

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-246**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-246

SUPPL #

HFD # 180

Trade Name METOZOLV ODT

Generic Name metoclopramide hydrochloride Orally Disintegrating Tablet

Applicant Name Wilmington Pharmaceuticals

Approval Date, If Known September 4, 2009

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(2)

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

YES  NO

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

The sponsor conducted the following bioequivalence (BE) and bioavailability studies (BA) studies:

1. Protocol 10643701 (pivotal study #1) was a randomized, two-way crossover study under fasting conditions comparing the BE and BA of a single dose of METOZOLV ODT to the reference listed drug (RLD) Reglan.

2. Protocol NA464 (pilot study) was a randomized, two-way crossover pilot pharmacokinetics BE study under fasting conditions comparing a single dose prototypic formulation of METOZOLV ODT to RLD Reglan (note: the formulation used is different from the to-be-market formulation).

3. Protocol 10743701 (pivotal study #2) was a randomized, three-treatment, three-period crossover study under both fasting and fed conditions comparing the BA of METOZOLV ODT to the RLD Reglan.

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

N/A

d) Did the applicant request exclusivity?

YES  NO

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

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?

N/A

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# 17-854 Reglan Tablet

NDA# 21-793 Reglan ODT

NDA#

## 2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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"):

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 # YES  ! NO   
! Explain:

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





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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MAUREEN D DEWEY  
09/04/2009

JOYCE A KORVICK  
09/04/2009

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

NDA/BLA#: 22-246

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Division of Gastroenterology Products

PDUFA Goal Date: 9-11-2009

Stamp Date: 3/11/2009

Proprietary Name: Metozolv ODT

Established/Generic Name: metoclopramide hydrochloride

Dosage Form: 5 mg, 10 mg

Applicant/Sponsor: Wilmington Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

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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): 2

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** relief of symptomatic GERD

**Q1:** Is this application in response to a PREA PMR?

Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

Supplement #: \_\_\_\_\_

PMR #: \_\_\_\_\_

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

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

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

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

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

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

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

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

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

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

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

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

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

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

# Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

Justification attached.

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

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

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

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

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

\* Other Reason: \_\_\_\_\_

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

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

**Attachment A**

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

**Indication #2: relief of symptoms associated with diabetic gastroparesis****Q1:** Does this indication have orphan designation?

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

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

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

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

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

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

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

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 <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

# Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

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

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

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

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

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

\* Other Reason: \_\_\_\_\_

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

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

(Revised: 6/2008)

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

-----  
Nancy Snow  
7/21/2009 04:03:35 PM

## Dewey, Maureen

---

**From:** DeLeon, Joyce\*  
**Sent:** Friday, September 04, 2009 11:11 AM  
**To:** CDER DDMSIMT Public Folder  
**Cc:** Stark, Cristi L; Strongin, Brian K; CDER-DRTL-ALL; Dewey, Maureen  
**Subject:** PER PM REQUEST RE: Change in Name and Dosage Form for NDA 22-246

Good Morning All,

**DDMSIMT - Please add the dosage form per PM request (email below).**

**Maureen- The tradename has been changed.**

Thank You,  
Joyce

---

**From:** Dewey, Maureen  
**Sent:** Friday, September 04, 2009 11:05 AM  
**To:** CDER-DRTL-ALL  
**Cc:** Stark, Cristi L; Strongin, Brian K  
**Subject:** Change in Name and Dosage Form for NDA 22-246

Hello,

The following application is being approved today:

NDA 22-246 Tradename **METOZOLV ODT**  
The former name ZYDUS was a placeholder

Please update the product name in DARRTS from Zydus to METOZOLV ODT.

The DOSAGE FORM is **Orally Disintegrating Tablet**

Many thanks,

Maureen Dewey  
Regulatory Project Manager  
301-796-0845

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION	
NDA # 22-246 BLA #	NDA Supplement # BLA STN #
If NDA, Efficacy Supplement Type:	
Proprietary Name: Metozolv ODT Established/Proper Name: metoclopramide hydrochloride Dosage Form: 5 mg, 10 mg	Applicant: Wilmington Pharmaceuticals Agent for Applicant (if applicable):
RPM: Maureen Dewey, MPH	Division: Division of Gastroenterology Products
<p><b>NDA:</b> 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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 17-854 Reglan Tablets NDA 21-793 Reglan ODT (pharmaceutical equivalent)</p> <p>Provide a brief explanation of how this product is different from the listed drug. Dosage form (Orally Disintegrating Tablet)</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>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.</b></p> <p><input checked="" type="checkbox"/> No changes      <input type="checkbox"/> Updated Date of check:</p> <p><b>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.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)	9/11/2009 9/4/2009
❖ 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 ( <i>specify type and date for each action taken</i> )	<input checked="" type="checkbox"/> None

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

<p>❖ Promotional Materials (<i>accelerated approvals only</i>)                  Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
❖ Application <sup>2</sup> Characteristics	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>                  Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: _____</p>	
<p>❖ Date reviewed by PeRC (<i>required for approvals only</i>)                  If PeRC review not necessary, explain:  <b>It does not trigger PREA, because it is not a new indication, new dosage form, new route of administration, new dosing regimen, or new active ingredient.</b></p>	<p>N/A (no pediatric indication)</p>
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes, date</p>
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes                  (Kim Rawlings/Lee Lemley)</p>
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Class labeling changes.</p>
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release (2/26/09)  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other Health Communication</p>

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

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10- year limitation expires:
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	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"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	<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 the rest of the patent questions.

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

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

Yes     No

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

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

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

Yes     No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input checked="" type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	9/8/2009
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/>
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/>
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action- CR 2/26/2009 Action - AP 9/4/2009
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	8/27/2009
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	11/5/2007
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	6/30/2009 AP Class Labeling
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	8/27/2009
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	3/10/2009
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)</li> </ul>	9/12/2008; 3/10/2009; 6/16/2009; 7/02/2009; 08/07/2009; 8/20/2009
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 5/16/2008 <input checked="" type="checkbox"/> DMEPA 05/4/2009 <input checked="" type="checkbox"/> DRISK 5/22/09 <input checked="" type="checkbox"/> DDMAC 06/16/2009 <input checked="" type="checkbox"/> SEALD Labeling 11/18/2008; 07/06/2009
<ul style="list-style-type: none"> <li>❖ Proprietary Name                             <ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	7/18/2008; 2/6/2009; 5/4/2009 Letter sent 8/1/2008
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	4/11/2008
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> 9/4/2009
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> 7/21/2009
<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Postmarketing Requirement (PMR) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Postmarketing Commitment (PMC) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	<input checked="" type="checkbox"/>
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/>
❖ Minutes of Meetings	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date</i>)</li> </ul>	No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> 4/17/2007
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	<input checked="" type="checkbox"/> Pre-IND Mtg 11/4/2004
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/>
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 9/4/2009
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> Comments in Clinical Review 8/24/2009
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> Comments in Clinical Review 8/24/2009
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> 8/24/2009
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> Clinical Review of 2/17/09 (Section 1.3.3, p.7)
❖ 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	<input checked="" type="checkbox"/> Clinical Review of 2/17/09 (Section 4.6, p.14)
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	<input checked="" type="checkbox"/> Clinical Review dated 8/24/2009 (page 32); FDAAA Class REMS Review dated 8/26/2009 <input checked="" type="checkbox"/> REMS MEMO 2/26/2009 <input checked="" type="checkbox"/> Sponsor submitted 7/10/2009
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/>
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ 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)	<input checked="" type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ 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)	<input checked="" type="checkbox"/> 11/3/2008; 06/23/2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> 01/09/2009
<b>Nonclinical</b> <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> 10/1/2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 12/14/2007; 1/30/2009; 2/25/2009; 8/24/2009
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	9/8/2008
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ 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> )	<input checked="" type="checkbox"/> 7/31/2008 Acceptable
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	<input checked="" type="checkbox"/> N/A
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	<div style="background-color: #cccccc; height: 20px;"></div>
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: 1/7/2009; 1/8/2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:           <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

## 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.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22246

ORIG-1

WILMINGTON  
PHARMACEUTICA  
LS INC

METZOLV ODT

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

/s/

MAUREEN D DEWEY

09/08/2009

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 22-246 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Metozolv (ODT)  
Established Name: metoclopramide  
Strengths: 5mg, 10 mgApplicant: Wilmington Pharmaceuticals  
Agent for Applicant (if applicable):

Date of Application: 01/29/2008 (Resubmission after Withdrawal)

Date of Receipt: 01/30/2008

Date clock started after UN:

Date of Filing Meeting: 3/11/2008

Filing Date: 3/28/2008

Action Goal Date (optional): November 30, 2008

User Fee Goal Date: ~~November 30, 2008~~  
February 27, 2009

Major Amendment: 11/13/2008

Indication(s) requested: Symptomatic GERD, diabetic gastroparesis

Type of Original NDA:	(b)(1) <input type="checkbox"/>	(b)(2) <input checked="" type="checkbox"/>
AND (if applicable)		
Type of Supplement:	(b)(1) <input type="checkbox"/>	(b)(2) <input type="checkbox"/>

**NOTE:**

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

Review Classification:	S <input checked="" type="checkbox"/>	P <input type="checkbox"/>
Resubmission after withdrawal?	<input checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Chemical Classification: (1,2,3 etc.)	3	
Other (orphan, OTC, etc.)		

