 mg once daily, preferably taken before the first meal of the day. The stability studies support an expiration-dating period of 24 months for both the 100 and 300 mg strengths of INVOKANA when stored at controlled room temperature [25°C (77°F)], with excursions permitted between 15°C and 30°C packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.

## **C. Basis for Approvability or Not-Approval Recommendation**

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved on the following basis:

- Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substance
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product

The Establishment Inspection work for the relevant manufacturing and testing facilities has not been completed. Thus, the CMC recommendation for approval does not reflect any facility inspection issues.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

**III. Administrative**

**A. Reviewer's Signatures**

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

**B. Endorsement Block (OGD only)**

N/A

**C. CC Block (OGD only)**

N/A

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/s/  
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SHELDON B MARKOFSKY  
02/08/2013

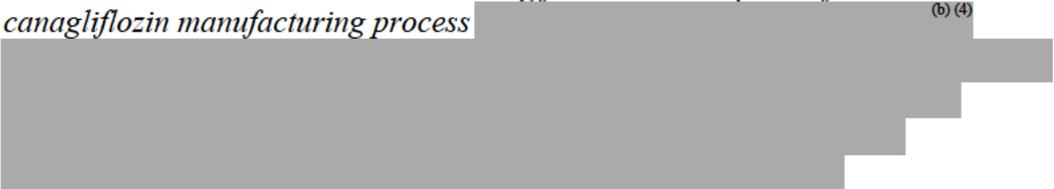
DANAE D CHRISTODOULOU  
02/08/2013

Concur with the reviewer's conclusions and recommendations

CMC IR for NDA 204042 (canagliflozin)

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your NDA 204042 for canagliflozin and have the following comments and requests for additional information. Please respond promptly in writing to your NDA file so we may continue our evaluation of your application.

**Drug Substance (DS)**

- 1) *Submit additional details that are missing from the description of the canagliflozin manufacturing process* (b) (4)  

- 2) *Describe any* (b) (4) *that may be carried out in the manufacture of your DS.*
- 3) *State which* (b) (4) *used in the proposed manufacture of the DS* (b) (4)  

- 4) *For the equipment used in each step in your proposed manufacture of the DS, provide the following:*
  - *The size and capacity of the equipment*
  - *The materials of construction that come in contact with contents being processed*
  - *The design/operating principle, as appropriate*
- 5) *Provide a protocol and specification for the establishment of any new primary reference standards for the canagliflozin DS.*
- 6) *You have submitted only 3 months of stability data for the validation batches packaged with the* (b) (4) *. Accordingly, you should revise your post-approval stability commitment so that the first post-approval commercial batch is tested at 40°C/75% RH at the 3 and 6 month time points, and 25°C/60% RH testing is monitored at 3, 6, 9, and 12 month time points, if canagliflozin is packaged with this* (b) (4) *. If you employ the* (b) (4)  *and the first post-approval commercial batch remains within its specification under these conditions, you may subsequently carry out stability testing on future commercial batches every 12 months at 25°C/60% RH.*
- 7) *Provide the analytical procedure used for the determination of the level of* (b) (4)  *in the DS as well as appropriate validation of the method.*

## Drug Product (DP)

- 1) *Justify why you did not include an in-process control, with an appropriate acceptance criteria for the weight gain of the tablets after film coating.*
- 2) *Your manufacturing process as described under Section P.3.3 does not provide a complete description of the commercial scale DP manufacturing process and in-process controls. In accordance with 21CFR 314.50(d)(ii)(c), You should either provide a master batch record OR update the process description in section P.3.3 such that it is comparably detailed to the master batch record.*

*Alternatively, you can clarify whether the executed batch production record provided in section 3.2.R is the same as that of the commercial scale master batch record, and then confirm that the process parameter ranges as provided in the executed batch production record in section 3.2.R supplements the DP manufacturing process description provided in section P.3.3, and provides operating ranges/set points for the process parameters not included in section.P.3.3. Notification of all changes beyond the ranges provided for in the submission, including changes to non-critical process parameters, should be communicated to the Agency in accordance with 21 CFR 314.70.*

