

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203441Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203441

SUPPL # NA

HFD # 180

Trade Name GATTEX

Generic Name teduglutide

Applicant Name NPS Pharmaceuticals

Approval Date, If Known 12-21-12

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)(1)

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:

d) Did the applicant request exclusivity?

YES NO

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

7 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#

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.)

Not applicable

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:

Trials 004, 005, 020, 021

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.")

004	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
005	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
020	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
021	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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?

All essential trials YES NO

(004, 005, 020, 021)

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"):

004, 005, 020, 021

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?

All essential investigations !
IND # 58213 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?

Not applicable

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: Matthew Scherer

Title: Regulatory Project Manager

Date: 12-20-12

Name of Office/Division Director signing form: Joyce Korvick

Title: Deputy Safety Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MATTHEW C SCHERER
12/20/2012

JOYCE A KORVICK
12/20/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203441 Supplement Number: NA NDA Supplement Type (e.g. SE5): NA
Division Name: Division of Gastroenterology and Inborn Errors Products PDUFA Goal Date: 12/31/12 Stamp Date: _____

Proprietary Name: GATTEX
Established/Generic Name: teduglutide
Dosage Form: Injection
Applicant/Sponsor: NPS Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on enteral support

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

└ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications.

Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Identify the pediatric subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

Revised: 6/2008)

Module 1.3.3 (ITEM 16): DEBARMENT CERTIFICATION

NPS Pharmaceuticals certifies that the services of any person debarred under subsection 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act has not, nor will be, used in any capacity in connection with this New Drug Application.



Sandra C. Cottrell, MA, PhD

Vice President, Regulatory Affairs & Drug Safety
NPS Pharmaceuticals
550 Hills Drive, 3rd Floor
Bedminster, New Jersey 07921

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 203441 BLA #	NDA Supplement # NA BLA Supplement #	If NDA, Efficacy Supplement Type: NA
Proprietary Name: GATTEX Established/Proper Name: teduglutide [rDNA origin] Dosage Form: Injection		Applicant: NPS Pharmaceuticals Agent for Applicant (if applicable): NA
RPM: Matthew Scherer		Division: Division of Gastroenterology and Inborn Errors Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is _____ 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1 (NME)</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input checked="" type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input checked="" type="checkbox"/> ETASU <input checked="" type="checkbox"/> MedGuide w/o REMS (outside of REMS) <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Information Advisory</p>

³ Answer all questions in all sections in relation 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	Included
Documentation of consent/non-consent by officers/employees	Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval, 12-21-12
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included, submitted 12/20/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included, submitted 11/30/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included, submitted 12/20/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	MG, IFU included, submitted 11/30/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling • Original applicant-proposed labeling 	Included, submitted 12/19/12, 11/9/12 Included, submitted 11/30/12
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Communications: 2/21/12, 12/19/11 Reviews: 11/19/12, 7/27/12, 2/21/12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 4/2/12 <input checked="" type="checkbox"/> DMEPA 12/17/12, 2/17/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 11/30/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 11/29/12 <input checked="" type="checkbox"/> SEALD 12/20/12 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review³/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review 1/27/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included , 12/2012
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

❖ 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 <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	12/20/12, 12/17/12, 12/14/12, 12/4/12, 11/21/12(2), 11/15/12, 11/13/12, 10/24/12, 9/27/12, 8/24/12, 8/10/12, 6/26/12, 6/15/12, 6/11/12, 6/4/12, 5/15/12, 4/9/12, 2/10/12, 12/14/11
❖ Internal memoranda, telecons, etc.	NA
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	None
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	NA
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 4/25/11, 10/19/10
• EOP2 meeting <i>(indicate date of mtg)</i>	None
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	None
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	10/16/12
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	12/21/12
Division Director Summary Review <i>(indicate date for each review)</i>	12/20/12
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	11/13/12
PMR/PMC Development Templates <i>(indicate total number)</i>	1 PMR (template included) 1 PMC (template not necessary)
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL review 11/13/12
• Clinical review(s) <i>(indicate date for each review)</i>	11/15/12, 10/31/12, 1/9/12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See 10/31/12 Clinical Review (p19)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	11/20/12 (Oncology), 4/27/12 (Division of Pharmacovigilance), 4/27/12 (QT-IRT)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	Not applicable

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	Submitted 12/18/12 REMS Memo 12/19/12 12/19/12, 12/3/12, 11/20/12
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	12/7/12
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	12/10/12, 2/9/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	10/24/12 (Immunology), 9/19/12, 1/11/12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	7/24/12, 2/24/12
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	8/9/12
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	8/3/12, 12/30/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	Included in P/T review, page 179
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		12/20/12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		1/12/12
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		12/14/12, 7/30/12
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		3/30/12, 1/11/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See 7/30/12 Quality review p263
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 12/14/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input checked="" type="checkbox"/> Completed 11/21/12 <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

...e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

1 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.

Scherer, Matthew

From: Scherer, Matthew
Sent: Thursday, December 20, 2012 12:43 PM
To: 'Sandra Cottrell'
Subject: Update: NDA 203441 (Gattex) - requested revisions to the PI

Attachments: NDA203441 GATTEX FINAL Label.doc

Good afternoon Dr. Cottrell,

Attached, please find the Gattex FPI with requested revisions to fix some typographical and formatting errors. Please submit the final label to the NDA.

Regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993



NDA203441
GATTEX FINAL Label.c

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/s/

MATTHEW C SCHERER
12/20/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Monday, December 17, 2012 4:52 PM
To: Sandra Cottrell
Cc: Diane Fiorenza; Scherer, Matthew; Grewal, Jagjit
Subject: NDA 203441 Gattex - FDA label revisions 12/17/12

Importance: High

Attachments: FDA PI Revision 12-17-12.doc; FDA Med Guide Revisions 12-17-12.doc; FDA IFU Revisions 12-17-12.docx

Dear Dr. Cottrell,

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Subcutaneous Injection, 5 mg.

Attached are FDA's revisions to your proposed package insert label, medication guide, and instructions for use. Please review the revisions and respond with your acceptance and/or proposed changes by 12:00PM tomorrow (December 18, 2012).

I can be reached via email or at the below phone number with any questions.



FDA PI Revision 12-17-12.doc (...
FDA Med Guide Revisions 12-17-...
FDA IFU Revisions 12-17-12.doc...

Regards,

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration
Phone: (301) 796-0846 || Fax: (301) 796-9904
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
12/17/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Subcutaneous Injection, 5 mg.

We also refer to your December 6, 2012, December 7, 2012, December 12, 2012, and December 13, 2012 submissions, containing your proposed REMS document, REMS supporting document, REMS website landing page, post-training and knowledge assessment questions, and Patient and Caregiver Counseling Guide.

Complete and submit the following required revisions from the Agency to the amendment to the proposed GATTEX REMS Document, appended education material (Patient and Caregiver Counseling Guide), and the REMS supporting document (see the Attachments, including track changes, to this Advice letter). Accept and submit the revisions below by 12:00PM on December 17, 2012, at the latest. If meeting this submission date is not possible, notify the Agency as soon as possible as to the expected submission date of these revised materials.

In the REMS Document:

1. II. REMS Elements, A, Communication Plan, 1., A Dear Healthcare Professional letter:
 - a. Insert the sentence clarifying that “NPS will also identify and send the DHCP letter to all other GATTEX prescribers within 60 days of the date of initial prescription, and again at 12 and 24 months after their initial prescription.” See the **Attachments** including track changes to the REMS Document.

b.



2. II. REMS Elements, B, Elements to Assure Safe Use, ETASU for healthcare providers who prescribe GATTEX will receive training:

- a. II. REMS Elements, B. ETASU, 1, a., b. c., d., and e., (b) (4)



3. In the *Patient and Caregiver Counseling Guide* (received on December 13, 2012/Supplement 53/Sequence 57), NPS Pharmaceuticals is informed that once incorporated into an approved REMS program, the proposed materials must *only* include a web address link which represents a direct link to the REMS materials. For example, the web address must not represent the commercial or promotional website for the product, GATTEX. Furthermore, the REMS specific website should not be the sole source of approved REMS materials. To further clarify, there is *no direct link* from the REMS website landing page back to the product, GATTEX website address.

4. Appended REMS materials

- a. GATTEX REMS website landing page:



(b) (4)

REMS Supporting Document

5. Revise the description of the REMS Document to be consistent with required revisions to the REMS Document (see **Attachments**, including track changes to the REMS Document)
6. Insert explanation in the REMS supporting document to explain that NPS will also identify and send the DHCP letter to all other GATTEX prescribers within 60 days of the date of initial prescription, and again at 12 and 24 months after their initial prescription written for GATTEX.

Provide the following information:

(b) (4)

7. Revise the REMS assessment plan (including track changes) to be acceptable to the Agency (see Attachments, including track changes to the REMS supporting document).

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES: REMS Document (including track changes)
REMS Supporting Document (including track changes to the REMS
assessment plan)

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/s/

JOYCE A KORVICK
12/14/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Tuesday, December 04, 2012 10:40 AM
To: 'Sandra Cottrell'
Subject: NDA 203441 (Gattex) - Comments on REMS slide decks

Dear Dr. Cottrell,

We are in the process of reviewing the *Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide* submitted on October 31, 2012 (Supporting Document 044/Sequence 040). The following are required revisions to the that must be incorporated into your appended REMS education materials for the GATTEX REMS to be acceptable to the Agency. Submit these revised REMS education materials incorporating the Agency's comments by close of business on December 7, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised materials.

See the comments and revisions to the proposed *Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide* appended REMS materials corresponding to the comments below:

A. Proposed Prescriber Education Slide Deck

1. Slide 1: Acceptable

2. Slide 2:

- In the Table of Contents (TOC), 1st Topic, delete [REDACTED] (b) (4) and replace it with "Indication"
- In the 2nd Topic, insert the word, "Serious" in front of "Adverse Events of Special Interest"
- In the 3rd Topic, insert the word, "Possible" in front of "Acceleration of Neoplastic Growth"
- In the 4th Topic, insert the word, "Possible" in front of "Enhanced Growth of Colorectal Polyps"
- In the 5th Topic, delete, [REDACTED] (b) (4) "Obstruction" and replace it with, "Gastrointestinal"
- In the 7th Topic, delete, [REDACTED] (b) (4) and replace it with, "Fluid Overload"

3. Slide 3:

- Delete the title, [REDACTED] (b) (4) and all proposed text related to this Topic.
- Replace the slide title with, "Indication"
- Insert the following text in the slide, "GATTEX (teduglutide) is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support."

