

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-246

CHEMISTRY REVIEW(S)



NDA 22-246

**Metozolv (metoclopramide hydrochloride)
Orally Disintegrating Tablets,
5 mg and 10 mg**

Wilmington Pharmaceuticals, Inc.

Division of Gastroenterology Products



Table of Contents

Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s).....	6
B. Description of How the Drug Product is Intended to be Used.....	6
C. Basis for Approvability or Not-Approval Recommendation.....	6
III. Administrative.....	6
A. Reviewer's Signature	7
B. Endorsement Block.....	7
C. CC Block.....	7
Chemistry Assessment	7
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	7
S. DRUG SUBSTANCE [Metoclopramide Hydrochloride (b) (4)]	7
P. DRUG PRODUCT [Metozolv, Orally Disintegrating Tablets (ODT)].....	7
A. APPENDICES	8
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	8
A. Labeling & Package Insert.....	8
III. List Of Deficiencies To Be Communicated: None.....	11



Chemistry Review Data Sheet

1. NDA 22-246
2. REVIEW #: 2
3. REVIEW DATE: 25-Aug-2009
4. REVIEWER: Marie Kowblansky, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	05-NOV-2007
Amendment (BC)	16-JUL-2008
Amendment (BC)	26-AUG-2008
Amendment (BC)	08-SEP-2008
Amendment (BZ)	09-OCT-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Complete Response	March 11, 2009
Amendment (BC)	April 16, 2009
Amendment (BZ)	June 16, 2009
Amendment (LC)	August 7, 2009
Amendment (LN)	August 14, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Wilmington Pharmaceuticals, Inc.
Address: 1213 Culbreth Drive, Suite 230
Wilmington, NC 28405
Representative: Eugene T. Haley, Chief Executive Officer
Telephone: (910) 509-0097

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Metozolv
- b. Non-Proprietary Name (USAN): metoclopramide hydrochloride
- c. Code Name/# (ONDQA only):

Chemistry Review Data Sheet

d. Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3 (new formulation)
- Submission Priority: S (standard)

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

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Tablets, orally disintegrating

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

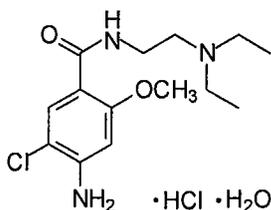
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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



CAS Name:	4-Amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxybenzamide
CAS Registry Number:	54143-57-6
Molecular Formula:	C ₁₄ H ₂₂ ClN ₃ O ₂ · HCl · H ₂ O
Molecular Weight:	354.27



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)	II	[REDACTED]	(b) (4)	1	Adequate	30-APR-2008 G.W .Holbert	LOA: 20-JAN-2006
(b)	III			1	Adequate	13-MAR-2001 C.M Bertha 7-SEP-2005 A.B. Shaw	LOA: 26-JAN-2006
(b)	IV			1	Adequate	16-MAY-2006 R.P. Frankewich	LOA: 10-OCT-2007

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION No.	DESCRIPTION
IND	70,578	Zydus® Orally Disintegrating Tablet, 5 & 10 mg

18 STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	07-FEB-2008	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
DMEPA	N/A		
Methods Validation	N/A per ONDQA policy		
EA	Categorical exclusion granted	31-JUL-2008	G.W. Holbert
Microbiology	N/A		



The Chemistry Review for NDA 22-246

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP. Labels and labeling have all the required CMC information. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

A description of the drug substance and product may be found in Review #1. The current review deals with CMC deficiencies that were noted in Review #1 and included in the CR letter that was issued February 26, 2009. These include 1) the submission of a post-approval stability protocol and commitment for the product, and 2) revision of packaging labels. Also, the sponsor has submitted additional stability data, with a request to extend the expiration dating period beyond the (b) (4) requested in the original submission. These data have been evaluated in the current review, with the conclusion that they support a 30-month expiration dating period for both product strengths, as requested by the sponsor.

