CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203188Orig1s000

CHEMISTRY REVIEW(S)

KALYDECO (ivacaftor) Tablets
150 mg
NDA 203188
Chemistry, Manufacturing, and Controls
Division Director's Summary Basis of Action

Applicant: Vertex Pharmaceuticals Inc.
130 Waverly Street
Cambridge, MA 02139

Indication: KALYDECO **(**Ivacaftor) is intended to treat cystic fibrosis (CF), which is caused by a defect in chloride transport. The drug targets a particular site in the CF transmembrane conductance regulator (CFTR) that has been altered by a single mutation that changes glycine 155 to aspartic acid (G155D). Ivacaftor is effective only in this subpopulation of CF patients. The labeling requires that patients be tested and found positive for this mutation. The drug product (150 mg) is to be taken orally twice a day. The recommended dose of KALYDECO for both adults and pediatric patients age 6 years and older is one 150 mg tablet taken orally every 12 hours with fat containing food.

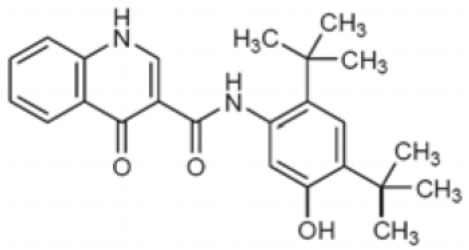
Presentation: Kalydeco Tablets are packaged in bottles (60 tablets) or blisters (4 tablets per card).

EER Status:	Recommendations:	**Acceptable as of Jan 17, 2012.**
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Requested for dissolution, assay, impurities and physical form (drug product) and (b) (4) impurity (drug substance).
	DMETS-	Acceptable
	Biopharm–	See review.
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Background: This NDA was submitted as a rolling submission. The CMC information was submitted to the Agency in July 27, 2011, but the complete NDA including clinical data was submitted on Oct. 18, 2011. The drug substance and drug product are prepared using a Quality by Design (QbD) Strategy for better assurance of quality from a manufacturer and patient perspective. Several CMC related meetings were held with the company before the NDA was submitted to come to agreements with the proposed QbD approach.

Drug Substance:
The active ingredient in KALYDECO tablets is ivacaftor which has the following chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4- oxoquinoline-3-carboxamide. Its

molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



The drug substance is a white-to-off-white powder that is practically insoluble in water (<0.05 microgram/mL). (b) (4) [redacted] (b) (4)

The applicant has identified Critical Quality Attributes (CQAs) for the drug substance and incorporated them into the specifications. They have performed experiments to identify and evaluate potential critical processing parameters and their effect on the CQAs. In addition they have identified and justified a number of attributes usually included in specifications as non-critical. These are (b) (4) [redacted]

The manufacturing development identified a number of process parameters that are controlled within their Normal Operating Ranges (NORs) and Proven Acceptable Ranges (PARs). Experimental data was provided to show that operating at the PAR for a given step had no impact on the quality of the drug substance. The applicant states that the manufacturing directions are intended to remain within the NORs.

The drug substance specifications include the following attributes: Appearance, Assay, (b) (4) [redacted] (b) (4) Impurities.

The drug substance is manufactured by (b) (4) [redacted] The facility was found acceptable from a cGMP point of view.

The drug substance is packaged in (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] The retest period is (b) (4) [redacted]

Drug Substance: Satisfactory

Drug Product:
KALYDECO is available as a light blue capsule-shaped, film-coated tablet for oral administration containing 150 mg of ivacaftor. Each tablet is printed with the characters

"V 150" on one side and is plain on the other. Each tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

As indicated above, to make the drug substance (b) (4)

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

Bulk ivacaftor bulk drug product is packaged in a (b) (4) For commercial distribution, the tablets are packaged in a 60-count high-density polyethylene (HDPE) bottle (75cc) with molecular sieve desiccant (b) (4), foil lined induction seal closure or thermoform blister (b) (4)/foil).