4. Slide 4:

- In the title, insert the word, "Serious" in front of "Adverse Events of Special Interest"
- Delete the [REDACTED] (b) (4) at the end of the title and [REDACTED] (b) (4)
- Delete the word, [REDACTED] (b) (4) in the first bullet point header; replace it with "Possible" in front of "Acceleration of neoplastic growth and enhanced growth of colorectal polyps"
- In the 2nd sub-bullet, delete, [REDACTED] (b) (4) "obstruction" and replace it with, "Gastrointestinal"

5. Slide 5:

- In the title, insert the word “Possible” in front of “Acceleration of Neoplastic Growth”
- [REDACTED] (b) (4)
- In the 3rd bullet point, remove the extra space between “3 patients” and “on”
- [REDACTED] (b) (4)

6. Slide 6:

- In the title, insert the word “Possible” in front of “Acceleration of Neoplastic Growth”
- Delete [REDACTED] (b) (4)
- Insert the following text below sub-header, “Possible Acceleration of Neoplastic Growth”:
 - Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia
 - Based on benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, GATTEX therapy should be discontinued.
 - In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), GATTEX therapy should be discontinued.
 - In patients with active non-gastrointestinal malignancy, the clinical decision to continue GATTEX should be made based on risk-benefit considerations
 - In patients at increased risk for malignancy, the clinical decision to use GATTEX should be considered only if the benefits outweigh the risks

7. Slide 7:

- In the title, delete the word, [REDACTED] (b) (4) and replace it with “Possible”
- Revise 1st sub-bullet, [REDACTED] (b) (4) to read as “2 villous adenomas”
- Revise 2nd sub-bullet text, [REDACTED] (b) (4) to read “2 hyperplastic”
- [REDACTED] (b) (4)

8. Slide 8:

- Insert the word, “Possible” in front of “Enhanced Growth of colorectal Polyps”
- Delete [REDACTED] (b) (4) from sub-header, “Colorectal Polyps”
- Insert the following text below the sub-header:
 - Colonoscopy of the entire colon with removal of polyps must be done within 6 months prior to starting treatment with GATTEX
 - A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX
 - Subsequent colonoscopies should be done every 5 years or more often as needed. If a polyp is found, adherence to current polyp follow-up guidelines is recommended
 - In case of diagnosis of colorectal cancer, GATTEX therapy should be discontinued

9. Slide 9:

- In the title, delete [REDACTED] (b) (4) "Obstruction" and replace it with, "Gastrointestinal"
- [REDACTED] (b) (4)
- Delete all proposed text in this slide and replace it with following text:
 - 12 patients experienced one or more episodes of intestinal obstruction/stenosis:
 - 6 in SBS placebo-controlled studies
 - 3/77 (3.9%) on GATTEX, 0.05 mg/kg/day
 - 3/32 (9.4%) on GATTEX, 0.05 mg/kg/day
 - None in placebo-group
 - Onset 1 day to 6 months
 - 6 in the extension studies (all on GATTEX, 0.05 mg/kg/day)
 - Onset 6 days to 7 months
 - Of all of these patients, 1 patient required endoscopic dilatation; and none required surgical intervention

1. Slide 10:

- Delete the title, [REDACTED] (b) (4) "Obstruction" and replace it with, "Gastrointestinal Obstruction"
- Delete [REDACTED] (b) (4) from sub-header, "Intestinal Obstruction"
- Delete the proposed content under the sub-header and replace it with the following text:
 - Intestinal obstruction has been reported in clinical trials
 - In patients who develop intestinal or stomal obstruction, GATTEX should be temporarily discontinued while the patient is clinically managed
 - GATTEX may be restarted when the obstructive presentation resolves, if clinically indicated

2. Slide 11:

- [REDACTED] (b) (4)
- Content in this slide is, otherwise, acceptable

3. Slide 12:

- Delete [REDACTED] (b) (4) in the sub-header, "Gallbladder and Bile Duct Diseases"
- Content in this slide is otherwise, acceptable

4. Slide 13:

- [REDACTED] (b) (4)
- In the 1st sub-bullet, insert [REDACTED] (b) (4) to read as, "All 3..."
- Delete 2nd sub-bullet proposed text and replace it with, "None of these events resulted in study withdrawal"

5. Slide 14:

- Delete, (b) (4) in the sub-header, “Pancreatic Diseases”
- Content is, otherwise, acceptable

6. Slide 15:

- Delete the proposed title and replace it with “Fluid Overload”
- (b) (4)
- Under the 2nd major bullet, delete all text (b) (4).

7. Slide 16: Delete this slide and figure.

8. Slide 17: Acceptable.

9. Slide 18:

- Delete the proposed title and replace it with “Fluid Overload”
- Delete (b) (4) from sub-header, “Cardiovascular Disease”

10. Slide 19:

- (b) (4)
- Content is, otherwise, acceptable

11. Slide 20:

- Delete (b) (4) from sub-header
- Delete proposed text and insert the following text:
 - Altered mental status in association with GATTEX has been observed in patients on benzodiazepines in clinical trials.
 - Patients on concomitant oral drugs (e.g., benzodiazepines, phenothiazines, etc.) requiring titration or with a narrow therapeutic index may require dose adjustment while on GATTEX.

B. Proposed Patient and Caregiver counseling Guide

1. Front Cover: Remove the (b) (4) from the front cover
2. Page 2: Remove the title, (b) (4) and all text below the heading.
3. Page 3: Entitled, **Understanding the Risk of GATTEX**, text should focus only on the safety risks and important safety information per the substantially final proposed labeling that includes a Medication Guide.
4. Page 4: Entitled, (b) (4), remove the entire heading and all text below the heading.
5. Page 5: Entitled, **The GATTEX Discussion**, text should focus only on the safety risks and important safety information per the substantially final proposed labeling that includes a Medication Guide.



(b) (4)

Best Regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

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/s/

MATTHEW C SCHERER
12/04/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, November 21, 2012 9:44 AM
To: 'Sandra Cottrell'
Subject: NDA 203441 (Gattex) - draft wording for registry PMR

Attachments: registry PMR.doc

Hi Sandy,
Please see the attached document that includes draft wording for the registry PMR. We may be able to set aside some time Thursday afternoon, 11-29-12, to discuss.

Kind regards,
Matt



registry PMR.doc
(28 KB)

PMR number TBD

A prospective, multi-center, long-term, observational, registry study, of short bowel syndrome patients treated with teduglutide in a routine clinical setting, to assess teduglutide's long-term safety. Design the study around a testable hypothesis to rule out a clinically meaningful increase in colorectal cancer risk above an estimated background risk in a suitable comparator. Select and justify the choice of appropriate comparator population(s) and corresponding background rate(s) relative to teduglutide-exposed patients. Provide sample sizes and effect sizes that can be ruled out under various enrollment target scenarios and loss to follow-up assumptions. The study's primary outcome should be colorectal cancer, and secondary outcomes should include other malignancies, colorectal polyps, bowel obstruction, pancreatitis, gall bladder disease, heart failure, and long-term effectiveness. Follow patients for a period of at least ten years from the time of enrollment. Provide annual progress updates of registry patient accrual and a demographic summary until enrollment target is reached, and provide periodic study updates thereafter. Submit the final protocol and statistical analysis plan to the FDA for review and concurrence prior to study initiation.

Please plan and conduct this study according to the following schedule:

Final Protocol Submission: 09/2013

Study Completion: 3/2029

Final Report Submission: 3/2031

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/s/

MATTHEW C SCHERER
11/21/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, November 21, 2012 1:52 PM
To: 'Sandra Cottrell'
Subject: NDA 203441 (Gattex) - Interim comments on proposed REMS

Attachments: 11-20-12 GATTEX REMS Doc_track chgs_OGC_cy.doc; 11 20 12 Gattex DHCP letter.doc; 11 20 12 Gattex Dear Professional Society Letter.doc

Good morning Dr. Cottrell,

We are in the process of reviewing your proposed REMS submissions dated September 5, 2012 (SDN 032/eCTD Sequence 029) and October 29, 2012 (SDN 044/eCTD Sequence 040). The following are required revisions to the proposed REMS and must be incorporated into your REMS proposal for the REMS to be acceptable to the Agency. Submit your revised REMS proposal incorporating the Agency's comments by close of business on November 30, 2012 so we may continue to review this portion of your NDA.

Proposed REMS

See the attached **REMS Document** that incorporates some of the comments below:

A. Proposed REMS

1. REMS Document:

- a. Goal: Insert "and patients" (italicized text) as follows: "To inform prescribers *and patients* about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with GATTEX."

2. REMS Elements:

- a. Communication Plan: comments on the communication plan follow:

1. The communication plan will be limited to the *Dear Healthcare Professional letter* and *Dear Professional Society letter*.
2. Incorporate the Agency's track changes in the *Dear Healthcare Professional letter* and *Dear Professional Society letter*. In addition to the track changes, we revised the *Dear Healthcare Professional letter* to indicate that both the *Full Prescribing Information* and *Medication Guide* are enclosed. (See the **Attachments**)
3. The target providers for the letters should also include Internists, Family Practice and General Surgeons.
4. Revise the language that describes distribution of the *Dear Healthcare Professional letter* as follows: "In order to facilitate prescriber training and education, a Dear Healthcare Professional (DHCP) letter will be distributed within 60 days of approval of GATTEX or at the time of product launch. The letter will be sent again at 12 and 24 months after product approval. This letter will be distributed via direct mail and electronic delivery and will be accessible via the GATTEX REMS website (www.GATTEXREMS.com)."
5. The communication plan must include that the *Dear Healthcare Professional letter* and the *Dear Professional Society letter* will be provide to MedWatch at the same time they are provided to the healthcare professional and the professional society leadership.

b. Element To Assure Safe Use

1. Prescriber training will be made available to all potential prescribers of GATTEX. This should be included under the ETASU A. Healthcare providers who prescribe GATTEX will receive training.
2. The *Prescriber Education Slide Deck* and the *Patient and Caregiver Counseling Guide* (submitted to the Agency in a REMS Amendment dated October 29, 2012) will be forthcoming in a subsequent communication from the Agency. These training materials should be available from direct links off the GATTEX REMS website. Hard copy of each appended REMS material should be available, upon request. See comments below in the section, REMS supporting document.
3. NPS will ensure that training is available to healthcare providers who prescribe GATTEX. Training will consist of the Prescriber Education Slide Deck and post-training knowledge assessment questions. NPS will ensure that prescribers can report that they have completed the Prescriber Education Slide Deck and the post-training knowledge assessment questions (4 to 5 questions).
4. Develop a GATTEX REMS-specific website (www.GATTEXREMS.com) and submit screen shots of your website for review (e.g., landing page and any additional web pages) landing page and screenshots of your website for review.
 - a. Ensure that all FDA-approved, appended GATTEX REMS materials will be available through the GATTEX REMS specific website.
 - b. The required REMS-specific website should not be linked back to the product website.

c. Timetable for Submission for Assessments

Revise your timetable to 12 months from the date of initial approval of the REMS and annually thereafter. _

B. REMS Supporting Document

1. REMS Assessment Plan

- Revise the REMS assessment plan to include an assessment that is required to include survey assessment of patients' understanding of the serious risks associated with GATTEX, including recommended screening prior to starting GATTEX therapy and monitoring during GATTEX therapy.
- Include information in the assessments on the number of healthcare providers who have completed the Prescriber Education Slide Deck and the results of the post-training knowledge assessment questions (see comments above under the ETASU for Prescriber Training).

2. Other:

- The REMS supporting document must be consistent with all changes made to the REMS Document and appended materials.
- Explain in the REMS supporting document how you will introduce and make the training materials available to prescribers, how you plan to use these training materials, and in what venue(s) you plan to use these training materials for prescribers.
- Submit results of the post-training knowledge assessment of prescribers who completed the training material (Prescriber Education Slide Deck).

C. Resubmission Instructions

1. Submit the amendment to the proposed REMS for GATTEX.
2. Include all of your REMS materials in the submission. For example, your REMS Document, all materials that are appended that are appended to your REMS Document (including the newly requested materials), and your REMS supporting document.
3. For any REMS materials that are being revised, provide both a clean version and tracked changes version of each material.
4. Submit all REMS materials in MS Word format. If certain documents, such as the REMS website are only in PDF format, they may be submitted as such. However, our preference is that as many materials as possible be provided in MS WORD.

REMS Document



11-20-12 GATTEX
REMS Doc_track...

Dear Healthcare Professional letter



11 20 12 Gattex
DHCP letter.do...