- 3) *You stated in the submitted analytical UPLC and HPLC methods for Assay, Impurities, and Degradation Products that, "equivalent reagents may be applied, if performance as specified in system suitability is met and a comparable separation of all relevant compounds is demonstrated." Please explain what you mean by "equivalent reagents." That is, do you mean that another chemical solvent can be used in place of (b) (4)*
- 4) *Designate which of the two analytical procedures (UPLC or HPLC) is the Regulatory Method and which is the Alternative Method for the analysis for Assay, Impurities, and Degradation Products for your tablets.*

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/s/  
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JENA M WEBER  
12/12/2012

## CMC Information Request for NDA 204042

We are concerned about the (b) (4) (b) (4) which you first reported to the Agency in your amendment dated 10-23-12. We have the following comments and request additional information by COB November 30<sup>th</sup> 2012.

- 1) *Based on our ongoing review of the submitted data, we do not believe you can justify setting the limit for (b) (4), an impurity that resulted in a positive Ames test, based on the levels of (b) (4) in the human diet alone. Additional justification is requested to support a level of (b) (4) above the threshold of toxicological concern of (b) (4).*
- 2) *Provide information on the amount of impurity that builds up as a function of drug product storage time. Accordingly, provide the levels of (b) (4) found in your current primary stability program at both 25<sup>o</sup>C/60%RH and 40<sup>o</sup>C/75%RH. Continue to monitor for the presence of the impurity at the 18, 24, and 36 month time points in batches, stored at 25<sup>o</sup>C/60%RH in your primary stability program.*
- 3) *Comment on the reliability of using older stored samples to estimate amount of (b) (4) impurity present on Day 1 of batches used in the pivotal clinical and nonclinical studies.*
- 4) *Since both drug product strengths are made from (b) (4), the limits for (b) (4)*
- 5) *The acceptance criteria for many of the characteristics for the analytical procedure for (b) (4) in the drug product are noted, in the validation of the method, as "to be reported". Provide the missing acceptance criteria.*
- 6) *Provide the stability of the (b) (4) reference-standard-solution, described in the validation section, for the determination of the levels of this impurity in the drug product.*
- 7) *The following information should be provided for your (b) (4) reference standard:*
  - a) *Brief description of its synthesis*
  - b) *Proof of its structure*
  - c) *Stability data to support a proposed retest date*

*d) The specification for the current reference standard as well as the protocol and specification for the establishment of any new primary reference standard of this substance*

8) *Since canagliflozin contains a [REDACTED] (b) (4) [REDACTED], and since this NDA is for a new molecular entity (NME) with which we have limited experience, provide a release and stability specification for [REDACTED] (b) (4) in the drug substance..*

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/s/  
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MARY H PARKS  
11/19/2012

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	204-042
<b>Submission Date</b>	May 31, 2012
<b>Product name, generic name of the active</b>	Canagliflozin (JNJ-28431754)
<b>Dosage form and strength</b>	Immediate-Release Tablet (100 mg and 300 mg)
<b>Applicant</b>	Janssen Research and Development LLC
<b>Clinical Division</b>	DMEP
<b>Type of Submission</b>	Original New Drug Application
<b>Biopharmaceutics Reviewer</b>	Houda Mahayni, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?	x		
6.	Does the application include a IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?	x		
9.	Is there any in vivo BA or BE information in the submission?	x		
<b>B. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
10.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

11.	Is the NDA fileable from the product quality-biopharmaceutics perspective? If the NDA is not fileable, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	x		
12.	Is the NDA fileable from the biopharmaceutics perspective? If the NDA is not fileable, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	x		
13.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

*{See appended electronic signature page}*

Houda Mahayni, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

08/10/12  
Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

08/10/12  
Date

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/s/  
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HOUDA MAHAYNI  
08/10/2012