The pharmaceutical development identified a number of processing parameters and materials that might have an impact on the CQAs. NORs and PARs were identified. None of the parameters had an effect on degradation of the drug substance.

(b) (4)

After review of all data submitted to the application, the biopharmaceutics team within ONDQA recommends that the applicant perform *F2* statistical in vitro testing for tablets that are

(b) (4)

(b) (4)

The Tablet is controlled for the following attributes: Appearance, Identification. Assay, Degradation Products, Uniformity of Dosage Units, Dissolution, Physical Form, (b) (4) and Microbial Limits.

The drug product is very stable when stored in its packaging (HDPE bottles and blisters) with an expiration period of 30 months.

(b) (4)

Both sites are acceptable from a cGMP point of view.

The final labeling for carton and container submitted on Jan 16th 2012 are adequate from a CMC perspective.

Drug Product: Satisfactory.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

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/s/

ERIC P DUFFY
01/20/2012

Chemistry Review Cover Sheet

NDA 203188
Kalydeco (ivacaftor) Tablet
Arthur B. Shaw, Ph.D.
DNDQA III/Branch VIII/DPARP

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APPEARS THIS WAY ON ORIGINAL

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Chemistry Review Data Sheet

1. NDA 203188

2. REVIEW #:1

3. REVIEW DATE: January 18, 2012

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Pre-submission	07/21/2011	Pre-submission
Original	10/18/2011	
IR Filing issues	12/14/2011	Spec for reagents and solvents In-process tests for (b) (4) Testing for (b) (4)
Amendment	12/22/2011	Response to 12/14/2011 letter
IR Fax	12/22/2011	Request info about (b) (4) and forced degradation studies
Amendment	12/29/2011	Info abou (b) (4) and forced degradation
IR e-mail	01/03/2012	Request dissolution profile data
IR Letter	01/06/2012	(b) (4) Hardness PAR and NOR (b) (4) CTD More on reagents and solvents Specs for HPCMAS
Amendment	1/09/2012	Response to 1/01/2012 letter
IR e-mail	1/10/2012 (DARRTS 1/11/2012)	Request for hardness and bulk density for clinical batches
Amendment	1/11/2012	Response to 1/10/2012 e-mail
IR e-mail	1/12/2012	Not in DARRTS
Amendment	1/16/2012	Response to 1/12/2012 IR Letter Revised IPC for hardness Revised dissolution specification

Reference ID: 3072977

7. NAME & ADDRESS OF APPLICANT:

Vertex Pharmaceuticals
Incorporated
130 Waverly Street
Cambridge, MA 02139

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kalydeco
b) Non-Proprietary Name (USAN): Ivacaftor
c) Code Name/# VX-770
d) Chem. Type/Submission Priority
- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: No pharmacologic class has been agreed upon

11. DOSAGE FORM: Tablet

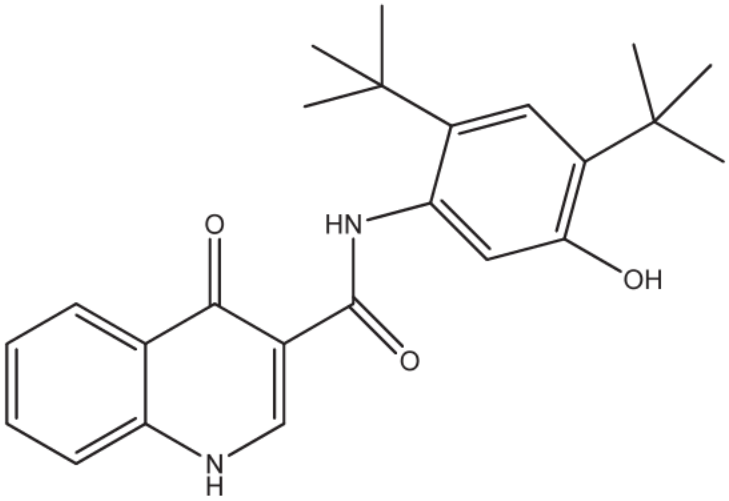
12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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



