CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-037

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-037 SUPPL # 000 HFD # 130

Trade Name Intuniv

Generic Name guanfacine

Applicant Name Shire

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-032 Tenex

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study SPD503-301, SPD503-304

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study SPD503-301, SPD503-304

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 63,551	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 63,551	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Shin-Ye Sandy Chang
Title: RPM
Date: June 18, 2009

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: DPP Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
7/10/2009 08:37:52 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22037 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Intuniv Established/Proper Name: guanfacine Dosage Form: extended-release tablets		Applicant: Shire Agent for Applicant (if applicable): James Ewing
RPM: Sandy Chang		Division: Psychiatry Products

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): IND (b) (4) IND 63,551 NDA 19-032 Tenex Provide a brief explanation of how this product is different from the listed drug. Intuniv is an extended release formulation while Tenex is an immediate-release formulation of guanfacine ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☒ No changes ☐ Updated Date of check: August 28, 2009 **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	September 29, 2009 September 2, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR: July 27, 2009; AE: June 27, 2007

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	July 8, 2009
✓ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☒ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	September 2, 2009
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR July 27, 2009; AE June 27, 2007;
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	August 24, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] Fill in blanks with dates of reviews, letters, etc.

• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	August 27, 2009
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	August 26, 2009; May 5, 2009; April 18, 2007; November 14, 2006 May 6, 2009; October 23, 2006
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☒ DRISK July 15, 2009 ☐ DDMAC ☐ CSS ☒ Other reviews SEALD July 10, 2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	July 27, 2009; January 16, 2007
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included (Pediatric Record)
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg September 17, 2007; March 9, 2006; November 30, 2005; August 5, 2005; June 15, 2005; March 29, 2005; February 2, 2003
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None September 1, 2009; July, 28, 2009; June 19, 2007
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None June 18, 2007
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	June 12, 2007
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	N/A
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT-IRT: July 28, 2009; June 12, 2009; June 13, 2007
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None June 30, 2009
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested June 1, 2007; May 17, 2007; April 10, 2007
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None June 13, 2007
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None June 14, 2007
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None July 14, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None July 7, 2009; June 20, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None June 16, 2009
• Product quality review(s) *(indicate date for each review)*	☐ None August 12, 2009; June 8, 2009, June 18, 2007, May 25, 2007
• ONDQA Biopharmaceutics review *(indicate date for each review)*	May 15, 2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	August 24, 2006
☐ Review & FONSI *(indicate date of review)*	

☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: July 23, 2009; June 20, 2007 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-037 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: Intuniv
Established Name: guanfacine
Strengths: 1 mg, 2 mg, 3 mg, 4 mg

Applicant: Shire Development, Inc.
Agent for Applicant (if applicable): James Ewing

Date of Application: January 26, 2009
Date of Receipt: January 27, 2009
Date clock started after UN:
Date of Filing Meeting: February 19, 2009
Filing Date:
Action Goal Date (optional): User Fee Goal Date: July 27, 2009

Indication(s) requested: Treatment of Attention Deficit and Hyperactivity Disorder (ADHD) in children and adolescents 6-12 years old.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: August 24, 2006 YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 for b2 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ N/A ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 63,551; (b) (4)

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 8, 2002 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 28, 2004; May 18, 2005; February 28, 2006; September 12, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) March 10, 2004; January 3, 2008 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ N/A ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ N/A ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 19, 2009

NDA #: 22-037

DRUG NAMES: Intuniv (guanfacine) extended-release tablets

APPLICANT: Shire

BACKGROUND: Shire has submitted a Complete Response addressing the deficiencies issued in our June 20, 2007, Approvable letter.

ATTENDEES: Thomas Laughren, Mitchell Mathis, Robert Levin, Donghao Lu, Thomas Oliver, Raman Baweja, Linda Fossom, Ikram Elayan

ASSIGNED REVIEWERS (including those not present at filing meeting) : Robert Levin, Donghao Lu, Thomas Oliver, Raman Baweja, Linda Fossom, Ikram Elayan, Patrick Marroum, Devi Kozeli, Abolade Adeolu

Discipline/Organization	**Reviewer**
Medical:	Robert Levin
Secondary Medical:	Lindberg, Cheri
Statistical:	
Pharmacology:	Linda Fossom
Statistical Pharmacology:	
Chemistry:	Thomas Oliver
Environmental Assessment (if needed):	
Biopharmaceutical:	Raman Baweja
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Sandy Chang
Other Consults:	QT IRT: Devi Kozeli OSE/DRISK: Abolade Adeolu ONDQA: Patrick Marroum

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: Cycle 1 inspection May 17, 2007.
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Shin-Ye Sandy Chang, Pharm.D.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

SHIN-YE CHANG
07/27/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-037

INFORMATION REQUEST LETTER

Shire Development Inc.
Attention: Michael S. Spitz, RAC, Senior Management, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mr. Spitz:

Please refer to your August 24, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, (b) mg, 3mg, (b) mg and 4 mg Extended-Release Tablets.

We also refer to your submission dated January 26, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The new dissolution method submitted to the Agency was reviewed and the proposed dissolution method is acceptable. We recommend that the dissolution method and specifications be as follows. Please provide an updated product specification:

USP apparatus II at 75 rpm
Medium: pH 2.2 HCl buffer
1 hour: (b) (4)
4 hours: (b) (4)
8 hours: (b) (4)
(b) (4) not less than (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
6/9/2009 02:00:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-037

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Michael S. Spitz
Senior Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to your 24 August 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD-503 (guanfacine hydrochloride).

We also refer to your submissions dated 21 November 2006, 23 January 2007 and 20 March 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In your drug substance specifications, please add a test and an acceptance criterion for individual unspecified impurity.
2. In your drug product specifications, please add a test and an acceptance criterion for friability testing and revise the post-approval stability protocol accordingly.
3. The drug product labels list (b) (4) as the established name but the strength corresponds to the Guanfacine base. Revise the product nomenclature so that the product strengths will match the established name. You may choose Guanfacine as the established name with the corresponding strengths of 1, 2, (b) (4) 3, (b) (4) and 4 mg (and with a footnote indicating it is present as Guanfacine HCl salt). Alternatively, you may choose (b) (4) as the established name with corresponding strengths that are equivalent to the amount of (b) (4)
4. It is noted that out of 9 batches manufactured at DSM (3 batches each for 1, 2 and 3 mg strengths), 3 batches (one batch each for 1, 2 and 3 mg strengths) conformed at level 2 for content uniformity. Please provide appropriate information to show that proper in process controls on blend uniformity/content uniformity are implemented during the commercial manufacturing.

5. Relatively high amount of [redacted] (b) (4) is used in the drug product. Potentially, if a patient takes four 1-mg tablets or two 2-mg tablets (in stead of one 4-mg tablet) for 4 mg/day dose, the daily intake of [redacted] (b) (4) Therefore, the acceptance criterion for monomers in the [redacted] (b) (4) specification needs to be limited to [redacted] (b) (4) ppm. Otherwise, please provide data to demonstrate the safety of these monomers at higher levels.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
5/17/2007 02:51:24 PM

Curtis, Felecia

From: Curtis, Felecia
Sent: Thursday, January 25, 2007 11:08 AM
To: 'Spitz, Mike'
Cc: Curtis, Felecia
Subject: NDA 22-037 Clinical, Statistical, and Biopharmaceutical Information Request (email)

NDA 22-037
INFORMATION REQUEST LETTER

Shire Pharmaceutical Development, Inc.
Attention: Mike Spitz
Regulatory Affairs
1901 Research Boulevard
Suite 500
Rockville, MD 20850

Dear Mr. Spitz:

Please refer to your August 24, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD503.

We are reviewing the Clinical, Statistical, and Biopharmaceutical s sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical
1. Any available details for the cases of syncope and loss of consciousness (pediatric and adult subjects).

It would be helpful to have any additional details added to narratives. Also, I would like to request patient profiles for all subjects with syncope or loss of consciousness. Helpful data would include demographics, medical history, concomitant medications, actual dosing, adverse events, as well as all vital signs recorded during the study (weights, heights, blood pressures, heart rates). We would also appreciate having all ECG, clinical labs, and PK drug exposure data for the subjects in question in patient profile form.