ANGELICA DORANTES  
08/10/2012

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**NDA 204042 (canagliflozin)**

**NDA** 204042  
**Applicant:** Janssen Pharmaceuticals Inc.  
**Stamp Date:** 31-MAY-2012  
**PDUFA Date:** 31-MAR-2013  
**Established Name:** canagliflozin  
**Proposed Proprietary Name:** [none indicated]  
**Dosage form and strength:** Tablet, 100 gm and 300 mg (anhydrous)  
**Route of Administration:** Oral  
**Indications:** Treatment of type 2 diabetes

**OVERALL PRODUCT QUALITY CONCLUSIONS AND  
RECOMMENDATIONS**

**CMC Lead: Su (Suong) Tran**

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**RELATED REVIEW DOCUMENTS:**

**a. Drug Master Files listed on 356h form:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	10-Jan-12	
	III		29-Aug-11		
	III		19-Aug-11		
	III		28-Jul-11		
	III		25-Aug-11		
	III		29-Jul-11		
	III		19-Aug-11		
	III		19-Aug-11		
	III		19-Aug-11		
	III		19-Aug-11		
	III		29-Mar-12		

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
NDA 204042 (canagliflozin)

**b. Recommended Consults**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Clin Pharm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	EER submitted to OMPQ on 06-JUN-2012
Pharm/Tox	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Not applicable. No impurity limit is above qualification thresholds and no genotoxic alert is present.</i>
Methods Validation	<input type="checkbox"/>	<input type="checkbox"/>	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<i>The categorical exclusion claim will be assessed by Primary Reviewer.</i>
New Drug Micro	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
CDRH	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other	<input type="checkbox"/>	<input type="checkbox"/>	

**c. Other Applications or Submissions to note (if any):**  
IND 76479

**d. Previous Communications with the Applicant to note (if any):**

Major issues discussed in FDA's 23-SEP-2011 letter include:

- FDA requested quality information on the (b) (4).
- FDA agreed that the executed batch records from one primary stability batch of each strength would be adequate in the NDA.
- The NDA would include information to support a biowaiver request to compare the (b) (4) use in Phase 1 studies and the (b) (4) used in later IND phases.

Major issues discussed in FDA's 07-DEC-2010 letter include:

- FDA agreed that (b) (4) are acceptable as starting materials of the drug substance.

**Does the submission contain any of the following elements?**

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Combination Products	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Nanotechnology	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
PET	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
QbD Elements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
SPOTS	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**Is a team review recommended?**

Yes	No	Suggested expertise for team
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review  
NDA 204042 (canagliflozin)

### CMC Summary and Critical Issues

This is an electronic NDA, filed as a 505(b)(1) application.

The drug substance canagliflozin hemihydrate is a small synthetic New Molecular Entity. It is an inhibitor of sodium-glucose co-transporter-2, which is responsible for reabsorbing glucose filtered by the kidneys.

The drug product is a 100 mg or 300 mg (anhydrous) immediate-release tablet for oral administration.

Inactive ingredients of the core tablet are croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, (b) (4)

(b) (4). The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, Macrogol/PEG, talc, iron oxide yellow, E172 (100 mg tablet only) and (b) (4)

The product will be packaged in 30-, 90-, and 500-count bottles and 10-count blisters for storage at room temperature.

**Maximum daily dose is 300 mg.**

#### Drug substance:

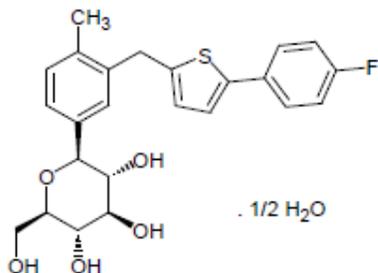
USAN:  
Associated Chemical Name

Canagliflozin  
(1S)-1,5-anhydro-1-C-(3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl)-D-glucitol hemihydrate

IUPAC Name:

(1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

- Structural formula



- Molecular formula: C<sub>24</sub>H<sub>25</sub>FO<sub>5</sub>S·1/2 H<sub>2</sub>O
- Molecular weight: 453.53 (444.52 + (0.5 × 18.02))

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The drug substance is non-hygroscopic and insoluble in aqueous media [REDACTED] (b) (4)

**Manufacturing process.** [REDACTED] (b) (4)

[REDACTED] The proposed starting materials were found acceptable by FDA in the 07-DEC-2010 letter.