Form 3397 (User Fee Cover Sheet) submitted: YES  NO 

User Fee Status:	Paid <input type="checkbox"/>	Exempt (orphan, government) <input type="checkbox"/>
	Waived (e.g., small business, public health) <input checked="" type="checkbox"/>	

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

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

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

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

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

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

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

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

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

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

Additional comments:

3. This application is an eCTD NDA. YES

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO   
IR Letters sent: 1/24/08; 12/3/2008

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

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

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

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

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

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

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO

- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **No, sent notification 3/11/2008**

- List referenced IND numbers: IND70,578

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections. **Sent notification 3/11/2008**

- End-of-Phase 2 Meeting(s)? Date(s) 11/4/2004 (Pre-IND Meeting) NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 4/17/2007 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO   
Ongoing Discussion with Katie Gelperin, M.D.
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

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

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: March 11, 2008

NDA #: 22-246

DRUG NAMES: Metozolv (metoclopramide) ODT

APPLICANT: Wilmington Pharmaceuticals

**BACKGROUND:**

On November 5, 2007, received November 6, 2007, Wilmington Pharmaceuticals submitted NDA 22-246 for Metoclopramide Orally Disintegrating Tablets (ODT) 5 mg, 10 mg. On January 2, 2008, the Agency notified Wilmington Pharmaceuticals that their application, NDA 22-246, did not contain patent certifications for Reglan ODT and that the applicant failed to list this drug as an additional drug relied upon. The Agency provided the sponsor with their regulatory options, including the opportunity to withdraw and resubmit the application with the appropriate patent certifications and identifying Reglan ODT as a reference listed drug (RLD). The Agency explained that if they choose to withdraw their application, the applicant may still reference information of the withdrawn application, but noted that the applicant is required to refresh their user-fee waiver. Wilmington Pharmaceuticals withdrew the application on January 3, 2008. On January 29, 2008, received January 30, 2008, Wilmington Pharmaceuticals resubmitted NDA 22-246.

**ATTENDEES:**

Joyce Korvick, M.D.  
Ruyi He, M.D.  
Fathia Gibril, M.D.  
Tamal Chakraborti, Ph.D.  
Sushanta Chakder, Ph.D.  
Khairy Malek, Ph.D.  
Tapash Ghosh, Ph.D.  
Sue Chih Lee, Ph.D.  
Solomon Iyasu, M.D.  
Katie Gelperin, M.D.  
Ann Corken, M.D.  
Mike Welch, Ph.D.  
Marie Kowblanski, Ph.D..  
John Metcalf, Ph.D.

ASSIGNED REVIEWERS:

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Fathia Gibril
Statistical:	Mike Welch
Pharmacology:	Tamal Chakraborti
Chemistry:	Gene Holbert
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Tapash Ghosh
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	John Metcalfe
DSI:	Khairy Malek
OPS:	N/A
Regulatory Project Management:	Maureen Dewey
Other Consults:	
OSE – Katie Gelperin, Anne Corken-Mackey	
SEALD Labeling	
ORP – Janice Weiner	

Per reviewers, are all parts in English or English translation? YES  NO

If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site audit(s) needed? YES  NO

If no, explain:

• Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

• Biopharm. study site audits(s) needed? Site 106 YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

• GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

• Establishment(s) ready for inspection? YES  NO

• Sterile product? YES  NO

If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List: Labeling comments.

**ACTION ITEMS:**

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

Maureen Dewey, M.P.H.  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own

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

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

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

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA#(s):  
**NDA 17-854 Reglan Tablets USP and NDA 21-793 Reglan ODT (Form 356h)**

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?  
**NDA 21-793 REGLAN ODT (Approved 2005; Not Marketed)** YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s): **NDA 21-793 Reglan ODT**

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

**According to the Orange Book, there are numerous marketed and unapproved metoclopramide products, in tablet, oral solution and intravenous formulations (5mg, 10 mg).**

*If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

**NDA 21-793**

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

**NDA 21-793**

*If "Yes," to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

The applicant states that their 505(b)2 application relies on findings of safety and effectiveness for Metoclopramide. There were no clinical studies performed. The applicant performed bioavailability studies to demonstrate "bioequivalence" to Reglan Tablets.

YES  NO

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO

**Based on previous advice given to the sponsor in pre-NDA meetings, this was found acceptable by the Division of Gastroenterology Products and Office of Regulatory Policy.**

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

**The applicant certifies that there are no relevant patents for NDA 17-854 Reglan Tablets**

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

**The applicant certifies to the following patents for NDA 21-793 Reglan ODT Tablets**

Patent number(s): **6,024,981 and 6,221,392**

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii):
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.  

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?  

YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-246 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Metozolv (ODT)  
Established Name: metoclopramide  
Strengths: 5mg, 10 mg

Applicant: Wilmington Pharmaceuticals  
Agent for Applicant (if applicable):

Date of Application: 01/29/2008 (Resubmission after Withdrawal)  
Date of Receipt: 01/30/2008  
Date clock started after UN:  
Date of Filing Meeting: 3/11/2008  
Filing Date: 3/28/2008  
Action Goal Date (optional): November 30, 2008 User Fee Goal Date: November 30, 2008

Indication(s) requested: Symptomatic GERD, diabetic gastroparesis

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

**NOTE:**

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

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

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

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

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

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

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

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

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

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES

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

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

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

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

Additional comments:

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

Additional comments:

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

- Exclusivity requested? YES, \_\_\_\_\_ Years NO

*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  NO

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

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

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

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

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

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO

- PDUFA and Action Goal dates correct in tracking system? YES  NO

If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **No, sent notification 3/11/2008**

- List referenced IND numbers: IND70,578

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections. **Sent notification 3/11/2008**

- End-of-Phase 2 Meeting(s)? Date(s) 11/4/2004 (Pre-IND Meeting) NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 4/17/2007 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO   
Ongoing Discussion with Katie Gelperin, M.D.
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

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

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: March 11, 2008

NDA #: 22-246

DRUG NAMES: Metozolv (metoclopramide) ODT

APPLICANT: Wilmington Pharmaceuticals

**BACKGROUND:**

On November 5, 2007, received November 6, 2007, Wilmington Pharmaceuticals submitted NDA 22-246 for Metoclopramide Orally Disintegrating Tablets (ODT) 5 mg, 10 mg. On January 2, 2008, the Agency notified Wilmington Pharmaceuticals that their application, NDA 22-246, did not contain patent certifications for Reglan ODT and that the applicant failed to list this drug as an additional drug relied upon. The Agency provided the sponsor with their regulatory options, including the opportunity to withdraw and resubmit the application with the appropriate patent certifications and identifying Reglan ODT as a reference listed drug (RLD). The Agency explained that if they choose to withdraw their application, the applicant may still reference information of the withdrawn application, but noted that the applicant is required to refresh their user-fee waiver. Wilmington Pharmaceuticals withdrew the application on January 3, 2008. On January 29, 2008, received January 30, 2008, Wilmington Pharmaceuticals resubmitted NDA 22-246.

**ATTENDEES:**

Joyce Korvick, M.D.  
Ruyi He, M.D.  
Fathia Gibril, M.D.  
Tamal Chakraborti, Ph.D.  
Sushanta Chakder, Ph.D.  
Khairy Malek, Ph.D.  
Tapash Ghosh, Ph.D.  
Sue Chih Lee, Ph.D.  
Solomon Iyasu, M.D.  
Katie Gelperin, M.D.  
Ann Corken, M.D.  
Mike Welch, Ph.D.  
Marie Kowblanski, Ph.D..  
John Metcalf, Ph.D.

ASSIGNED REVIEWERS:

**Discipline/Organization**

**Reviewer**

Medical:	Fathia Gibril
Statistical:	Mike Welch
Pharmacology:	Tamal Chakraborti
Chemistry:	Gene Holbert
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Tapash Ghosh
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	John Metcalfe
DSI:	Khairy Malek
OPS:	N/A
Regulatory Project Management:	Maureen Dewey
Other Consults:	
OSE – Katie Gelperin, Anne Corken-Mackey	
SEALD Labeling	
ORP – Janice Weiner	

Per reviewers, are all parts in English or English translation? YES  NO

If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? Site 106 YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

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

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List: Labeling comments.

**ACTION ITEMS:**

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

Maureen Dewey, M.P.H.  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own

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

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

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

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA#(s):  
**NDA 17-854 Reglan Tablets USP and NDA 21-793 Reglan ODT (Form 356h)**
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

**NDA 21-793 REGLAN ODT (Discontinued)** YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s): **NDA 21-793 Reglan ODT**

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

**According to the Orange Book, there are numerous marketed and unapproved metoclopramide products, in tablet, oral solution and intravenous formulations (5mg, 10 mg).**

*If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
**NDA 21-793**

*If "Yes," to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

The applicant states that their 505(b)2 application relies on findings of safety and effectiveness for Metoclopramide. There were no clinical studies performed. The applicant performed bioavailability studies to demonstrate "bioequivalence" to Reglan Tablets.

YES  NO

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

**Based on previous advice given to the sponsor in pre-NDA meetings, this was found acceptable by the Division of Gastroenterology Products and Office of Regulatory Policy.**

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

**The applicant certifies that there are no relevant patents for NDA 17-854 Reglan Tablets**

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

**The applicant certifies to the following patents for NDA 21-793 Reglan ODT Tablets**

Patent number(s): **6,024,981 and 6,221,392**

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii):
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.  