B. Description of How the Drug Product is Intended to be Used

See Review #1

C. Basis for Approvability or Not-Approval Recommendation

The pending issues from Review #1 (as noted above) have been resolved with no remaining deficiencies.

III. Administrative



Chemistry Assessment Section

A. Reviewer's Signature

Signed electronically in DFS.

B. Endorsement Block

Marie Kowblansky, Ph.D., August 24, 2009
Moo-Jhong Rhee, Ph.D.

C. CC Block

(b) (4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS

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

/s/

MARIE KOWBLANSKY
08/24/2009

MOO JHONG RHEE
08/24/2009
Chief, Branch III

MEMO TO FILE

To: NDA 22-246 ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets

From: Marie Kowblansky, PhD

Through: Moo-Jhong Rhee, PhD, Branch Chief, ONDQA, DPAIL, Branch III

Date: 2/25/2009

Subject: Correction to final CMC Review

The final review of NDA 22-246 (placed into DFS on January 30, 2009) included four CMC deficiency comments that were to be included in the CR letter for the NDA. The following text was inadvertently included in deficiency # 2

The blister and carton label should be revised as follows:

*Metozolv ODT
(metoclopramide) Orally Disintegrating Tablets
XX mg**

**contains yy mg metoclopramide hydrochloride equivalent to xx mg metoclopramide*

Deficiency # 2 should be revised to read

The blister and carton label should be revised as follows:

*Metozolv ODT
(metoclopramide hydrochloride) Orally Disintegrating Tablets
XX mg**

**contains yy mg metoclopramide hydrochloride equivalent to xx mg metoclopramide*

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

/s/

Marie Kowblansky
2/25/2009 02:48:34 PM
CHEMIST

Moo-Jhong Rhee
2/25/2009 02:58:12 PM
CHEMIST
Chief, Branch III



NDA 22-246

**Metozolv (metoclopramide hydrochloride)
Orally Disintegrating Tablets,
5 mg and 10 mg**

Wilmington Pharmaceuticals, Inc.

**Gene W. Holbert, Ph.D.
Division of Gastroenterology Products**



Table of Contents

Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s).....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
III. Administrative.....	8
A. Reviewer’s Signature	8
B. Endorsement Block.....	8
C. CC Block.....	8
Chemistry Assessment.....	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE [Metoclopramide Hydrochloride (b) (4)	9
P DRUG PRODUCT [Metozolv, Orally Disintegrating Tablets (ODT)]	19
A APPENDICES	62
R REGIONAL INFORMATION	62
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	63
A. Labeling & Package Insert.....	63
B. Environmental Assessment Or Claim Of Categorical Exclusion	66
III. List Of Deficiencies To Be Communicated.....	66
Attachment.....	68



Chemistry Review Data Sheet

1. NDA 22-246
2. REVIEW #: 1
3. REVIEW DATE: 22-JAN-2009
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	05-NOV-2007
Amendment (BC)	16-JUL-2008
Amendment (BC)	26-AUG-2008
Amendment (BC)	08-SEP-2008
Amendment (BZ)	08-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Wilmington Pharmaceuticals, Inc.
Address: 1213 Culbreth Drive, Suite 230
Wilmington, NC 28405
Representative: Eugene T. Haley, Chief Executive Officer
Telephone: (910) 509-0097

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Metozolv
- b. Non-Proprietary Name (USAN): metoclopramide hydrochloride
- c. Code Name/# (ONDQA only):
- d. Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3 (new formulation)
 - Submission Priority: S (standard)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Tablets, orally disintegrating

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

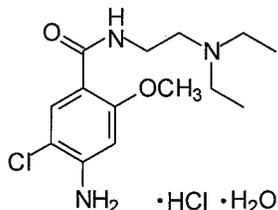
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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



CAS Name: 4-Amino-5-chloro-*N*-[(2-diethylamino)ethyl]-
2-methoxybenzamide
CAS Registry Number: 54143-57-6
Molecular Formula: C₁₄H₂₂ClN₃O₂ · HCl · H₂O
Molecular Weight: 354.27



