

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-198

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

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

NDA/BLA#: 22-198 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Gastroenterology PDUFA Goal Date: May 2, 2007 Stamp Date: May 2, 2007
Products Target Date: Sep 12, 2008

Proprietary Name: Sancuso

Established/Generic Name: granisetron

Dosage Form: transdermal system

Applicant/Sponsor: Strakan International (ProStrakan)

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: prevention of nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy for up to 5 consecutive days

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

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

Does the division agree that this is a complete response to the PMC/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.

APPEARS THIS WAY ON ORIGINAL

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 checked="" type="checkbox"/>	Other	0 yr. __ mo.	2 yr. __ mo.	<input checked="" 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.

Many childhood cancers are uncommon and it is difficult to standardize a multi-center study or conduct a single center protocol in a sufficient number of patients. It is thus impractical to conduct studies in this age group.

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 checked="" type="checkbox"/>	Other	<u>2</u> yr. __ mo.	<u>17</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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): <u>PK Study due February 29, 2012. Efficacy and Safety Study due January 31, 2013</u>							

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 THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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).

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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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}
Thomas Moreno
 Regulatory Project Manager

(Revised: 6/2008)

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

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

/s/

Thomas N Moreno
9/15/2008 03:28:29 PM

EXCLUSIVITY SUMMARY

NDA # 22-198

SUPPL #

HFD # 180

Trade Name Sancuso

Generic Name granisetron hydrochloride

Applicant Name Strakan

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 20-239 Kytril injectable; injection
 NDA# 20-305 Kytril tablet; oral
 NDA# 21-238 Kytril Solution; oral

2. Combination product.

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

YES NO

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

NDA#
 NDA#
 NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Investigation #1 (Study 392MD/8/C) and Investigation #2 (Study 392MD/15/C): Compare the efficacy, safety and tolerability of a granisetron TDS with oral granisetron in Chemotherapy Induced Nausea and Vomiting (CINV) following a single day administration of moderately emetogenic chemotherapy.

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2

YES

NO

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

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

Investigation #1 and #2

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

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

Investigation #1

!

!

IND # 70,582

YES

! NO

! Explain:

Investigation #2

!

!

IND # 70,582

YES

! NO

! Explain:

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

Investigation #1

YES

Explain:

! NO

! Explain:

Investigation #2

YES

Explain:

! NO

! 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: Thomas Moreno

Title: Regulatory Project Manager

Date: June 13, 2008

Name of Office/Division Director signing form: Donna Griebel

Title: Director, Division of Gastroenterology Products

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

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

/s/

Donna Griebel
9/15/2008 05:42:30 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
BLA # NDA # 22-198	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Sancuso Established Name: granisetron Dosage Form: transdermal system		Applicant: Strakan International
RPM: Thomas Moreño		Division: Gastroenterology Products Phone # 301-796-2247
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>20-239 Kytril (granisetron HCl), Injectable 20-305 Kytril (granisetron HCl), Tablet 21-238 Kytril (granisetron HCl), Oral Solution</p> <p>Provide a brief explanation of how this product is different from the listed drug. Different Dosage Form</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: June 2, 2008</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> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date		May 2, 2008
❖ Action Goal Date (if different)		September 12, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

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

Version: 3/13/08

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 2: New Active Ingredient NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<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, exception for review granted (<i>file Center Director's memo in Administrative Documents section</i>) If yes, OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: <input type="checkbox"/>	April 23, 2008
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OPE/DRM (approvals only)	<input type="checkbox"/> Yes, date
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs only: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs 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> • 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>) • 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>) • 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>) • 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 <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date 10-year limitation expires:
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<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 checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" 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 checked="" 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 checked="" 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 to the next section below (Summary Reviews).

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

<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>	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	September 16, 2008
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	September 12, 2008
❖ Documentation of consent/non-consent by officers/employees	September 12, 2008
Decisional Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	None
❖ Division Director Summary Review (<i>indicate date for each review</i>)	September 12, 2008
❖ Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	None
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval: September 12, 2008
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Not applicable
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	August 14, 2008
• Original applicant-proposed labeling	July 2, 2007
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert (<i>write submission/communication date at upper right of first page of PPI</i>)	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Not applicable
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	July 15, 2008
• Original applicant-proposed labeling	See Package Insert: July 2, 2007
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	None

❖ Medication Guide (<i>write submission/communication date at upper right of first page of MedGuide</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	None
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	None
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	None
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	None
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	Not applicable
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
❖ Labeling reviews and any minutes of internal labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP Name Review: March 17, 2008 <input checked="" type="checkbox"/> DMEDP Name Review: September 5, 2008 <input checked="" type="checkbox"/> DMEDP Safety Review: April 15, 2008 <input checked="" type="checkbox"/> DRISK Patient Labeling Review: May 27, 2008 <input checked="" type="checkbox"/> DDMAC Review: May 6, 2008 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	RPM Review: None CMC Review: August 8, 2008
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included: September 15, 2008
<ul style="list-style-type: none"> • AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	Not Applicable
❖ Pediatric Page (<i>a new Pediatric Page for each review cycle</i>)	<input checked="" type="checkbox"/> Included: September 15, 2008
❖ 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
❖ Postmarketing Commitment (PMC) Studies	
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	July 9, 2008
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	September 10, 2008
❖ Postmarketing Requirement (PMR) Studies	
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	July 28, 2008
<ul style="list-style-type: none"> • Incoming submissions/communications 	August 14, 2008

❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	Filing Letter: August 30, 2007 Information Request Letter: October 4, 2007 Information Request Letter: April 3, 2008 Tradename Review Letter: September 10, 2008
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing	<input checked="" type="checkbox"/> No meeting
• Pre-NDA/BLA meeting (<i>indicate date</i>)	February 22, 2007
• EOP2 meeting (<i>indicate date</i>)	<input checked="" type="checkbox"/> No meeting
• Other (e.g., EOP2a, CMC pilot programs)	Pre-IND Meeting: January 11, 2005 CMC Meeting: December 14, 2006
❖ Advisory Committee Meetings	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	None
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ PAL/BUD Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ CMC/product quality review(s) (<i>indicate date for each review</i>)	July 7, 2008
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC review page 47
• <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>)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: July 7, 2008 See CMC review page 49 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ BLAs: Facility-Related Documents	
• Facility review (<i>indicate date(s)</i>)	<input type="checkbox"/> Requested
• Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) (<i>indicate date completed, must be within 60 days prior to AP</i>)	<input type="checkbox"/> Accepted <input type="checkbox"/> Hold

❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	June 11, 2008 <input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	None Included in P/T review, page
❖ Nonclinical inspection review summary (DSI)	<input checked="" type="checkbox"/> None requested

Clinical Information	
❖ Clinical Team Leader Review(s) (indicate date for each review)	July 24, 2008
❖ Clinical review(s) (indicate date for each review)	July 14, 2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	See clinical review: July 14, 2008, page 18
❖ Clinical reviews from other review disciplines/divisions/Centers (indicate date of each review)	Division of Pharmacovigilance I September 11, 2008
❖ Clinical microbiology reviews(s) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Safety update review(s) (indicate location/date if incorporated into another review)	Not needed. As agreed, since there were no ongoing studies. See pre-NDA meeting minutes March 20, 2007.
❖ REMS review(s) (including those by OSE) (indicate location/date if incorporated into another review)	None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Biostatistics	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical Review(s) (indicate date for each review)	July 1, 2008
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (indicate date for each review)	July 3, 2008

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

Thomas N Moreno
9/16/2008 02:41:36 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-198

DISCIPLINE REVIEW LETTER

Strakan International, Ltd.
c/o ProStrakan
Attention: Mary Ellen Norwich, Ph.D.
Vice President, US Regulatory Affairs
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norwich:

Please refer to your new drug application (NDA) dated June 29, 2007, received July 2, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sancuso (granisetron) transdermal system.

The results of the Proprietary Name Risk Assessment found that the proposed name, Sancuso, has some similarity to other proprietary drug names, but the findings of the Failure Modes and Effects Analysis indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Sancuso, for this product. However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the medication error prevention staff rescinds this Risk Assessment finding and recommends that the name be resubmitted for review.

Additionally, the Division of Drug Marketing, Advertising and Communications found that the proprietary name, Sancuso, is acceptable from a promotional perspective.

As this is a new dosage form for granisetron, we anticipate the possibility of medication errors resulting in duplicate granisetron therapy (i.e., patients receiving oral or intravenous granisetron while wearing a Sancuso patch), especially at product launch. Therefore, the Division of Medication Error Prevention and Analysis recommends that you include in your product launch a component aimed at healthcare practitioners' awareness that the Sancuso patch contains granisetron and that they should avoid administering other granisetron containing products to patients wearing a Sancuso patch.

If you have any questions, call Thomas Moreno, Regulatory Health Project Manager
at (301) 796-2247.

Sincerely

{See appended electronic signature page}

R. Wesley Ishihara
Acting Chief, Project Management Staff
Division of Gastroenterology 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/

Richard W Ishihara
9/10/2008 10:40:17 AM

ProStrakan

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

**NDA 22-198
SANCUSO™ (Granisetron
Transdermal System)**

Amendment 21

**Amendment to a pending
application: Post Marketing
Commitments Revision**

10 September 2008

Dear Dr. Griebel:

Please refer to NDA 22-198 submitted June 29, 2007, according to Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act and 21 CFR 314.50 for SANCUSO™ (Granisetron Transdermal System) for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to five consecutive days, and to your August 28, 2008 e-mail message informing us of the requested revisions to the Post Marketing Commitments.

To confirm, ProStrakan accepts the following clinical pharmacology post-marketing commitments:

1. An appropriate *in vitro* or clinical pharmacokinetic study to determine the impact of heat on the delivery of granisetron from the transdermal system.

Protocol Submission: by end of 10/08
Study Start: by end of 12/08
Final Report Submission: by end of 03/09

2. A clinical pharmacokinetic study to assess granisetron exposure in human subjects with differing levels of body fat.

Protocol Submission: by end of 10/08
Study Start: by end of 02/09
Final Report Submission: by end of 12/09

ProStrakan

3. A clinical pharmacokinetic study to assess granisetron exposure in elderly individuals (over age 65) that includes an even age distribution across the geriatric population.

Protocol Submission:	by end of 10/08
Study Start:	by end of 02/09
Final Report Submission:	by end of 12/09

This submission has been prepared in eCTD format using PDF navigation (no XML), and is being submitted through the FDA Electronic Submission Gateway. The overall size of this submission and verification that it is virus free is provided in an attachment.

If you have any questions and/or comments, please feel free to contact me directly at (908) 234-1096, x203 or at mary.norvitch@prostrakan.com.

Sincerely,



Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs

From: Moreno, Thomas
Sent: Wednesday, July 09, 2008 4:18 PM
To: 'Mary Ellen Norvitch'
Cc: Moreno, Thomas
Subject: NDA 22-198 Sancuso PMCs

Dear Dr. Norvitch,

Regarding NDA 22-198 for Sancuso, we have the following draft Post Marketing Commitment requests. At our teleconference on July 10, at 2:00 PM, we will state our final requests.

1. _____

Given that this product is intended for multi-day use, we ask you to commit to the conduct of a study to determine the impact of heat on drug delivery. Such a study could be done using a validated in vitro model upon prior agreement by the Agency as to the model and protocol design. _____

b(4)

b(4)

2. While an in vivo pharmacokinetics study in healthy adults and a limited sampling study in subjects receiving chemotherapy have already been conducted, there is a lack of pharmacokinetic data from patients who have altered skin integrity due to advanced age or poor nutritional status related to chronic illness. _____

_____ It is possible that individuals with varying nutritional status and resultant differences in subcutaneous fat would have marked differences in pharmacokinetics. We have concerns that altered delivery of drug may arise in patients with altered skin integrity or extremes in subcutaneous fat. This could lead to altered efficacy in those individuals. We ask you to commit to conducting the following two studies:

b(4)

2a. An in vivo pharmacokinetic study in subjects with differing levels of body fat _____

b(4)

2b. An in vivo pharmacokinetic study in elderly individuals

Should the results of these studies indicate an altered delivery that could be correlated to body mass (IBW, etc) or age, this information would be important to include in the label.