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?  

YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

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Maureen Dewey  
4/11/2008 04:33:45 PM  
CSO



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

**ADVICE LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your March 10, 2009 complete response for NDA 22-246 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets 5 mg, 10 mg.

We also refer to the Agency's Advice/Information Request letter dated August 18, 2009.

We further refer to your submission (027), dated August 7, 2009 containing your response to the Agency's letter dated July 30, 2009. The Agency has reviewed this submission, which includes the artwork for your proposed blister sleeve included in Attachment 1.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Cristi L. Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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CRISTI L STARK  
08/19/2009



NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your March 10, 2009 complete response for NDA 22-246 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets 5 mg, 10 mg.

We also refer to your submission dated June 16, 2009 and July 2, 2009.

We are reviewing the carton and container labels in your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

**CARTON LABELING**

The carton labeling has been satisfactorily revised.

**BLISTER SLEEVE**

1. A net quantity statement (e.g., 10 orally disintegrating tablets) should be added to each blister sleeve.
2. The blister sleeve should contain a location for the prescription label to be placed so that it does not cover any of the tablet blisters or any of the important information on the blister sleeve.
3. Increase the size of the strength (e.g., 5 mg) to increase its prominence and relocate the strength adjacent to the proprietary and established names. We recommend it be placed in line with the proprietary and established name.

## **BLISTER BACKING**

We agree with your use of a packaging sleeve that contains all the required information about your product, however, the individual blister labels will need to contain the following information:

- Proprietary name
- Established name
- Strength
- Lot number
- Expiration date
- Barcode

Since the outer packaging sleeve will contain the full established name it will be acceptable for you to omit “orally disintegrating tablet” from the individual blister backing. Therefore, it should read: Metozolv ODT (metoclopramide HCL) x mg

Submit the revised Blister Sleeve and Blister labeling by **August 10, 2009**.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Cristi L. Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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MAUREEN D DEWEY  
07/30/2009

CRISTI L STARK  
07/30/2009



NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your March 10, 2009, complete response for NDA 22-246 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets 5 mg, 10 mg.

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

Division of Medication Error Prevention Analysis

1. Although your labels and labeling contain the required statement alerting the dispenser to provide the Medication Guide with the product for all strengths and formulations, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
  - a. "Dispense the enclosed Medication Guide to each patient." or
  - b. "Dispense the accompanying Medication Guide to each patient."
  
2. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:
  - a. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
  - b. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

Chemistry, Manufacturing and Controls

3. Please refer to the carton art work that you submitted on March 10, 2009.

The 5 mg carton should read:

\*Contains 5.91 mg metoclopramide hydrochloride equivalent to 5 mg metoclopramide.

The 10 mg carton should read:

\*Contains 11.82 mg metoclopramide hydrochloride equivalent to 10 mg metoclopramide.

4. For the blister package you will need to use (metoclopramide HCl) orally disintegrating tablet, not (metoclopramide HCl) tablet as you propose. If it is necessary, it will be acceptable for you to split (metoclopramide HCl) orally disintegrating tablet into two lines, as long as you use the same font.

We remind you that this information is needed in order to complete our review.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Brian Strongin  
6/11/2009 05:37:55 PM



NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your March 10, 2009 complete response for NDA 22-246 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets 5 mg, 10 mg.

We also refer to your submission dated March 10, 2009.

We are reviewing the REMS section of your submission and have the following comments and information requests. We request a prompt written response by July 20, 2009 in order to continue our evaluation of your REMS.

**Goal of REMS**

1. Revise your REMS goal as edited in the attached REMS file. This language is consistent with the REMS goals for all metoclopramide products.

**Medication Guide**

2. The Medication Guide distribution procedure is not acceptable. The use of electronic consumer medication information services is not reliable; not all pharmacies use them. Medication Guides are required to be disseminated with each new or refill prescription. Using these services would not guarantee that the Medication Guides are available for distribution at all pharmacies. Moreover, FDA learned in a recent study on Consumer Medication Information that information was sometimes truncated or missing. Medication Guides must follow and be printed in the approved format and content as specified in 21 CFR 208.20.

Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each

packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose.

For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
  - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
3. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): “Dispense the enclosed Medication Guide to each patient.” or “Dispense the accompanying Medication Guide to each patient.”

#### **Timetable for Submission of Assessments**

4. Please submit your detailed plan to evaluate patients’ understanding about the safe use of metoclopramide at least 3 months before you plan to conduct the evaluation. The submission should include:
- All methodology and instruments that will be used to evaluate patients’ understanding about the safe use of metoclopramide. This should include, but not be limited to:
    - Sample size and confidence associated with that sample size
    - How the sample will be determined (selection criteria)
    - The expected number of patients to be surveyed
    - How the participants will be recruited
    - How and how often the surveys will be administered
    - Explain controls used to minimize bias
    - Explain controls used to compensate for the limitations associated with the methodology
  - The survey instruments (questionnaires and/or moderator’s guide).
  - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please see appended REMS proposals for additional track changes. Submit the revised Proposed REMS with appended materials and documents by **July 20, 2009**. It is preferable that the entire REMS and appended materials be submitted as a single WORD document. If certain documents

are only in PDF format, they may be submitted as such, but the preference is a single WORD document.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Cristi L. Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

2 Pages Withheld as b(4) Trade Secret/Confidential



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/s/

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Cristi Stark  
7/7/2009 02:20:05 PM



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation ODE III

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** May 20, 2009

<b>To:</b> Eugene Haley/Dave Burns	<b>From:</b> Maureen Dewey
<b>Company:</b> Wilmington Pharmaceuticals	Division of Gastroenterology Products
<b>Fax number:</b> 910-509-0771	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 910-509-0097	<b>Phone number:</b> (301) 796-0845

**Subject:** Agency proposed Labeling for NDA 22-246

**Total no. of pages including cover:**

**Comments:**

Gene and Dave:

Please see the enclosed proposed safety labeling changes to the Metozolv ODT package insert. Please review the changes proposed by the Agency and incorporate accordingly.

Please respond to the proposed changes by sending a Word copy with your proposed Track Changes (if any) to me (email: [maureen.dewey@fda.hhs.gov](mailto:maureen.dewey@fda.hhs.gov)) by **Tuesday, May 26, 2009 10:00 am**.

A teleconference will be held to discuss any proposed changes to this section on **Tuesday, May 26, 2009 at 3:00 PM**. An additional teleconference will be held on **Thursday, June 18<sup>th</sup> @ 1:00 pm** to discuss the rest of the label and the Medication Guide.

Please feel free to contact me at (301) 796-0845 if you have any questions.

Thank you, Maureen Dewey

**Document to be mailed:** YES  NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

**WARNING: TARDIVE DYSKINESIA**

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS

**WARNINGS:****Tardive Dyskinesia (see Boxed Warnings)**

Treatment with metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities. Although the risk of TD with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 12 weeks. Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, although in some patients, TD may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.



NDA 22-246

**PROPRIETARY NAME REQUEST  
- WITHDRAWN**

Wilmington Pharmaceuticals  
ATTENTION: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, North Carolina 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA 22-246) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets 5 mg and 10 mg.

We acknowledge receipt of your March 23, 2009, correspondence on March 24, 2009, notifying us that you are withdrawing your request for a review of the proposed proprietary name Metozolv ODT. This proposed proprietary name request is considered withdrawn as of March 24, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648.

For any other information regarding this application, contact Maureen Dewey, Regulatory Health Project Manager.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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Donna Griebel  
3/31/2009 12:56:27 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

We acknowledge receipt on March 11, 2009 of your March 10, 2009 resubmission to your new drug application for Metozolv ODT (metoclopramide) Orally Disintegrating Tablets, 5 mg and 10 mg.

We consider this a complete, class 2 response to our February 26, 2009 action letter. Therefore, the user fee goal date is September 11, 2009.

If you have any questions, call Maureen Dewey, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Health Project Manager,  
Division of Gastroenterology Products  
Center for Drug Evaluation and Research



**DEPARTMENT OF HEALTH & HUMAN  
SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA 22-246) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv ODT (metoclopramide) Orally Disintegrating Tablets 5 mg, 10 mg.

We refer to your submission dated April 8, 2008, containing a notice of certification to patent holder and application holder.

We also refer to your submission dated April 21, 2008, containing documentation of the receipt of notice.

We further refer to your submission dated October 8, 2008, in which you replied to our request for clarification of the patent certifications made in your application.

You have submitted a "Paragraph IV Certification" to rely upon the previous finding of safety and effectiveness for NDA 17-854 and NDA 21-793. According to 21 CFR 314.50(i)(1)(i)(A)(4), you will comply with the notification requirements outlined in 21 CFR 314.52 for each patent owner and the holder of the approved application. According to FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), the holder of the applications being relied upon is Alaven Pharmaceutical LLC. Therefore, you must provide notice (and subsequent documentation of receipt of notice) to Alaven Pharmaceutical LLC as the holder of the approved applications.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call me, at 301-796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey  
12/3/2008 02:54:43 PM



Food and Drug  
Administration  
Rockville, MD 20857

NDA 22-246

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide) Orally Disintegrating Tablets.

On October 23, 2008, we received your October 22, 2008 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 27, 2009.

If you have any questions, please call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey  
11/13/2008 04:29:46 PM



NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA 22-246) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide Orally Disintegrating Tablets) 5 mg, 10 mg.