2. We would appreciate any possible additional discussion or analyses which might address the efficacy findings in subjects ages 13-17 years old (statistical power, lower exposures to drug, lower compliance, missing data patterns). We realize that this has already been addressed to some extent, and that it may be difficult to fully explain the findings.

Biopharmaceutical

"Please submit the blood level information on Guanfacine collected in study SPD503-206

and SPD503-305. The information should be in the pattern submitted for study SPD503-107 (PKCONC.XPT). The data should be submitted as SAS transport file."

Statistical

1. In clinical study reports for studies 301 and 304, statistical analyses on the primary endpoint include analysis of ADHD-RS-IV total scores by actual daily dose in mg at Endpoint (last post-randomization treatment week of the dose titration and dose maintenance phases). Please also perform an exploratory analysis by actual daily dose only for the patients who actually achieved the targeted dose level (the dose they were randomized to). Please also provide the indicator variable in a dataset to distinguish patients who achieved the daily dose they were randomized to from the patients who did not achieve their dose level.

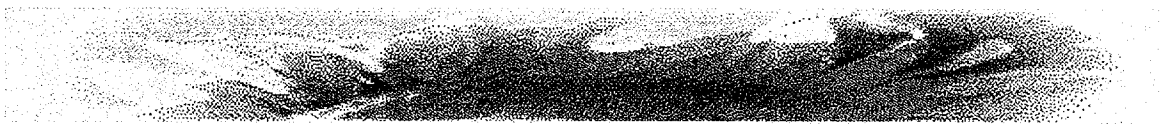
2. Please summarize the dropout reasons and plot response profiles of both dropouts and completers to explore the missing data mechanism.

If you have any questions, call me at 301-796-0877.

Sincerely,

{See appended electronic signature page}

Felecia Curtis
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Felicia Curtis
1/25/2007 11:11:02 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-037

INFORMATION REQUEST LETTER

Shire Development Inc.
Attention: Michael Spitz, RAC
Senior Director, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to your 8/24/06 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD503, (guanfacine hydrochloride).

We are reviewing the Statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For the two pivotal efficacy studies 301 and 304, please provide the following items:

- Data sets that contain derived variables needed for efficacy evaluations
- Please provide the IND and serial submission numbers for protocols, amendments and SAPs.
- In addition, we cannot find some key data sets or variables in your submission for study 301.

  For example, (a) the data set "rdmcode" in the "EFF_301_2.txt" SAS program, and
  (b) the data set "adhd.dr" and the variable "adhdtoti" in "T_EFF_2_1_1.txt" SAS program.

- Please make sure all required elements for efficacy evaluations in both studies are included.

If you have any questions, call Felecia Curtis, RN, RPM, at 301-796-0877.

Sincerely,

Felecia Curtis

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/s/

Felicia Curtis
10/2/2006 03:03:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,551

Shire Development, Inc
Attention: Michael S Spitz, RAC
Senior Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD503 (guanfacine hydrochloride) extended released tablets.

We also refer to the meeting between representatives of Shire and the FDA on September 13, 2007. The purpose of the meeting was to discuss your pediatric development plan for guanfacine in combination therapy with psychostimulants to treat ADHD.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 796-0240

Sincerely,

{See appended electronic signature page}

Thomas Laughren, MD
Division Director
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

IND 63,551
Drug: Guanfacine (SPD-503) Tablets
Indication: ADHD
Sponsor: Shire
Type C Meeting
Type of Meeting: Face to Face
Date: September 12, 2007
Time: 3:00 – 4:00 PM
Location: White Oak, Building 22, Room 1419

Shire requested a meeting with the Agency in a submission dated 5-14-07. The briefing package was submitted in correspondence dated 8-10-07.

Participants –

FDA.

Dr. Thomas Laughren	Director, DPP
Dr. Mitchell Mathis	Deputy Director, DPP
Dr. Ni Khin	TL, Medical
Janet Cliatt	Regulatory Project Manager
Barry Rosloff	TL, Pharmacology
Ikram Elayan	Pharmacology
Raman Baweja	TL, OCP
Peiling Yang	TL, Statistics
George Kordzakhia	Statistics

Shire

Kimberly Farrand, MPH	Sr. Clinical Scientist
Andrew Lyne, MSc, CStat	Director, Global Biometrics
Patrick Martin, MD	Vice President, Clinical Pharmacology
Rebecca Newberry	Regulatory Affairs Associate
Tracy Rockney, JD	Sr. Director, Regulatory Affairs
Michael Spitz, RAC	Sr. Manager, Regulatory Affairs
Timothy Whitaker, MD	Vice President, Global Clinical Medicine

Background:

This is a follow-up discussion to the SPD503 (guanfacine ER) pediatric development program meeting between Shire and the Agency on 8-3-05, where several study concepts were discussed in the context of obtaining Pediatric Exclusivity. One of the key studies that FDA expressed interest in was co-administered use of SPD503 with stimulants to treat ADHD, noting that, if positive, one study could also support an adjunctive use claim.

On 5-3-07, Shire submitted a PPSR with an add-on (SPD503 added on to stimulant use) study design synopsis (SPD503-313) that the company anticipates will address Pediatric Exclusivity requirements. Shire expects FDA feedback on the PPSR in the next couple of months. The background package for this meeting provides the same SPD503-313 study design synopsis as the PPSR, but the purpose of the meeting on 9-12-07 is to discuss the proposed design in the context of establishing an SPD503 adjunctive use claim, including efficacy, safety and appropriate instructions for use.

This background package includes a study design for a planned add-on study (SPD503-313), which will evaluate efficacy and safety of adding SPD503 to stimulant therapy in an ADHD population demographically similar to that studied in the SPD503 monotherapy program (6-17 yrs; ~25% female; ~25% adolescents). This will be a double-blind, randomized, placebo-controlled, flexible-dose (SPD503 doses of 1, 2, 3, or 4 mg/day) add-on study (n=333, i.e., about 100 patients/group). Patients must be treated with a psychostimulant (either Adderall XR or Concerta) for at least 4 weeks and have a suboptimal, partial response to be considered for study 313. Patients will continue on their psychostimulant and be randomized to add-on of placebo, SPD503 AM, or SPD503 PM. The purpose of AM and PM dosing arms is to establish if timing of dose makes a difference. The first 5 weeks will be a dose optimization phase, with the next 3 weeks being for maintenance. The primary outcome measure will be the ADHD-RS.

Questions:

Question 1 background: If the results of the study 313 are positive, Shire will submit an sNDA to add language to the INDICATIONS and USAGE section of the SPD503 label that provides for the use of stimulants in combination with SPD503 to treat ADHD.

Question 1A: Would the Agency accept the proposed study as the only study needed in support of an sNDA? If not, what modifications to this protocol would be necessary?

Preliminary Comments: *On face, the proposed study would be acceptable. However, we do have some comments on the protocol (see additional comments at the end of the document). We will likely have additional comments once a full protocol is submitted.*

Discussion at Meeting: *Although the Agency is in general agreement with the 313 study design and statistical analysis plan, we would like to review the full protocol. The protocol could be submitted as a standard review or as a 45 Day Special Protocol Assessment to meet Shire's goal of final design resolution by Jan. 2008.*

We had two specific comments:

- The Agency stated that the partial responders approach (Appendix II, page 3 of the meeting briefing document, items 6-9 of inclusion criteria) would be acceptable.

- We also indicated that the plan to exclude patients having weights greater than 176 lbs (80 kg) would be acceptable.

Question 1B: Does the agency concur that the proposed labeling claim described in section 12 could be achieved if the study is positive?

Preliminary Comments: *If positive, the study will support an adjunctive therapy claim. The exact language for labeling would be established at the time of review.*

Discussion at Meeting: *The Agency indicated that a single SPD503 and stimulants study (Protocol 313) would be sufficient to obtain the desired coadministration labeling, and this would be submitted as an efficacy supplement.*

Question 1C: If the protocol was modified to include only children (6-12yrs), how would the labeling be affected?