Dear Professional Society letter



11 20 12 Gattex
Dear Professio...

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/s/

MATTHEW C SCHERER
11/21/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Thursday, November 15, 2012 2:38 PM
To: 'Sandra Cottrell'
Subject: RE: NDA 203441 (Gattex) - PI revisions
Attachments: PI - fixed 11-15-12.doc

Hi Sandy -

Please see the revised PI with the previously mentioned glitches addressed. Note that changes were made to 2 Dosing and Administration: 2.2 (rewording), 2.6 (removal), 4 Contraindications (removal), 5 W&P: 5.1 (strengthening and cleanup), other redundant sections removed, 6 Adverse Events (cleanup). I hope these changes are fairly simple and should be easy to integrate into your version.

Regards,
Matt

From: Sandra Cottrell [mailto:SCottrell@npsp.com]
Sent: Thursday, November 15, 2012 1:09 PM
To: Scherer, Matthew
Cc: Diane Fiorenza
Subject: Re: NDA 203441 (Gattex) - PI revisions

Matt

We are sending a clean copy today (and track changes) - cleaned up some redundancy etc I bet you are calling out. Suggest you wait till then - we spent a lot of time doing this. Ok?

Thank you for considering

Kind regards

Sandy

Please forgive typos. Sent from my iPhone

On Nov 15, 2012, at 12:59 PM, "Scherer, Matthew" <Matthew.Scherer@fda.hhs.gov> wrote:

Hi Sandy,
We noticed some glitches in the version sent to you. We will have some updates for you today.
Matt

From: Sandra Cottrell [mailto:SCottrell@npsp.com]
Sent: Tuesday, November 13, 2012 2:36 PM
To: Scherer, Matthew
Cc: Diane Fiorenza
Subject: RE: NDA 203441 (Gattex) - PI revisions

Dear Matt

I wanted to acknowledge receipt of your PI feedback. We are working and intend to reply as quickly as possible, noting specifically your Nov. 19th date. In this regard, I'd like to verify that we, like you, will be working in this document for now and not the Annotated version yet, nor will we

send yet an updated SPL format. Assuming this is ok?
As always, thank you for your support!
Kind regards,
Sandy

From: Scherer, Matthew [mailto:Matthew.Scherer@fda.hhs.gov]
Sent: Monday, November 12, 2012 7:50 PM
To: Sandra Cottrell
Subject: NDA 203441 (Gattex) - PI revisions

Dear Dr. Cottrell,

Attached, please find DGIEP's initial revisions to your proposed package insert in pdf and word format (each file has identical content). We have attempted to display our revisions in track changes. Please note the following:

- These revisions are preliminary; we may have additional edits as our reviews progress.
- There are notes throughout requesting clarification throughout the document.
- There are sections/subsections that we have marked as requiring additional consideration before we can recommend revisions (e.g., Contraindications, Pharmacodynamics, Patient Counseling Information).
- The Highlights and Table of Contents will need to be updated to reflect the included revisions (and the ongoing label negotiations).

Please respond to these label revisions in a prompt manner, preferably by Monday, November 19, 2012 so we may continue our review of the labeling portion of your NDA.

Kind regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

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/s/

MATTHEW C SCHERER
11/15/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Monday, November 12, 2012 7:50 PM
To: 'Sandra Cottrell'
Subject: NDA 203441 (Gattex) - PI revisions

Attachments: PI - FDA revisions sent 11-12-12.pdf; PI.doc

Dear Dr. Cottrell,

Attached, please find DGIEP's initial revisions to your proposed package insert in pdf and word format (each file has identical content). We have attempted to display our revisions in track changes. Please note the following:

- These revisions are preliminary; we may have additional edits as our reviews progress.
- There are notes throughout requesting clarification throughout the document.
- There are sections/subsections that we have marked as requiring additional consideration before we can recommend revisions (e.g., Contraindications, Pharmacodynamics, Patient Counseling Information).
- The Highlights and Table of Contents will need to be updated to reflect the included revisions (and the ongoing label negotiations).

Please respond to these label revisions in a prompt manner, preferably by Monday, November 19, 2012 so we may continue our review of the labeling portion of your NDA.



PI - FDA revisions
sent 11-12-...



PI.doc (406 KB)

Kind regards,

Matthew C. Scherer, MBA

Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

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/s/

MATTHEW C SCHERER
11/13/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, October 24, 2012 12:33 PM
To: 'Sandra Cottrell'
Subject: NDA 203441 (Gattex) - labeling comments

Attachments: labeling comments C-C IFU MG PI.pdf

Dear Dr. Cottrell,

Attached, please find the review team's comments and requests for revision on the Gattex labeling. In addition to comments on the container and carton labeling, we are also including preliminary comments on the package insert, medication guide and instructions for use. Please note that we will have additional comments on the package insert, MG and IFU; we may have further comments on the container carton labeling.

Please incorporate these revisions and submit revised labeling to the NDA.

Best regards,
Matt



labeling comments
C-C IFU MG P...

A. Prescribing Information

1. We recommend deleting [REDACTED] (b) (4) where it appears in *Dosage Forms and Strengths* of the Highlights and the Full Prescribing Information, as well as *How Supplied/Storage and Handling* Section in the Full Prescribing Information. The [REDACTED] (b) (4) statement used to define [REDACTED] (b) (4) of Gattex, may lead to confusion and errors when determining the required dose for the patients.
2. The word [REDACTED] (b) (4) used to define the final concentration after reconstitution with 0.5 mL sterile Water for Injection ‘i.e., [REDACTED] (b) (4) 10 mg/mL’, in *Dosage Forms and Strengths* Sections of the Highlights and the Full Prescribing Information, as well as *Description* and *How Supplied/Storage and Handling* Sections of the Full Prescribing Information, is ambiguous and does not help clarify what the concentration is after reconstitution. You need to define the word [REDACTED] (b) (4) and indicate if the use of this terminology is necessary.
3. Revise the third bullet point [REDACTED] (b) (4) in *Dosage and Administration* Section of the Highlights of the Prescribing Information, to use a positive statement such as ‘Gattex should be administered by subcutaneous injection only.’ Additionally, we recommend appending the statement ‘Discard unused portion.’ to ‘Single-use product’ statement. Thus, the third bullet point should read as follows: ‘For subcutaneous injection only. Single use product. Use within 3 hours after reconstitution. Discard any unused portion.’
4. It is not clear if the proposed 5 mg per vial strength of Gattex is the deliverable quantity of Gattex. Clarify if the total vial content is 5 mg or more, as well as the extractable amount of the product in ‘mg’ (i.e., the statement ‘A maximum of 0.38 mL of reconstituted solution can then be withdrawn from the vial.’ should specify the amount of the product in ‘mg’ that is delivered in 0.38 mL). As currently presented, it is unclear if a patient would receive 5 mg Gattex or less, in the proposed maximum extractable volume of Gattex (i.e., 0.38 mL).
5. Include the type and size of the plastic dosing syringe with needles (i.e. 1 mL, 26G 5/8 in) as well as the needles to be attached to the glass pre-filled syringes containing the Diluent (i.e. 22G, 1½ in) in *How Supplied/Storage and Handling* Section.
6. Revise the Prescribing Information to remove the abbreviations ‘sWFI’ and ‘SC’. The abbreviation ‘SC’ is on the ISMP ‘List of Error-Prone Abbreviations, Symbols, and Dose Designations’¹ because it has been mistaken as ‘SL’ or sublingual. As part of a national campaign to reduce medication errors related to error prone medical abbreviations, the FDA agreed not to approve labels and labeling that include the use of error-prone

¹ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

abbreviations. Therefore replace ‘sWFI’ with ‘sterile Water for Injection’ and ‘SC’ with ‘subcutaneous’.

B. Medication Guide

1. Replace the word (b) (4) with ‘injection’ or ‘dose’. The use of the word (b) (4) may be confusing. Additionally, words such as ‘injection’ or ‘dose’ have been used in other approved Medication Guides and are recognized by patients.
2. To improve clarity, we recommend revising the first seven bullet points under ‘How should I use Gattex?’ to appear as follows (please note the replacement of the word (b) (4) with dose):

‘For detailed instructions, see the Instructions for Use at the end of this Medication Guide.

- Use Gattex exactly as your healthcare provider tells you to.
 - Gattex will be mailed to you by a specialty pharmacy. Your healthcare provider will give you details when you enroll.
 - Gattex is injected under the skin (subcutaneous injection) 1 time each day at the same time.
 - Gattex has to be mixed with the Diluent provided in the pre-filled syringe, prior to injection.
 - Your healthcare provider will tell you how much Gattex to use.
 - Gattex must be injected within 3 hours after you mix it with the Diluent.
 - Inject your dose of Gattex under the skin (subcutaneous injection), as you are told by your healthcare provider. Do not inject Gattex into a vein or muscle.
 - If you miss a dose, take it as soon as you remember that day. Take your next dose the next day at the same time you take it every day. Do not take 2 doses at the same time.
 - If you use more than 1 dose, call your healthcare provider right away.’
3. Under ‘How should I store Gattex?’, we recommend replacing the statement (b) (4) in the third bullet point by ‘to take a dose’ or ‘to give an injection’, and replacing the statement (b) (4) to ‘you have mixed for a dose’ or ‘you have mixed for an injection’.

C. Instructions for Use

1. Revise the general format to include spaces between words where appropriate. As currently presented, there are various spacing errors throughout the Instructions for Use. For example the words ‘1 type’ or ‘your workspace’ are presented as one word with no space.

2. We recommend replacing the word ^{(b) (4)} with ‘injection’ or ‘dose’ throughout the Instructions for Use to remain consistent with the Medication Guide (after revised).
3. We recommend providing a statement such as ‘your healthcare provider will tell you how many vials of Gattex you will need for your injection’ under #1 *From your Gattex patient kit*. This statement will clarify the instructions for the patient, if the patient will need more than the maximum extractable volume of 0.38 mL per vial, for each injection.
4. We recommend replacing ‘prefilled glass syringe containing sterile Water for Injection’ (or different variations of this statement) with the name, ‘Diluent’ (after revising the prefilled syringe labels). Using the name, ‘Diluent’ (when the syringe label is revised to be called ‘Diluent’) can further simplify the instructions to follow by patients.
5. *How Do I Prepare a Dose of Gattex*- sections A. 5a and A. 5b, which explain how to open the two different types of the pre-filled syringes. You have not provided detailed instructions on what part of the syringe and the cap the patient should hold and which way the cap should be bent (i.e. bend the cap sideways until the cap comes off). Revise A.5a. and A.5b. under *How Do I Prepare a Dose of Gattex?* to provide more clarity regarding the instructions for use for the two different types of the Diluent syringes. The revised format of section A under *How Do I Prepare a Dose of Gattex?* should appear as follows, however you need to provide specific details, especially to the section 5a:
 - ‘A. **Attach the Needle to the Diluent glass syringe**
 5. Put the prefilled glass syringe and 22G 1 1/2in needle in front of you on your workspace.
 - Hold the prefilled glass syringe by the barrel.
 - a. If you have the Diluent syringe with the white snap-off cap: Snap or twist off the white cap. Only the top portion of the white cap should be snapped off. The lower portion of the white cap will remain in place (Figure 2a). Throw the cap away.
 - b. If you have the Diluent syringe with the gray screw top: Unscrew the top counter clockwise (to the left) (Figure 2b). Throw the top away.
6. Replace the abbreviation ‘IV’ with ‘intravenous’ in Section E. The use of abbreviations is error prone and can lead to confusion. Patients may misinterpret the intended meaning for something else.