Please also refer to your amendment dated September 8, 2008, in which you replied to our comment concerning child resistance by stating that you are "taking the necessary steps to ensure compliance with the requirements prior to marketing of the product."

We note that these steps might invalidate your stability studies. Please explain in detail exactly the steps you are planning to take.

We remind you that this information is needed in order to complete our review.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Wes Ishihara  
LT, U.S. PHS Commissioned Corps  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Richard W Ishihara  
9/26/2008 11:41:21 AM



NDA 22-246

INFORMATION REQUEST LETTER

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA 22-246) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide Orally Disintegrating Tablets) 5 mg, 10 mg.

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

1. Identification by High Pressure Liquid Chromotography (HPLC) retention time alone is not considered a specific identity test (refer to ICH Q6A 3.2.2 (c) "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"). Please add a second non-chromatographic identity test to the specification. The UV spectrum from the photodiode array detector will be acceptable for this purpose.
2. Please submit a stability update. Currently available stability data do not support a (b) (4) expiration date.
3. Please be aware that the blister packs need to comply with 16 CFR 1700.14(a)(10) for child resistance. Refer to the Guidance for Industry: "Container Closure Systems for Packaging Human Drugs and Biologics", (May 1999, Attachment A, <http://www.fda.gov/cder/guidance/1714fnl.htm>) for more information.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager,  
at 301-796-0845.

Sincerely,

*{See appended electronic signature page}*

Wes Ishihara  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Richard W Ishihara  
8/19/2008 01:31:54 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

**DISCIPLINE REVIEW LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene Haley  
Chief Executive Office  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide) ODT.

We also refer to your submissions dated May 20 and June 9, 2008.

Our review of the trade name, Metozolv ODT, is complete. The Proprietary Name Risk Assessment findings indicate that the proposed name, Metozolv ODT, does not appear to be vulnerable to name confusion that could lead to medication errors in the United States of America. As such, we do not object to the use of the proprietary name, Metozolv ODT, for this product.

If any of the proposed product characteristics as stated in your submission are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

Additionally, the Division of Drug Marketing, Advertising, and Communication has no objection to the proposed name, Metozolv ODT, from a promotional perspective. However, we request that you submit all container labels for review and comment when they become available.

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

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

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/s/

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Richard W Ishihara  
8/1/2008 11:05:31 AM



NDA 22-246

**INFORMATION REQUEST LETTER**

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your January 29, 2008, new drug application (NDA 22-246) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide Orally Disintegrating Tablets) 5 mg, 10 mg.

We also refer to your submission dated May 20 and June 9, 2008.

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

1. Please provide the Integrated Summary of all available information about the safety of the drug product (ISS) and summary tables for common adverse events, drug related adverse events, and serious adverse events for the three clinical studies performed. The cut off for common adverse events should be  $\geq 2\%$  of subjects.
2. Please identify the location of the case report forms (CRF) and full narratives for all patients who discontinued the study for any reason.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at 301-796-0845.

Sincerely

*{See appended electronic signature page}*

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

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/s/

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Brian Strongin  
6/23/2008 01:46:32 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-246

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive  
Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your new drug application (NDA) dated January 29, 2008, received January 30, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Metozolv (metoclopramide) Orally Disintegrating Tablets (5mg, 10 mg).

We also refer to your submission dated, February 26, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act of February 29, 2008, in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is November 30, 2008.

**Labeling**

The following issues have been identified in your proposed labeling.

Highlights Section:

- The Highlights must be limited in length to one-half page, in 8 point font type, two-column format. This also applies to Contents and the Full Prescribing Information (FPI). [21 CFR 201.57 (d)(8).]
- Current regulations [21 CFR 201.57] fully describe the format and content of labeling, including Highlights. There is no provision for a logo. Therefore, do not include logos (e.g. ®) in Highlights or FPI.

- The new rule [21 CFR 201.57 (a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Regarding Contraindications, “theoretical” possibilities must not be listed (i.e., sensitivity or intolerance to the drug). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section (4.3) in the FPI. [21 CFR 201.57 (a)(9) and (c)(5)]
- A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date will be the month/year that the application or supplement is approved. Please delete the word “Original”.

Full Prescribing Information (FPI):

- Do not include the pregnancy category (e.g., Category B) in the Table of Contents. [See comment #34 Preamble]
- Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.3.1 Adult PK). Use headings without numbering (e.g., Adult Pharmacokinetics). [21 CFR 201.59 (c)]
- Every table and figure throughout the FPI should be numbered.

We request that you submit an updated proposed label to reflect the recommendations and comments listed above by June 9, 2008. This updated version of labeling will be used for further labeling discussions.

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

If you have any questions, please call Maureen Dewey, Regulatory Project Manager,  
at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Julieann DuBeau, MSN, RN  
Chief, Project Management Staff (CPMS)  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Julieann DuBeau  
4/11/2008 10:34:29 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

Federal Express

Wilmington Pharmaceuticals  
ATTENTION: Eugene T. Haley, Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

On February 4, 2008, a third party notified the FDA that this office inadvertently sent them a copy of the 01/14/08 letter for your NDA that was intended for an FDA office.

In a telephone conversation on February 5, 2008, the recipient of the document agreed to return the original document and any copies that were made. The recipient further agreed not to retain any copies of the document or to use, distribute, or disclose the document or the contents thereof. The recipient returned the original document and confirmed these agreements in a letter to this office on February 8, 2008.

I apologize for this having happened. Please note that we take our disclosure responsibilities very seriously and make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have questions, please call me at (301) 796-0447.

Sincerely,

A handwritten signature in black ink, appearing to read "Marc J. Bloom", written over a horizontal line.

Marc J. Bloom, Director  
Division of Logistics Services  
Office of Real Property Services  
Office of Shared Services

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/s/

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Mia Prather  
2/26/2008 04:47:59 PM



NDA 22-246

**NDA ACKNOWLEDGMENT**

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive  
Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Metoclopramide Orally Disintegrating Tablets (ODT) 5 mg, 10 mg

Date of Application: January 29, 2008

Date of Receipt: January 30, 2008

Our Reference Number: NDA 22-246

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 28, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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

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

If you have any questions, call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey  
2/19/2008 04:09:55 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Haley:

We received your January 3, 2008, correspondence notifying us that you are withdrawing your unapproved new drug application (NDA) for Zydys (metoclopramide) prior to the date on which a decision would be made regarding filing of this 505(b)(2) application.

In accordance with 21 CFR 314.65, this application is withdrawn as of January 3, 2008. We note that Wilmington Pharmaceuticals, LLC (Wilmington) had been granted a small business waiver of the human drug application fee for NDA 22-246. We refer to a letter sent January 14, 2008, acknowledging your withdrawn application, and would like to provide the following clarifications.

If you decide to resubmit the application, we reiterate that this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. We request that you resubmit appropriate review copies of Module 1 of the application.

If you choose to resubmit, the resubmitted application should address the following deficiencies identified during our preliminary review of the withdrawn application:

- You should identify Reglan ODT (NDA 21-793), a pharmaceutical equivalent to your proposed Zydys ODT, as an additional listed drug relied upon in support of your 505(b)(2) application. Please be advised that you will need to comply with applicable regulatory requirements for each listed drug relied upon in support of your 505(b)(2) application (see 21 CFR 314.54), including, but not limited to, an appropriate patent certification or statement (see 21 CFR 314.50(i)).

FDA's letter dated January 22, 2008, granting your request for extension of the small business waiver should accompany a resubmission of your application.

If you have any questions, please feel free to call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey

1/24/2008 03:08:06 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-246

Wilmington Pharmaceuticals  
Attention: Eugene T. Haley  
Chief Executive Officer  
1213 Culbreth Drive, Suite 230  
Wilmington, NC 28405

Dear Haley:

We received your January 3, 2008, correspondence on January 3, 2008, notifying us that you are withdrawing your unapproved new drug application (NDA) for Zydis (metoclopramide) prior to its filing date.

In accordance with 21 CFR 314.65, this application is withdrawn as of January 3, 2008. If you have paid a user fee, we will refund 75% of your payment.

If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. However, because we retain only the archival copy of a withdrawn application in our files, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application but obtain a new user fee identification number. The new user fee identification number must be on the check as well as on the User Fee Cover Sheet in the resubmitted application. Submit the check for the appropriate user fee to the following address:

Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909

For courier delivery, write the NDA number, the FDA Post Office box number (P.O. Box 360909), and the user fee identification number on the check and deliver it to the following address:

Food and drug Administration (360909)  
Mellon Client Service Center, Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

In addition, the resubmitted application should address the following deficiencies identified during our preliminary review of the withdrawn application:

Your application lacked identifying Reglan ODT as an additional listed drug relied upon. If you choose to resubmit, please be advised that in accordance with 21 CFR 314.52, you must submit a paragraph IV certification.

If you have any questions, please feel free to call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey  
1/14/2008 10:03:03 AM

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If you have any questions, call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey

11/19/2007 05:39:01 PM

## MEMORANDUM OF TELECON

DATE: February 25, 2009

NDA 22-246

BETWEEN:

Name: Eugene Haley  
Phone: (910) 233-2322  
Representing: Wilmington Pharmaceuticals

AND

Name: Kristen Everett, CDR USPHS  
Safety Regulatory Project Manager (SRPM)  
Maureen Dewey, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology Products, HFD-180

SUBJECT: 24 hour advance notice of FDA Press Release

Kristen Everett notified Mr. Haley that the FDA will be releasing a press release regarding the risk of tardive dyskinesia for the class of metoclopramide products on Thursday, February 26, 2009. The press release will be posted at [www.fda.gov](http://www.fda.gov) under News and Events. Mr. Haley inquired whether this announcement would affect the approvability of NDA 22-246. The Agency noted that any questions specific to the application under review could be discussed at a teleconference scheduled for February 26, 2009 at 2:30 PM.