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)	II	[REDACTED]	(b) (4)	1	Adequate	30-APR-2008 G.W. Holbert	LOA: 20-JAN-2006
(b)	III			1	Adequate	13-MAR-2001 C.M Bertha 7-SEP-2005 A.B. Shaw	LOA: 26-JAN-2006
(b)	IV			1	Adequate	16-MAY-2006 R.P. Frankewich	LOA: 10-OCT-2007

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION No.	DESCRIPTION
IND	70,578	Zydus® Orally Disintegrating Tablet, 5 & 10 mg

18 STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	07-FEB-2008	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
DMEPA	N/A		
Methods Validation	Not required		
EA	Categorical exclusion granted	31-JUL-2008	G.W. Holbert
Microbiology	N/A		



The Chemistry Review for NDA 22-246

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product except for the post approval stability commitment. All facilities involved are in compliance with cGMP. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until the pending issues are resolved.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Metozolv (metoclopramide hydrochloride) Orally Disintegrating Tablets are white to off-white freeze dried tablets debossed with “5” or “10” to denote the strength of the tablet. Each tablet contains 5 mg or 10 mg of metoclopramide hydrochloride as the free base. Inactive ingredients include gelatin, mannitol, acesulfame potassium and mint flavor. With the exception of the flavoring, all excipients are compendial. The flavoring is composed of ingredients that are compendial and/or GRAS.

The product is packaged in aluminum blisters with peelable blister lidding. Each blister strip contains ten tablets which are packaged in cardboard cartons. Each carton contains 100 tablets.

Metozolv Orally Disintegrating Tablets are manufactured by Catalent Pharma Solutions (formerly Cardinal Health UK), Swindon, UK for Salix Pharmaceuticals Inc., Morrisville, NC. The manufacturing process consists of (b) (4)

The drug product specification includes tests for Appearance, Identification, Assay, Uniformity of Dosage Units by Content Uniformity, Dissolution Disintegration Time, Water Content, Related Substances, Microbial Purity and Absence of Pathogens.

Executive Summary Section

The application contains 12 months of long term stability data on three registration batches of 10 mg tablets and one batch of 5 mg tablets manufactured by Catalent. This is supported by 24 months of data on a fourth batch. There were no significant changes in any of the lots stored at the long term or intermediate condition. Some of the tablets stored under accelerated conditions had shrunk and failed dissolution.

The applicant's request for a waiver of *in vivo* bioavailability studies for the 5 mg strength is granted under the provisions of 21 CFR 320.22(d)(2).

The applicant has proposed a (b) (4) expiration dating period when stored at 20-25°C (68-77°F) and protected from freezing. Considering that there were no stability failures at the long term or intermediate condition and that the applicant has performed statistical analyses which predicted an expiration dating period of at least (b) (4) and that there is 24 month data available on one batch, a (b) (4) expiration dating period is acceptable.

The active drug substance is Metoclopramide Hydrochloride USP. Metoclopramide hydrochloride is a white or almost white crystalline solid melting at 183°C. It is freely soluble in water. There are no asymmetric centers. The drug substance is manufactured by (b) (4). The manufacturing process is described in Type II DMF (b)

B. Description of How the Drug Product is Intended to be Used

METOZOLV Orally Disintegrating Tablets are a dopamine antagonist drug indicated for:

- Relief of Symptomatic Gastroesophageal Reflux: short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.
- Diabetic Gastroparesis (Diabetic Gastric Stasis): the relief of symptoms associated with acute and recurrent diabetic gastroparesis (gastric stasis).
- Gastroesophageal Reflux Disease (GERD): 10 mg to 15 mg dose up to four times daily at least 30 minutes before eating and at bedtime. Therapy should not exceed 12 weeks in duration.
- Diabetic Gastroparesis (Diabetic Gastric Stasis): 10 mg dose four times daily at least 30 minutes before eating and at bedtime for two to eight weeks. Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to

**Executive Summary Section**

assure identity, strength, purity and quality of the drug product during the expiration dating period. However, post approval stability commitment is not acceptable and should be revised in the next review cycle. The Office of Compliance has issued an "Acceptable" overall recommendation for all the facilities involved. However, package labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until these pending issues are resolved.