D. All Container Labels and Carton Labeling

1. Revise the established name and the dosage form to have a prominence commensurate with the prominence of the proprietary name, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). Additionally, the established name and the dosage form should be revised as follows: '(Teduglutide [rDNA origin]) for Injection'
2. Provide information regarding the amount of the product delivered in the maximum extractable volume of 0.38 mL per vial, after reconstitution. The statement may appear as follows: 'After reconstitution with 0.5 mL sterile Water for Injection, each 0.38 mL contains x mg of Gattex.'
3. Revise the storage information statement 'Store at room temperature up to 25°C (77°F) which appears in the Prescribing Information, Medication Guide, carton labeling, and the pre-filled syringe label, to be in accordance with the USP definition of controlled room temperature (i.e. 20°C to 25°C (68°F to 77°F) per USP 10.30.60 *Controlled Room Temperature*). As currently presented, the storage statement is too general.
4. Put the finalized NDC number on the vial and syringe labels, and in the package insert.
5. The nomenclature of the dosage form should be changed to "for injection" on the container and carton labels, and in the package insert.

E. Container Labels

Pre-filled syringe labels

1. Revise the pre-filled syringe labels to include the word 'Diluent' as the prominent identifier for the pre-filled syringe containing sterile Water for Injection. As currently presented, the syringe label does not provide this, which may make it difficult for patients to identify what the pre-filled syringe contains. Additionally, include the statement 'for Gattex' in a less prominent presentation immediately under the name, 'Diluent', followed by the quantity, '0.5 mL'. The revised presentation should appear as follows (note the prominence of the name, Diluent as compared to the proprietary name, Gattex, and that of Gattex compared to 'Sterile Water for Injection, 0.5 mL):

"Diluent

for Gattex

Sterile Water for Injection, 0.5 mL"

2. Include the 'Rx only' statement on the pre-filled syringe label if space permits, as Sterile Water for Injection is considered a prescription product. Additionally, ensure the 'Rx only' statement is not printed in bold letters and does not have greater prominence than the other information on the syringe

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/s/

MATTHEW C SCHERER
10/24/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, September 27, 2012 5:07 PM
To: SCottrell@npsp.com
Cc: Scherer, Matthew; Grewal, Jagjit
Subject: NDA 203441 Gattex - request for information

Importance: High

Dear Dr. Cottrell,

I am contacting you on behalf of Matt Scherer. Matt is currently out of the office and will return next week.

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Subcutaneous Injection, 5 mg.

We are requesting information to examine the combined effect of parenteral nutrition reduction and teduglutide on liver enzyme levels (AST, ALT, GGT, AlkPhos, total bilirubin). Please provide a tabulation (or other appropriate format) of the data in Study 020 on mean liver enzyme changes from Baseline to Week 24, stratified by treatment group (placebo versus teduglutide 0.05) and responder status (responder versus non-responder). Note that there will be responders in the placebo group also. In addition, provide the marginal mean changes.

Please provide the requested information by October 9, 2012. I can be reached via email or at the below phone number with any questions.

Regards,

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration
Phone: (301) 796-0846 || Fax: (301) 796-9904
Email: Jagjit.Grewal@fda.hhs.gov

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JAGJIT S GREWAL
09/27/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Subcutaneous Injection, 5 mg.

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

1. We note that the neutralizing antibody assay could be interfered with by the presence of teduglutide (at a concentration of 1.5 ng/mL and above) and are concerned that the drug interference could lead to false negative assay results and impact the interpretation of the neutralizing antibody incidence. Provide data to support the lack (or presence) of drug interference in the clinical study samples. We recommend that you submit a dataset containing the sampling time of each immunogenicity sample and the associated teduglutide dosing time information, including dosing time on the day of the visit, dosing time on the day prior to the visit, and the elapse time of immunogenicity sampling since the previous dose.
2. We could not locate a report within the NDA documenting the methodology of the ELISA assay used to measure teduglutide concentrations in the plasma. Provide a brief description of your ELISA assay methodology and identify the location of its documentation within the NDA submission.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

Brian Strongin, RPh, MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
08/24/2012



NDA 203441

**REVIEW EXTENSION –
MAJOR AMENDMENT**

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your November 30, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Subcutaneous Injection, 5 mg.

On August 3, 2012, we received your August 3, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 30, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 12, 2012.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, MD, MPH
Deputy Safety Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JOYCE A KORVICK
08/10/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

We are reviewing the clinical pharmacology and clinical sections of your NDA and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a descriptive statistical summary of PK parameters for each clinical pharmacology study. Each summary should include median (range) and mean (SD). A sample format to present this summary is below.

	Dose (n=)	
	Mean (SD)	Median (range)
C_{max}		
T_{max}		
AUC_{0-t}		
$AUC_{0-\infty}$		
$T_{1/2}$		
CL/F		
$V_{d,ss}/F$		

2. Provide narratives for the 7 cases of intestinal obstruction observed in studies 005 and 021.
3. Provide pathology reports for the following polyps:
 - Subject 004-0138-0008
 - Subject 020-0207-1004
 - Subject 020-0109-1005
 - Subject 005-0103-0007
 - Subject 005-0145-0004
 - Subject 021-0208-1001
 - Subject 021-0138-1011

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/03/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

We are reviewing the immunogenicity assay information provided in your NDA and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In your antibody screening assay, you used 500 ng/ml ALX-0600 to assess percent inhibition in establishing the confirmatory assay. Provide data showing 500 ng/ml ALX-0600 is optimum in your assay.
2. In your neutralizing antibody assay, you did not provide data to support that the engineered cell line was well characterized to ensure responsiveness to the drug product during continuous culture. Provide data ensuring that the length of time required to stimulate cells and the cell culture used in the assay development were optimum for the assay.
3. In your cut-point analysis for neutralizing antibody assay, the mean nominal absorbance for unspiked samples were 310.5, 112.9 and 104.8 electrochemiluminescence units (ECLU) for run 7/8, run 11/12 and run 13/14 respectively (Table 2: cut point analysis). Explain the observed background differences of the study samples.
4. You provide data for study 020 on cross-reactivity between antibodies to ALX-0600 and native glucagon-like peptide -2 (GLP-2) by the native cross reactivity assay (Table 10: 5/6 AD+patients).
 - a) Provide information where the validation report for this assay is located in your NDA.
 - b) Provide data on cross –reactivity rates for clinical studies 04 and 021.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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RICHARD W ISHIHARA
06/15/2012

From: [Bugin, Kevin](#)
To: ["scottrell@npsp.com"](mailto:scottrell@npsp.com)
Cc: [Bugin, Kevin](#); [Scherer, Matthew](#)
Subject: NDA 203441 Gattex (teduglutide [rDNA origin]) - Statistics Information Request - June 11, 2012
Date: Monday, June 11, 2012 11:26:29 AM

Hello Dr. Cottrell,

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

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

- For the CL0600-020 patients who enrolled in the CL0600-021 study, please provide 4 Figures analogous to those provided within the final CSR of the CL0600-005 study i.e. Figures 14.4.1, 14.4.2, 14.4.5, and 14.4.6 on pages 843, 844, 847, and 848 respectively in the CL0600-005 CSR. The time points should range from randomization into the 24 week treatment period of the CL0600-020 study through the point of last data cutoff in the CL0600-021 study.

If you have any questions, call Matthew Scherer, at (301) 796-2307.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

+++++

If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

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/s/

KEVIN B BUGIN
06/11/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA), dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

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

1. Provide pharmacokinetics (PK) results and anti-drug antibody (ADA) data at Week 24 for patients who enrolled in the 72-hour nutrition absorption test in Study CL0600-004. This should include: A) raw individual PK data such as concentration-time data tables and figures; B) individual PK parameters and descriptive statistical summary per dose group; and C) summary graphic PK profiles per dose group.
2. For Study CL0600-020, provide a table of all patients with ADA data from both Weeks 12 and 24. Additionally, explain why Week 12 had only 16 immunogenicity samples while Week 24 had 34 immunogenicity samples.
3. Submit the datasets (.xpt format), NONMEM control stream and program codes used for APPENDIX 2 of the isi-study report (NPSP-RAS-017) entitled "Population PK Analysis to Assess the Effect of Antibodies on Pharmacokinetic Parameters of Teduglutide".

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
06/04/2012



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals
Attention: Sandra C. Cottrell, MA, Ph.D.
Vice President, Regulatory Affairs and Pharmacovigilance
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gattex® (teduglutide [rDNA origin]) Powder.

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.

A. Regarding the Drug Substance

1. Raw Materials:

- Provide the test methods and procedures used in the specifications of the master and working cell banks.

2. Specification:

- Add a test method and an acceptance criterion for heavy metals to the drug substance specification.
- Provide data to confirm peak purity of teduglutide in the HPLC method (b)(4) used to quantitate teduglutide concentration/peptide content in the drug substance and drug product.
- The acceptance criterion for teduglutide concentration/peptide content in the drug substance specification is not acceptable for stability studies. Provide an acceptance criterion (percentage of the release value) for teduglutide concentration/peptide content in the drug substance specification.
- Provide the equation used to calculate the levels of impurities present in the drug substance and drug product to the analytical procedure of HPLC (b)(4).
- Provide the equation used to calculate the relative potency of teduglutide to the analytical procedure of the biological assay.
- Provide the equation used to calculate the amount of (b)(4) in each well for the ELISA.

3. Stability:

- The retest period of the drug substance will be set on the stability data based on the above acceptance criterion for teduglutide concentration/peptide content in the drug substance specification.
- Tabulate the holding times and temperatures used for the intermediates of all the primary stability batches of the drug substance. The holding time and conditions for future production batches of the drug substance need to be comparable or less stressful to the drug substance

B. Regarding the Drug Product

1. Stability:

- Tabulate the holding times used for the bulk solution before filling for all the primary stability batches of the drug product. The proposed holding time for the bulk solution should be comparable to the ones used for manufacturing the primary stability batches of the drug product.
- Provide stability data on samples stored at room temperature after they have been stored at the recommended long-term storage condition for up to 33 months (aged drug product) to support the proposed room temperature storage condition (b) (4)
[REDACTED]

2. Packaging:

- Provide the configuration, acceptance criteria and suppliers for the dosing syringes and needles, and alcohol swabs.

C. Regarding the Method Validation

- Provide data to demonstrate linearity of the HPLC method used for quantitation of impurities [REDACTED] (b) (4) for all the known impurities in the drug substance and drug product.
- Provide validation results to include [REDACTED] (b) (4) impurity in the validation report of the HPLC method used to quantitate B impurities in the drug substance and drug product ([REDACTED] (b) (4)).
- Provide relative standard deviations for retention time and peak area for the validation of repeatability and intermediate precision of the HPLC method used for peptide mapping [REDACTED] (b) (4).
- The number passage of rG2R cell line used for the biological assay should be controlled between 2 to 22 instead of 2 to 30 based on the validation results.
- Clarify how the RSD for intermediate precision of the biological assay was calculated from two measurements in the validation report.
- Provide validation data to demonstrate the specificity of the biological assay using degraded samples of the drug substance and drug product because the validation results provided for degraded samples did not demonstrate that the method is stability-indicating.
- Provide the source and a certificate of analysis for [REDACTED] (b) (4) reference standard.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

CATHERINE A TRAN-ZWANETZ
05/15/2012

MOO JHONG RHEE
05/15/2012
Chief, Branch IV



NDA 203441

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA) dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

We also refer to proposed package insert submitted with this NDA. During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights of Prescribing Information (Highlights)

1. Information presented in the Warnings and Precautions and Drug Interactions sections regarding increased absorption of concomitant drugs is redundant. You should revise these sections to remove any redundant information.
2. Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in Highlights. Avoid other terms, such as “adverse events” or “treatment-emergent adverse events,” and note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
3. The Patient Counseling Information (PCI) Statement must include the verbatim statement: “See 17 for Patient Counseling Information” or if the product has FDA-approved patient labeling: “See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”). You should revise the PCI Statement to reference the Medication Guide.
4. A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of Highlights. The revision date is the month/year of application or supplement approval.