Preliminary Comments: *We strongly encourage you to include ages 6-17. If the study is limited to children, that fact would be reflected in labeling. However, you should note that the Agency's pediatric written request will likely require that you study children and adolescents aged 6-17 years old. In that event, if you restrict the age range in your proposed study, you would not meet the terms of the written request.*

Discussion at Meeting: *Shire agreed to include both children and adolescents aged 6-17 years old for study 313 (the same as the SPD503 monotherapy study).*

Question 2: Does the Agency agree that only one PDUFA fee will be charged for the concurrent review of the proposed study which may support both the fulfillment of a Pediatric Written Request [PWR] and a SPD503 / psychostimulants combination use sNDA?

Preliminary Comments: *Yes. The requirement to submit a PDUFA fee is based upon the submission of a supplement that requires clinical data (as defined by the Bundling Policy) for approval. It is independent of a submission providing for a response to a pediatric written request. If your supplement only provides for one claim (in this case, combination therapy with psychostimulants to treat ADHD), only one PDUFA payment will be required.*

Discussion at Meeting: *No discussion at the meeting.*

ADDITIONAL PRELIMINARY COMMENTS

Clinical

We recommend that you consider a longer tapering period for subjects treated with guanfacine 3 mg/day or 4 mg/day, due to potential risks of rebound elevations in blood pressure and heart rate.

- ***Discussion at Meeting:*** The Agency suggested that Shire extend the drug taper phase for subjects assigned to guanfacine 3 or 4 mg daily dose in order to be consistent with the anticipated monotherapy label (minimum of 3 days/mg), and recommended assessment of vital signs data at study end point. The sponsor agreed to this approach, and will collect data on discontinuation as part of this program.

Statistics

1. The primary efficacy measure for the study is the change in ADHD-RS-IV total score from baseline at study endpoint. In the study synopsis, the endpoint is considered as the last post-randomization treatment week at which a valid ADHD-RS-IV total score is collected. We recommend that you consider the primary efficacy measure as change from baseline to Visit 10 (Day 56), and that you plan to impute missing data using the LOCF approach.

2. Please plan to submit the SAP at the early stage of trial development to allow sufficient time for Agency to review and for you to finalize the plan. In your SAP, please pre-specify in detail sensitivity analyses to assess the robustness of the primary analysis results with respect to missing data.

- ***Discussion at Meeting:*** Shire agreed to these proposals.

Office of Clinical Pharmacology

The pharmacokinetics of guanfacine (SPD-503) coadministered with stimulants as per the proposed dosing regimen need to be characterized. We ask that you outline your clinical pharmacology program for characterizing such coadministration.

- ***Discussion at Meeting:*** We reiterated that PK data on the coadministered use will be required for the efficacy supplement filing (via either formal PK studies, or population PK or PK data collection in Study 313). The important aspect that was re-conveyed to the sponsor at the meeting was that the pharmacokinetics of guanfacine coadministered with stimulants would need to be characterized as per the proposed dosing regimen. However, we noted that it would be acceptable for Shire to proceed with study 313 even without such data. Additional PK studies can be done in parallel.

Pharmacology/Toxicology

A juvenile rat study evaluating the proposed combination(s) should be performed.

- ***Discussion at Meeting:*** The Agency reiterated that a juvenile rat study of stimulants/SPD503 combination is a requirement for the efficacy supplement filing. The Agency will work with Shire (review and discuss available data, meetings to discuss any potential study design considerations, etc.) prior to Shire initiating such a study. The toxicology study could be done while the 313 study is on-going.

ADDITIONAL DISCUSSION AT THE MEETING

- Shire's PPSR, which includes study 313 as the cornerstone of the PWR program is still under FDA review and Shire should get feedback regarding the PWR in the near future.

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/s/

Thomas Laughren
9/19/2007 02:42:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 63551

Shire Development, Incorporated
Attention: Michael S. Spitz, RAC
Senior Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD503 (guanfacine hydrocholoride).

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2006. The purpose of the meeting was to discuss the cardiovascular safety of SPD503.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Susan E. Player, Regulatory Project Manager, at (301) 796-1074.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES
IND 63,551

Date:	February 28, 2006
Location:	White Oak Conference Room 1313
Time:	10:00 – 11:00 AM
Firm:	Shire Development, Incorporated
Type:	Face to Face
Meeting:	Type C –FDA Feedback
Drug:	SPD503 (guanfacine)
Indication:	Attention Deficit Hyperactivity Disorder
Meeting Chair:	Thomas Laughren, M.D., Division Director, DPP
Meeting Recorder:	Susan Player, M.S., Regulatory Project Manager

Participants:

FDA:

Thomas Laughren, M.D.	Division Director, DPP
Ni Aye Khin	ActingTeam Leader, DPP
Roberta Glass, M.D.	Clinical Reviewer
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer
Raman Baweja, Ph.D.	OCPB Team Leader
Kofi Kumi, Ph.D	OCPB Reviewer
B. Nhi t Beasley, Pharm.D.	OCPB Reviewer
Jogarao V. Gobburu, Ph.D.	Pharmacometrics Team Leader, Office of Clinical Pharmacology
Mehul Mehta, Ph.D.	Division Director, DCP1, Office of Clinical Pharmacology
Ellis Unger, M.D.	Deputy Director, DCRP
Mehul Desai, M.D.	Clinical Reviewer, DCRP
Susan Player, M.S.	Regulatory Project Manager

Shire:

Steve Damment, Ph.D.	Senior Vice President, Biosciences
Jim Ermer, M.S.	Director, Pharmacology/Pharmacokinetics
Andrew Lyne	Director, Global Biometrics
Patrick Martin, M.D.	Vice President, Global Clinical Pharmacology and Pharmacokinetics
(b) (4)	Scientist, Clinical Research
Linda Mota	Associate Manager, Regulatory Affairs
Noreen Scherer	Director, Clinical Research
Michael Spitz	Senior Manager, Regulatory Affairs
Gerardo Torres, M.D.	Vice President, Medical Affairs
Timothy Whitaker, M.D.	Vice President, Clinical Research
Lisa Whittmer, Ph.D.	Senior Director, Regulatory Affairs

The following minutes include FDA's preliminary comments sent to the Shire via e-mail on 2/27/06 and additional discussion at the 2/28/06 meeting.

Meeting Objective
Discuss planned pre-sNDA submission for (b) (4) for the indication of ADHD.

Background
SPD503 is an extended release form of guanfacine that is being developed for ADHD. The purpose of this meeting is to discuss the cardiovascular safety of guanfacine based on available clinical and non-clinical data. The sponsor contends that there have been no signals of cardiovascular risk in either the non-clinical or clinical data accumulated thus far. They do, however, acknowledge a roughly 5-10 msec increase in QTc in association with the use of this drug in their clinical trials, depending on what correction is used. However, they argue that this is an artifact of the correction factors, and not a true drug effect. They feel that a thorough QT study is not needed; however, they want FDA's views on this matter. In anticipation of the possible need for a thorough QT study, they have proposed a rough outline for a study, and they seek our feedback on this design. They are proposing a 3-period crossover study involving baseline, SPD503 at 4 mg with food on day 1 (and with 1 mg/day increments as tolerated), and moxifloxicin 400 mg as a positive control. They may use ketoconazole to increase guanfacine exposure. If a QT study is needed, they want to discuss timing of such a study relative to the filing of an NDA.

