CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200732Orig1s000

CHEMISTRY REVIEW(S)

NDA 200-732

Zidovudine Tablets USP, 100 mg

Matrix Laboratories Limited

Maotang Zhou, Ph.D.

Division of Pre-Marketing Assessment II

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-732

2. REVIEW #1

3. REVIEW DATE: 31-Jan-2011

4. REVIEWER: Maotang Zhou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	23-Apr-2010
Telephone Amendment	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	23-Apr-2010
Telephone Amendment	

7. NAME & ADDRESS OF APPLICANT:

Matrix Laboratories Limited
1-1-151/1, 4th Floor
Sairam, Towers, Alexander Road
Secunderabad -500 003
Andhra Pradesh (AP)
India

Keith Giunta, Associate Director
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road, PO Box 4310
Morgantown, WV 26504-4310
Tel: 304-554-5899
Fax: 304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Zidovudine Tablets, USP

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject NDA [Type 505(b)(2)] is the reference listed drug, Retrovir® (Zidovudine) Tablets, 300 mg approved under NDA # 20-518, Retrovir® (Zidovudine) Capsules, 100 mg approved under NDA #19-655 and Retrovir® (Zidovudine) oral syrup 50 mg/mL approved under NDA #20-518 of GlaxoSmithKline (now VIIV Healthcare). The applicant has provided a Paragraph III certification and exclusivity statement. This NDA was filed to support the PEPFAR program.

10. PHARMACOLOGICAL CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

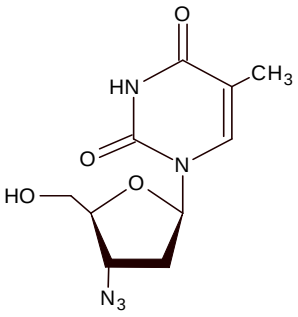
12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

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

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
3'-Azido-3'-deoxythymidine
$C_{10}H_{13}N_5O_4$
MW: 267.24



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENT
17751	II	Matrix	Zidovudine	3	Adequate	6/22/2010	Alan Fenselau
(b) (4)	IV		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	---	---
EES	Overall Acceptable	12/8/2010	E Johnson
Methods Validation	N/A	---	---
Labeling	Acceptable	1/31/2011	M. Zhou
Bioequivalence	Biowaiver Acceptable	8/2/2010	J. Duan
EA	Categorical Exclusion	1/31/2011	M. Zhou
Radiopharmaceutical	N/A	---	---

19. ORDER OF REVIEW

This NDA was submitted to the PEPFAR program and was granted standard review.

The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient/adequate information to assure identity, strength, purity, and quality of the drug product from the CMC perspective. An "Acceptable" site recommendation from the Office of Compliance has been made. The labels have adequate information as required. 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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Zidovudine (AZT) is a nucleoside reverse transcriptase inhibitor (NRTI) for treatment of human immunodeficiency virus (HIV). Zidovudine was the first drug to be approved for treatment of HIV infection. FDA approval of zidovudine was granted in 1987 for advanced HIV disease in adults and in 1990 for pediatric use. The brand name Zidovudine (Retrovir) was manufactured by GSK.

The chemical name of Zidovudine is 3'-azido-3'-deoxythymidine (AZT, azidothymidine). Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

The drug substance (Zidovudine, USP) is manufactured by Matrix Laboratories Limited, India (Matrix, India) at its (b) (4) facility. A copy of DMF (#17751) letter of authorization is provided in the NDA. The LOA lists Matrix Laboratories Limited as the manufacturer/DMF holder and (b) (4) The DMF has been reviewed on 6/24/2010 by Dr. Allan Fenselau and was found adequate. As of the date of this review, no additional updates or amendments have submitted to the DMF.

Drug Product

Zidovudine USP Tablets, 100 mg are white to off-white round, biconvex film-coated tablets debossed with "M" above and "55" below the score line on one side and plain on the other side. The single score line allows the tablet to be split into two equal halves for certain dosage requirements. The applicant has provided data to establish the breakability of the scored tablets including content uniformity of the split half tablets. The drug product is supplied in HDPE bottles of 60 tablets. The recommended

storage condition is 25 °C, excursions permitted to 15-30 °C. The current expiration dating period is 24 months.