Best Regards,

Thomas Moreno
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 301-796-2247

ProStrakan

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Amundson Road
Beltsville, MD 20705-1266

14 August 2008

**NDA 22-198
SANCUSO™ (Granisetron
Transdermal System)**

Amendment 20

**Amendment to a pending
application: Submission of
Revised Prescribing
Information, Revised Pediatric
Plan, Post-Marketing
Requirements, Revised Post-
Marketing Commitments and
Response to Information
Request**

Dear Dr. Griebel:

Please refer to NDA 22-198 submitted June 29, 2007, according to Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act and 21 CFR 314.50 for SANCUSO™ (Granisetron Transdermal System) for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to five consecutive days, and to our July 15, 2008 submission (Amendment 19). In addition, please refer to your July 28, August 1, August 6 and August 14, 2008 e-mail correspondence.

Attached please find the Prescribing Information (Attachment 1). We have accepted all changes presented in the version provided to us on August 14, 2008. In addition, please find the revised Pediatric Plan (Attachment 2) as well as the response to the information request made on August 1 (Attachment 3).

ProStrakan accepts the following post-marketing requirements:

1. A Single-Site, Randomized, Crossover, Thorough QTc Study that incorporates Placebo, Active Control, Bolus Infusion, and Transdermal Granisetron in Healthy Volunteers

Protocol Submission:	by September 30, 2008
Trial Start:	by March 31, 2009
Final Report Submission:	by December 31, 2009

ProStrakan, Inc
1430 US Highway 206, Suite 110
Bedminster, New Jersey 07921-2652, USA
Tel: +1 908 234 1096 Fax: +1 908 234 2835

ProStrakan

2. A deferred pediatric study under PREA: A Study to Examine the Pharmacokinetics of Granisetron Transdermal System (SANCUSO™) Compared to IV Dosing in 48 Pediatric Patients aged 2 to 17 years.

Protocol Submission: by February 28, 2010
Trial Start: by June 30, 2010
Final Report Submission: by February 29, 2012

3. A deferred pediatric study under PREA: A Study of the Efficacy and Safety of Transdermal Granisetron (SANCUSO™) Compared to Intravenous Granisetron for the Prevention of Chemotherapy Induced Nausea and Vomiting in 200 Pediatric Patients aged 2 to 17 years and over 400 Patient Treatment Periods.

Protocol Submission: by February 28, 2010
Trial Start: by June 30, 2011
Final Report Submission: by January 31, 2013

ProStrakan confirms its intention to work with FDA on finalizing the study protocols for its thorough QTc and pediatric post-marketing studies. The Applicant plans to pursue the opportunity to qualify for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act, and will be seeking the Division's advice in this regard.

In our July 15, 2008 submission, we made a post-marketing commitment to study the impact of heat on drug delivery. In order to allow sufficient time for protocol development in light of the delayed Action Date, we request that the protocol submission and study start dates be revised as noted below (i.e., delayed one month). The final report submission is unchanged.

The originally proposed dates for the two remaining PK post-marketing studies remain unchanged.

ProStrakan accepts the following clinical pharmacology post-marketing commitments:

1. Study to determine the impact of heat on drug delivery

Protocol Submission: by end of 10/08
Study Start: by end of 12/08
Final Report Submission: by end of 03/09

2. Pharmacokinetic study in subjects with differing levels of body fat

Protocol Submission: by end of 10/08
Study Start: by end of 02/09

ProStrakan

Final Report Submission: by end of 12/09

3. Pharmacokinetic study in elderly individuals

Protocol Submission: by end of 10/08

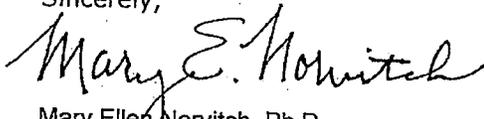
Study Start: by end of 02/09

Final Report Submission: by end of 12/09

This submission has been prepared in eCTD format using PDF navigation (no XML), and is being submitted through the FDA Electronic Submission Gateway. The overall size of this submission and verification that it is virus free is provided in an attachment.

If you have any questions and/or comments, please feel free to contact me directly at (908) 234-1096, x203 or at mary.norvitch@prostrakan.com.

Sincerely,



Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs

**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

MEMORANDUM

****Pre-Decisional Agency Information****

Date: May 6, 2008

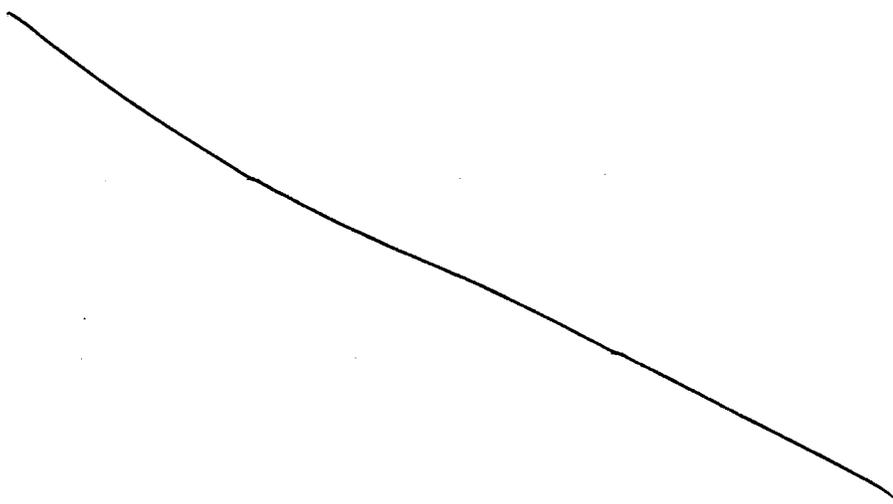
To: Frances Fahnbulleh Pharm.D.
Division of Gastroenterology Products

From: Samuel M. Skariah, PharmD – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for SANCUSO® (Granisetron Transdermal System)
NDA #22-198

DDMAC has reviewed the proposed product labeling (PI), patient labeling, and carton container labeling for SANCUSO® (Granisetron Transdermal System) (Sancuso) (version dated 06/2007) and we offer the following comments. Please feel free to contact me with any questions or clarifications.