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- Molecular formula: $C_{24}H_{28}N_2O_3$
- Molecular weight: 392.49 grams per mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)	IV	(b) (4)	(b) (4)	ACCEPTABLE	To be filed

The components of (b) (4) are all either NF or FD&C color.
DMFs for the packaging materials do not require review, per MAPP 5015.5. See Section P.7.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74633	Vertex-770

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	1/17/2011	N/A
Methods Validation	Submitted to (b) (4)	1/12/2012	Pending
EA	N/A		
Microbiology	N/A		

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The Chemistry Review for NDA 203188

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view. All sites are in compliance with CGMP.

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(s) and Drug Substance(s)

1. Drug Substance

The drug substance is a white-to-off-white (b) (4). It can also be prepared as (b) (4)

(b) (4)

The starting materials are qualified by extensive experiments showing that any potential, theoretical, and actual impurities (b) (4) are adequately controlled. (b) (4) (b) (4) It is controlled at NMT (b) (4) in the finished drug substance. This will result in patient exposure of NMT (b) (4) under the labeled dosing (300 mg ivacaftor/day). Note that this drug is intended for chronic use. In addition, (b) (4), which is used in the preparation of one of

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the starting materials, is controlled at a level of NMT (b) (4) in the staring material. (b) (4)

All of the (b) (4) impurities and (b) (4) arising from the (b) (4) have been evaluated by the toxicology reviewer and found acceptable. Ivacaftor is very stable and no degradation products have been observed under standard storage conditions.

The applicant has identified Critical Quality Attributes (CQAs) for the drug substance and incorporated them into the specifications. They have used Quality by Design (QbD) principles and experiments to identify and evaluate potential critical processing parameters and their effect on the CQAs. In addition they have identified and justified a number of attributes usually included in specifications as non-critical. These are (b) (4)

The manufacturing development identified a number of process parameters that are controlled within their Normal Operating Ranges (NORs) and Proven Operating Ranges (PARs). Experimental data was provided to show that operating at the PAR for a given step had no impact on the quality of the drug substance. The applicant states that the manufacturing directions are intended to remain within the NORs.

The drug substance is manufactured by (b) (4). The facility was found acceptable from a cGMP point of view.

2. Drug Product

The CQAs for the tablets include identity, assay, dissolution, and a blue color. The goal of the manufacturing process development, which used QbD extensively, was to ensure that the ivacaftor is present in the drug product in (b) (4) without affecting the purity of the drug substance. (b) (4) (b) (4)

The pharmaceutical development identified a number of processing parameters and materials that might have an impact on the CQAs. NORs and PARs were identified. None of the parameters had an effect on degradation of the drug

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substance, which is expected given its stability. Experiments were done to show control of contaminants of the (b) (4) . (b) (4)

The drug product is very stable when stored in its packaging (HDPE bottles and blisters) for up to 18 months at 25°C/60%RH, with an expiration period of 30 months.

(b) (4) oth sites are acceptable from a cGMP point of view.

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

Ivacaftor is intended to treat cystic fibrosis (CF), which is caused by a defect in chloride transport. The drug targets a particular site in the CF transmembrane conductance regulator (CFTR) that has been altered by a single mutation that changes glycine 155 to aspartic acid (G155D). Ivacaftor is effective only in this subpopulation of CF patients. The labeling requires that patient be tested and found positive for this mutation. The drug product (150 mg) is to be taken orally twice a day.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach the gastrointestinal tract to be absorbed into the systemic circulation.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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/s/

ARTHUR B SHAW
01/18/2012

PRASAD PERI
01/18/2012
I concur

Ivacaftor
VX-770
NDA 203188

CMC Planning Meeting
Overview
Arthur Shaw
October 12, 2011
ONDQA DNDQAIII
OND DAAP

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/s/

ALAN C SCHROEDER
10/20/2011
Initial Quality Assessment, see separate filing review. Signed for Dr. Prasad Peri.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 203188 (ONDQA)