[REDACTED] (b) (4)

**Comparability of the product used in the clinical studies, stability studies, and commercial product.**

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Structural characterization.**

The molecular weight, the empirical formula, and the molecular structure of R600348 drug substance were confirmed using the following techniques: high resolution mass spectrometry (MS), elemental analysis, infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. Ultraviolet (UV) spectroscopy data is added only to complement the spectral data set.

**Specification.** The drug substance specification is copied here.

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**Table 1: Specifications for the Drug Substance**

Parameters	Regulatory Acceptance Criteria	Test Methods
Appearance	White to off-white powder	Visual examination
Identification <sup>a</sup>		
IR	Complies with reference spectrum	Current USP <197K>
Assay	98.0-102.0% (w/w) calculated on anhydrous basis	HPLC-00005-V1
Chromatographic Purity		HPLC-00005-V1
Any Unspecified Impurity	Not more than (b) (4)	
Total impurities	Not more than (b) (4)	
Residual Solvents		
(b) (4)	Not more than (b) (4)	GC-005489-V1
Water Content	(b) (4)	KARL-00002-V1
Particle Size		LD-003457-V1
(b) (4)	Not less than (b) (4)	
(b) (4)	(b) (4)	
(b) (4)	Not more than (b) (4)	
Residue on Ignition/Sulphated Ash <sup>a</sup>	Not more than (b) (4)	Current USP <281>, 1g
Heavy Metals <sup>a</sup>	Not more than (b) (4)	Current USP <231> method II, 1g

<sup>a</sup> Initial release test only

**Impurities.**

**2.1.4. Toxicological Qualification of Impurities**

The qualification of impurities was not required as there have been no impurities with specified limits above the qualification threshold (b) (4) when using the proposed (b) (4). There are no impurities specified above the qualification threshold in the proposed commercial specifications.

**2.1.5. Genotoxicological Properties of Organic Impurities**

The genotoxic properties of all starting materials, intermediates, and impurities were evaluated based on their alert structures. The chemically reactive alert structures that could be present in the drug substance were evaluated for potential genotoxic activity using the DEREK computational method. The compounds tested are the starting materials (b) (4) potential impurities listed in Table 1 and combinations of solvents with reagents. The results of the assessment indicated there were no genotoxic alerts for the compounds tested.

The drug substance specification does not include testing for (b) (4)

(b) (4)  
 (b) (4)  
 (b) (4) This information will be confirmed by the reviewer.

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**Stability.** Up to 18-month long term stability data are submitted for the three primary drug substance stability batches with additional supporting data from three validation batches. The proposed retest period of (b) (4) at room temperature will be evaluated by the reviewer.

**Drug product**

The dosage form for the oral administration of canagliflozin is a film-coated tablet formulated for immediate release in two strengths, 100- and 300-mg. The tablets are manufactured (b) (4)

(b) (4) The tablets are capsule-shaped, film-coated with strength-specific colors, and debossed for tablet identification.

The active compound is canagliflozin, except where unit doses or batch quantities are shown as the quantity of hemihydrate for clarity. Each tablet strength contains canagliflozin drug substance as the hemihydrate equivalent to 100- and 300-mg doses of Canagliflozin (anhydrous), respectively.

