CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-037

CHEMISTRY REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 12, 2009

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 22-037

SUBJECT: Shire's Response to July 27, 2009 Complete Response Letter

RECOMMENDATION: Shire's response (on the CMC section) to July 27, 2009 complete response letter from FDA is acceptable. The drug product Intuniv (Guanfacine) extended-release tablet, 1, 2, 3 and 4 mg, is recommended as APPROVAL from a CMC perspective.

1. Dissolution specification

Following receipt of the Agency's CMC Information Request Letter (June 11, 2009), the Sponsor has evaluated the Agency's recommendation for adopting a final regulatory specification for drug product dissolution that proposes implementing (b) (4): not less than (b) (4)%." At this time, the Sponsor proposes the following approach in setting the final regulatory specification for drug product dissolution:

- Since the new dissolution method without (b) (4) has only recently been developed at the Agency's request, there are limited commercial scale manufacturing data available on which to set a meaningful specification.
- The Sponsor proposes to set an interim final time point specification of "24 hours: not less than (b) (4)%" to be implemented at the time of approval. The Sponsor commits to generate additional data at commercial scale on all dose strengths until a sufficient number of batches are available to permit a statistically valid process capability assessment for dissolution performance at (b) (4) versus 24 hours. At this time the Sponsor is still evaluating the number of batches required to achieve this but it is expected that it will take no longer than one (1) calendar year following the date of approval to accumulate and evaluate these additional data.
- The Sponsor commits to submitting a "CMC Special Report" no later than one (1) calendar year following approval in accordance with the regulations contained in 21 CFR §314.81(b)(3)(ii). This submission will contain all applicable drug product dissolution data in the new (b) (4) medium, the Sponsor's analysis for performance of the material at (b) (4) and 24 hours, and the Sponsor's proposal for a suitable final regulatory specification.
- Following submission of the "CMC Special Report," the Sponsor will request a teleconference with the Agency to discuss its interpretation of the accumulated drug product dissolution data for all approved dose strengths and the suitability of a specification based upon (b) (4) or 24 hours.

The Sponsor will not implement a final regulatory specification for drug product dissolution without concurrence from the Agency.

Evaluation: Acceptable (by Dr. Patrick J. Marroum, on August 11, 2009, see below).

****

From: Marroum, Patrick J
Sent: Tuesday, August 11, 2009 1:09 AM
To: Henry, Don
Subject: RE: cmc-request-letter-response.pdf - Adobe Acrobat Professional

Don:

The sponsor's response is fine.

Patrick

From: Henry, Don
Sent: Monday, August 10, 2009 2:30 PM
To: Marroum, Patrick J
Subject: FW: cmc-request-letter-response.pdf - Adobe Acrobat Professional

Patrick,

Please review the response from the sponsor regarding the dissolution specification. I believe this is what we had agree upon. Please let the team know whether it is acceptable

Thanks

Don
****

2. Labeling

There is no change made in the "description" and "how supplied" sections. The representative labels for 1 and 2 mg strength products can be seen below. The labels for 3 and 4 mg strength products are similar in design but the background colors are red and orange, respectively. The representative labels for 1 mg strength physician sample product can be seen below. The labels for 2 mg strength physician sample product are similar in design but the background color for "Physician Samples 7 Tablets 2 mg" text is light blue. **Evaluation: Adequate.**

(b) (4)

FRONT

(b) (4)

INSIDE

(b) (4)

BASE

(b) (4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22037	ORIG 1		INTUNIV
NDA 22037	ORIG 1		INTUNIV
NDA 22037	ORIG 1		INTUNIV

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/s/

DONGHAO R LU
08/13/2009

RAMESH K SOOD
08/13/2009

Intuniv
(guanfacine) extended-release tablets
NDA 22-037

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Shire Development Inc.
Wayne, PA 19087

Indication: Indicated for the treatment of ADHD.