Table of Contents

5. The word (b) (4) appears immediately above the header “1 INDICATIONS AND USAGE” and should be removed.

Full Prescribing Information (FPI)

6. The word ^{(b) (4)} appears immediately above the header “1 INDICATIONS AND USAGE” and should be removed.
7. Throughout the Full Prescribing Information, you should ensure that all identifying numbers are presented in bold print and precede the heading or subheading by at least two square em’s (i.e., two squares of the size of the letter “m” in 8 point type).
8. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
9. In the Clinical Studies section, and throughout the label, as appropriate, remove references to study phase (e.g., Phase 3) and avoid using internal company study titles (e.g., ^{(b) (4)}).
10. The Patient Counseling Information must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. Revise this statement to include a reference to the Instructions For Use in addition to the Medication Guide (i.e., “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”).

We request that you resubmit labeling that addresses these issues by April 20, 2012. The resubmitted labeling will be used for further labeling discussions.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
04/09/2012



NDA 203441

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

NPS Pharmaceuticals
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

ATTENTION: Sandra C. Cottrell, MA, Ph.D.
Vice President Regulatory Affairs & Drug Safety

Dear Dr Cottrell:

Please refer to your New Drug Application (NDA) dated and received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Teduglutide for Injection, 10 mg/mL.

We also refer to your correspondence, dated and received November 30, 2011, requesting review of your proposed proprietary name, Gattex. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Gattex will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 30, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Scherer at (301) 796-2307

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/21/2012



NDA 203441

FILING COMMUNICATION

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your New Drug Application (NDA) dated and received November 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg.

We also refer to your amendments dated November 30, 2011; December 22, 23, 2011; January 12, 13, 2012; and February 7, 9, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 30, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 13, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Study CL0600-020: a description of the number of subjects who were randomized after two optimization attempts, their treatment assignment, and their identification codes. Although the statistical analysis plan for Study CL0600-020 states “If a subject fails to remain stable for at least four consecutive weeks immediately prior to randomization, the subject may start the optimization period again” (Section 5.1), we were unable to find a descriptive analyses of these subjects.
2. Study CL0600-004: minutes for internal meetings that discussed study endpoint changes while the study was ongoing.
3. Study CL0600-04: a discussion of the results of the sensitivity analyses mentioned in Section 11.4.2.2 of the study report (page 76). If this has already been provided, please identify the section of the study report where the results of the sensitivity analyses are discussed.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Division Deputy Director
Division of Gastroenterology and Inborn Error
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
02/10/2012

From: Patel, Nitin M. (CDER/OSE)
Sent: Friday, December 16, 2011 10:54 AM
To: 'Sandra Cottrell'
Cc: Scherer, Matthew; Patel, Nitin M. (CDER/OSE)
Subject: RE: NDA 203441 Sample Request for DMEPA
Good Morning Sandy,

Yes your plans are acceptable.

Kind Regards

Nitin

Nitin M. Patel
OSE-SRPM covering Division of Gastroenterology and Inborn Errors Products
White Oak Bldg. #22, Room 4475
Tel: (301) 796-5412
Email: nitin.patel2@fda.hhs.gov

From: Sandra Cottrell [mailto:SCottrell@npsp.com]
Sent: Thursday, December 15, 2011 4:24 PM
To: Patel, Nitin M. (CDER/OSE)
Cc: Scherer, Matthew
Subject: RE: NDA 203441 Sample Request
Importance: High

Dear Nitin,

Thank you for replying – your answer was even faster than mine! ☺

May I confirm NPS will send one of each of the items you have requested, namely:

- An assembled 30-count patient kit containing 30 empty drug product vials (no label on the vial; but with the proposed vial label art work printed and provided separately) and 30 (b) (4) prefilled syringes with sterile water for injection (sWFI) for reconstituting product without label but art work label printed and provided. In addition the kit will include the planned commercially available ancillary supplies including 30 sterile disposable needles for use with the prefilled sWFI syringes, 30 disposable 1-mL dosing syringes with needle, and 68 alcohol swabs.
- A second assembled 30-count kit with no drug vials but rather the non-product spacer.
- An assembled 1-count patient kit containing an empty drug product vial (no label on the vial; but with the proposed vial label art work printed and provided separately) one (b) (4) prefilled syringe with sterile water for injection (sWFI) for reconstituting product (without label but with art work label printed and provided). In addition the kit will include the commercially available ancillary supplies including one sterile disposable needle for use with the prefilled sWFI syringe, one disposable 1-mL dosing syringe with needle, and four alcohol swabs.
- A 30-count (cold ship) carton of just drug vials containing 30 empty drug product vials (no label on the vial; but with the proposed vial label art work printed and provided).

(b) (4)

Please note that the samples NPS will provide by December 23, 2011, as you requested, will be "handmade units" meaning the cartons, while having the correct labels, will be manually produced and the other packaging material such as the spacer for the 30-count patient kit will also be from

prototype tooling along with hand crimped vials; the commercial units will be obviously much more "elegant" in appearance. The ancillary supplies (alcohol swabs and various needles) will however be those planned for commercialization.

The draft proposed label with medication guide and instruction for use will also be provided in this submission to you.

Please advise me if these plans are acceptable. Thank you!

Kind regards,
Sandy

Sandra C. Cottrell, MA, Ph.D.

Vice President Regulatory Affairs & Drug Safety
NPS Pharmaceuticals
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921
Tel. 908-450-5525 (direct)
Mobile 908-432-3807

From: Patel, Nitin M. (CDER/OSE) [mailto:Nitin.Patel2@fda.hhs.gov]

Sent: Wednesday, December 14, 2011 3:12 PM

To: Sandra Cottrell

Cc: Scherer, Matthew; Patel, Nitin M. (CDER/OSE)

Subject: RE: NDA 203441 Sample Request

Importance: High

Dear Sandy - Thank you for your prompt response. Please see below for DMEPA's response:

We propose to include in these sample kits empty 3-mL vials with (b) (4) no label on the vial; but the proposed vial label art work as provided in the NDA submission would be printed and provided with the sample kits). (We assume this option of empty vials is best in order to avoid shipping unapproved GATTEX drug in vials). Is this acceptable?

Yes, however, could you provide us with the 30-count kit that is assembled and is ready to be shipped to the patient, as well as the kit (without the drug) and the 30-count (cold ship) carton of vials, in the same manner the specialty pharmacy receives?

We propose to send 30 (b) (4) sWFI syringes in the 30-count patient kit and a (b) (4) sWFI syringe in the 1-count patient kit to allow pre-filled syringes from both suppliers to be seen. The submission to you of these samples will also include the printed proposed syringe labels as provided in the NDA. It should be noted that these labels have not been commercially printed as we are awaiting FDA review of the art work as submitted in the NDA. Is this acceptable?

Yes, however, can you verify if you will be utilizing only one supplier for the commercial product?

Does the Agency accept this position regarding the topic of "usability study"?

We will be able to provide a response upon review of the samples (when available) and the Patient Instruction for Use.

Kind Regards
Nitin

From: Sandra Cottrell [mailto:SCottrell@npsp.com]

Sent: Wednesday, December 14, 2011 8:33 AM

To: Patel, Nitin M. (CDER/OSE)

Cc: Scherer, Matthew

Subject: RE: NDA 203441 Sample Request

Dear Nitin,

Thank you for your message acknowledging receipt of our NDA-stage Request for Proprietary Name Review (in follow up to the Conditional Approval letter we received at the IND-stage of development). We are actively preparing to ship the items you requested but have a few questions and proposals for clarification.

The current submission (NDA 203441 Sequence 0000 submitted August 16, 2011 as a "rolling" CMC submission) provided draft labeling and a description of the various components for distributing the product to patients (and to our specialty pharmacies prior to completing the patient kits). To reiterate, these items are:

1. **30-count patient kit** containing the drug product in vials and the device component consisting of prefilled syringes with sterile water for injection (sWFI) for reconstituting product. In addition the kit contains commercially available ancillary supplies including 30 sterile disposable needles for use with the prefilled sWFI syringes, 30 disposable 1-mL dosing syringes with needle, and 68 alcohol swabs. (Drug vials are added when preparing for shipping to a patient.)
2. Non-product spacer carton label for section of 30-count patient kit prior to adding drug product vials
3. **1-count patient kit** containing the drug product in a vial and the device component consisting of one prefilled syringe with sterile water for injection (sWFI) for reconstituting product. In addition the kit contains commercially available ancillary supplies including one sterile disposable needle for use with the prefilled sWFI syringe, one disposable 1-mL dosing syringe with needle, and four alcohol swabs; no non-product spacer label is needed
4. 30-count (cold ship) carton of drug vials (b) (4)
5. (b) (4)
6. (b) (4)

As we read your email, it is our understanding in the context especially of evaluating medication errors for the patients, that you have requested one each of the 30-count patient kit (Item 1 above) and the 1-count patient kit (Item 3 above). Further, these kits will contain all the ancillary supplies (needles, dosing syringes with needles, alcohol swabs) and the drug vial (s). In summary the two kits contain:

	30-count kit	1-count kit
vials	30	1
sWFI syringes	30	1
needles for sWFI syringes	30	1
dosing syringes	30	1
alcohol swabs	68	4

In this regard we have these proposals/questions:

- We propose to include in these sample kits empty 3-mL vials with (b) (4) no label on the vial; but the proposed vial label art work as provided in the NDA submission would be printed and provided with the sample kits). (We assume this option of empty vials is best in order to avoid shipping unapproved GATTEX drug in vials). Is this acceptable?
- We propose to send 30 (b) (4) sWFI syringes in the 30-count patient kit and a (b) (4) sWFI syringe in the 1-count patient kit to allow pre-filled syringes from both suppliers to be seen. The submission to you of these samples will also include the printed proposed syringe labels as provided in the NDA. It should be noted that these labels have not been commercially printed as we are awaiting FDA review of the art work as submitted in the NDA. Is this acceptable?

Please note that the draft labels provided in the August 16th "rolling CMC" submission (NDA Sequence 0000) all used place holders (68875-xxx-xx) for the NDC codes on the draft labels provided, but (as noted in the Reviewer's Guide in NDA Sequence 0001), it is now planned to use

the alternative configuration (68875-xxxx-x). Moreover, NPS has assigned an NDC code to each item in anticipation of approval. These numbers are listed below for the two patient kits along with the components within the two kits. We have not produced labels with these codes pending FDA review of the overall proposed labels. The rationale for assignments is based on:

68875-xyy-z

XX=01=Gattex

YY=01=5mg/vial

Package Configuration	Proposed NDC code on Carton	NDC Code of kit components
30 Day Patient Kit	(b) (4)	(b) (4)
Unit Dose Kit		
(b) (4)		

Thank you for your support and guidance.

Kind regards,

Sandy

Sandra C. Cottrell, MA, Ph.D.