Shire Questions:

1. *As discussed with the Agency previously, Shire intends to file an NDA to support an indication of treatment of ADHD in pediatric patients. Based on the information provided in the background package, does the Agency agree that:*
   a. *existing non-clinical data are sufficient to support the NDA filing?*
   FDA Preliminary Comment: We are aware that Shire has conducted two juvenile animal studies, however, it is our impression that the first study was not adequate. The second study may fulfill this need; however, until we see some data from this study, we cannot reach any conclusion about the adequacy of the non-clinical data for filing the NDA.
   Discussion: Shire described the second study which was conducted in 2001. Animals were dosed from days 7 to 59 and the study included full assessments and toxicokinetics. However, the study did not assess reproductive effects and did not include a recovery group. Thus, it does not meet current guidance. Shire will submit the study results to the IND and we agreed to provide timely feedback on whether or not the study can be considered sufficient for filing.
   b. *existing clinical data and analyses are sufficient to support the NDA filing?*
   FDA Preliminary Comment: It is our impression that the available clinical data are likely sufficient for filing the NDA. A potential area of concern, however, is whether the blood pressure and heart rate effects of guanfacine in the pediatric population have been adequately characterized.
   Discussion: We agreed that they likely have sufficient data to file the NDA. Shire described the data they have accumulated regarding blood pressure and heart rate,

and the data they plan to submit with the NDA. We agreed that this should be adequate.

2. *The existing data from the SPD503 development program (including ECGs) as well as the extensive safety data relating to the use of Tenex® provide cardiovascular safety data for the planned NDA submission. Incremental, confirmatory data that further characterize the effects of SPD503 on the QT interval independent of heart rate may be obtained from a QT study.*
   -If a QT study is required, does the Agency find the proposed conceptual design to be acceptable (specifically with respect to dosage and dose duration, study population, and use of continuous 12-lead ECG recording)?
   FDA Preliminary Comment: If a QT study is done, it should fully cover the plasma exposures that are seen in pediatric patients. These exposures include those at the recommended doses as well as those from concomitant extrinsic factors such as ketoconazole or food. The proposed initial dose of 4 mg with daily 1 mg increases in dose in adults may not yield the highest exposure obtained children. This is because doses higher than 4 mg seem to be poorly tolerated in adults and because of the weight differences, it seems unlikely that concomitant ketoconazole and food with SPD503 will increase plasma levels as high as that obtained in children. A preliminary analysis of the ketoconazole study in adults compared to the dose escalation/dose tapering study (Study 203) in children shows lower concentrations in adults despite CYP3A4 inhibition (same 4 mg dose in both studies). This is presumably because the 6 – 12 year olds had a higher mg/kg dose (mean dose 0.107 mg/kg vs. 0.057 mg/kg in children vs. adults, respectively). The duration should be long enough to permit the highest doses tested to reach steady state. Normal adults would be an acceptable population, and the proposed ECG monitoring should be adequate. If a QT study is performed, it is recommended that heart rate-independent corrections be pre-specified in the protocol. You may want to consider the use of a heart rate independent method such as the Holter bin method. In addition, blood pressures and measurements for orthostatic changes should be performed at the time of peak plasma concentrations. It is suggested that the sponsor submit the QT protocol as a Special Protocol Assessment for Agency comment.
   Discussion: We again emphasized our view that a QT study is not likely to provide additional critical information, especially given the difficulty they would have in pushing the dose high enough in adults to achieve the plasma exposures seen in smaller children under the most extreme of circumstances (i.e., 4 mg dose, high fat meal, and maximal 3A4 inhibition). Shire expressed the view that, although such a study would be difficult, they felt they might be able to accomplish it. We indicated that whether or not they conduct such a study is their decision, as it would not be a requirement for filing the NDA.

3. *The clinical development program for SPD503 is complete (with the exception of one open-label study) and an NDA submission is currently being prepared. The data from a QT study are likely to be confirmatory that the increases in corrected QT from baseline are attributed to effects on heart rate and the inability to correct for this, rather than a direct effect on QT.*
   -Will the Agency comment on the latest date in the review that data from a QT study

would need to be provided (if required) so as to not affect the PDUFA date?
Preliminary Comment: The results from the pivotal studies suggest that guanfacine has a modest effect on prolonging the QTc interval using Bazett and Fridericia corrections; however, both of these corrections utilize a heart rate-based adjustment. In addition, the Agency has not reviewed the raw data or performed an in-depth analysis of your clinical program. If you wish to conduct a QT study in order to convince the agency that guanfacine does not have a QT prolonging effect, you must submit the results of such a study with the initial filing of the NDA in order for the results of such a study to be reviewed in the initial review cycle.
Discussion: We again emphasized that, if they wished to have us review the data from a thorough QT study in the initial review cycle, they would need to submit the results of the study with the initial filing of the application. Shire noted that our preliminary comments regarding the conduct of such a study were helpful, and they would like any additional advice we could provide. We agreed to provide a template for the ECG data that the company should provide, and we also agreed to analyze ECG data from their existing datasets in order to help them with their decision process of whether to conduct a thorough QT study.

4. *If a QT study is not provided as part of the original or amended NDA package for SPD503, what implications will there be on labeling (if any)?*
FDA Preliminary Comment: If a QT study is not provided, then it will be a review issue whether or not guanfacine prolongs the QTc interval. If, based on the available data, the Agency concludes that guanfacine does affect the QTc interval, then this finding would be incorporated in labeling.
Discussion: We again noted that, based on our preliminary look of their analysis, we did not consider this drug product to be a strong QT prolonger. However, we further noted that we could not reach a final judgement about where the ECG information should be located in labeling until we had actually reviewed the data. We did note that the data seemed unlikely to justify a Warning statement.

Action Items

- Shire will submit the results of the second juvenile animal study to the IND and FDA agreed to provide timely feedback on whether or not the study can be considered sufficient for filing.
- FDA agreed to provide a template for the ECG data that should be provided to the Agency for the Agency's analysis. FDA also agreed to analyze their ECG data from Shire's existing datasets in order to help them further with their decision process of whether to conduct a thorough QT study.

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/s/

Thomas Laughren
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,551

Shire Development Inc.
Attention: Michael Spitz, RAC
Senior Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to the Pre-NDA CMC meeting between representatives of your firm and FDA on October 13, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manger, at (301) 796-1152.

Sincerely,

{See appended electronic signature page}

Thomas Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Psychiatry Products
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES
IND #63,551

Date: October 13, 2005
Location: Conference Room 1309
Time: 1:00-2:15 PM
Firm: Shire Laboratories, Inc.
Type: Face to Face
Meeting: Pre-NDA CMC
Drug: SPD 503 (guanfacine hydrochloride)
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Meeting Recorder: Richardae Taylor, Pharm.D., Regulatory Project Manager

Participants:

FDA

Thomas Oliver, PhD	CMC Team Leader
Ray Baweja, PhD	Biopharm Team Leader
Kofi Kumi, PhD	Biopharm Reviewer
Chhagan Tele, PhD	CMC Reviewer
Richardae Taylor, PharmD	FDA Project Manager

SHIRE

Robert H Pullen, PhD	VP, Analytical Sciences
Amir H. Shojaei, PhD	Director, Pharmaceutical Sciences
Michael Spitz, RAC	Sr. Mgr, Regulatory Affairs
Erika A. Wambolt, Ph.D.	Director, Process Development
Lisa Wittmer, PhD	Sr. Director, Regulatory Affairs

Meeting Questions

Drug Substance

1. *The proposed particle size specifications are based on successful manufacture of registration scale batches. Are these proposed method and specifications acceptable?*

   The Agency recommended that the NDA include Shire's rationale for (b) (4); The distribution of (b) (4) should be included, since the choice of appropriate particle size specifications will have a clinical link as well as a manufacturing component. (b) (4)

2. (b) (4)

   (b) (4)

(b) (4)

3. *In response to FDA's EOP2 recommendation to develop an HPLC method for quantifying drug substance impurities, Shire has developed and validated a new HPLC method for the detection of guanidine. Is the proposed method and specification acceptable?*

The Agency recommended that the NDA justify why a not-more-than [NMT] (b) (4)% specification is acceptable (instead of the ICHQ3AR recommended 0.15% limit) for the API HPLC methods for impurities. Currently the HPLC methods that need to be addressed are for (b) (4) The FDA is initially not as concerned about the (b) (4) HPLC specification, which is also set at NMT (b) (4)%.

Shire explained that the impurity limits cannot be lower than the limits already established in the API manufacturer's DMF. FDA recommended that Shire provide nonclinical toxicology data, strong justification from the literature, or other information to support the safety of the specified limits. Ultimately, the adequacy of the impurity limits will be evaluated in conjunction with the Division's pharm/tox colleagues.

