CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40265

CORRESPONDENCE

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

July 30, 1997

RE: Methotrexate Sodium Injection (Preservative-Free), equivalent to Methotrexate, 25 mg/mL
ANDA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application (ANDA), in duplicate, for Methotrexate Sodium Injection (Preservative-Free), equivalent to Methotrexate, 25 mg/mL. This product is indicated in the treatment of various neoplastic diseases as well as the treatment of severe psoriasis.

This ANDA is being filed by Bigmar, Inc., a start-up pharmaceutical company with headquarters in the Columbus, Ohio area. The subject drug product is produced by Bigmar Pharmaceuticals SA, a Swiss division of Bigmar, Inc.

An analytical methods validation package, which includes three (3) additional copies of non-compendial assay procedures and their corresponding validation studies, is provided under separate cover.

Standard operating procedures (SOPs) are provided throughout this application as an aid in the review process. Revisions may be made to these SOPs after appropriate in-house review and approval. Changes which influence the manufacture of Methotrexate Sodium Injection (Preservative-Free), equivalent to Methotrexate, 25 mg/mL will be reported to the agency per the criteria established under CFR 314.70. A number of the SOPs provided in this application are written in Italian, the language spoken at Bigmar's Swiss manufacturing facility. English translations of those procedures immediately follow the corresponding Italian version.

In accordance with 21 CFR 314.94 (d)(5), we certify that a true field copy has been sent to our FDA district office in Cincinnati, Ohio. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions or comments concerning this application, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly
Manager, Regulatory Affairs

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

November 3, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

Re: ANDA 40-265
Methotrexate Sodium Injection USP, 25 mg (base)/mL (preservative free)
Gratuitous Amendment

Dear Sir or Madam,

The purpose of this correspondence is to amend the above referenced abbreviated application. Specifically, we wish to revise an exhibit batch stability data table provided on page 1805 of the original application. A minor transcription error was identified during an audit of the exhibit batch stability records. The error was limited to a single data entry.

A 3 month assay value for the exhibit batch sample stored at 40°±2°C was erroneously reported as %. The correct value is %. A corrected data table is provided as an attachment to this amendment. The revision does not affect the stability profile of the exhibit batch, or the requested product expiry period of 24 months.

The accuracy of transcribed stability data is now independently verified and acknowledged on the respective stability data tables. This practice, which was not in place at the time of ANDA submission, is expected to reduce the likelihood of such occurrences.

In accordance with 21 CFR Part 314.96(b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (614) 966-5800.

November 3, 1997

Sincerely,

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

September 17, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

NDA ORIG AMENDMENT

Re: ANDA 40-265
Methotrexate Sodium Injection USP, 25 mg (base)/mL (preservative free)
Gratuitous Amendment

Dear Sir or Madam,

The purpose of this correspondence is to amend the above referenced abbreviated new drug application. Specifically, we wish to provide additional information regarding the status of the laboratory facility located in Johnstown, Ohio.

Bigmar, Inc., 9711 Sportsman Club Road, Columbus, Ohio, 43031, was to be added as an analytical laboratory site on September 01, 1997, as noted on page 0335 of the original application (see Attachment A). Delays in the scheduled arrival of analytical equipment, caused by the recent United Parcel Service strike, requires the commissioning date to be deferred until October 15, 1997. The document entitled, "Location of Facilities," has been revised to accommodate the new start date. A copy of this document is provided under Attachment B.

In accordance with 21 CFR Part 314.96(b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

December 20, 1997

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

Re: ANDA 40-265
Methotrexate Sodium Injection USP, 25 mg (base)/mL (preservative free)
Gratuitous Amendment

Dear Sir or Madam,

The purpose of this correspondence is to amend the above referenced abbreviated application. Specifically, we wish to provide the following information which may aid in the review process:

A. Chemistry

B. Sterility Assurance

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

C. Labeling

1. *Revised Package Insert*

Revisions to Bigmar's package insert for Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preservative-Free) were made subsequent to the submission of the original ANDA. The

revisions have been incorporated into Bigmar's proposed labeling. Four copies of the draft labeling of the revised package insert and its corresponding side-by-side differences to the reference listed drug product are provided under Attachments C.1.a. and C.1.b, respectively.

D. Acknowledgments

1. *Future Submission Content*

In recent unrelated applications, the agency has asked that Bigmar refer to Policy and Procedure Guide #30-91, section 3(D) and #41-95, section 3(B)(6) for guidance on ANDA tabulation and the establishment of a batch record summary table in future submissions. Bigmar shall incorporate these sections in future submissions.

In accordance with 21 CFR Part 314.96(b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

NDA ORIG AMENDMENT
N/A

June 11, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 113
Rockville, MD 20855

RECEIVED
JUN 12 1998
GENERIC DRUGS

Re: ANDA 40-265
Methotrexate Injection, 25 mg/mL (preservative free)
Gratuitous Amendment

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced abbreviated new drug application (ANDA). Specifically, we wish to provide the following additional information, which may aid in the review process:

1. Dimethicone Certificate of Analysis (COA)

As noted in Bigmar's Major Amendment response, dated February 16, 1998 (page 026), the supplier of the silicone lubricant is Certificate of Analysis (COA) was included as part of the amendment. The COA did not include results for all NF 18 testing. Those results have since been provided and are enclosed under Attachment A 1.

The test results support the earlier claim that utilized to lubricate the elastomeric closures supplied to Bigmar by the meets the NF 18 monograph for Dimethicone.