Vice President Regulatory Affairs & Drug Safety
NPS Pharmaceuticals
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921
Tel. 908-450-5525 (direct)
Mobile 908-432-3807

From: Patel, Nitin M. (CDER/OSE) [<mailto:Nitin.Patel2@fda.hhs.gov>]

Sent: Friday, December 09, 2011 8:31 AM

To: Sandra Cottrell

Cc: Patel, Nitin M. (CDER/OSE); Scherer, Matthew

Subject: NDA 203441 Sample Request

Importance: High

Good Morning Dr Cottrell,

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GATTEX (teduglutide) Subcutaneous Injection. Please also refer to your Request for Proprietary Name Review dated November 30, 2011, received November 30, 2011.

Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) is currently reviewing the name and labeling including carton/container and kit. In order to proceed with the review DMEPA will need actual sample product of the 30-count and the 1-count patient kits. The safety evaluator is also inquiring whether you have conducted a usability study for your product if so please email a pdf copy in your response.

Please respond and ship the samples by December 23, 2011. You may ship the samples at the address below.

Please contact me if you have any questions.

Kindly

Nitin

Nitin M. Patel Pharm-D
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Surveillance and Epidemiology
10903 New Hampshire Avenue
White Oak Bldg. #22, Room 4475
Silver Spring, Maryland 20993
Tel: (301) 796-5412
Email: nitin.patel2@fda.hhs.gov

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/s/

NITIN M PATEL
12/19/2011



NDA 203441

NDA ACKNOWLEDGMENT

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Gattex (teduglutide [rDNA origin]) Lyophilized Powder for Injection, 5 mg

Date of Application: November 30, 2011

Date of Receipt: November 30, 2011

Our Reference Number: NDA 203441

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 29, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
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/

MATTHEW C SCHERER
12/14/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 058213

MEETING MINUTES

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gattex (teduglutide) Lyophilized Powder for SC Injection.

We also refer to the meeting between representatives of NPS Pharmaceuticals and the FDA on April 25, 2011. The purpose of the meeting was to discuss the content and format of your planned NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 25, 2011, 1:00 to 2:30 pm
Meeting Location: White Oak, Building 22, Room 1313
Application Number: IND 058213
Product Name: Gattex (teduglutide) Lyophilized Powder for SC Injection
Indication: Treatment of short-bowel syndrome
Sponsor/Applicant Name: NPS Pharmaceuticals, Inc.
Meeting Chair: Rob Fiorentino
Meeting Recorder: Matthew Scherer

FDA ATTENDEES

Donna Griebel, MD, Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, Deputy Director, DGIEP
Joyce Korvick, MD, MPH, Deputy Safety Director, DGIEP
Robert Fiorentino, MD, Acting Medical Team Leader, DGIEP
Zana Marks, MD, MPH, Medical Officer, DGIEP
Michael Welch, PhD, Deputy Director, Division of Biometrics III
Sushanta Chakder, PhD, Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, PhD, Pharmacologist, DGIEP
Susan Kirshner, PhD, Associate Chief, Laboratory of Immunology, Division of Therapeutic Proteins (DTP)
Farouk Sheik, PhD, Staff Fellow, DTP
Yow-Ming Wang, PhD, Team Leader, Division of Clinical Pharmacology III
Lanyan Fang, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology III
John Hill, PhD, CMC Reviewer, Office of New Drug Quality Assessment
Matthew Scherer, MBA, Senior Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES

Henry Chu, MS, Senior Director, Biostatistics and Data Management
Sandra Cottrell, MA, PhD, Vice President, Regulatory Affairs & Pharmacovigilance
Roger Garceau, MD, Senior Vice President of R & D and Chief Medical Officer
Bo Joelsson, MD, PhD, Vice President, Clinical Development, GI
Diane Fiorenza Jones, BS, RAC, Senior Director Product Development, Regulatory Affairs
Lee-ann Montano, BA, Director, Regulatory Operations
Anthony Sileno, MS, Head, R&D Operations
Nader Youssef, MD, Senior Medical Director

1. BACKGROUND

NPS Pharmaceuticals, Inc. (NPS) is developing Gattex (teduglutide) for the treatment of short-bowel syndrome (SBS) in adults. On February 4, 2011, NPS submitted a request for a Type B, pre-application meeting to discuss the content, format and logistics of an anticipated marketing application submission. At the time the meeting request was submitted, the Agency was still determining the appropriate regulatory pathway for Gattex (teduglutide) licensing. The Agency has since advised NPS that a New Drug Application (NDA) is the appropriate application. The Division of Gastroenterology Products sent preliminary responses to the meeting questions to NPS on April 21, 2011. Upon review of the preliminary responses, NPS determined that questions 1, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22 did not require further discussion.

2. DISCUSSION

The sponsor's questions are in "standard" font. The preliminary responses sent to NPS on April 21, 2011 are presented in **bold**. Meeting discussion is presented in *italics*.

Question 1: Does the Agency agree that the four positive secondary endpoints for study CL0600-020 (STEPS) can be included in the label?

FDA Response:

It is premature to discuss which secondary endpoints might go into a label at this time. Specifics of labeling will be a review issue.

Question 2: Does the Agency accept the proposed data-lock date for the BLA's 4-month safety update?

FDA Response:

No, your initial application should contain all the data intended to support the proposed efficacy claims including long-term data that demonstrate durability of benefit.

Given the potential for long term use of your drug, the application should contain an adequate number of subjects with sufficient duration of follow-up to support the safety database. Please clarify the total number of subjects across the development program who will have received at least 12 months of teduglutide at the time of submission.

Discussion

NPS clarified the total number of patients who will have received at least 12 months of exposure to teduglutide, see slide 4 (attached).

NPS further clarified that it would only update the safety data in the 4-month safety update, not efficacy data, as requested by the Agency.

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FDA recommended that NPS delay submission of the marketing application until ~64 patients with at least 12 months of teduglutide exposure are included in the initial safety and efficacy databases.

Question 3: To facilitate the efficiency of review at the 4-month safety update, would the Agency prefer an update to the ISE and an interim study report for Protocol CL600-021, or just an updated ISE?

FDA Response:

See our response to Question 2. We expect that reports of all studies intended to support efficacy would be included with your initial application.

Question 4: Would the Agency accept an updated label at the time of the 4-month safety update, reflecting increased exposure and potentially additional text on maintained or additional effectiveness of teduglutide on PN reduction?

FDA Response:

See our response to Question 2.

Question 5: Does the Agency agree to the proposed tables and listings, and general strategies for side-by-side presentations and limiting pooling efficacy results to subpopulations' data in support of preparing the ISE?

FDA Response:

In general, your plan seems reasonable.

Please refer to the Guidance for Industry: Integrated Summary of Effectiveness available at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Question 6: Does the Agency agree to the proposed tables and listings, and general strategies for pooling data in support of preparing the ISS?

FDA Response:

In general, your plan appears reasonable.

Question 7: Does the Agency agree to the proposed approaches for providing CRFs?

FDA Response:

Yes. Given the small number of subjects in each study, we request that all CRFs be included with the application. This may help to prevent delays in the review process.

Question 8: With reference to the currently proposed list of "adverse events of special interest" (as identified in Section 10.1.3 of this briefing document), does the Agency agree to the proposed adverse event terms?

FDA Response:

Yes. The proposed adverse event terms appear appropriate.

Question 9: Upon review of this topic in this briefing document, does the Agency agree that the approaches described for immunogenicity seem appropriate?

FDA Response:

You have provided limited information in the meeting package and we cannot assess the appropriateness of your immunogenicity testing at this time. Some general comments are provided below.

Your product, teduglutide, is an analog to naturally occurring human glucagon-like peptide-2 (GLP-2). We are concerned about anti-drug antibodies potentially cross-reacting with endogenous GLP-2. In subjects who show a serologic immune response, we recommend that you characterize whether the antibodies are specific to teduglutide or cross-reactive with endogenous GLP-2, and whether the antibodies are neutralizing in nature.

In the event that the antibodies react with both teduglutide and GLP-2 and that subjects show antibody positive at baseline, you should clarify how treatment-induced antibody response is determined when their anti-drug antibody titers rise over their anti-GLP-2 baseline, e.g., by providing the predefined threshold criteria to conclude that a subject has treatment-induced anti-drug antibodies.

You will need to show that the immunogenicity data collected during your phase 3 studies were obtained using validated assays. We recommend that you submit to the Agency for review your immunogenicity assay validation packages along with relevant development data (e.g., supporting the minimum required dilution, stimulatory dose in the neutralizing assay, etc.) and the SOP for routine assay performance prior to testing pivotal clinical samples.

You should characterize the impact of immunogenicity on pharmacokinetics (PK), efficacy and safety. You should monitor patients that show a serologic immune response to your product until they return to baseline on 2 consecutive measurements. These data, both serologic and clinical, should be included with your marketing application.

Please note that we may provide additional comments related to immunogenicity assessment at a later date.

Discussion

FDA recommended submitting the immunogenicity assay method(s) validation along with relevant supporting development data (e.g., selection of minimum required dilution and the selection of the stimulatory dose in the bioassay), and method SOPs for routine assay performance to the IND prior to submitting a marketing application. The FDA further noted that

it may be feasible to assess cross reactivity to native GLP-2 by inhibiting anti-serum responses in the binding assay using excess GLP-2 as a competitor.

Question 10: Will this proposal related to the datasets submission be acceptable to the Agency?

FDA Response:

Please provide the following full case report tabulation (CRT) for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include in your marketing application:

- 1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**
- 2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>). We recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.**
- 3. A well commented and organized software program written for each analysis dataset and efficacy table created.**

For all clinical pharmacology studies, you should submit analysis datasets and parameter datasets. In addition, we have the following general expectations for submitting pharmacometric data and models:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table that gives an overview of modeling steps should be provided.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as

THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion

FDA agreed that it would be acceptable to submit clinical pharmacology study datasets in SDTM 3.1.1.

Regarding the clinical study datasets, NPS proposed to submit the datasets in 3.1.1 and the analysis datasets in a "CRO/industry standards" format. FDA noted that this would be acceptable as long as they adhere to current standards.

Question 11: NPS Pharmaceuticals proposes to not re-issue the individual toxicology study reports, but rather will summarize and re-interpret these studies' results in Module 2.6 and 2.4 based on the current knowledge of the product. Does the Agency agree with this approach to handling preclinical studies?

FDA Response:

No, we do not agree. You need to submit amended study reports for modified interpretation of each individual study. These amended study reports should be submitted in Module 4 along with each original study report. Additionally, the amended study reports should contain re-interpretation of the results of the original findings, the rationale and justification for such re-interpretation and the impact of modified interpretation on the safety assessment of the drug.

Question 12: Does the Agency agree that a waiver request, relative to pediatric development as otherwise required under PREA, is not required for teduglutide based on its Orphan Designation for SBS?

FDA Response:

Yes. Since you have received Orphan Designation, this application will not trigger PREA. Therefore, a waiver is not necessary.

Question 13: Since FDA has estimated in the aforementioned guidance that it could take approximately 120 days to review a sponsor's PPSR, would the Agency accept a PPSR filing during the BLA review after the Filing Review Notification at Day 74?

FDA Response:

You are free to submit a PPSR for Agency consideration at any time. Please note that if you submit a PPSR prior to receiving drug approval, you should submit it to the IND, rather than to your marketing application.

You may wish to wait to submit your PPSR until after we taken action on your marketing application. We may not issue a Written Request during the review cycle if we have not fully reviewed the submitted adult data to inform the design of studies in the pediatric population.

Question 14: Is the proposed strategy acceptable in terms of size and linking relative to these earlier finalized documents, and do the documents appear in overall alignment with the Agency's expectations for an efficient review?