Drug Product

4. *The proposed dissolution method for SPD503 uses USP Apparatus II, HPLC (b) (4)>, 75 rpm, and 900mL of acid buffer media (pH 2.2). The proposed specification met the USP acceptance criteria at 1, 4, 8 and (b) (4) for all levels of testing. Is the proposed method and specification acceptable?*

Shire explained that the dissolution method was not limited by the low solubility of the drug product and that the method/conditions are justified because they provide a discriminatory test, (b) (4)

The Agency recommended that the NDA include pharmaceutical development and dissolution method development reports. The pharmaceutical development report should explain the steps in getting from the prototype formulation to (b) strengths with (b) blends. Shire stated that a limit of monomer test is conducted as a releases test for the methacrylic acid copolymer (b) (4) USP/NF (b) (4) The Agency requested that the Shire's NDA address (b) (4) monomer levels and excipient compatibility. The dissolution method report should explain how the proposed method and conditions were selected and must include a 3 media challenge in classical buffers, as Shire explained in the meeting. The dissolution method report should also justify the choice of (b) (4) Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requested that dissolution data also be provided in the PK section of the NDA.

OCPB is particularly interested in the release characteristics over time, and when reviewing (b) (4) will consider the PK characteristics of SPD503 in relationship to drug release/dissolution data.

5. *Shire proposes to eliminate microbial testing of SPD503 drug product since the batches tested according to USP <61> met the corresponding microbial limits and contamination is unlikely. Is this acceptable?*

FDA stated that it was reasonable to propose eliminating routine microbial testing of the drug product. In the NDA, Shire will justify this proposal using data from a large number of (approximately 60) batches. Ultimately, your proposal to remove this testing will be a review decision.

6. *Shire has the following questions regarding stability testing and stability results for SPD503:*

a. (b) (4)

Since (b) (4) blends are used to obtain the (b) (4) strengths, and because various bottling configurations have been put on stability, the Agency requested that the NDA clearly describe the rationale behind the selection of strengths and number of batches for the stability program. In general, the Agency agreed that Shire will have sufficient data on all strengths for commercial packaging (100-count) at the time of NDA submission.

(b) (4)

(b) (4)

b. *Is the proposed stability protocol acceptable*?

Although Shire conducts in-process friability testing, the Agency recommended adding a friability test to the (finished product) stability program. Ongoing or future stability protocols should be amended as applicable to collect friability data.

In response to a question from FDA, Shire confirmed that photostability data will be included in the NDA filing.

7. *The SPD503 clinical development program included use of the following tablet strengths: 1, 2, 3 and 4 mg.* (b) (4)

(b) (4)

(b) (4)

8. *Shire has the following questions regarding qualification of a secondary site of manufacture for the drug product:*

   a. (b) (4)

   b. Shire intends to submit 3 months stability data in the NDA filing to support secondary drug product manufacturer. This is justified based on the extensive long-term stability data available from the primary site of manufacture. Will the FDA allow for an update of these stability data during review of the NDA?

   c. *The stability package intended to support the secondary supplier will contain stability data on three lots of the highest strength of each common blend (2mg and 4mg), and a single lot of the other strength from each blend (1mg and 3mg). Will this approach provide adequate stability data to support manufacture of all four strengths (1, 2, 3 and 4mg tablets) at the secondary site of manufacture?*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

NDA Format of Quality Sections

Shire has the following question relating to the format of the CMC section of the NDA. The NDA will be presented in CTD format. The modules will be organized into the appropriate file/folder structure, in accordance with FDA guidance "NDA Submissions in Electronic Format."

9. *The NDA will reference a DMF for the API. This DMF may not yet be updated in CTD format. Is this acceptable?*

   The Agency agreed to this approach and indicated that the majority of DMFs have not been converted to CTD format.

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/s/

Thomas Oliver
11/30/2005 07:22:07 AM

MEETING MINUTES
IND #63,551

Date:	August 3, 2005
Location:	Conference Room E; WOC2
Time:	11:00 AM -12:00 PM
Firm:	Shire Laboratories, Inc.
Type:	Teleconference
Meeting:	Type C
Drug:	SPD 503 (guanfacine hydrochloride)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Meeting Chair:	Thomas Laughren, M.D., Division Director, DPP
Meeting Recorder:	Richardae Taylor, Pharm.D., Regulatory Project Manager

Participants:

FDA:

Dr. Thomas Laughren	Acting Director, DPP
Dr. Paul Andreason	Acting Deputy Director, DPP
Dr. Roberta Glass	Clinical Reviewer
Dr. Ramana Uppoor	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) Team Leader
Dr. Ta-Chen Wu	OCPB Reviewer
Dr. Richardae Taylor	Regulatory Project Manager

Shire Laboratories, Inc:

Mark Charles	Product General Manager, CNS STAT
Jeff Davidson	VP, Global Biometrics
Jennifer Konow	Manager, Clinical Programs
Victoria Marino, BSMT, CCRA	Assoc. Director, Clinical Programs
Mary F. Morrison, MD, MS	Sr. Director, Global Clinical Medicine
Linda Mota	Assoc. Manager, Regulatory Affairs
Michael Pennick, BSc	Biosciences Director
Michael Spitz, RAC	Senior Manager, Regulatory Affairs
Timothy Whitaker, MD	VP, Global Clinical Medicine
Lisa Wittmer, PhD	Senior Director, Regulatory Affairs

Meeting Objective: Discussion of pediatric development program for SPD 503.

Background:

Shire has largely completed the development program for extended release guanfacine for ADHD (see MM for 5-18-05 preNDA mtg) and plans to submit a 505(b)(2) NDA within the next 8-12 months. They have studied both children and adolescents, but as discussed, the positive efficacy findings come entirely from children. They noted that, in a 1-28-04 meeting, we indicated that we would issue a WR, but we didn't commit to when this would happen. In anticipation of what might be included, in addition to what

they already have done, they proposed several areas for discussion:

-Adolescents with ADHD

-Co-administration with stimulants (they will have some open label data with combined use)

-Safety and efficacy with afternoon or nighttime dosing (guanfacine in their development has been given in the am)

Questions:

1) Would the Division grant a PWR prior to the NDA filing if Shire submits a study plan including children and adolescents?

   Comment: We reassured Shire that we are willing, at some point, to issue a WR. The question is what is best from a public health standpoint. Our view generally is that we like to do this after an NDA has been submitted, and we have had a chance to review much of the available data, so that we can better assess what more is needed. Of course, this presumes that there is something else to ask for that was not submitted in the NDA. We assured them that this would be the case with their program, since they acknowledge that they have adequate efficacy data only in children and they need to do more for adolescents. So, a WR could, at the least, include a request for adolescent data.

2) If yes, could the studies submitted in support of the NDA filing also (partially or completely) fulfill the terms of a written request if appropriately designed?

   Comment: As noted, we indicated that we would not likely issue a WR before submission of the NDA.

3) If no, would the Division write a pediatric written request during or after the NDA review, and would this PWR likely request data above and beyond what was filed to support the initial pediatric indication?

   Comment: As noted, we indicated that we would likely issue a WR after submission of the NDA. We included the following as additional requests that might be considered for a WR:

   -Adolescents: As noted, the efficacy data for adolescents is very weak, and the explanation for this finding is unclear. They are currently exploring this issue, and agree that there are several explanations, including possibly dosing. So one topic for a WR might involve collecting additional data for adolescents.

   -Combined use of stimulants and guanfacine: We noted that it is our impression that alpha-2 agonists are often used in combination with stimulants for treating ADHD, and it would be useful to know if guanfacine is useful as adjunctive therapy. We indicated that they might consider doing an add-on study, and if positive, one such study would be enough to get an adjunctive claim. Such a study would also provide more systematic safety information for the combination

than they would be able to obtain with their open label studies.

-Evening dosing: As noted, in their program thus far, guanfacine has been dosed in the morning. However, they acknowledged that currently available immediate release guanfacine is used mostly in the evening, in combination with stimulants during the day. They would consider a placebo-controlled trial comparing morning and evening dosing of guanfacine. Patients could be stratified on the basis of the presence or absence of insomnia. They acknowledged that they might need to explore several doses, since the exposure to guanfacine during the day would be diminished for evening dosing compared to what is seen with morning dosing.