The teleconference concluded at 2:45 PM.

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Maureen Dewey, M.P.H.  
Senior Regulatory Health Project Manager

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/s/

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Maureen Dewey  
2/25/2009 03:48:25 PM  
CSO

**MEMORANDUM OF TELECON**

DATE: January 28, 2008

APPLICATION NUMBER: NDA 22-246

BETWEEN:

(b) (4)

Salix Pharmaceuticals

Stephana Patton

Wilmington Pharmaceuticals

Dave Burns, Tom Aluise, Eugene Haley

Phone: 866-365-4406

AND

Division of Gastroenterology Products

Ruyi He, M.D., Medical Team Leader

Fathia Gibril, M.D., Medical Officer

Maureen Dewey, M.P.H., Regulatory Project Manager

Office of Regulatory Policy, Division of Regulatory Policy I

Janice Weiner, J.D., M.P.H., Regulatory Counsel

Nam Kim, J.D., Regulatory Counsel

SUBJECT: Resubmission of NDA 22-246

Dave Burns notified the Agency that Wilmington Pharmaceuticals was ready to resubmit their application, NDA 22-246, with an appropriate patent certification to patents listed for Reglan ODT and identifying Reglan ODT as a pharmaceutical equivalent and as such, an additional listed drug in support of their 505(b)(2) application.

He stated that the new application will contain modifications to the following modules:

- 1.3 Administrative Information
- 1.3.5.2 Patent Certification
- 1.5.5 Withdrawal of an Unapproved NDA
- 1.6.3 Correspondence Regarding Teleconference with the Agency
- 1.12.11 Basis for Submission Statement
- 1.1.3 Updated User Fee Cover Sheet

- 1.3.2 Field Copy Certification
- 1.3.3 Debarment Certification

He inquired whether there were any additional items that needed to be addressed. Janice Weiner stated that the sponsor should update the Form 356h to include the Reglan ODT in addition to Reglan tablets as listed drugs relied upon in support of their 505(b)(2) application.

Ms. Weiner further clarified that the sponsor needs to comply with applicable regulatory requirements for each listed drug relied upon including an appropriate patent certification or statement, however, the type of patent certification (Paragraph III or IV) is entirely up to the sponsor.

Dave Burns noted that they will submit 18 copies of Volume 1, which will contain an updated Module 1. Additionally, they have made an amendment to Module 2, which will be submitted along with Module 1, both of which are contained in Volume 1 of the NDA. Further, the sponsor will provide five copies of tab-to-tab replacements of Module 3.

Gene Haley inquired whether the Agency will require the full sixty days for filing. Dr. He responded that the Agency will treat this application as any other NDA submission, which will require the full 60 days for filing.

(b) (4) wanted to ensure that there was no misunderstanding with respect to the patent certification and the fact that the application addresses the comparability of Zydys ODT to the Reglan tablet not Reglan ODT. Janice Weiner noted that the Agency recognized the unavailability of Reglan ODT for use as a comparator, and understands that the sponsor is using the Reglan tablet as a comparator to bridge to the Agency's findings of safety and efficacy for Reglan tablet and Reglan ODT in support of their 505(b)(2) application for a metoclopramide ODT product.

With respect to the sponsor's proposed paragraph IV patent certification, Janice Weiner noted that the sponsor is required to provide notice to the NDA holder and each patent owner in accordance with the regulations (21 CFR 314.52). It should be noted that the NDA holder and patent owner may be different entities. Dave Burns agreed.

The call was ended at 9:33 AM.

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Maureen Dewey, M.P.H.  
Regulatory Project Manager

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/s/

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Maureen Dewey  
1/30/2008 11:15:18 AM

## MEMORANDUM OF TELECON

DATE: January 2, 2008

APPLICATION NUMBER: NDA 22-246

BETWEEN:

(b) (4)

Salix Pharmaceuticals

Stephana Patton

Sam Bohannon

Wilmington Pharmaceuticals

Dave Burns

Tom Aluise

Eugene Haley

Phone: 866-365-4406

AND

Division of Gastroenterology Products

Daniel A. Shames, M.D., Division Director

Joyce Korvick, M.D., Deputy Director

Ruyi He, M.D., Medical Team Leader

Maureen Dewey, M.P.H., Regulatory Project Manager

Office of Drug Evaluation III

Bronwyn Collier, Associate Director for Regulatory Affairs

Maria R. Walsh, R.N., M.S., Project Management Officer

Office of Regulatory Policy, Division of Regulatory Policy I

Janice Weiner, J.D., M.P.H., Regulatory Counsel

Nam Kim, J.D., Regulatory Counsel

SUBJECT: Refusal to File

On January 2, 2008, the Agency notified Wilmington Pharmaceuticals that their application, NDA 22-246, failed to identify Reglan ODT as an additional listed drug relied upon and did not contain an appropriate patent certification to patents listed in the Orange Book for Reglan ODT. The Agency noted that it had previously advised Wilmington Pharmaceuticals in preliminary

responses provided in advance of their April 17, 2007, pre-NDA meeting with the Agency that Wilmington Pharmaceuticals would be required to certify to patents listed in the Orange Book for Reglan ODT (NDA 21-793), a pharmaceutical equivalent to their proposed Zydis ODT product. The Agency provided the sponsor with their regulatory options, including the opportunity to withdraw their application in advance of the 60 day filing date and resubmit the application with the appropriate patent certifications and identifying Reglan ODT as an additional listed drug relied upon. The Agency noted that this type of change is not permitted as an amendment.

Ms. Chance of Salix Pharmaceuticals inquired why a patent certification was required since Reglan ODT was not listed in the Orange Book. Janice Weiner clarified that Reglan ODT is, in fact, listed in the discontinued section of the Orange Book. Janice Weiner additionally pointed out that 505(j) application would have been a more appropriate submission for this product, as the applicant's proposed Zydis ODT product is a pharmaceutical equivalent to Reglan ODT. In light of earlier discussions with the sponsor, the Agency advised at the pre-NDA meeting that the sponsor would be permitted to proceed through the 505(b)(2) pathway. However, the sponsor could not circumvent its patent certification obligations by submitting a 505(b)(2) application instead of a 505(j) application. The sponsor commented that their proposed product is a "new dosage form" of the Reglan tablet, and appropriate for submission through the 505(b)(2) pathway. The Agency responded that Reglan ODT had been approved before their application was submitted.

Salix Pharmaceuticals explained that their original belief was that the application was no longer relying on Reglan ODT as a listed drug because they had provided literature support for the sections of their annotated draft labeling that previously referenced information from the Reglan ODT labeling. Janice Weiner explained that the comment in the pre-NDA meeting responses regarding reliance on Reglan ODT labeling in their annotated draft labeling was an additional basis for identifying Reglan ODT as a listed drug relied upon. The subsequent revision to their annotated labeling in Module 1 was noted; however, referencing published literature rather than Reglan ODT labeling for certain information did not eliminate the need to identify Reglan ODT as a listed drug because it is a pharmaceutical equivalent. Ms. Weiner further explained that a pharmaceutical equivalent had the same active ingredient, dosage form, and dose strength and referred the applicant to 21 CFR 320.1 for further information.

Additionally (b) (4) inquired whether pursuing the 505(b)(2) mechanism instead of the 505(j) would "handicap" the sponsor in any way? After conferring internally with the other meeting attendees while the telephone was on "mute," Janice Weiner responded that identification of Reglan ODT as an additional listed drug relied upon for this 505(b)(2) application would not result in additional requirements at this time beyond identification of the listed drug pursuant to 21 CFR 314.54 and applicable regulatory requirements, namely an appropriate patent certification.

The applicant inquired whether it was feasible to file a patent certification to Reglan ODT by the filing date, January 4, 2008, as an amendment. Janice Weiner reiterated that under section 505(b)(4)(A) of the Food, Drug, & Cosmetic Act (FD&C Act), added by the Medicare Modernization Act, an applicant may not amend a 505(b)(2) application to seek approval of a

drug that relies on the Agency's finding of safety and/or effectiveness for a drug that is different from the drug identified in a previous submission of the application. Therefore, the identification of Reglan ODT as an additional listed drug relied upon is not the type of change that may be made in an amendment to a 505(b)(2) application.

Bronwyn Collier explained that if they choose to withdraw their application, the applicant may still reference information in the withdrawn application, but noted that the applicant is required to refresh their user-fee waiver.

The Regulatory Project Manager requested that if they choose to withdraw NDA 22-246, Wilmington Pharma should send their withdrawal letter via facsimile before the filing date of January 4, 2008.

Gene Haley stated that Wilmington Pharmaceuticals intended to withdraw the application.