Presentation: Intuniv (guanfacine) extended-release tablets are available as oblong tablets available in 1 mg, 2 mg, 3 mg, and 4 mg strengths. The tablets strengths are differentiated based on color and/or shape. The tablets will be available as 100 count tablets packaged in 75 cc. HDPE bottles. The tablets will also be available as physician samples as 7 tablets (1 mg) or (b) (4) (2 mg) packaged in 30 cc. HDPE bottles.

EER Status: Acceptable

Consults: ONDQA Biopharm: Dissolution acceptable
Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Post-Approval Agreements: None

Drug Substance:

The drug substance, Guanfacine hydrochloride, has chemical name, N-amidino-2-(2,6)-dichlorophenyl acetamide monohydrochloride. It has a molecular formula of $C_9H_9Cl_2N_3O \cdot HCl$ and a relative molecular mass of 282.56 g/mol (its free base MW = 246.08). It is white to off-white powder which exhibits no polymorphic forms. The drug substance is manufactured at (b) (4). The drug substance will be provided by (b) (4) The CMC information has been referenced to DMF (b) (4) The DMF was reviewed and found acceptable by the CMC reviewer.

Conclusion: Acceptable.

Drug product:

The drug product is designed as extended-release tablets. The product will be available in four strengths as described above. The tablet strengths are differentiated based on the color and/or shape. A (b) (4) approach is used for the 1 and 2 mg (0.76% w/w Guanfacine HCl), and 3 and 4 mg (1.71% w/w Guanfacine HCl) products. The basic excipients used in all strengths are same except the coloring agents. The excipients used are hypromellose (b) (4) microcrystalline cellulose, lactose (b) (4) (b) (4) methacrylic acid copolymer (b) (4) fumaric acid and glyceryl behenate. The quality of all excipients is ensured either through their conformance to the compendial standard or appropriate in-house standards. The manufacturing is straight forward and includes (b) (4) and packaging. The manufacturing process includes appropriate in-process controls with adequate acceptance limits. The quality of the final product is also ensured though acceptable final product testing. The final product specification includes tests and acceptable acceptance criteria for appearance, average content (HPLC), non-parent peaks (HPLC), identification HPLC/UV), content uniformity (HPLC) and multi-point dissolution.

The guanfacine hydrochloride extended release tablets are packaged in square, white high-density polyethylene (HDPE) bottles that also contain a 1-gram silica gel desiccant canister and 9-gram or 16-gram cotton coil for the 30cc and 75cc bottles, respectively. The 30cc and 75cc bottles are fitted with 24mm and 33mm white, plastic, child resistant closures containing an induction seal liner, respectively.

All analytical methods used are appropriately validated.

When stored at 25°C (77°F), excursions permitted to 15° to 30°C (59 to 86°F), the product has an assigned expiration period (shelf life) of 48 months.

Conclusion: Acceptable

Overall Conclusion: The application is acceptable and recommended for approval from CMC perspective

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

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/s/

Ramesh Sood
6/16/2009 01:52:20 PM
CHEMIST

NDA 22-037

(Review #2)

Intuniv™ (Guanfacine Hydrochloride) Oral Extended-Release Tablet 1, 2, (b) (4), 3, (b) (4), and 4 mg

Shire Development Inc.

Division of Psychiatry Drug Products

Donghao (Robert Lu), Ph.D.

Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-037

2. REVIEW NUMBER: 2

3. REVIEW DATE: 11 June 2007

4. REVIEWER: Donghao (Robert) Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-037	24-AUG-2006
NDA 22-037 (Amendment 006, CMC)	23-JAN-2007
NDA 22-037 (Amendment 012, Labeling)	12-MAR-2007
NDA 22-037 (Amendment 014, CMC, Stability)	20- MAR-2007

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-037 (Amendment 018, CMC, Response)	25- MAY-2007
NDA 22-037 (Amendment 019, CMC, Labeling)	29- MAY-2007
NDA 22-037 (Amendment 021, CMC, Response)	11- JUN-2007