-Longer-term efficacy data: We suggested that it also might be useful to have longer-term efficacy data, and they might consider adding randomized withdrawal study. We noted that we are rethinking this issue of when long-term data are needed, and we plan to bring this issue to the PDAC in the near future. Thus, longer-term data may become a requirement in near future.

-The sponsor noted their concern that, with only 3 years of exclusivity, they may not have sufficient time to complete the requirements of a WR unless they could receive it before submitting the NDA. Alternatively, we agreed to continue our discussions with them to help in defining more precisely what would be needed in the WR so they could possibly begin some of these programs even before receiving the WR.

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/s/

Thomas Laughren
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,551

Shire Development Inc.
Attention: Michael Spitz, RAC
Senior Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Spitz:

Please refer to the End-of-Phase 3 meeting between representatives of your firm and the FDA on May 18, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manger, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES
IND #63,551

Date:	May 18, 2005
Location:	Conference Room E; WOC2
Time:	1:00-2:30 PM
Firm:	Shire Laboratories, Inc.
Type:	Face to Face
Meeting:	Type B End-of-Phase 3 Meeting
Drug:	SPD 503 (guanfacine hydrochloride)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Meeting Chair:	Russell Katz, M.D., Division Director, DNDP, HFD-120
Meeting Recorder:	Richardae Taylor, Pharm.D., Regulatory Project Manager

Participants:

FDA:

Dr. Russell Katz	Division Director, DNDP
Dr. Thomas Laughren	Psychopharm Clinical Team Leader
Dr. Paul Andreason	Psychopharm Clinical Team Leader
Dr. Roberta Glass	Clinical Reviewer
Dr. Kun Jin	Biometrics Team Leader
Dr. Ramana Uppoor	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) Team Leader
Dr. Ta-Chen Wu	OCPB Reviewer
Dr. Mehta Mehul	OCPB Supervisor
Dr. Richardae Taylor	Regulatory Project Manager

Shire Laboratories, Inc:

Douglas Hay, PhD	VP, Regulatory Affairs
Andrew Lyne, MSc CStat	Biostatistics Director
Victoria Marino, BSMT, CCRA	Assoc. Director,Clinical Programs
Mary F. Morrison, MD, MS	Senior Director, Global Clinical Medicine
Arnaud Partiot, MD, PhD	Sr. VP, Clinical Research and Development
Michael Pennick, BSc	Biosciences Director
Michael Spitz, RAC	Senior Manager, Regulatory Affairs
Timothy Whitaker, MD	VP, Global Clinical Medicine
Lisa Wittmer, PhD	Senior Director, Regulatory Affairs

Meeting Objective

Discussion of clinical and biopharmaceutics results from key studies in the SPD 503 development program for pediatric ADHD.

Background:

SPD503 is extended release (ER) form of guanfacine which has been developed for ADHD in ages 6-17. It is an alpha-2A-adrenergic agonist which is purported to have greater selectivity for alpha-2A than clonidine. The ER form provides flatter input with lower Cmax than the marketed immediate release (IR) form (Tenex).

Development Program:

- Have completed (or are ongoing) 9 phase 1, 5 phase 2, and 4 phase 3 studies
- Phase 3:

- 301: Double-blind, parallel group, placebo-controlled, age 6-17, ADHD; 4 groups, i.e., 3 fixed doses of SPD (2, 3, 4 mg/day) vs. placebo; about 80/group; up to 3 weeks of up-titration, then 2 weeks maintenance, then 3 weeks down-titration; all 3 groups appear to be statistically superior to placebo in change from baseline in ADHD-RS (used Dunnetts) at 5 weeks.

- 304: Similar to 301, except 4 dose groups (1,2,3,4); about 60/group; all 4 groups appear to be statistically superior to placebo in change from baseline in ADHD-RS (used Dunnetts) at 5 weeks.

- While both studies appeared to be highly significant overall, the effect in both studies appears to be coming entirely from 6-12 age group (also 75% of both samples); no apparent effect in 13-17; unclear if higher placebo effect, failure is due to underdosing, or just does not work in adolescents; Shire is considering need for weight-based dosing in future adolescent studies.

- 303 & 305: open label extensions

- Total Exposures:
  - Ph 1: 311
  - Ph 2-3: 839
  - Total: 1150

- Safety Issues:
  - Abrupt Cessation/Rebound:
    - Shire did an abrupt cessation study in young adults (couldn't do in children); had earlier collected data in children who were down-titrated; they looked at first week after end of down-titration [apparent minor increases in systolic and diastolic BP (mean about 6-7%)]; in adult study, compared abrupt d/c from 4 mg vs. slow down-titration (both groups had minor and similar increases to those seen in pediatric studies in both BP and HR); also have data from down-titration in 301, and results are similar.

    - Syncope: 6 patients experienced 7 syncopal events in open-label extension phases of phase 3 studies; also 1 adult in phase 1 study; studies ongoing, so cannot estimate rate (per PY) as yet; about n=450 in open label extensions; usual doses of 3-4 mg; they further note that syncope is common in this age group (15-25% experience fainting at some point), and also that syncope was reported with open-label extension for atomoxetine (0.4% [7/1933]); tended to occur during chronic exposure, either after postural change, in warm environment, or when stressed;

    - Somnolence, Sedation, and Fatigue: somnolence and sedation both dose-related; fatigue not apparently dose-related; all 3 occurred to an important extent; used Pediatric Daytime Sleepiness Scale (PDSS) in 304; despite somnolence, patients scored in normal range on PDSS; to address FDA concerns about the effects of sedation on function, sponsor has initiated study 206; looks at attention, cognition, and daytime sedation in children and adolescents being treated with SPD; simulated classroom setting; looking at doses of 1, 2, and 3 mg; 9 wks; flexible dose design, with patients titrated to optimal dose; will look at changes over course of a day and over duration of study; want to know if can submit with 4-mo safety update.

- Risk Benefit Issues:
  - All doses studied (1, 2, 3, and 4 mg) have been shown effective; post-hoc analyses using weight-based doses suggest dose response for efficacy (greater efficacy with greater weight-based dose); similar analyses for AEs showed similar dose response; they seem to want to in some manner provide for weight-based dosing in labeling.

- PK Issues:
  - Food effect: leads to increased levels (about 40% increase in AUC); but 301 and 304 done without regard to food intake, and demonstrated (in their view) a reasonable risk/benefit profile.

Questions:

Efficacy:

1. Efficacy Questions
   a. Although full data from the completed pivotal studies (301 and 304) need to be reviewed, does the Agency agree that data on the primary outcome measure presented in the briefing package suggest that efficacy has been demonstrated at SPD503 doses of 1-4mg, in the target patient population (diagnosis of ADHD ages 6-17)?

      Comment: We agreed that, on face, both studies appear to be positive, however, we also cautioned that, as always, this is a matter of review.

   b. Shire is considering an alternative NDA filing scenario whereby the initial filing would target an indication specifically in children ages 6-12. Does the Agency agree that the efficacy data are adequate to support this approach?

      Comment: We agreed that the effect appears to be coming from the 6-12 age group, with little indication of efficacy in the smaller adolescent subgroup. The sponsor clarified that even a breakdown of the adolescent subgroup on the basis of mg/kg dose ranges did not reveal any positive efficacy finding. Nevertheless, we noted that it is not clear how to interpret this result, or how to handle it in labeling. We did confirm that this discrepancy would not be a filing issue, but rather, something to be resolved in the course of the review.

Safety:

2. Does the Agency agree that the rebound effects on blood pressure and heart rate have been adequately characterized by the SPD503-102 data, and are reassuring with respect to the use of the product in the pediatric population (6-17 yrs.) for the proposed indication?

   Comment: We noted that they appear to have made a reasonable effort to collect data on this question. Nevertheless, we noted that our ultimate view on this matter would be a matter for review.