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Maureen Dewey, M.P.H.  
Regulatory Project Manager

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## MEMORANDUM OF TELECON

DATE: June 15, 2006

APPLICATION NUMBER: IND 70,578 Zydis® (metoclopramide) Orally Dissolving Tablets  
BETWEEN:

Name: Eugene Haley, CEO  
Bob Zeid, Regulatory Affairs Consultant  
Phone: (866) 365-4406 / (910) 509-0097  
Representing: Wilmington Pharmaceuticals, LLC

AND

Name: Mary Ann Holovac, R.Ph., Director, Drug Information  
Office of Generic Drugs  
Maureen Dewey, MPH, Regulatory Project Manager,  
Division of Gastroenterology Products

SUBJECT: Clarification of Therapeutic Equivalence Evaluations (TE)  
Ratings by the Agency

### BACKGROUND:

On January 27, 2006, received January 31, 2006, Wilmington Pharmaceuticals submitted an IND for Zydis® (metoclopramide) Orally Dissolving Tablets indicated for symptomatic gastroesophageal reflux, diabetic gastroparesis (diabetic gastric stasis), (b) (4)

. Wilmington Pharmaceuticals intends to conduct bioequivalence studies with Reglan® (metoclopramide) Tablets as the reference listed drug (RLD) and submit a 505(b)(2) application.

On June 10, 2005, NDA 21-793 for Reglan® (metoclopramide) Orally Disintegrating Tablets (ODT) was approved. NDA 21-793 is a 505(b)(1) application that showed bioequivalence with NDA 17-854 Reglan® (metoclopramide) Tablets and relied on the Agency's finding of safety and efficacy for NDA 17-854.

THE CALL: The sponsor asked the following question:

The sponsor would like to understand the process by which the Agency determines TE ratings, and specifically to understand the approach to the issuance of an AB rating in a 505(b)(2) filing.

Gene Haley summarized that the reference listed drug (RLD) for their filing is the original Reglan® Tablet, not the Reglan® ODT product. We explained that the Zydis® product, if approved, would not receive an AB rating against the RLD Reglan® Tablets.

IND 70,578  
T-con June 15, 2006  
Page 2 of 2

In a 505(b)(2) filing in which the filed product is an oral *disintegrating* tablet (ODT) dosage form for which the RLD is a *traditional* oral tablet, the ODT product will not be AB rated against the oral tablet RLD.

Further, it was explained that in order to become AB rated to Reglan<sup>®</sup> ODT, Wilmington Pharmaceuticals should submit an Abbreviated New Drug Application (ANDA) instead of a 505(b)(2). If the Wilmington Pharmaceuticals product Zydis<sup>®</sup> showed pharmaceutical equivalence and bioequivalence to Reglan<sup>®</sup> ODT then Zydis<sup>®</sup> will be AB rated.

The sponsor summarized the discussion and the call was ended.

It should be noted that Reglan<sup>®</sup> ODT is not currently in the marketplace. If it enters the marketplace, then the Zydis<sup>®</sup> product, if approved, would be a single source and not rated as therapeutically equivalent to any other product.

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Maureen Dewey, MPH  
Regulatory Project Manager

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Maureen Dewey  
7/7/2006 12:02:22 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 70,578

Wilmington Pharmaceuticals, LLC  
Attention: Eugene Haley, CEO  
1213 Culberth Drive, Suite 230  
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your Investigational New Drug Application (IND) file for Zydis<sup>®</sup> (metoclopramide) Orally Disintegrating Tablets, 10 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 17, 2007. The purpose of the meeting was to discuss the development of Zydis<sup>®</sup> (metoclopramide) Orally Disintegrating Tablets, 10 mg.

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) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, MPH  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## Memorandum of Meeting Minutes

**Meeting Date:** April 17, 2007  
**Meeting Time:** 1:00-2:00 p.m.  
**Meeting Location:** White Oak Conference Room 1415  
**Application Number:** IND 70,578  
**Drug Name:** Zydys<sup>®</sup> (metoclopramide) Orally Dissolving Tablet  
**Type of Meeting:** Type B  
**Meeting Chair:** Fathia Gibril, M.D.  
**Meeting Recorder:** Maureen Dewey, M.P.H.

### **BETWEEN:**

#### **Division of Gastroenterology Products**

Brian E. Harvey, M.D., Ph.D., Director  
Fathia Gibril, M.D., Medical Team Leader  
Keith St. Amand, M.D., Medical Officer  
Tamal Chakraborti, Ph.D., Pharmacologist Reviewer  
Maureen Dewey, MPH, Regulatory Project Manager

#### **Office of Clinical Pharmacology and Biopharmaceutics**

Tapash Ghosh, Ph.D., Biopharmaceutics Team Leader

#### **Office of New Drug Quality Assessment (ONDQA)**

Rajiv Agrawal, Ph.D., Chemistry Reviewer  
Marie Kowblansky, Ph.D, Pharmaceutical Lead

#### **Office of Regulatory Policy**

Janice Weiner, J.D., Regulatory Counsel

**AND**

#### **Wilmington Pharmaceuticals LLC:**

Eugene T. Haley, Chief Executive Officer, Wilmington Pharmaceuticals. LLC

(b) (4)

Joining by telephone:

(b) (4)

**PURPOSE:** To discuss the development plan for Zydys<sup>®</sup> (metoclopramide) Orally Dissolving Tablets indicated for symptomatic gastroesophageal reflux, diabetic gastroparesis (diabetic gastric stasis),

(b) (4)

(b) (4)

## **BACKGROUND:**

On February 6, 2007, received February 6, 2007, Wilmington Pharmaceuticals submitted a pre-NDA meeting request for Zydis® (metoclopramide) Orally Dissolving Tablets indicated for symptomatic gastroesophageal reflux, diabetic gastroparesis (diabetic gastric stasis), [REDACTED] (b) (4)

On March 12, 2007, received March 13, 2007, the sponsor submitted a background package containing specific pre-NDA questions relating to the content and format for a 505(b)(2) application.

Responses to the questions posed by the sponsor were faxed to the sponsor on April 16, 2007.

**Discussion Points:** Following introductions, Wilmington Pharmaceutical's questions from the March 12, 2007 background package were addressed. The format of these minutes provides for Wilmington Pharmaceutical's questions in regular typeface, followed by FDA's responses in **bolded** print, followed by the April 17, 2007, meeting discussion in *italic and bolded* print.

## **DISCUSSION:**

**CLINICAL: COMPLIANCE WITH THE PEDIATRIC RESEARCH EQUITY ACT (PREA) OF 2003**

**Question 1:** The tablet formulation of the reference listed drug, Reglan®, is not clinically indicated for [REDACTED] (b) (4)

[REDACTED] (These are indications of the marketed potential formulation of metoclopramide but not of the RLD Reglan [metoclopramide] tablets.) Furthermore, these indications are not part of the Zydis® application or proposed labeling. Therefore, the pediatric assessment to be performed by Wilmington Pharmaceuticals for Zydis® (metoclopramide tablets, USP) Orally Disintegrating Tablets will not include pediatric studies for these indications. Is this acceptable?

### **Response:**

**At this time, it is the opinion of the Agency that this application does not trigger PREA. Therefore, no pediatric studies are required.**

**Question 2:** Can labeling for pediatric use of Zydys® (metoclopramide tablets, USP) ODT be supported by safety data from the use of potential and oral solution formulations of metoclopramide in pediatric patients, as reported in the literature?

**Response:**

**You may be able to use safety data from the literature to support your product's safety, but this information would need to be submitted to us for review before an assessment could be made regarding the adequacy of this data for labeling. If you intend to rely on published literature describing a listed drug(s) to support your 505(b)(2) application, you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54, and comply with applicable regulatory requirements for 505(b)(2) applications (see Additional Regulatory Comments).**

**Question 3:** Wilmington Pharmaceuticals intends to defer conducting pediatric studies until after approval of Zydys® for use in adults (as was permitted for Schwarz Pharma for their ODT metoclopramide formulation in NDA 021793). This will allow ample time to prepare the pediatric plan. Is this acceptable?

**Response: See response to Question 1.**

**Question 4:** We plan to submit the request for deferral and/or partial waiver after the NDA has been filed but still prior to approval; is this acceptable? If the request for deferral and/or waiver must be included at the time of the NDA filing, should they be submitted separately or included in the NDA?

**Response: See response to Question 1.**

**Question 5:** We understand that a Written Request for pediatric studies must be issued prior to submitting the results of those studies in order for the studies to potentially qualify for pediatric exclusivity. However, does the Written Request have to be issued prior to the NDA filing in order for the sponsor to have met their obligations to conduct a pediatric assessment, apart from issues of exclusivity?

**Response:**

**No. Although studies performed to satisfy a Written Request may be used to meet the obligations of PREA, the Written Request need not be issued before NDA filing or approval. Please note that the Best Pharmaceuticals for Children Act has a Sunset date of October 1, 2007.**

**Question 6:** May the supporting data for a partial waiver (for instance, a request to waive use in infants) be outlined in the Proposed Pediatric Study Request asking for a Written Request and then be filed in detail later, either in the NDA or in an amendment post-approval?

**Response: See response to Question 1.**

**Question 7.** The parenteral and oral formulations of metoclopramide are used extensively in pediatric patients as an anti-emetic or for treatment of GERD. We plan to submit published reports on distribution, metabolism, excretion, and safety of metoclopramide, including reports of toxicity of certain doses in neonates and infants, to justify a waiver in neonates and infants if it is shown (1) that the lowest dose (5 mg) of Zydys® product is greater than a toxic dose in these pediatric sub-populations and (2) that the ODT dosage form cannot be further titrated to a lower dose, thus excluding its utility in neonates and infants. If the data are found to show this, would this approach to this age group be acceptable?