HIGHLIGHTS



b(4)

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 1

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/s/

Sam Skariah
5/6/2008 01:47:53 PM
DDMAC REVIEWER



NDA 22-198

INFORMATION REQUEST LETTER

Straken International, Ltd.
Attention: Mary Ellen Norwich
VP, Regulatory Affairs
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norwich:

Please refer to your June 28, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sancuso (granisetron transdermal patch) which delivers 3.6 mg over 24 hours.

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.

Comments and Information Requests:

1. Drug product specification:

The acceptance criterion for "Adhesive Strength" should be revised to reflect the Phase 3 clinical batch data.

2. Drug product manufacturing process:

In the description of the drug product manufacturing process the _____ time, after adding the granisetron solution to the _____ solution, was given as _____ Whereas in the executed batch record, it was given as _____ Please revise the mixing time in the executed batch record to 60 ± 15 minutes.

b(4)

Please provide the exposure time in each of the _____ settings during the _____ (Section 3.2.P.3.3).

b(4)

3. Labeling:

The labels for pouch and carton should include NDC numbers.

The labels are required to include a barcode that contains at a minimum the NDC number encoded in it (21 CFR § 201.25). You must comply with the bar code rule within 60 days of the NDA approval.

For more information, please refer to "Guidance for Industry: Bar Code Label Requirements, Questions and Answers (Revision 1, October 2006)."

4. Expiration dating period:

Based on the submitted primary and supporting stability data, the maximum expiration dating period that can be allowed at this time is 24 months. Please amend the NDA with this expiration dating period.

If you have any questions, call Frances Fahnbulleh, Regulatory Health Project Manager, at 301-796-0942.

Sincerely,

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

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/s/

Moo-Jhong Rhee
4/3/2008 04:00:05 PM
Chief, Branch III



INFORMATION REQUEST LETTER

NDA 22-198

Straken International Ltd.
Attn: Armand Girard
Senior Development Director
1005 Radley Drive
West Chester, PA 18392

Dear Mr. Girard:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sancuso® (granisetron) Transdermal System, (52 cm² patch containing 34.3 mg of granisetron) delivering 3.6 mg per 24 hours.

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

Please provide the following information for studies 392MD/15/C and 392MD/8/C:

- 1) a. In your submitted data set ADEP for Study 392MD/15/C, please provide the definition for the levels (1, 2, 3, 4, 5, OVERALL PEEP, and OVERALL) of the variable PERIOD. In addition, please indicate which period level was used for the primary endpoint analysis.

b. In your submitted data sets for Study 392MD/8/C, please indicate which data set includes the primary endpoint (proportion of patients achieving total control of CINV) for the period of 24 to 120 hours (delayed phase). If you did not submit this efficacy data set, please do so. In your submitted efficacy data set, please include two variables for ITT and PP populations.
- 2) a. For Study 392MD/15/C, please submit the statistical efficacy analysis (SAS) programs used to generate Table 24 to Table 38 (total of 15 tables).

b. Similarly, for Study 392MD/8/C, please submit the statistical efficacy analysis programs used to generate Table 13 to Table 20 (total of 8 tables).

c. If you used variables from other data sets, in addition to those described in 1) above, to generate the requested tables, please provide those additional data sets.

- 3) a. We realize that you provided literature articles in regard with the effects of palonosetron and ondansetron. However, in the Study 392MD/15/C, Oral 2mg Granisetron was the active control arm. Accordingly, please justify the non-inferiority margin of 15% you selected for Oral 2mg Granisetron in light of ICH E10 recommendations as provided below.
- b. The ICH E10 guidance states that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size is only possible when there is a historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. Ideally, a margin should be identified based on past experience in placebo-controlled trials with adequate design under conditions similar to those planned for the new trial.
- c. Please provide any algorithm you employed to calculate the non-inferiority margin of 15% using the historical studies you selected based upon ICH E10.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, M.B.A, RPh
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
10/4/2007 04:22:08 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-198

Straken International Ltd.
Attn: Armand Girard
Senior Development Director
1005 Radley Drive
West Chester, PA 18392

Dear Mr. Girard:

Please refer to your June 29, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sancuso® (granisetron) Transdermal System, (52 cm² patch containing 34.3 mg of granisetron) delivering 3.6 mg per 24 hours.

We also refer to your submissions dated July 23 and August 23, 2007.

The following information applies to the application listed above:

- Name of Drug Product: Sancuso® (granisetron) Transdermal System
- Review Priority Classification: Standard (S)
- Date of Application: June 29, 2007
- Date of Receipt: July 2, 2007
- Our Reference Number: NDA 22-198

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 31, 2007 in accordance with 21 CFR 314.101(a). The user fee goal date will be May 02, 2008.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

NDA 22-198

Page 2

We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above 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 Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Giuseppe Randazzo, Project Manager, at (301) 796-0980.

Sincerely,

(See appended electronic signature page)

Brian Strongin, M.B.A, RPh
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
8/30/2007 09:44:53 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND #70,582

Straken Pharmaceuticals Limited
Attn: Armand Girard
Senior Development Director
1005 Radley Drive
West Chester, PA 18392

Dear Mr. Girard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SancusoTM Transdermal System (granisetron base).

We also refer to the meeting between representatives of your firm and the FDA on February 22, 2007. The purpose of this meeting was to discuss the planning and filing of a 505(b)(2) NDA for SancusoTM Transdermal System in eCTD format.

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

If you have any questions, call me at (301) 796-0980.