FDA Response:

The specifications state the files should not exceed 100 MB, but since the specifications were written, computers have been upgraded and it is acceptable to send file up to 200 MB as long as it does not take long to open or navigate through the file. However, if it does, the files should be split and be named with a convention similar to "1234-study-report-Part-1."

Please note that for datasets please refer to the Study Data Specifications (PDF - 199KB) (updated 4/1/2010). For questions that pertain to data, please contact eData@fda.hhs.gov.

Please make sure you provide sufficient navigation (bookmarks, hyperlinks, TOCs) as well as descriptive leaf titles in the index.xml and stf.xml files for both legacy and non-legacy documents. The submission needs to comply with FDA and ICH specifications. For example, the tabular listing in module 5.2 should be linked to the referenced studies. Since the eCTD is very granular, providing sufficient navigation using hyperlinks is essential to help ensure an efficient review. Providing reference links from the Module 2 summaries to the information in other modules is essential to an efficient review.

Text-based documents are recommended and preferred. By not providing text-based documents, reviewers have limited ability to search and copy or paste from documents. Please see page 6 of the **Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications** regarding scanned .pdf files and the use of **Optical Character Recognition (OCR)**, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>.

Please also reference the **PDF Specifications** website, located at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>.

A reviewer's guide is not required, but can be helpful to provide a high level overview of an application of what is provided in modules 1 through 5 and should include hyperlinks. For example, for module 5 it could reference the pivotal studies, ISS, ISE and explain how data is being submitted (SDTM or non-SDTM). Additionally, the guide could provide reference links to any other documents which may be specific to the particular application being submitted. The reviewer's guide usually consists of 3 to 10 pages, but there have been some that are up to 30 pages. If you provide a Reviewer's guide, it should be a separate document in the cover letter section under section 1.2 with a clear and descriptive leaf title.

Question 15: While NPS Pharmaceuticals understands that the FDA determines whether a Priority or Standard Review designation will be assigned within 45 days of the company's request that accompanies the submission, and thus will not definitively respond during this

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meeting, does the Agency agree that in principal there is a justification for asking for such consideration for Priority Review?

FDA Response:

Review priority will be determined at the time of NDA filing. If you desire to pursue priority designation, your formal request should include a detailed rationale for why you believe Gattex offers a *significant* improvement compared to products currently marketed. For additional information, please see the Office of New Drugs MAPP 6020.3: Review Classification Policy: Priority (P) and Standard (S) (July 2007), available at the following link:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf>

Question 16: Would the Agency accept the SPL labeling to first be submitted at the 4-month safety update without issuing a Refusal to File for the absence of the SPL label at initial submission?

FDA Response:

Per 21 CFR 314.50 (l)(1)(i), you are required to submit your proposed package insert in SPL format with your marketing application. We expect your marketing application to be complete at the time of submission.

Question 17: Would the Agency comment on the proposed approach to labeling in Section 6 Adverse Reactions (as noted above) and specifically the pooling strategy for the proposed Table in label Section 6.2?

FDA Response:

In general, your proposed labeling plan appears to be reasonable. However, details of the actual label will be a review issue, including the choice of cut-offs for the incidence of adverse events that are reported.

Question 18: Will the Agency accept for this BLA submission the Module 1.16 RMP being written consistent with the European format?

FDA Response:

Any proposed REMS should be in the FDA-specified format, available at the following link:

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM188155.pdf>

Please also see the response to Question 19.

Question 19: Will the Agency make any preliminary comments on the sections of the RMP and the proposed approaches outlined for the REMS and other voluntary risk mitigation measures?

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FDA Response:

You have provided a proposed RMP that generally follows the EU format with modifications for FDA REMS requirements.

The proposal includes the following: Medication Guide, Communication Plan (DHCP letter) and a REMS website.

We acknowledge your intention to submit a proposed risk evaluation and mitigation strategy (REMS). At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be.

A complete review of the proposed REMS in conjunction with the full clinical review of the marketing application will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your marketing application.

If you plan to submit a REMS with the original marketing application submission, please submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal.

Please see the Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>

Question 20: Does the Agency wish the mouse carcinogenicity protocol to be submitted in the BLA, and if yes, is the location so noted acceptable?

FDA Response:

The mouse carcinogenicity protocol does not need to be included in your marketing application submission.

Question 21: Does the Agency wish the protocol for study CL0600-021 to be submitted in the BLA, and if yes, is the location so noted acceptable?

FDA Response:

Yes. The location is acceptable.

Question 22: Does the Agency wish to have a post-approval commitment by NPS Pharmaceuticals for a Clinical Study Report for Protocol CL0600-021 (STEPS 2)?

FDA Response:

Please see our response to Question 2.

Additional comments

1. Clinical Pharmacology comments:

Based on the past discussions, we understand that the drug substance or manufacture process changed during the clinical development process. As such, there is a need to demonstrate the comparability between different drug products. The comparability assessment may involve PK/PD studies and/or clinical studies as stated in previous communications.

As there is a lack of dose response with the studied doses (0.05 and 0.10 mg/kg) of your product, we recommend that you justify your proposed dosing regimen (e.g., exposure-response analysis).

Discussion

FDA requested that NPS include data justifying dose selection in the marketing application. These data should include AUC and PD parameters.

- 2. Within your application, you should also present a comprehensive set of analyses of clinically meaningful indicators of nutritional status to support the observed outcome of change in PN volume from baseline.**

Discussion

NPS agreed to present the measures of nutritional status listed on slide 3 (attached) in the marketing application.

FDA noted that these analyses could be supportive of the primary endpoint and should be included in the ISE.

- 3. Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.**

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3. OTHER COMMENTS

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4. ISSUES REQUIRING FURTHER DISCUSSION

None.

5. ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit immunogenicity validation data	NPS	Per NPS's timeline

6. ATTACHMENTS AND HANDOUTS

NPS's slide presentation is attached.

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MATTHEW C SCHERER
05/23/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration
Silver Spring MD 20993**

IND 058213

MEETING MINUTES

NPS Pharmaceuticals, Inc.
Attention: Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs and Drug Safety
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gattex (teduglutide) Lyophilized Powder for SC Injection.

We also refer to the meeting between representatives of your firm and the FDA on October 19, 2010. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls section of an anticipated new drug application (NDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: October 19, 2010, 3:00 to 4:00 p.m.
Meeting Location: White Oak Building 22, Conference Room 1313
Application Number: 058213
Product Name: Gattex (teduglutide) Lyophilized Powder for SC Injection
Indication: Treatment of short-bowel syndrome
Sponsor/Applicant Name: NPS Pharmaceuticals, Inc.
Meeting Chair: Robert Fiorentino
Meeting Recorder: Matthew Scherer

FDA ATTENDEES

Robert Fiorentino, M.D., M.P.H., Acting Medical Team Leader, DGP
Zana Marks, M.D., M.P.H., Medical Team Leader, DGP
Marie Kowblansky, Ph.D., CMC Lead, Office of New Drug Quality Assessment
John Hill, Ph.D., CMC Reviewer, Office of New Drug Quality Assessment
Sayed (Sam) Al Habet, RP.h., Ph.D., Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology III
Matthew Scherer, M.B.A., Regulatory Project Manager, DGP
Victoria Tsuritis, Pharmacy Intern
Giuseppe Randazzo, M.S., Regulatory Scientist, Office of Drug Evaluation III

SPONSOR ATTENDEES

Sandra Cottrell, Vice President, Regulatory Affairs & Drug Safety
Diane Fiorenza Jones, Senior Director Product Development, Regulatory Affairs
Joseph Rogus, Vice President, Technical Operations and Supply Chain Management
Peter Valentinsson, Senior Director, Pharmaceutical Development
Rick Wilcocks, Director, Technical Services

(b) (4)

1. BACKGROUND

NPS Pharmaceuticals, Inc. (NPS) is developing Gattex (teduglutide) for the treatment of short bowel syndrome (SBS). On July 28, 2010, NPS submitted a request for a Type B, pre-NDA meeting to discuss Chemistry, Manufacturing and Controls section of an anticipated new drug application (NDA) as well some regulatory issues. The Division of Gastroenterology Products (DGP) granted this meeting on August 19, 2010 and received the background package on September 13, 2010. Preliminary responses to the meeting questions were sent to NPS on October 15, 2010. Upon review of the preliminary responses, NPS determined that questions 3, 8b, 10, 11, 13, 14, 15, 16, 17, 18, 19 and 20 did not require further discussion.

2. DISCUSSION

Drug Substance

Question 1: Does the Agency agree that the proposed testing and frequency of testing are sufficient to indicate plasmid stability in both the Master Cell Bank and Working Cell Bank? (See Section 10.1.1)

FDA Response:

We cannot evaluate your proposed testing schedule until we receive the following additional information:

- **A table summarizing the developmental history of the master and working cell banks, noting changes in the cell banks (including, but not limited to changes in the gene sequence, changes in copy number, changes to the plasmid/vector, etc.)**
- **A table summarizing the vial numbers, history of use and disposition for both the master and working cell banks**

Guidance about frequency and type of testing is provided in ICH guidances Q5A, Q5B, Q5C, Q5D, and Q5E.

Discussion

The FDA indicated that the proposed specification, test methods and testing frequency appear to be adequate. These should be submitted with the NDA.

The FDA recommended that the master cell bank (MCB) should be conserved and that testing should be every five years to conserve these important vials. NPS should have a standard operating procedure (SOP) for the working cell banks (WCBs) that clearly specifies the procedures for generating the WCBs from the MCB. The SOP should indicate the number of WCB vials to be generated from each MCB vial. The FDA further stated that one lot of end of production cells should be tested to further qualify the WCB. The Agency indicated that

bracketing of end of production testing, based on fermentation scale, was an acceptable approach if appropriate. The Agency suggested MCBs should be stored at 2 sites covered by separate power grids.

Question 2: Does the Agency agree with the proposal for demonstrating comparability between the two proposed commercial drug substance manufacturers (b) (4)? (See Section 10.1.2)

FDA Response:

Your proposed approach to demonstrating comparability of drug substance from the two sites by extensive characterization studies, in addition to routine commercial release testing, is reasonable. Before you submit your NDA, please provide a comparability protocol, with pre-specified acceptance criteria that will be used to determine comparability of the drug substances from the two sites and submit all supporting data. Where applicable, tabular and graphical presentations/analyses of the data should be submitted prior to submitting your NDA.

Depending on the data provided, it may also be necessary to demonstrate drug substance comparability with animal studies and/or a PK/PD study in humans prior to NDA submission.

In addition, you should be aware that blending of two or more drug substance batches is not recommended unless a clearly defined protocol has been provided for evaluation.

Discussion

NPS noted that it submitted a comparability assessment in 2002. Additional comparability information was also presented with process validation studies in 2005 and 2007.

FDA acknowledged that not all of the above-referenced CMC data has been fully reviewed. NPS agreed to resubmit any comparability data which will support any future manufacturing changes; however, given that NPS has data from approximately 50 batches, FDA agreed that a summary of the data would be preferable.

The FDA requested that NPS develop and submit a comparability protocol be written and submitted support potential major manufacturing changes at the two sites (b) (4) as well as to support other subsequent changes for the drug substance or drug product.

FDA reinforced that the onus to establish comparability is on NPS and recommended that it submit a summary of the comparability data prior to submitting the NDA. The FDA clarified that the comparability testing should align with ICH guidance Q5E that describes a "tiered approach" including physical/chemical testing; animal PK/PD and toxicology testing; and then human PK/PD, which all should be aligned and supporting comparability. The absence of this development continuity could result in a refusal-to-file.