7. NAME & ADDRESS OF APPLICANT:

NAME:	Shire Development Inc.
ADDRESS:	725 Chesterbrook Blvd., Wayne, PA 19087
REPRESENTATIVE:	Michael S. Spitz, Senior Manager
TELEPHONE:	484-595-8156

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Intuniv**
NON-PROPRIETARY NAME (USAN)	**Guanfacine Hydrochloride**
CODE NAME/ NUMBER (ONDC ONLY)	**SPD503**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3S**

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Selective, postsynaptic agonist of alpha-2A-adrenergic receptors (for treatment of ADHD)

11. DOSAGE FORM: Extended-Release Tablets

12. STRENGTH/POTENCY: 1, 2, (b) (4) 3, (b) (4), and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

__x__Not a SPOTS product

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

Name (USAN):	Guanfacine hydrochloride
Name (CAS):	N-amidino-2-(2,6)-dichlorophenyl acetamide monohydrochloride
	Benzeacetamide, N-(aminoiminomethyl)-2,6-dichloro-, monohydrochloride
Mol. Formula:	$C_9H_9Cl_2N_3O \cdot HCl$
Mol. Wt.:	**282.56** g/mol.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE
(b) (4)	II	(b) (4)	Guanfacine HCl	1	Adequate	22-FEB-07
	III		(b) (4)	4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	IV			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	IV			4	N/A	
	III			4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	**63,551**	
IND	(b) (4)	
NDA	**19-032**	**TENEX (Dr. Reddy's Labs, Inc)**

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	22-Feb-07	Donghao Lu, Ph.D.
ODS DMETS	Changed to "INTUNIV"	1-DEC-07	Walter Fava R.Ph.
EA	Acceptable	10-Apr-07	Donghao Lu, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 22-037

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Intuniv (Guanfacine) extended-release tablet, 1, 2, (b) (4) 3, (b) (4) and 4 mg, is recommended as APPROVABLE from a CMC perspective, pending an overall acceptable recommendation from the office of compliance.

All other CMC issues had been adequately resolved.

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

There are no Phase IV commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Guanfacine hydrochloride. The chemical name is N-amidino-2-(2,6)-dichlorophenyl acetamide monohydrochloride. It has a molecular formula of $C_9H_9Cl_2N_3O \cdot HCl$ and a relative molecular mass of 282.56 g/mol (its free base MW = 246.08). The starting materials for the manufacture of guanfacine hydrochloride are (b) (4) and (b) (4). (b) is also a major process impurity/degradant.

The drug substance is provided by (b) (4). A Drug Master File (DMF), DMF # (b), is available from (b) (4) and Letter of Authorization was provided (LOA date: 5/25/2006). The last review on DMF # (b) was carried out on 3-AUG-1994 (Dr. Norman Gregory) and the DMF was found adequate. Since then, there were several amendments and annual report. These updated documents are reviewed separately by this reviewer (2/20/2007) and found adequate.