Sincerely,

{See appended electronic signature page}

Giuseppe Randazzo
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: February 22, 2007

Meeting Type: B – Face-to-Face

Meeting Category: Pre-NDA

Meeting Location: FDA/CDER
White Oak Building #22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Application Number: I 70,582

Product Name: Sancuso™ Transdermal System (granisetron base)

Received Briefing Package January 25, 2007

Sponsor Name: Straken Pharmaceuticals Limited

Meeting Requestor: Armand Girard and David Zuchero

Meeting Chair: Dr. Hugo Gallo-Torres

Meeting Recorder: Giuseppe Randazzo

Meeting Attendees:
FDA Attendees:
Brian Harvey, M.D., Ph.D., Division of Gastroenterology Products (DGP)
Joyce Korvick, M.D. M.P.H., (DGP)
Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Gastrointestinal Medical Team Leader (DGP)
Nancy Snow, M.D., Ph.D. Medical Reviewer (DGP)
Mike Welch, Ph.D., Acting Statistical Team Leader, Division of Biometrics II
Tapash Ghosh, Ph.D., Acting Biopharmaceutical Team Leader
Shushanta Chakder, Ph.D., Pharmacologist Reviewer (DGP)
Stanley Shepperson, PharmD., Senior Regulatory Manager (OGD)
Janice Weiner, JD, Regulatory Counsel, Division of Regulatory Policy II (DRPII)
Giuseppe Randazzo, Project Manager (DGP)

External Attendees

Mrs. Gemma Clark Clinical Operations Director, ProStrakan
Ms. Amanda Cook Regulatory Manager, ProStrakan
Dr. Ian Duguid Regulatory Affairs Director, ProStrakan

b(4)

Dr. Allison Jeynes-Ellis Head of Clinical Development, ProStrakan

b(4)

1.0 BACKGROUND

On December 20, 2006, Straken Pharmaceuticals Limited submitted a pre-NDA, type-B meeting request (serial number 016), which was received on December 21, 2006. The purpose of this meeting was to discuss the planning and filing of a 505(b)(2) NDA for Sancuso™ Transdermal System in eCTD format.

The briefing package with non-clinical, clinical, and regulatory questions was received on January 25, 2007.

2.0 DISCUSSION

Non-clinical

- a.1 In the NDA ProStrakan proposes to cross reference to the FDA's non-clinical findings for granisetron (Kytrel®) injectable and oral formulations (NDA 20-239 and NDA 20-305). In addition, ProStrakan plans to perform a literature search covering the period 1995 (date of Kytrel® NDA 20-305 approval) to date. The findings of the search will be reported as narratives, however tabular summaries will not be provided. Does the FDA agree with this approach as a part of the 505(b)(2) application?

Response for 02/22/07 meeting:

Yes, your approach as a part of the 505(b)(2) application is acceptable. You may rely upon studies not conducted by or for you and to which you have not obtained a right of reference of use [i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug(s)] to support your nonclinical development program.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug(s), you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (i.e., relative bioavailability study)

between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies that you have no right of reference to but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm>. It should be noted that the regulatory requirements for a 505(b)(2) application (including but not limited to provision of an appropriate patent certification) apply to each listed drug upon which a sponsor chooses to rely. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408).

- a.2 We believe that the non-clinical data package to be submitted in the NDA and described in the meeting information package is sufficient to support the filing of this 505(b)(2) NDA. Do you agree?

Response for 02/22/07 meeting:

Yes. We agree with your proposal to rely, in part, upon published literature and the Agency's finding of safety and/or effectiveness for Kytril (granisetron) injectable and oral formulations to support the filing of a 505(b)(2) application (see also response to question a.1.). However, we note that your meeting information package inappropriately proposes to reference data in the Summary Basis of Approval (SBA) for Kytril. A 505(b)(2) applicant may rely upon the Agency's finding of safety and/or effectiveness for a listed drug, as reflected in the approved labeling for the listed drug.

Clinical (the attachments referenced below are provided in the Clinical section of the briefing package)

- b.1 Does the Agency have any comments on the proposed draft labeling for Sancuso™ included in Attachment 2?

The draft labeling has been prepared in accordance with the Final Rule of January 24, 2006 for prescription drug labeling (71FR3922), with the current prescribing information for Kytril® presented for comparison. The 'clinical studies' and 'adverse reactions' sections will be completed when the Phase III trial results have been confirmed and all the safety data reported (including data from 392MD/26/C – Sensitization & Irritation study). Specific items will be identified

in the section 'patient counseling information' when the labeling is complete. The 'highlights' section will also be added to the draft submitted in the NDA.

Response for 02/22/07 meeting:

We have no comments about your draft labeling at this time. We will review the labeling when it is submitted with the NDA. Please keep in mind that your label will be based upon the data submitted in your marketing application.

- b.2 ProStrakan plans to include information for the patient in the package insert. An outline of our proposal is included in Attachment 3. Does the FDA have any comments on this proposed outline?

Response for 02/22/07 meeting:

We have no comments about your draft package insert at this time. Whether all sections will be included in the final PPI will be reviewed at the time of your NDA submission.

- b.3 Does the Agency agree with the pediatric waiver request included as Attachment 4?

Response for 02/22/07 meeting:

Yes, we agree with your request to waive studies in patients birth to 12 years. However, there may be a role for this product in patients 13 to 17 years of age. From a regulatory perspective, this adolescent range could be deferred until further information is obtained. You cite recruitment and protocol standardization problems. You also note that the patch may become dislodged, the need for adult supervision with regard to patch application and removal, and the increased sensitivity of children's skin compared to that of adults. You also note that the design of the patch does not allow it to be divided, so dose adjustments cannot be made. Finally you conclude that "the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients."

- b.4 Does the Agency have any comment on the electronic data set provided on disk?

Response for 02/22/07 meeting:

The structure and content of submitted data sets will be reviewed in detail at the time of filing. The submitted data and documentation should conform to the guidance on eCTD submissions. See: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

- b.5 Does the Agency agree with the proposal to analyze the safety data for healthy subjects and cancer patients separately in the ISS?

Response for 02/22/07 meeting:

Yes, we agree to your proposal for a separate analysis for these 2 groups.

- b.6 As there will be no on-going clinical studies at the time of NDA submission, ProStrakan proposes not to provide a 4 month safety update. Does the Agency agree with this proposal?

Response for 02/22/07 meeting:

We agree.

- b.7 As a single pivotal efficacy study will form the basis of this NDA, does the Agency agree to waive the requirement for an Integrated Summary of Efficacy and instead accept the provision of a detailed report on the subjects studied in the Phase III study?

Response for 02/22/07 meeting:

No, please provide an ISE as appropriate for your clinical data.