III. Administrative**A. Reviewer's Signature**

Signed electronically in DFS.

B. Endorsement Block

Gene W. Holbert, Ph.D. 21-JAN-2009
Moo-Jhong Rhee, Ph.D.

C. CC Block

62 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

/s/

Gene Holbert
1/30/2009 10:53:38 AM
CHEMIST

Moo-Jhong Rhee
1/30/2009 12:15:29 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 22-246
Applicant: Wilmington Pharmaceuticals
Stamp Date: 11/6/2007
Received by PAL: 11/14/2007
Review Date: 11/30/2007
PDUFA Date: 09/06/2008
Filing Meeting: 12/20/2007
Proposed Trademark: To be determined
Established Name: metoclopramide hydrochloride
Dosage Form: Orally Disintegrating Tablets
Route of Administration: oral
Indication: gastroesophageal reflux and diabetic gastroparesis

P.A.L.: Marie Kowblansky, PhD

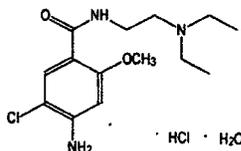
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

A. Summary

Metoclopramide Hydrochloride Orally Disintegrating Tablets (ODT) is intended for treatment of gastroesophageal reflux or diabetic gastroparesis, with a recommendation to administer one tablet up to four times daily. The tablets are manufactured in two strengths: 5mg or 10mg of metoclopramide (added as the hydrochloride salt), using Catalent Pharma's Zydys® Fast-Dissolve proprietary technology, where the tablets are formed in-situ in the blister package. This technology is used in a number of currently approved products including Zofran, Zyprexa, Claritin, Pepside, and others. The current drug product was studied under IND 70,578, and is being filed as a 505(b)(2) application using Reglan® (metoclopramide) Tablets (NDA 17-854) as the reference listed drug. Since this product is a new formulation of a currently approved drug, this is classified as a Type 3 application in the Chemical Classification Code.

Drug Substance

The active drug substance, which will be manufactured by [REDACTED] (b) (4), is metoclopramide hydrochloride, USP



The drug substance is freely soluble in water, with solubility decreasing with increasing pH as it is converted to the free base. Only limited chemistry, manufacturing, and controls information

regarding this drug substance is provided in the submission; reference is made to (b) (4) for complete CMC information. The proposed registration specification for the drug substance will require testing for identification (IR and colorimetric), water content (b) (4) residue on ignition (b) (4) residual solvents (b) (4) chromatographic purity by TLC (no single impurity will exceed (b) (4)), and titrimetric assay (b) (4). This specification is in complete conformance with the USP monograph for metoclopramide hydrochloride (but USP requires 101% as the upper assay limit, (b) (4)). Although no specific impurities are identified in the USP monograph, the structures of six potential impurities are identified in the submission.

The (b) (4) specification for the drug substance is more extensive than the USP specification proposed above. In addition to the above tests and acceptance criteria, (b) (4) has other requirements, including acceptance criteria for particle size, HPLC testing for related substances (with limits of no more than (b) (4) for each of the identified impurities and a limit of (b) (4) for unidentified impurities), and a less liberal limit of (b) (4), but the assay method for the drug substance remains a titrimetric method. The tabulated data for four batches of drug substance from (b) (4), however, only include impurities determined by TLC and no particle size data.

Yet another specification for the drug substance is required by Catalent (the product manufacturer). This specification incorporates all the USP requirements with additional testing for pH, chlorides, heavy metals, and solubility.