2. Drug Product

The drug product is Intuniv™ (guanfacine hydrochloride) oral extended-release tablet, 1, 2, (b), 3, (b), and 4 mg. It is a once daily, extended release formulation of guanfacine hydrochloride in a matrix tablet form. There are (b) dose strengths, 1, 2, (b), 3, (b) and 4 mg (expressed as the base equivalent of guanfacine). For (b), 3 and (b) mg tablets, they have the same appe**arance with difference in color: 5/16" round tablets debossed with "503" on one side and** (b) (4) **"3mg",** (b) (4) **on the other side,** respectively, with a color in (b) (4), green, (b) (4) respectively. For 1 mg tablet, **it has the appearance of 9/32"** round, white to off-white **tablets debossed with "503" on one side and "1mg" on the other side.** For 2 mg tablet, it has the appearance of **0.486" x 0.240" caplet shaped, white to off-white tablets debossed with "503" on one side and "2mg" on the other side. For 4 mg tablet, it has the appearance of 0.486" x 0.240" caplet shaped, green tablets debossed with "503" on one side and "4mg" on** the other side. The guanfacine hydrochloride (also named as SPD503) extended release tablets are packaged in square, white high-density polyethylene (HDPE) bottles that also contain a 1-gram silica gel desiccant canister and 9-gram or 16-gram cotton coil for the 30cc and 75cc bottles, respectively. The 30cc and 75cc bottles are fitted with 24mm and 33mm white, plastic, child resistant closures containing an induction seal liner, respectively. The manufacturing process for Intuniv ER tablets consists of (b) (4) and (b) (4) of the active ingredient with excipients followed by (b) (4). Three critical parameters are monitored during the manufacturing process (weight, hardness, and friability). The validation of the manufacturing process involves the assessment of blend uniformity, tablet content uniformity, tablet weight, tablet hardness and friability. The critical excipients for (b) (4) are Hypromellose (b) (b) (4) and Methacrylic acid copolymer (b) (4) (b) (4) Hypromellose (b) is used as the (b) (4) Methacrylic acid copolymer is used as a (b) (4) (Guanfacine has pH dependent solubility).

B. Description of How the Drug Product Is Intended to Be Used

Intuniv™ is indicated for the treatment of ADHD in children and adolescents. The clinical efficacy was established in ten studies in subjects (6-17 years old) with Attention Deficit Hyperactivity Disorder (ADHD) and eight studies in healthy adult **volunteers. Intuniv™ is an extended-release** tablet and should be dosed once daily. It **is recommended that the dose of Intuniv™ be** maintained within the range of 1 mg to 4 mg per day, depending on clinical response and the dose should begin at 1 mg and adjust in increments up to 1 mg/week. When stored at 25°C (77°F), excursions permitted to 15° to 30°C (59 to 86°F), the product has an expiration period (shelf life) of (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Shire Development Inc. has submitted sufficient and appropriate information to support the approval of the drug product. The physical and **chemical characteristics, impurity profile, and stability for Intuniv™ (guanfacine)** extended-release tablets, 1, 2, (b), 3, (b) and 4 mg, are adequately demonstrated in this NDA. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug products. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. (b) (4)

Shire has adequately addressed the CMC comments (see Review #1). Their responses and the CMC evaluations for these responses are described below.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

Donghao Lu
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CHEMIST

Ramesh Sood
6/18/2007 01:29:55 PM
CHEMIST

NDA 22-037

Intuniv™ (Guanfacine Hydrochloride)
Oral Extended-Release Tablet
1, 2, 2.5, 3, 3.5, and 4 mg

Shire Development Inc.

Division of Psychiatry Drug Products

Donghao (Robert Lu), Ph.D.

Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-037

2. REVIEW NUMBER: 1

3. REVIEW DATE: 10 April 2007

4. REVIEWER: Donghao (Robert) Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	**19-032**	**TENEX (Dr. Reddy's Labs, Inc)**

18. STATUS:

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EA	Acceptable	10-Apr-07	Donghao Lu, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 22-037

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I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Intuniv (Guanfacine Hydrochloride) oral extended-release tablet, 1, 2, (b) (4), 3 (b) (4), and 4 mg, is recommended as APPROVABLE from a CMC perspective, pending the acceptable recommendations from label and EES reviews, as well as the acceptance on sponsor's responses for our CMC review comments (see the end of this document).