- b.8 The Phase III study report will contain detailed line listings of patient data. Will the Agency accept this listing in the place of Case Report Form Tabulations?

Response for 02/22/07 meeting:

No. You should submit Case Report Form Tabulations.

Additional discussion at 2/22/07 meeting: Prior to submitting the NDA Straken will submit a CRF tabulations template for our review and comment.

- b.9 A rationale for not performing photoallergenicity and phototoxicity studies in humans is included in Attachment 5. Does the Agency agree that this approach is acceptable?

Response for 02/22/07 meeting:

A waiver from performing phototoxic and photoallergenicity studies in humans would be appropriate since you intend to include in the label to avoid direct exposure to sunlight. Avoidance of direct exposure to sunlight is based on photoclastogenic potential of granisetron base demonstrated in the in vitro photogenotoxicity of granisetron base in Chinese Hamster Ovary cells (CHO) study. The patch should be applied to areas where there is adequate protection

from sunlight. Patients should not expose any area where the patch was applied to natural or artificial sources of sunlight.

According to the briefing package, absorption and transmission spectra indicate that the drug substance in the product has a low level of absorption over 310-320nm. Phototoxic and photoallergenicity studies are usually required if any component of the drug product absorbs light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible). However, you are requesting a waiver from performing additional photosafety studies with Sancuso™ in either patients or healthy subjects based on the intent to include in the label to avoid direct exposure to sunlight due to the photoclastogenic potential of granisetron base.

The photoclastogenic potential of granisetron base was assessed in Chinese Hamster Ovary cells (CHO), CHO cells, in the absence or presence of UVA:UVB irradiation (700mJ/cm²), and harvested at 20 hours from the beginning of treatment (approximately one and a halftimes the average CHO cell cycle). In irradiated cells, a highly statistically significant increase in the percentage of cells with chromosome damage was observed at 200 and 300 µg/mL (13 and 33% of cells, respectively, as compared to 2.5% in irradiated vehicle control cells). This finding suggests that there is a potential for photoactivation of granisetron and therefore justifies the statement in your proposed label to avoid direct exposure to sunlight.

- b.10 Does the Agency have any comments on the proposed draft format for the Human PK/Bioavailability information, as included in Attachment 6?

Response for 02/22/07 meeting:

The format for the Human PK/Bioavailability information seems reasonable at this time. However, you have not submitted details of the PK studies. Also you referenced literature articles in the proposed label and our review will include an analysis of these articles. In addition, we remind you to submit information on the following:

- SAS transport datasets for all PK (BA/Dose proportionality) studies.
- Information needed on how the patch performs (with regards to PK and adhesion) in different environmental conditions that may include (but not limited to) those experienced in a health club (e.g., sauna, whirlpool, treadmill, warm/cold water showering) and weather conditions may include (but not limited to) the effect of heat, humidity, effect of sun burning, shaving and other potential factors on the PK of the drug.

- The absence of actual data addressing these conditions should be supported either by adequate justification, or appropriate labeling information.

b.11 Does the Agency agree with ProStrakan's justification in Attachment 7 to not include a RiskMAP in the NDA?

Response for 02/22/07 meeting:

The transdermal system represents a new route of administration for an approved product and the benefit risk profile will be determined during the review cycle.

If you and/or we believe that there are product risks that merit more than conventional professional product labeling [i.e., package insert (PI) or patient package insert (PPI)] and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

Additional Clinical question sent February 13, 2007:

b.12 Based on the information provided, Strakan seeks FDA agreement that machine read ECGs introduced through protocol amendment into study 392MD/15/C are acceptable for reporting purposes.

Response for 02/22/07 meeting:

Unfortunately we were unable to address this question at this time. We recommend you submit the data as an information amendment to the IND and we will comment at that time. Our review will include consultation with the QT Interdisciplinary Review Team (QTIRT).

Electronic submission format

c.1 Does the Agency agree that it is acceptable to provide a hybrid electronic submission (*hyperlinked PDF files with no xml backbone*)?

Response for 02/22/07 meeting:

While the agency strongly encourages electronic submissions and eCTDs, a hybrid submission consisting of paper and electronic information is acceptable. Hyperlinked PDF files with no XML backbone is also acceptable.

3.0 ISSUES REQUIRING FURTHER DISCUSSION
N/A

1/11
1/11
en

4.0 ACTION ITEMS

Please read dialogue above in the **DISCUSSION** section.

5.0 ATTACHMENTS AND HANDOUTS

N/A

APPEARS THIS WAY ON ORIGINAL

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/s/

Ruyi He
3/20/2007 10:32:30 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70, 582

Strakan Pharmaceuticals Limited
Atten: William Sietsema, Ph.D.
Vice President, Clinical and Regulatory Strategic Planning
441 Vine Street, Suite 1200
Cincinnati, OH 45202

Dear Dr. Sietsema:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Granisetron Transdermal Patch (TDS).

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2006. The purpose of the meeting was to discuss the CMC approach for Sancuso.

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

If you have any questions, call Linda D. Athey, Regulatory Health Project Manager for Quality, at (301) 796-2096.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 14, 2006
TIME: 10:00 AM to 11:00 AM
LOCATION: Food and Drug Administration, White Oak Campus
APPLICATION: IND 70,582
DRUG NAME: Sancuso Transdermal System (Granisetron base)
TYPE OF MEETING: CMC Type B
MEETING CHAIR: Marie Kowblansky, Ph.D.
MEETING RECORDER: Linda D. Athey

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH
Office of New Drug Quality Assessment:

Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead, DPMA II
Linda D. Athey, Regulatory Health Project Manager for Quality, DPMA II

PROSTRAKAN ATTENDEES:

Amanda Cook, Regulatory Manager
Ian Duguid, Ph.D., Regulatory Affairs Director
Doreen Wood, Project Leader

William Sietsema, Ph.D., US agent

b(4)

BACKGROUND:

ProStrakan Pharmaceuticals (ProStrakan) is developing a Sancuso Transdermal System Granisetron base proposed for chemotherapy induced nausea and vomiting. ProStrakan requested a Chemistry, Manufacturing and Controls (CMC) Type B meeting on October 18, 2006, to discuss the CMC approach for Sancuso. ProStrakan submitted a pre-meeting CMC briefing document dated November 15, 2006, received November 15, 2006, providing additional information on discussion topics and questions. FDA provided written responses to all questions outlined in the briefing document in an email dated December 1, 2006.