Drug Product

The finished drug product is a freeze-dried tablet containing 5mg or 10mg of metoclopramide. The tablets are debossed on one side with "5" or "10" to reflect the metoclopramide content. The two tablet formulations are "dose-proportional", that is, the relative proportions of all the components are identical in the two tablets, with the final weight of the 5 and 10 mg tablets respectively being 19.2 and 38.5 mg.

Ingredient	Function	Amount,% (w/w)
Metoclopramide (as the monohydrate HCl salt) USP ²	Active ingredient	(b) (4)
Sodium chloride ¹		(b) (4)
Gelatin NF		
Mannitol USP		
Mint Flavor (b) (4)		
Acesulfame potassium NF		
(b) (4)		
Sodium hydroxide NF		

(b) (4)

All inactive components are compendial with the exception of mint flavor, but the applicant states that this flavor has been commonly used in food, confectionery, and pharmaceutical applications (including other Zydys®-based products). Specifications for this component are provided.

Formulation changes during process development included (b) (4)

The pivotal BE studies to which the applicant refers are comparisons of the commercial Zydys-metoclopramide formulation with Reglan tablets, the reference listed drug.

The manufacturing process involves (b) (4),

According to the applicant, the key tablet properties are appearance, disintegration time, and tablet strength, which are primarily determined by the properties of the bulk suspension. Consequently, the formulation changes discussed above were introduced to optimize suspension properties.

The product will conform to the following specification:

Test	Method #	Specification
Appearance	AM253	(b) (4)
Identification (HPLC)	AM621	
Assay	AM621	
Uniformity of Dosage Units: Content Uniformity	AM621 (USP <905>)	
Dissolution	AM670	
Disintegration Time	AM059 (USP <701>)	
Water Content	AM677 (USP <921>)	
Related Substances	AM621	
Microbiological Purity	AM430 (USP <61>)	
Absence of Pathogens	AM431 (USP <61>)	

NMT – Not more than

CFU – Colony forming units

While the drug substance is assayed by a non-specific titration method, the determination of metoclopramide and related substances content in the drug product utilizes a stability indicating HPLC method. With a total daily dose of (b) (4), the ICH threshold for drug product impurities is (b) (4) for reporting impurities, (b) (4) for identification, and (b) (4) for qualification. To date, no peaks greater than (b) (4) have been observed in samples on stability testing. Consequently, the proposed impurity acceptance criteria are acceptable.

The proposed (b) (4) disintegration time, although higher than observed in the drug product batch data, is in accord with recommendations in FDA's Draft guidance (2007) for Orally Disintegrating Tablets and consequently considered acceptable. The test is performed using the USP Disintegration method <701> with small modification due to the buoyancy of the tablet.

The applicant proposes (b) (4) expiry for both tablet strengths, providing 12 months of room temperature stability data and six months of accelerated stability data for one lot of the 10 mg tablet, and three months of room temperature- and accelerated stability data for an additional three lots of 10 mg tablets and for one lot of 5 mg tablets. Additional data will be submitted during the review cycle. On evaluation of the limited data that have been submitted thus far, no trends indicative of product instability are noted.

Wilmington Pharmaceuticals claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of metoclopramide at the point of entry into the aquatic environment will be below 1 part per billion.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

While the name Zydys® (metoclopramide) Orally Disintegrating Tablets is used throughout the submission, this clearly is not suitable as Zydys refers to the technology used in manufacturing the product. This is a temporary name until a final name is provided. When the final name is submitted it will need to be evaluated for conformance to FDA requirements.

B. Critical issues for review

Based on this initial assessment, the following issues will need closer scrutiny:

Regarding the drug substance

---The applicant proposes multiple specifications for the drug substance, one specification (the registration specification) showing conformance to USP requirements, one used by the drug substance manufacturer (b) (4) and one used by the drug product manufacturer. This reviewer favors the use of the more restrictive (b) (4) specification as the registration specification, since the USP specification relies on an antiquated non-specific titration method for assay and a TLC assay for quantitating impurities. In addition, the product batches presented in this application used drug substance that conformed to the (b) (4) specification; future changes of drug substance suppliers, who may have less stringent specifications than (b) (4), may lead to a product with unacceptable properties.