**Response:**

**See response to Question 1. However, if you decide to submit a Proposed Pediatric Study Request (PPSR), we agree that your 5 mg dose of ODT could be toxic for infants. You may need to provide evidence that reasonable attempts to produce a pediatric formulation (which would allow for a lower dose) for neonates and infants have failed.**

**Alternatively, you could include in your PPSR a proposal to conduct your pediatric assessment in older children first (i.e., children over 2 years of age). If you can demonstrate safety and effectiveness of your product in this subpopulation, you could then proceed to the neonatal/ infant study.**

**Question 8:** If a partial waiver for a sub-population (for instance, neonates and infants) is granted, should the proposed labeling include a statement to this effect prior to completing other pediatric studies that would be conducted post-approval?

**Response: See response to Question 1.**

**Clinical: Clarification of ISS & ISE Standards for a 505(b)(2) in CTD Format**

**Question 9:** Per 21 CFR 314.50(d)(5)(v-vi), the ISS (integrated summary of safety) and ISE (integrated summary of efficacy) are required but there has been considerable discussion about the proper placement in the CTD format. This was clarified in a 2006 presentation by FDA<sup>1</sup>:

The location of the clinical safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (Structure and Content of Clinical Study Reports). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis. If the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, the CTD

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<sup>1</sup> Justina A. Molzon, M.S. Pharm., J.D., Associate Director for International Programs, CDER, FDA presented at the 42<sup>nd</sup> Annual Meeting of the Drug Information Association (DIA) in Philadelphia, PA (2006).

Module 2 section would fulfill the need for an ISS/ISE. In some cases, it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5.

Since the safety and efficacy of the Zydis<sup>®</sup> application will be principally supported by the Agency's previous findings for the reference listed drug, Reglan<sup>®</sup> for the same indications, the Sponsor is proposing the ISS and ISE be included in Module 2 (Clinical Overview and Summary) as part of the general discussion of metoclopramide use in both in symptomatic GERD and diabetic gastroparesis. Thus, these would not be in Module 5. Does the FDA agree with this approach?

**Response:**

**No. We recommend that the ISS and ISE be included in Module 5. Your Clinical Overview and Summary sections in Module 2 may refer extensively to the ISS/ISE so that duplication is minimized, but you should still provide a brief summary of your product's overall safety and efficacy profile in Module 2.**

**CLINICAL: CASE REPORT TABULATIONS (CRT) REQUIREMENTS FOR A 505(B)(2)**

**Question 10:** Per 21 CFR §314.50(f)(1) case report tabulations (CRT) are required for: ...data from each adequate and well-controlled study under §314.126 (Phase 2 and Phase 3 studies as described in §§312.21(b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in §312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. ...the applicant may delete those tabulations which the Agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness.

Since the safety and efficacy of the Zydis<sup>®</sup> application will be supported by the Agency's previous findings of safety and efficacy for Reglan<sup>®</sup> and the only study conducted by the Sponsor is a definitive BE study, the requirement for CRT may not apply. Does the FDA agree?

**Response:**

**Please submit CRTs with your application.**

**See Additional Regulatory Comments regarding reliance on the Agency's finding of safety and effectiveness for Reglan to support your proposed 505(b)(2) application.**

## CHEMISTRY & MANUFACTURING

**Question 11:** This pre-NDA meeting packet contains stability data through the 9-month time point for a 10 mg lot (# 413808; (b) (4)) manufactured at the Cardinal Health facility in February 2006. The data show a projected expiry period of (b) (4) for material stored at both 25°C/60% RH and 30°C/65% RH. The potency was also demonstrated to have a projected expiry period of approximately (b) (4) for material stored at 40°C/75% RH.

Plans are underway to complete production of two more 10 mg lots and a 5 mg lot in 2007. The NDA, tentatively set to be filed in mid-2007, would include 12-month stability data from a 10 mg lot at both 25°C/60% RH and 30°C/65% RH conditions as well as 6-month data at 40°C/75% RH. The other two 10 mg lots and a 5 mg lot would include at least 3-month data for both controlled room temperature and accelerated conditions. The rationale for this approach is that:

- The API and finished product (from present and previous formulations) have well-demonstrated stability at both controlled room temperature and under accelerated conditions.
- Stability updates will be submitted to the unapproved NDA so by the time the initial review cycle is complete there will be 9 to 12-month data on the two remaining 10 mg lots and the 5 mg lot.
- Stability data from a single 5 mg lot should be sufficient for registration purposes since the formulation is dose-proportional and there are no differences in container/closure systems or methods of manufacture. Thus, there are no plans to submit NDA stability for three 5 mg lots as is being done for the 10 mg strength.
- The 3-month accelerated data (for two 10 mg lots and a 5 mg lot) will allow projected expiry determinations out to 12 months; 6-month accelerated data will allow projected expiry determinations up to 24 months.
- The 12-month data (at controlled room temperature) for at least one 10 mg lot will provide crucial supporting data for the other lots with less long-term stability data.

Is this plan acceptable?

**Response:**

**Your proposal to provide 12 months of stability data for one 10 mg batch, three months of data for two additional 10 mg batches, and 3 months of data for one 5 mg batch at the time of NDA submission, and to supplement these data during the review cycle is generally acceptable. To determine expiration dating, we generally recommend that at least 12 months of room temperature and six months of accelerated stability data be provided for three batches of product at the time of submission. Please reference, *Guidance for Industry: Q1C Stability Testing for New Dosage Forms* (November 1996) (<http://www.fda.gov/cder/guidance/1319fnl.pdf>).**

**We request that any supplemental data be submitted as soon as possible to allow adequate time for review and adherence to the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* (<http://www.fda.gov/cder/guidance/5812fnl.htm>).**

**Additional data submitted within three months of the PDUFA date will likely result in a three month extension of the review clock. Expiration dating will be based on our evaluation of your originally submitted data and any supplemental data that is accepted for consideration.**

**We cannot comment on your projected expiry in the absence of actual data. Since the two tablet strengths are prepared from the same bulk solution, the limited data that you will be providing for the 5 mg tablet may be sufficient in conjunction with the data for the 10 mg tablets to allow for expiration dating of the 5 mg tablet. However, you should be aware that if the data reveal any significant differences in the stability of the two strengths, you will have insufficient data for assigning a reasonable expiry for the 5 mg product.**

**Question 12:** The NDA will be organized as a Common Technical Dossier (CTD). The section for API process development (Section 3.2.S.2.6) will be incorporated into the NDA by letter of authorization from (b) (4) to refer to their DMF (b) (4). Some process development data may need to be requested specifically from the API manufacturer in addition to the DMF files, but this should not pose a problem as (b) (4) (b) (4) has been a US-approved producer of metoclopramide HCl API for several years. Is this acceptable?

**Response:**

**Yes, this is acceptable. We request that for ease of review, information on Structure, General Properties, and Specifications be provided directly to the NDA.**

**Question 13:** With respect to production records, the NDA will contain "...the proposed or actual master production record, including a description of the equipment to be used for the manufacture of a commercial lot of drug product." in accordance with 21 CFR 314.54(a)(1)(i). With respect to executed batch records would the Agency prefer copies of all three 10 mg lots and the 5 mg lot or just records from a single 10 mg and 5 mg lot each?

**Response:**

**One representative executed batch record for each strength will be sufficient.**

**Additional Comments:**

- 1. Please provide assurance that all excipients are dissolved and/or evenly distributed throughout the bulk prior to dispensing into the blister wells. Perform in-process tests for wet dose weight and dry tablet weight to assure that the nozzle dispenses the correct amount of the solution into**

the wells and that the (b) (4) process is robust. Also provide in-process testing for hardness to assure tablet integrity after (b) (4). Keeping in mind the moisture sensitivity of the dosage form, perform seal integrity of blister pack as an in-process test.

2. You must include the debossing information in the drug product specifications for appearance.
3. A test should be added to the specifications to demonstrate that the tablets can be removed from the blisters without breakage.

## ADMINISTRATIVE & FORMAT

**Question 14:** The NDA format will be as a Common Technical Dossier (CTD) and may be provided in electronic form (eCTD) or a combination of paper and electronic. All sections of the CTD will be completed but the level of detail required for each section will either be not applicable; cross-referenced to the previous findings of safety and efficacy by FDA; cross-referenced to published reports; or detailed in the application. A CTD table of contents is provided in this pre-NDA meeting packet (see Appendix 2) that cross-references each section to the data that will be provided. However, the key components of each CTD module are as follows:

- Module 2 (CTD Summaries) will contain a summary of:
  - clinical experience in adults with Symptomatic Gastroesophageal Reflux and Diabetic Gastroparesis (Diabetic Gastric Stasis) from published reports. The purpose is to provide a current review of the uses and limits of metoclopramide in these patient populations that will satisfy the ISE and ISS requirements for filing.
  - pivotal BE study data and pilot BE study data comparing the Zydys<sup>®</sup> formulation to Reglan<sup>®</sup>
  - non-clinical summary based on published literature
  - CMC data
- Module 3 (Quality) will contain a brief summary of the API section (with cross-references to DMF (b) (4) for details). A complete section will be provided for finished product.
- Module 4 (Non-Clinical) will rely on the Agency's previous findings for the reference listed drug (RLD), Reglan<sup>®</sup> Tablets.
- Module 5 (Clinical) will contain the reports for Protocols NA-464 (pilot BE study) and Protocol 10643701 (pivotal BE study). Electronic files will be

provided for Protocol 10643701 as SAS Transport files (Version 5) formatted per SAS TS-140 (XPORT). A Readme file will define the layout for each of the following files.