DISCUSSION:

In response to the IND meeting package dated November 15, 2006, the following CMC comments/responses were given to the sponsor. The format provides the sponsor's comments/questions in italics followed by FDA's responses in plain lettering. Questions, responses, and additional comments are indicated with headings.

Question 1:

ProStrakan proposes to market a patch with an unmarked backing (as placed on the skin), packaged within a pouch and a carton bearing appropriate labeling information. Does the Agency agree with the approach of using an un-marked backing?

FDA Response 1:

Your proposal to market the patch with an unmarked backing with the label on the pouch and on the carton is not acceptable.

Discussion 1:

Correction to the above response was made by FDA, indicating that due to safety concerns it was not acceptable to market the product with an unmarked backing. The discussion centered on whether a trade name should be used for this purpose, the full established name, or just an identifying code. The sponsor's preference is to use an identifying code. FDA agreed to provide guidance on this issue as an addendum to the meeting minutes.

Post-Meeting Addendum:

Consistent with our labeling requirements for other transdermal patches that have been approved, we would require the backing to be imprinted with the trade name, established name, and drug delivery rate. However, since you plan to market the patch in only one strength, the trade name will be sufficient for your product. If in the future you decide to market this product at another strength, you will need to include all the above information for this product and the new product.

Question 2:

Does the Agency agree that the manufacturing controls and methods used for the Phase III clinical trial and ICH stability batches are appropriate for the routine control of the drug product for release onto the US market?

FDA Response 2:

The information you have submitted in the briefing package appears reasonable, but the adequacy of your manufacturing methods and controls can only be assessed when you have submitted more detailed information regarding the process.

Discussion 2:

No further discussion.

Question 3:

Does the Agency agree that the finished product specifications and methods used for the Phase III clinical trial and ICH stability batches are appropriate for routine control of the drug product for release onto the US market?

FDA Response 3:

At the present time we have the following comments regarding your proposed drug product specifications:

- You propose different release and stability specifications for your product. Please be aware that FDA requires that your product conform to the same regulatory specification at release and throughout the shelf life of the product:

- The limits for related substances in your commercial product should conform to ICH recommendations, which for your product would require identification of all impurities at levels above 0.2% and toxicological qualification for all impurities above 0.5%. Therefore, your proposed limit of $\frac{1}{1000}$ for each single unidentified impurity will not be acceptable.
- You indicate that you will be setting specifications for certain parameters (such as dissolution, adhesion, and peel force) once 12 month stability data are available". This is acceptable. However, please be aware that the acceptance criteria for these parameters in the commercial product will need to be based on the product used in the Phase III clinical trials.

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Discussion 3:

The release and stability specifications will be identical.

Impurity specification thresholds for identification and qualification will be based on the daily delivered dose according to ICH, not on the amount of drug substance in the patch. Data demonstrating the delivered daily dose will be submitted.

There was no additional discussion. We are in agreement.

Question 4:

ProStrakan intends to include in the NDA a process validation protocol and results to demonstrate the consistency of drug product runs conducted during the manufacture of the Phase III clinical trial and ICH stability batches. Details of pouch labeling/printing procedures for the commercial batch are also included. Process validation of 3 batches will be performed prior to commercialization. Does the Agency agree with this approach for presentation of data in the NDA and generation of the data for the validation batches?

FDA Response 4:

In your NDA submission you will need to provide documentation justifying critical steps in the manufacturing process. However, for questions regarding process validation please contact the District Office.

Discussion 4:

No additional discussion.

Question 5:

ProStrakan intends to submit the NDA containing 12 months ICH stability data for three batches of the proposed marketed formulation of the drug product (as used in the Phase III clinical study), produced in the US manufacturing site proposed for commercialization. Twenty four months data for drug product manufactured by a previous European manufacturer, using identical formulation, will also be provided. Does the Agency agree that this stability package will be suitable to support a 24 month shelf life, in principle, provided there is no indication of instability from the data?

FDA Response 5:

Yes. A 24-month shelf life is possible based on the stability data and supporting stability data that you plan to submit. However, please be reminded that you also need to include at least six months of accelerated stability data.

Discussion 5:

The firm will provide the accelerated stability data.

Question 6:

ProStrakan believes that a DMF is not required for the packaging components not in immediate contact with the adhesive matrix (the slip sheet and pouch laminate), although USP plastics and extractables testing will be included in the NDA for these components. Does the Agency agree that a DMF is not needed for these packaging components?

FDA Response 6:

All packaging components need to be adequately described, identifying the composition and specifications (including tests) to which they will conform. (Reference to 21CFR may be sufficient for this purpose.) This information can be provided directly in the NDA or by reference to a DMF.

Discussion 6:

No further discussion.

DECISIONS (AGREEMENTS) REACHED:

See specific question.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

Attachment:
Sancuso CMC Meeting with FDA slides.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 70,582

Prostrakan Pharmaceuticals Ltd.
Attention: Nancy Chew, MS, RAC (US Agent, Regulatory Affairs, North America LLC)
6217 Roxboro Road
Durham, NC 27503

Dear Ms. Chew:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Granisetron Transdermal Delivery System.

We also refer to the meeting between representatives of your firm and the FDA on January 11, 2005. The purpose of the meeting was to discuss your drug development plans prior to submitting your IND.

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

If you have any questions, call Dr. Betsy Scroggs, Regulatory Project Manager, at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 11, 2005
Time: 4:00 PM to 5:00 PM
Location: Parklawn 3rd Floor-Conference Room "C"
Application: P-IND 70,582
Type of Meeting: Type B (Pre-IND)
Meeting Chair: Dr. Hugo Gallo-Torres
Meeting Recorder: Dr. Betsy Scroggs

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Joyce Korvick, Acting Division Director
Dr. Hugo Gallo-Torres, GI Team I Medical Team Leader
Dr. Gary Della'Zanna, Medical Officer
Dr. Ronald Honchel, Pharmacology Reviewer
Dr. Betsy Scroggs, Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. Suliman Al-Fayoumi, Clinical Pharmacology Reviewer

Office of Generic Drug Products (HFD-604)

Mr. Donald Hare, R.Ph., Consumer Safety Officer

External Constituent Attendees and Titles representing Prostrakan Pharmaceuticals Ltd.