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

There are no Phase IV commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

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2. Drug Product

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B. Description of How the Drug Product Is Intended to Be Used

Intuniv™ is indicated for the treatment of ADHD in children and adolescents. The clinical efficacy was established in ten studies in subjects (6-17 years old) with Attention Deficit Hyperactivity Disorder (ADHD) and eight studies in healthy adult volunteers. Intuniv™ is an extended-release tablet and should be dosed once daily. It is recommended that the dose of Intuniv™ be maintained within the range of 1 mg to 4 mg per day, depending on clinical response and the dose should begin at 1 mg and adjust in increments up to 1 mg/week. When stored at 25°C (77°F), excursions permitted to 15° to 30°C (59 to 86°F), the products have an expiration period (shelf life) of (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Shire Development Inc. has submitted sufficient and appropriate information to support the approval of the drug product. The physical and **chemical characteristics, impurity profile, and stability for Intuniv™ (guanfacine** hydrochloride) oral extended-release tablets, 1, 2, (b) (4), 3, (b) (4) and 4 mg, are adequately demonstrated in this NDA. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug products. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. (b) (4)

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

Donghao Lu
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Ramesh Sood
5/29/2007 10:14:11 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-037**
Applicant:	Shire Development Inc.
Letter Date:	24-AUG-06
Stamp Date:	24-AUG-06
PDUFA Date:	24-JUN-07
Trademark:	(b) (4)
Established Name:	Guanfacine hydrochloride
Dosage Form:	1-, 2-, (b) (4), 3-, (b) (4), and 4 mg Extended-Release Tablets
Route of Administration:	Oral
Indication:	ADHD
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary

Guanfacine hydrochloride (NDA 19-032, Tenex tablets, Dr. Reddys Labs) was approved for the treatment of hypertension on October 27, 1986. The purpose of this NDA program was to develop a once daily, extended release formulation of guanfacine hydrochloride for the treatment of ADHD. The sponsor had a CMC Pre-NDA meeting (13-OCT-05), which focused on: particle size, polymorphs, dissolution, impurities, qualification of a second DP manufacturing site, and the stability protocol. In addition, the sponsor submitted a special protocol (stability). Minutes for the meeting and review of the special protocol (Dr. Chhagan Tele) can be found in DFS.

Drug Substance

The sponsor references DMF (b) (4) for information on the drug substance (LoA dated 25-MAY-06). Guanfacine hydrochloride is a white to off-white powder and exhibits low solubility (~1mg/mL). The sponsor indicates there is no evidence of polymorphic forms. The drug substance will be manufactured commercially at (b) (4)). The sponsor has set a specification limit of NMT 0 (b) (4) for four impurities (b) (4) These specification limits (especially those for (b) (4)) will need to be discussed with pharm/tox. The particle size range will need to be evaluated and found acceptable. It appears the DMF was last reviewed in 1994 and at that time was found adequate. Since that time, there have been a number of amendments and annual reports, which will need to be evaluated.

Drug Product

Guanfacine hydrochloride extended release tablets will be available in (b) (4) strengths: 1 mg, 2 mg, (b) (4) mg, 3 mg (b) (4) mg, and 4 mg for the treatment of ADHD. The recommended dose should be within the range of 1 mg to 4 mg per day (the starting dose is 1 mg with adjustments of 1 mg/week). The formulation is not proportional across all

(b) tablet strengths. The 1 mg and 2 mg (b) (4) and the 3 mg and 4 mg (b) (4) The (b) (4) (b) (4) Extended Release Tablets were formulated as matrix tablets that would release drug over the pH range of the gastrointestinal tract. The sponsor cites (b) (4) excipients that (b) (4) 1) hypromellose (b) (4), 2) (b) (4) (methacrylic acid copolymer (b) (4)), 3) fumaric acid (an (b) (4), and 4) glyceryl behenate (b) (4) (b) (4). The manufacture of the drug product consists of: (b) (4) and packaging. For commercial manufacture, the same blending and tableting process will be followed, except the blending times and final blender loads will be optimized prior to process validation. The SPD503 extended release tablets will be packaged commercially in square, white 75 cc HDPE bottles that contain a 1 g silica gel desiccant canister and a 16-gram cotton coil. The SPD503 extended release tablets will be packaged for physician samples in square, white 30 cc HDPE bottles that contain a 1 g silica gel desiccant canister and a 9-gram cotton coil. The sponsor lists (b) (4) and Shire U.S. Manufacturing Inc. (Owings Mills, MD) as the manufacturers of SPD503 extended release tablets. The (b) (4) site will manufacture only 1 mg, 2 mg and 3 mg strengths.