3. In the open-label portion of the Phase 3 studies, a small number of patients reported syncopal events that are possibly related to SPD503. Although clinically important, these episodes generally appear to be related to postural changes / orthostatic hypotension and/or vasovagal events, and do not seem to be correlated with evidence of cardiac arrhythmia. Based on the information available, how does the Agency view these events in context of the overall safety profile?

Comment: We noted that their explanation of these events seemed reasonable on face, however, we noted that how we ultimately view these events is a matter for review.

4. Somnolence and Effect on Function
   a. Sedation, somnolence and fatigue are common, related and may be dose-dependent. However, these events are generally mild to moderate and generally do not lead to treatment discontinuation. Therefore, functional impairment, if it occurs, is expected to be limited. Does the Agency agree with Shire's interpretation of the available data on CNS effects associated with the doses (1-4 mg) studied in the Phase 3 program?

      Comment: We again noted that these findings would be a matter for review. However, we did emphasize to the sponsor the importance of trying to determine what events were actually captured under the different AE terms, i.e., sedation, somnolence and fatigue, and to appropriately lump or split based on what they found.

   b. Shire has initiated a study (206) to further characterize the potential functional consequences of the CNS side effects observed in phase 3 trials. Is it acceptable to the Agency that Shire report these results in the 4-month safety update to the NDA?

      Comment: Although we did note some of the shortcomings of study 206, in particular, the fact that it is a flexible-dosing study, we did, nevertheless, express our view that it may provide some useful information about the potential for cognitive impairment. Consequently, we strongly encouraged them to include the results of this study with the application, and noted that this could be a filing issue. They noted that an earlier study, 202, involving a single fixed dose of the IR form, may provide some additional information on lack of cognitive impairment with this drug.

Dose and Benefit/Risk:

5. Does the Agency agree that the preliminary safety and efficacy data support the proposed 1-4mg dose range of SPD503 for the treatment of children (and adolescents) with ADHD?

   Comment: We noted that the ultimate approvability and the appropriate recommended dose range for this product would be a matter for review.

6. As the Agency has previously expressed interest in dosing SPD503 by weight (Type C meeting on Jan. 28, 2004), based on available data, would the Agency support additional guidance regarding weight-based optimization of dose in the "Dosage and Administration" section of the SPD503 label?

   Comment: We expressed our concern that patients were not randomized to weight-based doses, thus the analyses, although suggestive, are not definitive. On the other hand, we acknowledged that it is difficult to know how the results could have been biased because pts were randomized to fixed doses, and thus, also, in a sense, fixed mg/kg doses. Thus, we noted that it is possible that we may be able to interpret these results as fixed mg/kg dosing. Nevertheless, we noted that how we view these results with regard to labeling is a matter for review.

7. Results from the food effect study (104), demonstrate that SPD503 AUC and Cmax are higher when dosed with food than without. However, the patients from the two pivotal studies were dosed without regard to food, and the primary (ITT) analyses of these studies support efficacy and safety of SPD503. Does the

Agency agree that available data support dosing SPD503 without regard to food intake?

Comment: The impact of high-fat meal on AUC (~40%↑) and Cmax (~75%↑), as demonstrated in Study 104, will be included in the Pharmacokinetics section of the label. We noted that clearly exposure is predictive of adverse events, so the fact that patients who eat a high fat breakfast will have substantially higher exposures is a concern. Thus, we indicated that the appropriateness of "dosing SPD503 without regard to food intake" related to the "Dosage and Administration" in the labeling will also be a matter for review. The sponsor indicated that they will attempt to make a PK argument that this may not be an important concern during steady-state dosing.

8. Shire has performed bioequivalence, dose-proportionality, PK, and drug interaction studies (each evaluated in a fasted state, per Agency guidance), as well as a food-effect study. Synopses for the Phase 1 program are provided in section 4.2 of this briefing package. Shire believes this program is adequate to support an NDA filing for SPD503. Does the Agency concur?

Comment:

- (b) (4)
- In addition, the sponsor should provide a summary to show dose-proportionality in the dose range for the NDA submission.
- Per current standard of recommendation for drug metabolism and interactions, the sponsor is recommended to investigate the inhibition potential of SPD503 on CYP2C8 and P-gp, and the induction potential on major CYP enzymes. Since these issues had not been raised in the previous meeting of 2002 (some of these are new scientific standards), OCPB will not make it an NDA filing issue. However, the sponsor should investigate this at the earliest possible time or during the NDA review cycle. The study can be conducted first in vitro; additional in vivo study may be necessary depending on the outcome.
- OCPB has previously requested adequate information on hepatic impairment, but it appears that the sponsor has not provided data on this. The sponsor should justify in the NDA submission as to why such study is not necessary.
- Per previous OCPB recommendation, the sponsor should also develop an adequate discriminatory in vitro dissolution method based on dissolution profiles generated in multiple media and data with different agitation speeds as part of the NDA submission. Adequate dissolution data should be provided on batches used in pivotal BA/BE studies. This was not discussed at this meeting since this was previously communicated.

Conclusions:

- Minutes will be provided to sponsor within 30 days from the date of this meeting in accordance with MAPP 4512.1.

Minutes Preparer **Concurrence, Chair (or designated authority)**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

Russell Katz
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Meeting Minutes
SPD503 Clinical Issues Teleconference between Shire and FDA
Telecon. Date: 23 February 2005

The following minutes were prepared by Shire and will be archived as official minutes of this teleconference. We have added comments for clarification (highlighted and underlined in red below).

Product: SPD503 (guanfacine hydrochloride) tablets; IND 63,551

Shire attendees:

(b) (4)	Clinical Consultant
Kimberly Fiske	Clinical Programs Manager
Arnaud Partiot, MD	Sr. VP, Clinical Research and Development
Michael Spitz	Sr. Manager, Regulatory Affairs
Valerie Waltman	Manager, Regulatory Affairs
Tim Whitaker, MD	VP, Global Clinical Medicine
Lisa Wittmer, PhD	Director, Regulatory Affairs

FDA attendees (Div. of Neuropharmacological Drug Products, ODE-I, CDER):

Paul Andreason, MD	Medical Team Leader
Roberta Glass, MD	Medical Reviewer
Richardae Taylor, PharmD	Regulatory Project Manager

Background information:
On 27 Jan 2005, after reviewing the statistical analysis plan for Shire's SPD503 study 304, the FDA's Neuropharm. Division provided statistical and clinical review comments related to study 304 as well as clinical considerations for the overall SPD503 development program. At Shire's request, the Division granted an informal teleconference to discuss clinical comments regarding CNS effects and sexual functioning.

Summary of teleconference discussions:

I. CNS Effects

After Introductions, Shire acknowledged the need to characterize CNS effects observed in the clinical program, particularly somnolence and sedation, but asked the Division for additional specificity regarding their concerns.

Initially, the Division indicated a concern about next day sedation in pediatrics and recommended that Shire perform studies to evaluate time course of effects, at multiple hourly points, in the day following dosing. The Phase 1 study designs used to evaluate sleep aids, e.g. Sonata (zaleplon), were referenced as acceptable models to follow. However, after hearing that Shire was not employing a nighttime dosing regimen, the Division's study design recommendations shifted from next day to same day (and most importantly, the school day) evaluations of sedation/somnolence, psychomotor skills, cognitive function and possibly driving (simulation) studies.

The Division was informed of Shire's ongoing efforts with various experts to explore characterizing these effects in pediatric patients who suffer from ADHD. One test being considered by Shire to include in a study design is a pictorial visual analog scale

recommended by Dr. Roth, which would include both a self-report and parent/caregiver report aspect. The Division indicated that Dr. Roth is a well known resource for this topic, and respect his expertise. We could not in this meeting guarantee that we would accept Dr. Roth's proposed endpoint without the Division Director's concurrence.