NDA Number: 203188	Supplement Number and Type: N.A.	Established/Proper Name: ivacaftor (tablet)
Applicant: Vertex Pharmaceuticals Inc.	Letter Date: 7/27/11 (presubmission for CMC)	Stamp Date: 7/27/11

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:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		

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4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	revie w issue		Note: associated IND is #74633 **6/30/08 EOP1 meeting**: sponsor agreed to provide specifications [redacted] (b) (4) of starting materials [redacted] (b) (4) and [redacted] (b) (4) and quality control agreements with each supplier. Specifications [redacted] (b) (4) of starting materials are provided. Reviewer should determine if the QC agreements are provided. **9/18/2009 CMC EOP2 meeting**: we asked for stability data to support the [redacted] (b) (4) expiry for the [redacted] (b) (4) The adequacy of the amount of data provided is a review issue. What is the effect of a [redacted] (b) (4) ? This should be evaluated by the reviewer. [redacted] (b) (4) (b) (4) (b) (4) To be evaluated by reviewer. **1/25/11 CMC pNDA meeting:** NDA should include a description of process controls for microbiological safety. Additional in-process controls may be required. The potential for microbial growth during manufacture should be investigated. Microbial safety/quality are discussed in 3.2.P2.5, and this is a review issue.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		on form FDA 356h
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? **This question is not applicable for synthesized API.**			Not applicable

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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		title & telephone number provided for each contact person, but not fax number or e-mail address
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		title & telephone number provided for each contact person, but not fax number or e-mail address

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9.	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: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		title & telephone number provided for each contact person, but not fax number or e-mail address
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Present in part of the facilities table along with form FDA 356h

* 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.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Section 1.12.14

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	x		
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	not an approvability issue

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	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?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		The final formulation of the proposed commercial product (3 lots) was used in pivotal clinical studies and in primary NDA stability batches. See 3.2 P.2.2.1.4
23.	Have any biowaivers been requested?		x	A biowaiver request was not seen in this preliminary scan of the NDA. This does not seem to be a concern. Note that a single 150 mg immediate release tablet is proposed.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		The applicant should be requested to provide statements that the materials of construction of the packaging materials meet the requirements for food contact in 21 CFR and appropriate USP tests per MAPP 5015.5
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	review issue		Some statistical analyses were performed to determine poolability (per ICH Q1E) and trends, and statistical significance of slopes. It is indicated that there are 18 months shelf life data to support a 30 month expiry, although it is not clear precisely how the expiration dating period was calculated, including extrapolation from 18 to 30 months.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		

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28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	not an approvability issue

Reference ID: 3032119

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		DMF references are provided, but they may not need to be reviewed depending whether sufficient information is provide in the NDA.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	5/27/11	
	III			7/17/09	
	III			5/14/10	DMF sections referenced but not dates
	III			8/28/09	submission dates not given
	III			5/31/11	submission dates not given
	III			5/31/11	submission dates not given
	III			5/12/10	submission dates not given
	III			6/09/11	submission dates not given
	III			6/10/11	submission dates not given
	III			9/10/10	submission dates not given
	III			6/9/11	specific

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		Closures			submission date not given
(b) (4)	III	(b) (4)	(b) (4)	6/10/11	DMF updated on 4/5/11.
	III			6/10/11	submission dates not given
	III			6/9/11	dates of submission not given

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?		x	This is still a presubmission.
33.	Have the immediate container and carton labels been provided?		x	This is still a presubmission.

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J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See separate initial quality assessment (slides prepared by Dr. Arthur Shaw)

{See appended electronic signature page}

Alan Schroeder, Ph.D.
CMC Lead
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Prasad Peri, Ph.D.
Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

Date

Reference ID: 3032119

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/s/

ALAN C SCHROEDER
10/20/2011
Signing for myself and on behalf of Dr. Prasad Peri. The NDA is fileable from a CMC perspective.