- Rawdata.xpt
- KE.xpt
- PK.xpt
- Times.xpt

The remaining sections of Module 5 (for safety and efficacy reports supporting the application) will rely on the Agency's previous findings for the reference listed drug (RLD), Reglan<sup>®</sup> Tablets.

Based on the outline above and the detail provided in Appendix 2, we believe the overall content will satisfy both the requirements for filing an NDA as well as the critical body of data sufficient for initial filing and review. Is this acceptable?

**Response:**

- **Submission of data in .XPT format is acceptable. Please refer to "Study Data Specifications" guidance at the following website.  
<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>**
- **Please note that CTD stands for Common Technical Document. Please clarify whether your submission will be an electronic submission in CTD format, or whether you will have an .XML backbone file.**
- **Module 2: Non-clinical summary based on published literature: The application should include up to date information available in public domain.**
- **Module 4: (Non-Clinical) will rely on the Agency's previous findings for the reference listed drug (RLD), Reglan<sup>®</sup> Tablets: Module 4 should contain any new information, such as published literature. Please refer to the Pre-IND Meeting Minutes of November 4, 2004.**
- **Module 5: Please submit annotated CRF with a defined file to explain the data set. Please refer to the "Study Data Specifications" guidance to create the folder structure for storing the datasets.**

**Additional Clinical Pharmacology Comments:**

- **You conducted one pilot and one pivotal bioequivalence (BE) study with the proposed 10 mg ODT product using 10 mg Reglan conventional tablet as the RLD and mentioned that the proposed 10 mg ODT was found bioequivalent with the 10 mg Reglan tablet. However, the overall BE study design is not clear.**

More specifically, it is not clear whether proposed 10 mg ODT was taken with or without water.

- You proposed to use the language [REDACTED] (b) (4) [REDACTED] You commented that the language is comparable to the language in the Schwarz Pharma ODT labeling. The proposed labeling language should be supported by data generated from your product.
- Effect of food on metoclopramide is not mentioned in the Reglan tablet label. If food does affect bioavailability (BA) of metoclopramide, then you should conduct a food effect study on the ODT as per Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies (<http://www.fda.gov/cder/guidance/5194fnl.htm>). In that case, the ODT should be administered according to intended label use/instructions.

*Additional Discussion:*

*The Division reiterated that a cross-over food effect study would be beneficial for your product's review and label. You may conduct this study either in healthy normal volunteers or in patients.*

- The bioequivalence study was conducted only with the 10 mg ODT; however, you are seeking approval of both 5 mg and 10 mg strengths. You will need to request a biowaiver for the approval of 5 mg with required documentation.

**Additional Regulatory Comments:**

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, 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. You should establish a "bridge" (e.g., comparative 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 for which you have no right of reference 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/index.htm>. 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.

**On page 28 of the background materials provided in advance of this pre-NDA meeting, you stated: "The Zydys ... ODT application will contain a patent certification as outlined above for the RLD and may also include certification for the approved ODT formulation of metoclopramide (Schwartz Pharma) as well." We note that you will be required to certify to patents listed in the Orange Book for Reglan ODT (NDA 21-793), a pharmaceutical equivalent to your proposed Zydys ODT product. We further note that the annotated draft labeling for your proposed Zydys ODT product incorporates information from the Reglan ODT labeling regarding pregnancy and teratogenic effects and nursing mothers (see Appendix 1 of the background materials).**

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Fathia Gibril  
5/10/2007 11:11:53 AM

## MEMORANDUM OF TELECON

DATE: September 2, 2005

APPLICATION NUMBER: PIND 70,578

BETWEEN:

Name: Gene Haley, Chief Executive Officer  
Phone: (910) 509-0097  
Representing: Wilmington Pharmaceuticals, LLC

AND

Name: Susan Daugherty, Regulatory Project Manager  
Division of Gastroenterology Products (DGP), HFD-180

SUBJECT: Sponsor's correspondence dated August 4, 2005.

BACKGROUND: On November 4, 2004, a pre-IND meeting was held between representatives of Wilmington Pharmaceuticals and DGCDP to discuss the development plan for (b) (4) (metoclopramide) Orally Dissolving Tablets indicated for symptomatic gastroesophageal reflux, diabetic gastroparesis (diabetic gastric stasis), (b) (4). The sponsor intends to conduct bioequivalence studies with Reglan Tablets as the reference listed drug and submit a 505(b)(2) application.

On June 10, 2005, NDA 21-793 for Reglan (metoclopramide) Orally Disintegrating Tablets was approved. NDA 21-793 is a 505(b)(1) application that showed bioequivalence with NDA 17-854 Reglan (metoclopramide) Tablets and relied on the Agency's finding of safety and efficacy for NDA 17-854.

On August 4, 2005, received August 8, 2005, the sponsor submitted a general correspondence containing the following:

"As previously discussed at the Zydys Metoclopramide pre-IND meeting on November 4, 2004, we intend to file an NDA via the 505(b)(2) route and gain approval based on bioequivalence (BE) to the Reference Listed Drug (RLD), Reglan 10 mg oral tablets. The bioequivalence of our dosage form to the RLD was preliminarily established in a pilot study, NA464, which we discussed during our pre-IND meeting.

In preparation for the pivotal BE study and production of clinical supplies, we transferred our manufacturing to Cardinal Health's Swindon, UK facility and scaled up in order to use material representative of the commercial process. Based on current timing, we estimate clinical trial material should be available by early 2006. Thus, we anticipate filing an IND in the first quarter of 2006 to perform the pivotal BE study.

PIND 70,578  
T-con 9-2-05

However, these plans were made prior to the June 10, 2005 approval of the Schwarz Pharma NDA 21-793 for Reglan ODT and we would therefore like to confirm the following regarding the Zydys Metoclopramide program.

1. Our plan remains the same in that we will conduct the pivotal BE study comparing Zydys Metoclopramide ODT to the RLD, Reglan 10 mg oral tablets, not the Reglan ODT formulation. Thus, the NDA will be based on labeling stemming from the approved Reglan 10 mg oral tablets, not the Reglan ODT. Do you agree?
2. When we met in November 2004 and discussed our preclinical program requirements, you concurred that the existing body of preclinical data in the Reglan 10 mg oral tablet labeling would be sufficient and that there would not be any requirement to perform new preclinical studies as long as the products were demonstrated to be bioequivalent. However, the Reglan ODT labeling contains preclinical information not found in the Reglan tablets prescribing information. It is not clear that these additional data were (1) conducted by the Sponsor or collected from the public domain or were (2) a reflection of any bioequivalence issues in Reglan ODT compared to the RLD, Reglan tablets (10 mg). Regardless, we still do not anticipate any new preclinical studies for our program but would like to understand more about the context of those studies that were done in conjunction with the Reglan ODT formulation. Based on this input, we can evaluate similar components or key considerations that should be addressed in our NDA summaries of safety and efficacy.

Thus, can you confirm that the preclinical studies performed in conjunction with the Reglan ODT formulation are a reflection of BE issues rather than a safety consideration of the ODT dosage form, *per se*? If that is not the case, then could you further elaborate on any safety aspects of the ODT dosage formulation that prompted these additional studies?"

The purpose of today's call is to answer the questions posed by the sponsor.

THE CALL: I informed Mr. Haley that Reglan Tablets NDA 17-854 would still be the reference listed drug for their application. In addition, I informed Mr. Haley that the new preclinical data contained in the Reglan ODT label were the result of literature disclosures, and will be required in the Zydys (metoclopramide) Orally Disintegrating Tablets label. These data will eventually be added to the existing Reglan 10mg tablet label as well as the labels for the generic equivalents of the Reglan 10mg tablet.

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Susan Daugherty  
Regulatory Project Manager

## Dewey, Maureen

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**From:** Pincock, Laura  
**nt:** Monday, August 31, 2009 12:00 PM  
Korvick, Joyce A  
**Cc:** Dewey, Maureen; Everett, Kristen; Toyer, Denise P; Holquist, Carol A  
**Subject:** RE: proprietary name review for METOZOLV ODT

Hi Joyce,

Since we are not much over the 90 day timeframe for a re-review and given your wish to approve this week, DMEPA does not need to perform another pre-action review at this time.

Thank you for checking with us.

Regards,

-Laura

V/R,

Laura L. Pincock, R.Ph., Pharm.D.  
Commander, U. S. Public Health Service

ting Team Leader/Drug Safety Evaluator

(301-796-0522

\*laura.pincock@fda.hhs.gov

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**From:** Korvick, Joyce A  
**Sent:** Sunday, August 30, 2009 1:54 PM  
**To:** Pincock, Laura  
**Cc:** Dewey, Maureen; Everett, Kristen; Toyer, Denise P  
**Subject:** proprietary name review for METOZOLV!  
**Importance:** High

Hi Laura,

I was just reviewing all the documents in order to approve this drug this week, and the last proprietary name review I found was dated 5/4/2009. The standard sentence is that we can approve within 90 days .....

if I calculate this then 90 days was **August 4th!**

Can you help us with this again, as you see we are now entering the first week of September. You may have a more recent document? If not, please advise.