NPS clarified that it only combined batches from the same manufacturer and that each batch was subjected to release testing prior to combining. FDA recommended that NPS not combine different drug substance batches. FDA noted that, if NPS must combine drug substance batches, it must provide a detailed protocol of the batch combination process in the NDA submission. Release testing will be required of the blended batches.

Question 3: Upon review of the table within this briefing document, does the Agency agree to the strategy supporting a (b) (4) shelf-life for drug substance batches manufactured at either (b) (4)? (See Section 10.1.3)

FDA Response:

Your proposal to submit 60 months of stability data from each manufacturing site is reasonable to support a (b) (4) month expiry. However, you should be aware that expiration dating will be based on trends observed in the real-time stability data for drug substance stored at the proposed storage condition and in the proposed container/closure system.

Discussion

No further discussion.

Drug Product

Question 4: Does the Agency agree to the proposed NDA approach to support a transition from the use of vials of sWFI, as was used during clinical trials, to a commercial approach in which the same vial of drug product and dosing syringe used clinically will be supplied with a prefilled, (b) (4) syringe designed to deliver 0.5 mL of sWFI? (See Section 10.2.1)

FDA Response:

From the information provided, the proposal to switch from a vial of sWFI to pre-filled syringes containing sWFI is acceptable. However, you will need to provide a description/illustration of how the pre-filled syringes and the vials of Gattex are to be co-packaged.

Discussion

The FDA stated that details of how the pre-filled sWFI syringes would be co-packaged with the drug product would need to be provided in the NDA. If possible, NPS should provide packaging samples in addition to the required mock labeling.

The FDA reminded NPS to assure that the vendor(s) had submitted their DMFs prior to the NDA submission.

Question 5: Upon review of the table within this briefing document, does the Agency agree to the proposed strategy supporting a (b) (4) month shelf-life for drug product batches manufactured at (b) (4) at a batch scale of up to (b) (4) vials using teduglutide drug substance supplied by either (b) (4)? (See Section 10.2.2)

FDA Response:

No, it is not likely that your data will support a (b) (4) month expiration period for your drug product because you plan to submit only 18 months of stability data for product manufactured at (b) (4). It is possible, however, that some supporting stability data for product manufactured at (b) (4) may be considered in determination of a final expiry date.

The required stability data should be real-time stability data for the proposed commercial formulation stored in the proposed container/closure system at the intended storage condition.

Discussion

No further discussion.

Question 6: Does the Agency agree to the proposed validation approach intended to support use of drug substance from (b) (4) for drug product manufactured at (b) (4) at a nominal commercial batch size of (b) (4) vials? (See Section 10.2.3)

FDA Response:

The proposal, as described, is adequate. However, you are advised to contact the FDA Office of Compliance regarding validation of the commercial process.

Discussion

The FDA commented that there may be specific criteria used by facilities inspectors regarding the inspection of two facilities that manufacture the same product. All testing laboratories should also be prepared for inspection.

The FDA advised NPS to request a meeting with the Office of Compliance and also provide the Office of Compliance with details of the "combining" procedure for multiple batches of API.

Analytical

Question 7: Does the Agency agree with the proposal to treat teduglutide as a biological, rather than a small molecule drug, from an analytical perspective with respect to attributes measured, analytical methods, and the setting of specification acceptance criteria? (See Section 10.3.1)

FDA Response:

Please clarify what differences you expect by treating “teduglutide as a biological, rather than a small molecule”. Both OBP and ONDQA adhere to the ICH guidances Q6B and Q5C when reviewing recombinant DNA technology products.

Discussion

No further discussion.

Question 8a: Does the Agency agree with the proposed approach to specify the biological potency of teduglutide drug substance using this numerical relative biological potency to a reference standard?

FDA Response:

Yes, based on the information you have provided, your approach seems adequate; however please be aware that an acceptable potency range of (b)(4) percent of reference, or (b)(4), is required. To assist in the interpretation of these potency data, indicate if this drug has a wide or narrow therapeutic window. Final evaluation of the acceptability of your proposed potency will depend on the data provided in the NDA.

Discussion

NPS acknowledged the requirement for a potency range of (b)(4)% and noted the challenges of meeting this requirement with the currently-used “tandem bioassay”.

FDA recommends NPS strive for an (b)(4)% potency range and justify any inability to reach this specification in the NDA submission. FDA further recommended that NPS develop an HPLC-based assay that will not be subject to the error propagation resulting from the currently-used tandem assay. All details of the current assay should be included in the NDA. NPS should comply with the guidelines as described in the ICH guidance for cell banks.

Question 8b: Does the Agency agree that the biological potency of the drug product need not be routinely tested provided a good correlation is provided between the chemical-based assays and the bioassay of the drug product? (See Section 10.3.2)

FDA Response:

Routine potency testing as part of lot release is required. This does not preclude requests in the future seeking regulatory relief (routine lot release testing) as more manufacturing experience is gained. Your request should include validation data concurrently obtained at the time of batch release, linking potency to another attribute such as chromatographic peak height or area under-a-curve.

Discussion

No further discussion.

Question 9: Does the Agency agree with the proposal that the reference standard, in turn, be controlled by a specification range placed upon the specific activity of the reference standard? (See Section 10.3.2)

FDA Response:

Yes, we agree. Full biochemical characterization data for the reference standard will need to be provided in the NDA. These data need to include, but not be limited to, examples of calculations to determine potency/activity, chromatographic profiles, impurity profiles, etc. Justifications for all specifications need to be provided.

Discussion

NPS described challenges associated with determination of reference standard potency and noted that it does not observe transient instability but it does observe variability in the reference standard. FDA remarked that the potency assay for the reference standard should be as accurate as possible. Accurate assessment of the reference standard potency will simplify lot release testing. NPS should provide as much data as possible to support the reference standard potency accuracy.

The FDA suggested that NPS consider the following approaches: to certify/re-qualify the reference standard; control routine lot release by requiring the potency assay to be as accurate as possible; and to test the historical data with statistics. The FDA noted that the onus was on NPS to provide a convincing case that the proposed range is the best it can be. It is NPS' responsibility to identify the controls to be used to assure the reference standard integrity. This information should be included in the NDA submission.

Question 10: Does the Agency agree with the proposed approach to replace the current quantitative methods for L-histidine, mannitol, and phosphate with a compendial osmolality method as part of the teduglutide for injection specification? (See Section 10.3.3)

FDA Response:

Your proposal is acceptable, however supporting data demonstrating the sensitivity of the osmolality measurement to changes in any of the excipients L-histidine, mannitol, and phosphate needs should be provided in with your NDA.

Discussion

No further discussion.

Question 11: Does the Agency agree with the proposal to place a minimum of one of every 20 commercial drug substance and drug product batches produced per year on stability to be followed with the proposed marketed product stability protocols that will be included in the NDA for review and acceptance? (See Section 10.3.4 and Tables 9 and 10 for stability schedules.)

FDA Response:

We require that, initially, a minimum of three commercial batches of drug product manufactured using different lots of drug substance manufactured at each of the two qualified drug substance manufacturers (a total of six batches) be enrolled into the commercial stability protocol. After this, one batch of drug product manufactured using drug substance from each manufacturer (a total of two batches) must be enrolled annually into the commercial stability protocol. You are also reminded that as a biologic drug, neither the bulk drug substance nor the final drug product can be re-tested in order to extend the shelf-life.

Discussion

No further discussion.

Question 12: Does the Agency agree with the proposed approach for new analytical methods for monitoring aggregation, opalescence, and uniformity of dosage units and possible introduction into the corresponding specifications, along with the strategy for establishing acceptance criteria? (See Section 10.3.5)

FDA Response:

A measure of aggregate formation and uniformity of dosage units will be required as a part of the drug product quality specifications for routine lot release and stability testing. Concurrent evaluation of new analytical methodologies is acceptable.

Discussion

NPS acknowledged the FDA comments. NPS noted that is has developed (b) (4) and compendial (b) (4) methods to measure aggregation.

The FDA agreed that alternative tests could be acceptable if NPS demonstrates that they adequately measure aggregation and recommended that NPS concurrently validate any new tests to minimize the chance of batch loss.

FDA agreed that (b) (4) and USP Particulate Matter testing in lieu of existing released tests for aggregation may be acceptable. It recommended that NPS refine the USP Particulate Matter test at various stages of the manufacturing process to tighten the release specifications.

Question 13: Does the Agency agree that there is no need to re-assign the value of the current reference standard from (b) (4) vial or the values of earlier reference standards, nor to change all the values for drug dosing and drug concentration in the NDA filing and company records? (See Section 10.3.6)

FDA Response:

We agree that there is no need to re-assign the value of the current reference standard from (b) (4) however our decision may be re-evaluated when you provide information about the therapeutic window of this drug (please see answer to question #8).

Discussion

No further discussion.

Question 14: Does the Agency agree with the proposal to use the newly determined reconstitution factor for future batches and future stability data points, but not to retrospectively reassign the protein content for earlier drug product batch release and stability data? (See Section 10.3.7)

FDA Response:

Based on the data provided, this proposal is adequate.

Discussion

No further discussion.

Question 15: Does the Agency agree with the proposed approach for correcting the database for drug substance impurities associated with optimization of the integration parameters for analytical method QC-ANP-GLP-2111? (See Section 10.3.8)

FDA Response:

Based on the provided data, this proposal is adequate.

Discussion

No further discussion.

Regulatory Development Considerations

Question 16: Would the Agency support initiating review of this “rolling submission” for teduglutide? If yes, will the Agency provide a Letter of Agreement to this partial submission when issuing their official minutes from this meeting?

FDA Response:

Per 21 CFR 314.50(d)(1)(iv), any sponsor can “submit a complete chemistry, manufacturing, and controls section 90-120 days before the anticipated submission of the remainder of the application.” The FDA will review such early submissions as resources permit. A “Letter of Agreement” is not necessary.

Discussion

No further discussion.

Question 17: Does the Agency agree to this strategy for limited components to be in Module 1 in the CMC NDA submission?

FDA Response:

This approach appears to be acceptable.

Discussion

No further discussion.

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Question 18: Does the Agency agree to this strategy for resubmitting the request in the full NDA submission, or should this name request be included in the initial CMC submission if a rolling submission is pursued?

FDA Response:

Your proposal to re-submit the original proprietary name request document upon submission of the full NDA submission is acceptable.

Discussion

No further discussion.

Question 19: Regardless of a rolling submission, is it correct that the PAI process and scheduling of inspections will not start until the full NDA is accepted for filing?

FDA Response:

The prior approval inspection process and scheduling generally do not start until the full NDA is accepted for filing. However, there are exceptions; therefore facilities need to be ready for inspection upon submission of any new marketing application.

Discussion

No further discussion.

Question 20: Does the Agency agree to this approach for fulfilling the obligation of submitting a field copy of Module 3 and meeting the obligation of Field Copy Certification in the NDA?

FDA Response:

This approach appears to be acceptable.

Discussion

No further discussion.

Additional comments from the FDA

In the NDA application you will need to provide at least six hours of stability data for the reconstituted drug product to support your proposed (b) (4) holding period prior to

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use.

Discussion

No further discussion.

3. ISSUES REQUIRING FURTHER DISCUSSION

None

4. ACTION ITEMS

None

5. ATTACHMENTS AND HANDOUTS

NPS' slide presentation is attached.

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MATTHEW C SCHERER
11/30/2010