Dr. Ian Duguid, Regulatory Affairs Director
Dr. Adam Watkinson, Drug Delivery Research Manager

Ms. Nancy Chew, MS, RAC, (US Agent)

Background:

On September 20, 2004 the firm submitted a Meeting Request and on October 28, 2004 a subsequent background package which contained specific questions to be addressed. The purpose of today's meeting is to address the firm's questions contained in the October 28, 2004 background package.

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The firm's questions are followed by FDA's responses in **bolded** text as follow.

1. Does the Division agree that the drug product, Granisetron TDS, is eligible for NDA review under the 505(b)(2) provisions?

FDA Response: Yes, since you are proposing a change in active ingredient, delivery system, dosage form, this proposed application would be eligible. However, granisetron is not approved for the proposed treatment regimen, or indication.

2. Will the Agency accept reference to nonclinical and clinical portions of the Kytril[®] Tablets and Injection NDAs?

FDA Response: Yes, the findings of safety and efficacy of the listed drug can be referenced with appropriate data bridging the new route of administration and the listed drug. However, preclinical bridging studies comparing the transdermal (using the proposed patch formulation) to the intravenous route of administration will need to be performed in multiple species because the route, dosage form, and duration are different from what has been approved. If this submission is accepted as a 505(b)(2) application, you will need to submit all nonclinical information available in the public domain. Data from a relative bioavailability study in humans comparing your product with the listed drug should be provided.

3. Please comment on the adequacy of the proposed clinical development plan to support an NDA for the proposed indication.

FDA Response: The proposed clinical development plan is not adequate to support approval of Granisetron TDS for a new indication and treatment regimen. The Division recommends at least two well-controlled trials to assess the safety and efficacy of Granisetron TDS for the prevention chemotherapy-induced acute and delayed nausea and vomiting.

Kytril[®] tablets (granisetron hydrochloride) is currently indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. The recommended adult dose is 2 mg up to 1 hour before chemotherapy or 1 mg up to 1 hour before chemotherapy and 1 mg 12 hour after the first.

You should supply reference to support that the proposed "standard of care" is current "standard of care."

Additionally, you should supply the following:

- a. **Relative bioavailability study as mentioned in the response to question 2.**
 - b. **Data examining the site of application differences in pharmacokinetics should be provided if different sites of application are used.**
 - c. **Data assessing the adhesive strength of the patch for the length of wear should be provided.**
 - d. **Assess if there are any age and gender differences in the pharmacokinetics.**
4. The Area-Under-the-Curve (AUC) for Granisetron that will be produced by the final formulation/patch size applied for five days may be greater than that seen following Kytril® administration for five days. Although potentially greater, the five-day AUC with the patch will be within justifiable safety limits based upon published literature. Please comment.

FDA Response: For clinical studies, the relative bioavailability study indicates higher bioavailability of the transdermal patch, safety data from clinical trial(s) should be provided. For preclinical studies, it would depend on the results from the bridging studies (i.e., how AUC for the transdermal route compares to the intravenous route).

5. ProStrakan proposes to conduct a clinical study in healthy subjects to investigate the sensitization and irritation associated with the use of Granisetron TDS concomitant with the phase 3 program. Please comment on this proposal.

FDA Response:

Topical safety studies in humans should be conducted with the final, to-be-marketed formulation and, for this reason, are generally conducted later in development, e.g. in parallel with Phase 3 studies. Thus, your proposed timing of conduct of the sensitization and irritation study is acceptable; however, you should ensure that the study is conducted with the final, to-be-marketed formulation.

Generally, the required topical safety studies (and recommended minimum number of subjects) are:

- a. **cumulative irritancy (at least 30 evaluable subjects),**

- b. contact sensitization (at least 200 evaluable subjects),
- c. photoallergenicity (at least 50 evaluable subjects), and
- d. phototoxicity (at least 30 evaluable subjects).

For a product applied via a transdermal delivery system, the need for phototoxicity and photoallergenicity testing would depend on whether the patch is translucent or opaque. If your product is translucent, phototoxicity and photoallergenicity testing would be required. However, if no component of your product absorbs in the ultra violet-A (UVA), ultra violet-B (UVB), or visible light spectra, then phototoxicity and photoallergenicity studies may be waived (copies of the absorption spectra should be submitted to the IND).

6. Does the Division agree that the extensive preclinical data available in the Kytril[®] NDA will fully support a 505(b)(2) new drug application? Please comment on our nonclinical development plan.

FDA Response: Please describe your full nonclinical development plan, including irritation and sensitization studies. We also remind you that a 505(b)(2) application references FDA's findings of safety and efficacy for an approved drug, not the data itself, so long as an acceptable bridging study is in the 505(b)(2) application.

7. Has the Division any concerns regarding Chemistry, Manufacturing and Controls (CMC) of the Granisetron TDS system?

FDA Response:

- a. The submission does not contain complete CMC details of the drug substance and the drug product. Therefore, this information should be provided for our review.
- b. Initial CMC data regarding the drug substance and drug product specifications need to be revised (Volatile Solvents Limits, drug product impurities, etc.).
- c. Drug master file (DMF) regarding the manufacturing process of the drug substance should be provided.
- d. Stability data from development/commercial batches should be provided.

Meeting note: RPM to set up post-meeting CMC informal teleconference if needed to clarify remaining CMC responses.

8. If the Granisetron TDS is shown to be effective in the prevention of acute nausea and vomiting following a single dose of chemotherapy and the blood levels of granisetron are maintained at a constant level over several days would this be sufficient, from FDA's point of view, to support labeling indicating that the product can also be used in the prevention of acute nausea and vomiting associated with chemotherapy administered on consecutive days?

FDA Response: See response to Question #3.

Minutes Preparer: Betsy Scroggs

Chair Concurrence: Hugo Gallo-Torres

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

/s/

Betsy Scroggs
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