The applicant's ANDA #78-922 for its adult strength, Zidovudine Tablets, 300 mg, has previously been reviewed and was tentatively approved by OGD. The applicant's pediatric strength Zidovudine Tablets, 100 mg, which are the subject of this NDA, have been developed from the adult-strength tablets by scaling down dose proportionately and performing dissolution profile mapping of the lower strength tablets with the higher strength tablets. The dissolution profiles which support the biowaiver for the pediatric strength tablets have been reviewed by Dr. John Duan of QNDQA Biopharmaceutics Review Team, ONDQA and found acceptable.

The drug product is a film-coated tablet containing 100 mg Zidovudine. Inactive ingredients include microcrystalline cellulose, sodium starch glycolate, magnesium stearate, (b) (4), Polyethylene Glycol (b) (4), and (b) (4). All excipients are compendial and are the same as those used in the adult-strength tablets (300 mg).

The drug product will be manufactured, tested, and packaged by Matrix Laboratories Ltd., Maharashtra, India. An Overall Recommendation of Acceptable has by made by Office of Compliance. The manufacturing process and controls are adequately described in submission.

Acceptable specifications for appearance, identity, dissolution, content uniformity, related compounds, assay, loss on drying, and residual solvents are provided and justified. The analytical procedures are adequately described. The current USP methods are employed in most of the drug product testing. Satisfactory batch analyses are provided for three drug product batches.

The drug product is packaged in white HDPE bottles containing 60 tablets. Each bottle is closed with a induction sealing liner and a white (b) (4) screw cap. While a non-child resistant closure is used for the drug product marketed outside the US, (b) (4) will be used if drug product is to be marketed in the US.

At the time of submission, the applicant provided 12 months long term (30°C/75% RH) and 6 months accelerated (40°C/75% RH) stability data. The long-term studies will be continued for 24 months, and may be continued for 60 months if an extension of shelf life is to be requested. The stability samples are tested for description, assay, dissolution, LOD, and related substances. The acceptance criteria are in compliance with the current version of USP. All testing results are shown to be within the specifications and no obvious trends are observed. Based on the stability data, an expiration dating period of 24 months when stored at 25°C is acceptable. Long term stability data on the (b) (4) are provided to support the commercial bulk holding time of (b) (4)

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

Zidovudine in combination with other antiretroviral agents is indicated for the treatment of AIDS.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The sponsor has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have "Acceptable" site recommendations on December 8, 2010.

All labels have the required information.

Although the applicant has stated that they do not intend to market this product in the US, this product will receive approval (rather than tentative approval) because the patents for zidovudine have expired.

III. Administrative

A. Reviewer's Signature
Maotang Zhou, Ph.D., Review Chemist

B. Endorsement Block
Stephen P. Miller, Ph.D., Acting Branch Chief

C. CC Block

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

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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.

/s/

MAOTANG ZHOU
01/31/2011

STEPHEN P MILLER
01/31/2011
I concur - this NDA is recommended for approval from the CMC perspective.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 200-732 **Supplement Number and Type:** **Established/Proper Name: Zidovudine tablets 100 mg**

Applicant: Matrix **Letter Date: 22-Apr-2010** **Stamp Date: 23-Apr-2010**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			DMF 17751has been referenced for the API and a LOA has been provided.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			
14.	Does the section contain information regarding the characterization of the DS?			
15.	Does the section contain controls for the DS?			
16.	Has stability data and analysis been provided for the drug substance?			
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		The 100 mg formulation is a dose proportional scale-down version formulation of the approved adult dose of Zidovudine tablets USP, 300mg, ANDA 78-922.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		Method validation performed for the adult dose is extended to the 100 mg formulation and hence validation has been performed only on system suitability, precision and accuracy. Report MVR-ZDVT-AY-001 (used for adult dose) has been referenced for other parameters.
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			NA
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			NA

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		

DMF #*	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
17751	II	Matrix Laboratories Ltd.	Zidovudine USP	11-26-09	
(b) (4)					

* (b) (4)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		There is no proposal to use cartons.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			A recommendation to use cartons will be made. No other review issues have been identified at this time.

{See appended electronic signature page}

Balajee Shanmugam
(Acting) Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

{See appended electronic signature page}

Stephen Miller
Branch Chief Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200732	ORIG-1	MATRIX LABORATORIES LTD	Zidovudine 100mg tablets

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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.

/s/

BALAJEE SHANMUGAM
06/04/2010
FilingReviewN200732

STEPHEN P MILLER
06/24/2010