The applicant claims that particle size is not a critical attribute for this product. However, since the manufacturing process involves (b) (4) metoclopramide, one would expect that the particle size of metoclopramide would have an effect (b) (4). A determination should be made if data to support the applicant's claim have been provided in the submission. This determination should take into consideration the (b) (4) specification which includes acceptance criteria for particle size.

Regarding the Drug Product

-- Since orally disintegrating tablets are very fragile, it may be appropriate to add a test for hardness, either to the final specification or as an in-process test, to ensure that tablets can be removed from the package without breakage. Consideration should be given to this proposal.

-- If mint flavor cannot be found in the inactive ingredients data base, it may be necessary to consult with the toxicology reviewer to determine if this non-compendial excipient is considered safe. Also, a determination will need to be made whether the specifications for this excipient provide adequate control to ensure acceptable performance and safety.

-- The applicant has provided very limited stability data. At a meeting with FDA (April 2007) the applicant was advised that stability data for only one batch of the 5 mg tablet would be sufficient in view of the dose proportionality of the 10mg and 5mg tablets. However, FDA cautioned that should any divergence between the stability trends of the 10mg and 5 mg tablets be observed in the data, stability data for two additional 5mg batches would be required. Additionally, the applicant was discouraged at the meeting from providing less than 12 months of stability data at the time of NDA submission, with an explanation that additional data received during the review cycle may or may not be considered in assigning expiration; that would depend on when the data were received.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

12/14/2007
Date

Moo-Jhong Rhee, PhD
Branch Chief

12/14/2007
Date

Manufacturing Sites

Name & Address	Operations	Drug Establishment Registration Number	Contact	Ready for Pre-Approval Inspection (PAI)
(b) (4)				Yes
<p>Catalent Pharma Solutions (formerly Cardinal Health UK 416 Ltd) Frankland Road Blagrove Swindon, SN5 8RU UK</p>	<p>Drug product manufacture Primary packaging Quality Control testing of incoming materials and drug product Stability storage & testing</p>	<p>FEI # FCUK729 3003812585 CFN # 62938</p>	<p>Site: Mr. Andrew Tapper Head of Quality Telephone: + 44 (0) 1793 548200 e-mail: andy.tapper@catalent.com US agent: Mrs Mary Foster VP Regulatory Compliance Catalent Pharma Solutions Inc. Telephone: 215 613 3526 e-mail: mary.foster@catalent.com</p>	Yes
<p>Catalent UK Packaging Limited (formerly Cardinal Health UK 417 Limited) Sedge Close, Headways, Great Oakley, Corby, Northants, NN18 8HS UK</p>	<p>Secondary packaging of finished product</p>	<p>FEI # pending CFN # pending</p>	<p>Site: Dave Waddington Director QA and Regulatory Direct telephone: +44 (0)1536 424302 Mobile: +44 (0)7786 164885 Fax: +44 (0) 1536 461011 e-mail: dave.waddington@catalent.com US agent: Mrs Mary Foster VP Regulatory Compliance Catalent Pharma Solutions Inc. Telephone: 215 613 3526 e-mail: mary.foster@catalent.com</p>	Yes
<p>Catalent Packaging Services 3001 Red Lion Road Philadelphia, PA 19114</p>	<p>Secondary packaging of finished product</p>	<p>FEI # 2530802 /1000522077/ 3004900127 Labeler code # 11014</p>	<p>Site: Mr. Gregory Lane Director QA Direct telephone: 215-613-3178 Mobile: 267 325 2283 Fax: 215 613 3127 e-mail: gregory.lane@catalent.com</p>	Yes
(b) (4)				Yes

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

/s/

Marie Kowblansky
12/14/2007 02:07:38 PM
CHEMIST

Moo-Jhong Rhee
12/14/2007 02:19:08 PM
CHEMIST
Chief, Branch III