Critical Issues for Review

- The sponsor has set a specification limit of NMT (b) (4)% for the four drug substance impurities (b) (4) (b) (4) These specification limits (especially those for (b) (4)) will need to be discussed with pharm/tox and found acceptable.

- The role of particle size on product performance will need to be evaluated, to ensure adequate controls are in place for consistent product performance. The sponsor will need to demonstrate that particle size (e.g., shape under the curve) as measured in clinical, stability and commercial batches is rationally controlled to ensure product performance (as outlined in labeling).

(b) (4)

- The compatibility of the excipients used in the drug product will need to be evaluated.

• The sponsor utilizes [redacted] and [redacted] However, the composition was not provided in terms of each of the excipients. The sponsor will need to provide the formulations in terms of each excipient (wt/wt %). The adequacy of [redacted] and [redacted] will need to be examined.

• The green pigment powder, which is used in the 3 mg and 4 mg strengths, will need to found acceptable.

•The sponsor cites four excipients [redacted]: hypromellose [redacted] (methacrylic acid copolymer [redacted], fumaric acid, and glyceryl behenate. The sponsors understanding and control of each of these excipients will need to be closely examined. [redacted]

• The [redacted] polymer contains a number of residual monomers, which should be adequately controlled, so that daily exposure is within the realm of already approved drugs (refer to previous NDAs, e.g., within HFD-130).

• The sponsor incorporates a [redacted]% processing overage of guanfacine hydrochloride. The sponsor's justification for including this overage will need to be evaluated in conjunction with the testing results.

• The 1-[redacted], 3-, and [redacted] mg tablets are round and the 2 mg and 4 mg tablets are oblong. The effect of shape should be evaluated across the various specifications, especially, in regards to dissolution, since a patient could receive two 1 mg or one 2 mg tablet. The sponsor has chosen four time points (1h, 4h, 8h, and 24h) for dissolution measurement. The adequacy of the dissolution specification will need to be evaluated in conjunction with the Biopharm reviewer.

• The drug product strengths are debossed with [redacted] on one side and "503" on the other side. The reviewer will need to verify whether these debossings represent the commercial product.

• Any differences in the drug product release testing results should be evaluated in terms of strength and site of manufacture.

• It appears the dose strengths are expressed as guanfacine base (i.e., 1 mg tablet contains 1 mg guanfacine, i.e, 1.14 mg guanfacine HCl). Since the 1 mg bottle labels cite guanfacine hydrochloride and 1 mg, it appears the product is labeled incorrectly. The reviewer will need to evaluate this issue and modify any labeling problems.

• The reviewer should refer to the Special Protocol (Stability) review by Dr. Chhagan Tele, for an outline of the stability data to be included in the NDA and the approved

stability protocol. The sponsor utilizes both desiccant and a cotton coil in the HDPE bottles. As the tablets are not film coated, special attention should be paid to: appearance (e.g., fading, chipping), dissolution, impurities and friability over time. Any differences between sites, strengths, and packaging configurations should be evaluated, when assigning the expiry.

• Even though the sponsor states that, "the proposed production of SPD503 tablets does not increase the use of the active moiety to an extent which results in the estimated concentration of the substance at the point of entry into the aquatic environment to a level of 1 ppb or greater", no categorical exclusion has been claimed. A categorical exclusion will need to be claimed with the correct class action cited (see 25.31).

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. Additional manufacturing site information will be requested from the NDA sponsor. Once this information is received, I will enter the sites into EES. My recommendation would be for a single reviewer to be assigned to the NDA. As Dr. Chhagan Tele participated in the pre-NDA meeting and evaluated the Special Protocol (Stability), he would be a prudent reviewer choice.

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/s/

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