When asked if mg/kg or weight-based dosing had been considered, Shire indicated that as a result of earlier discussions with the Agency, the design of the second pivotal study (304) had been updated from the first pivotal study design (301) to include randomization using a weight-based stratification. It was also noted that the Pediatric Daytime Sleepiness Scale [PDSS] was also added to the 304 study to evaluate sleepiness. {Post meeting note: In the 304 study, the patients were stratified to treatment in three weight groups: < 75 lbs; 75 to <110 lbs.; and 110 lbs. and above. The two lower weight groups were eligible to receive a target dose of 1 mg in a 1:1 ratio. A secondary efficacy analyses of the age subgroups (6-12 and 13-17 years) was also performed.} FDA recommends that the lower weight group NOT be randomized to the highest dose of 4 mg which is higher than the labeled dosing for adults for the marketed form of guanfacine (Tenex).

Shire stated that substantial information on the sedative/somnolence effects will be obtained from studies already performed. Based on this, Shire asked the Division to comment on whether an additional safety study to assess potential CNS effects was a requirement for NDA filing or needed for development of informative labeling. Based on data available thus far, the Division suggested that in order to ensure that sedation and sleepiness are fully characterized, an additional study specifically evaluating CNS effects is recommended.

The FDA recommended that Shire consider the following when designing the safety study:

- Enrolling both pediatric age groups (6-12 and 13-17) years, utilizing either an ADHD patient or normal subject population
- Assessing both cognitive function, such as sustained attention, and sedation
- Evaluating all recommended doses in either a fixed dose titration or dose optimization design depending on the study objectives. (No strong recommendation was made for this safety study, but fixed dose studies are generally more informative for regulatory purposes if an objective of the study is to examine dose response.)
- Evaluating the time course of effects (to characterize effects immediately after dosing and during the school day, and determine if sedation is transient and/or habituated)
- Possibly including active control, (e.g., diphenhydramine) if considered to be appropriate, to demonstrate adequate sensitivity of the study to discern an impairing level of sedation/somnolence.

II. Sexual Functioning

Due to the ethics and feasibility of studying sexual function in pediatric clinical trials, Shire will rely on (spontaneous) adverse event data to characterize potential effects in this area. The Division acknowledged the difficulties in designing a pediatric study, and did not require a study for NDA approval. However, they indicated that an additional study, perhaps in healthy adult volunteers, should be considered.

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/s/

Paul Andreason
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MEMORANDUM OF MEETING MINUTES

Meeting Date: October 8, 2002
Location: WOCII 4th Floor Conference Room
Application: I 63,551 Guanfacine for ADHD
Type of Meeting: End of Phase 2
Meeting Chair: Russell Katz, MD
Meeting Recorder: Lana Chen, RPh

FDA Attendees
Russell Katz, MD, Division Director
Thomas Laughren, MD, Psychiatry Team Leader
Andrew Mosholder, MD, Clinical Reviewer
Judith Racoosin, MD, Safety Team Leader
Jerry Boehm, MD, Safety Reviewer
Barry Rosloff, PhD, Pharmacology Team Leader
David Hawver, PhD, Pharmacology Reviewer
Melissa Banks, PhD, Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Leader
Vaneeta Tandon, PhD, Clinical Pharmacology Reviewer
Sally Yasuda, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Regulatory Project Manager

Sponsor Attendees
(b) (4) Clinical Program Manager
Susan Clausen, PhD, Director, Clinical Programs
Neil Frazer, MD, Vice President, Clinical Research
Suma Krishnan, Senior Manager, Regulatory Affairs
Rick Lilly, PhD, St Vice President, Regulatory Affairs
Guillermo Millicovsky, PhD, Director, Pre-Clinical Development
Simon Tulloch, MD, Sr. Vice President, US Research & Development
Yuxin Zhang, PhD, Sr. Director, Biostatistics
Mike Pennick, PhD, Preclinical Sciences Manager

Meeting Objectives:

The Sponsor requests Agency guidance on the design of the two proposed pediatric pivotal phase 3 studies in ADHD.

Discussion Points:

The meeting opened with the sponsor noting that 19% of total guanfacine use in the U.S. is believed to be for ADHD, often at dosages of 4 mg/day.

Question 1. Design of the proposed pediatric pivotal studies.

Dr. Katz indicated that the proposed designs were generally acceptable, and asked how much previous experience there was with doses of 4 mg/day. Shire indicated that twenty children had received 4 mg/day in a clinical trial, for a duration of 1 week. The total planned exposure to 4 mg/day will be approximately 230 pediatric subjects. Dr. Katz recommended adding growth hormone and cortisol levels as part of the safety assessments, based on the fact that guanfacine has been used as a probe to stimulate growth hormone, and there are some data suggesting an effect on cortisol as well.

Question 2. Statistical analysis plan.

The Division noted that the overall alpha of $p < 0.05$ needs to be protected, and that an alternative to Dunnett's procedure should be used if the data are not normally distributed. Also, any secondary outcome measures for which a claim is desired should be specified *a priori*. We provided a detailed discussion of our requirements for getting secondary outcomes into labeling, i.e., prior agreement with the division on key secondary outcomes, analyses plans that provide for sequential testing of these outcomes, and replication of positive outcomes.

Question 3. Adequacy of the pediatric database.

Shire clarified that they expect to have 450 subjects exposed to any dose, 230 exposed to 4 mg/day, and 200 subjects exposed for a duration of 6 months (at various doses). By the time of the 4-month safety update, they expect to have 150 subjects exposed for a year, 295 exposed for 6 months, and 600 exposed for any duration of time. Open label safety data will include ECG monitoring, vital signs, height and weight, and 30 days follow-up post treatment. We indicated that this plan should be adequate, given that guanfacine is an approved drug with extensive exposure.

Question 4. Adequacy of the proposed adult database.

Dr. Katz indicated that the proposed adult pivotal study is acceptable.

Comments regarding the proposed PK studies:

- The Sponsor's proposal to conduct a single food effect study (SPD 503.102) with a 4 mg dose (using one 4 mg tablet) and a bioequivalence study (SPD 503.103) comparing a 1x4 mg tablet to 4x1 mg tablets is acceptable. However, comments on the study design cannot be provided as only an outline of the protocol has been provided. The diet in the food effect study as well as the statistical analysis plan for both studies have not been mentioned. The sponsor is encouraged to submit the protocol for acceptance.

- The sponsor is encouraged to conduct the in vitro metabolism studies early on in their drug development. Relevant drug-drug interaction studies may need to be conducted depending on

the outcome of these metabolism studies.

Comments for additional PK studies needed to support NDA filing:

- The PK characteristics of guanfacine should be characterized in children at all ages (6-17 yrs) with ADHD. This can be done along with the Phase 3 studies using sparse sampling with at least the highest dose, if not at all doses.

- It is also recommended to obtain PK/PD information in both children and adults in a subset of patients from the Phase 3 studies by taking sparse samples at the clinically studied doses.

- Although some dose proportionality information is available for the 1 mg and 4 mg doses, additional information on the middle doses is recommended. This can be done by collecting random samples from the Phase 3 studies at each dose level.

- An adequate discriminatory in vitro dissolution method should be developed based on dissolution profiles generated in multiple media and data with different agitation Speeds. Adequate dissolution data should be provided on batches used in pivotal BA/BE studies.

- Adequate information on special populations, such as hepatic impaired patients, age, gender and race should be generated.

Question 5. Rebound hypertension.

We had an extensive discussion about the two studies designed to look at rebound hypertension (SPD 503.204 and 205). They had been planning only monitoring up to 8 hours on days 1 through 3 off drug. We argued for continuous inpatient monitoring for the first 2 days off, and they agreed to modify the protocols to address our concerns.

Question 6. Preclinical Program

Shire was advised to qualify any excipients and impurities not contained in the currently marketed products, according to ICH guidelines.

Finally, the Division had some further comments not related to the questions on the agenda. The Division noted that in the pilot study 202, deportment improved but not attention, suggesting that there may be a calming effect without specific improvement in attentional deficits. The sponsor indicated that, on another measure of attention, i.e., the PERMP, there was an effect on attention.

Action Items:

The Sponsor will consider revising their phase 3 protocols regarding the above comments from the Division.

Minutes Preparer:

Lana Chen, R.Ph.
Project Manager, DNDP

Chair Concurrence:

Thomas Laughren, MD
Team Leader, Psychiatry
(designated signatory)

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/s/

Thomas Laughren
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