Table 2: Quantitative Ingredient Statement per 100-mg Unit Dose  
 (GFI 28431754-ZAE-CA-005 Film-Coated Tablets)

Component	Quality Reference <sup>a</sup>	Role	% w/w	mg/unit
<b>Core Tablet</b>				
(b) (4)				
Canagliflozin	Company standard	Active (b) (4)		(b) (4)
Microcrystalline Cellulose	NF/Ph. Eur.			
Lactose Anhydrous	NF/Ph. Eur.			
Croscarmellose Sodium	NF/Ph. Eur.			
Hydroxypropyl Cellulose	NF/Ph. Eur.			
(b) (4)	USP/Ph. Eur.			
Magnesium Stearate <sup>d</sup>	NF/Ph. Eur.			(b) (4)
<b>Filmcoating</b>				
(b) (4) Yellow	Company standard USP/Ph. Eur.			(b) (4)
<i>Total Tablet Weight</i>				208.00

<sup>a</sup> Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

<sup>b</sup> Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous).

<sup>c</sup> (b) (4)

<sup>d</sup> Vegetable sourced

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Table 3: Quantitative Ingredient Statement per 300-mg Unit Dose  
 (GFI 28431754-ZAE-CA-006 Film-Coated Tablets)

Component	Quality Reference <sup>a</sup>	Role	Theoretical	
			% w/w	mg/unit
<b>Core Tablet</b>				
(b) (4)				
Canagliflozin	Company standard	Active		(b) (4)
Microcrystalline Cellulose	NF/Ph. Eur.			
Lactose Anhydrous	NF/Ph. Eur.			
Croscarmellose Sodium	NF/Ph. Eur.			
Hydroxypropyl Cellulose	NF/Ph. Eur.			
(b) (4)	USP/Ph. Eur.			
Magnesium Stearate <sup>d</sup>	NF/Ph. Eur.			(b) (4)
<b>Filmcoating</b>				
(b) (4)				
White	Company standard			(b) (4)
	USP/Ph. Eur.			
			<i>Total Tablet Weight</i>	618.00

<sup>a</sup> Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

<sup>b</sup> Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous).

<sup>c</sup> (b) (4)

<sup>d</sup> Vegetable sourced

Table 4: Composition of the (b) (4) Yellow

Ingredient	Quality Reference	Composition	
		% w/w	mg/unit
Polyvinyl Alcohol-Partially Hydrolyzed	USP/Ph. Eur.		(b) (4)
Titanium Dioxide	USP/Ph. Eur.		
Macrogol /PEG 3350	NF/Ph. Eur.		
Talc	USP/Ph. Eur.		
Yellow Iron Oxide E172	EU Directive 2008/128/EC/NF		

Table 5: Composition of the (b) (4) White

Ingredient	Quality Reference	Composition	
		% w/w	mg/unit
Polyvinyl Alcohol-Partially Hydrolyzed	USP/Ph. Eur.		(b) (4)
Titanium Dioxide	USP/Ph. Eur.		
Macrogol /PEG 3350	NF/Ph. Eur.		
Talc	USP/Ph. Eur.		

**Established name and dosage strength.** The proposed established name of the product is “canagliflozin”, which is acceptable because it correlates with the dosage strength of the anhydrous form, as per current CDER policy on nomenclature.

**Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the phase 3 clinical/primary stability batches and the commercial product have the same formulation (including color and debossing). These batches were manufactured using the (b) (4) at the commercial site and scale (Gurabo PR).

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The 100-mg stability batches are: 0HG2281-X, 0HG2282-X, and 0HG2283-X. The 300-mg stability batches are: 0HG2278-X, 0HG2279-X, and 0HG2280-X.

**Manufacturing process of the drug product.**

(b) (4)

The phase 3 clinical/primary stability batches and the commercial product were manufactured using the commercial process at the commercial site and scale.

**Drug product specification.** The drug product specification is copied here.

Table 1: Specifications for Canagliflozin Tablets

Test Parameter	Regulatory Acceptance Criteria	Test Methods
<b>Identification<sup>a</sup></b>		
IR	Complies with reference spectrum	IR-00125-V1 <sup>b</sup>
<b>Appearance</b>		
100-mg	Yellow, capsule-shaped tablet debossed with "CFZ" on one side and "100" on the other side	Visual examination
300-mg	White to off-white, capsule-shaped tablet debossed with "CFZ" on one side and "300" on the other side	Visual examination
Assay	90.0-110.0% of label claim	UPLC-00014-V1 <sup>c</sup> or HPLC-01-V1 <sup>d</sup>
<b>Chromatographic Purity</b>		
Each Unspecified Degradation Product	NMT (b) (4)	UPLC-00014-V1 <sup>c</sup> or HPLC-01-V1 <sup>d</sup>
Total Degradation Products	NMT (b) (4)	UPLC-00014-V1 <sup>c</sup> or HPLC-01-V1 <sup>d</sup>
Dissolution	Q= (b) (4) (b) (4)	DISS-01-V1 <sup>d</sup>
Uniformity of Dosage Units <sup>a</sup>	Conforms to current USP <905>	Current USP <905> Weight Variation

(b) (4)

- **Limits on degradation products.** The applicant states that, based on stress stability and primary stability data, no degradation occurs. A limit of (b) (4) is proposed for an unspecified degradant to comply with the ICH identification threshold for the maximum daily dose of 300 mg.
- **Dissolution.** All dissolution-related information (including data, test method, and acceptance criteria) will be reviewed by the [Biopharm team](#).
- **Water content and microbial limits.** No testing for water content or microbial limits is included in the drug product specification. The applicant states that the drug substance is non-hygroscopic

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and the water activity of the drug product stayed below (b) (4) for 12 months at room temperature. The water activity is well below the USP<1112> thresholds for microbial growth.

**Container closure systems for product distribution.**

Table 6: Intended Commercial Packaging Configurations for 100-mg Tablets

Package Type	Count
(b) (4)	7
(b) (4)	30
(b) (4)	90
(b) (4)	500
(b) (4)	Not applicable

Table 7: Intended Commercial Packaging Configurations for 300-mg Tablets

Package Type	Count
(b) (4)	7
(b) (4)	30
(b) (4)	90
(b) (4)	500
(b) (4)	Not applicable

- **Safety of the packaging components.** The applicant states that the components (bottle, cotton, blister materials) comply with applicable indirect food additives regulations.
- **Suitability of the packaging components.** The primary stability batches were packaged in the proposed commercial container closure systems.
- **DMFs.** The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

**Stability of the drug product.** A sufficient amount of stability data is submitted for filing purposes (12-month at 25 °C/60% RH and 6-month at 40 °C/75% RH for three commercial-scale batches of each dosage strength). The container closure systems of the stability batches and the commercial product are different in size. A bracketing design was used for the stability container closure sizes (copied below) based on the water vapor transmission rate. The commercial container closure sizes were selected based on the stability data. Both stability and commercial container closure systems have the same components (per the applicant's citing of the stability data to show suitability and compatibility of the commercial systems). The reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

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For the 100-mg stability batches:

Stability Package	
Count (ct)	Package (mL)
(b) (4)	

For the 300-mg stability batches:

Stability Package	
Count (ct)	Package (mL)
(b) (4)	

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**FILING REVIEW CHECKLIST**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>B. FACILITIES*</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6	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? <b>This question is not applicable for synthesized API.</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
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9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>D. MASTER FILES (DMF/MAF)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<i>See table on cover page.</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
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<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
13.	Does the section contain a description of the DS manufacturing process?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
18.	Has stability data and analysis been provided for the drug substance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>F. DRUG PRODUCT (DP)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
28.	Have any biowaiver been requested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
NDA 204042 (canagliflozin)

<b>G. METHODS VALIDATION (MV)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>H. MICROBIOLOGY</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>I. LABELING</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>J. FILING CONCLUSION</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
39.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<b>See first page.</b>

This document will be signed in DARRTS by the following:

CMC Lead  
Branch Chief

*{See appended electronic signature page}*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUONG T TRAN  
08/02/2012

ALI H AL HAKIM  
08/02/2012