2. Addition of Upright Testing to the Stability Protocol

Bigmar has committed to store and test production lots placed into the stability program in the inverted and upright positions. That commitment along with revised stability protocols and "Sampling Instructions" documents were provided as part of the Major Amendment response, dated February 16, 1998.

The "Stability Program / Policy " SOP has been revised to reference testing of samples stored in the upright position. The revised document replaces the SOP found on pages 1818 – 1822 of the original application and is located under Attachment A. 2.

In accordance with 21 CFR Part 314.96 (b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (740) 966-5800.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

May 29, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 113
Rockville, MD 20855

Re: ANDA 40-265
Methotrexate Injection, 25mg/mL (preservative free)
Gratuitous Microbiology Amendment

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced abbreviated new drug application (ANDA). Specifically, we wish to provide additional information, which may aid in the review process.

Bigmar Inc. has received directives following the Agency's Microbiology review of ANDA 40-258. Relevant questions and observations have been applied to the above referenced ANDA. Each observation and its corresponding response are enclosed.

In accordance with 21 CFR Part 314.96 (b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (740) 966-5800.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Bigmar Inc.

711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

February 16, 1998

ORIG AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

Re: ANDA 40-265
Methotrexate Injection USP, 25 mg/mL (preservative free)
Major Amendment

Dear Sir or Madam,

The purpose of this correspondence is to amend the above referenced application in response to a deficiency letter dated January 29, 1998. The letter indicated that our response should be submitted as a **major amendment**.

To facilitate the review, each observation and corresponding response is provided as an attachment to this amendment. Necessary supportive documentation is also provided for each response.

As requested, side-by-side comparison of the previously submitted labeling and current revised labeling (annotated and explained) is included in this amendment response. In addition, twelve (12) copies of final printed labeling and four (4) copies of draft insert labeling are also included.

In accordance with 21 CFR Part 314.96(b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

We believe that this correspondence provides a thorough response to the above referenced letter dated January 29, 1998. If you have any questions regarding this correspondence, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures

RECEIVED
GENERIC DRUGS

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

February 9, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

ORIG AMENDMENT

Re: ANDA 40-265
Methotrexate Injection USP, 25 mg/mL (preservative free)
Additional Correspondence

Dear Sir or Madam,

The purpose of this correspondence is to amend the above referenced abbreviated new drug application (ANDA) as requested by the Cincinnati District Office of the Food and Drug Administration. In a letter dated February 2, 1998, the District Office asked that Bigmar Incorporated identify the specific tests which may be performed at the laboratory facilities referenced in a series of pending ANDAs. The above referenced application was included in that list.

The District Office indicated that this information must be included within the ANDA before approval of the Bigmar Incorporated laboratory facility, located in Johnstown, Ohio, would be recommended.

The requested clarification is provided as an attachment to this correspondence. The documentation identifies the specific tests which may be performed at the testing facilities already listed in the application. No new facilities have been referenced.

In accordance with 21 CFR Part 314.96(b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures

RECEIVED
FEB 10 1998
GENERIC DRUGS

Pharmaceuticals Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

September 16, 1998

FPL
NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 40-265
Methotrexate Injection USP (non-preserved)
25 mg/mL (2mL, 4mL, 8mL and 10mL fill volumes)
Facsimile Amendment Response to Chemistry, Microbiology and Labeling Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated August 19, 1998. The Agency indicated that Bigmar's response should be submitted as a facsimile amendment.

To facilitate your review, each observation and corresponding response is provided as an attachment to this amendment. Necessary supportive documentation is also provided for each response.

In accordance with 21 CFR Part 314.96(b), Bigmar Inc. certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

We believe this amendment provides a thorough response to the Agency's letter dated August 19, 1998. Please contact me at the above address or at (740) 966-5800 if you have any questions regarding this correspondence.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

RECEIVED
SEP 18 1998
GENERIC DRUGS

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

November 20, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FA

RE: ANDA 40-265
Methotrexate Injection USP (non-preserved) 25mg/mL
Facsimile Amendment Response to Microbiology and Chemistry Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated October 23, 1998. The Agency indicated that Bigmar's response should be submitted as a facsimile amendment.

To facilitate your review, each observation and corresponding response is provided as an attachment to this amendment. Necessary supportive documentation is also provided for each response.

In accordance with 21 CFR, Part 314.96(b), Bigmar, Inc, certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

We believe this amendment provides a thorough response to the Agency's letter dated October 23, 1998. Please contact me at the above address or at (740) 966-5800 if you have any questions or comments concerning this amendment.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

November 25, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] AMENDMENT
N/FA

RE: ANDA 40-265
Methotrexate Injection USP (non-preserved) 25mg/mL
Response to Labeling Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to provide revised product labeling in response to Agency comments received via facsimile on November 4, 1998.

The revised labeling, including a side-by-side comparison to Bigmar's last labeling submission is provided as an attachment to this correspondence.

In accordance with 21 CFR, Part 314.96(b), Bigmar, Inc, certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

Please contact me at the above address or at (740) 966-5800 if you have any questions or comments concerning this amendment.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

RECEIVED
DEC 0 2 1998
GENERIC DRUGS

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

FA

January 03, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 40-265
Methotrexate Injection USP (non-preserved)
25 mg/mL, 2mL, 4mL, 8mL and 10mL fills
Telephone Amendment Response to a Labeling Request

Dear Sir or Madam:

The purpose of this correspondence is to provide samples of actual final printed cartons and vial labels for the above referenced Abbreviated New Drug Application. The enclosed samples were requested by the Agency's Ms. Theresa Watkins by telephone on December 09, 1998.

In accordance with 21 CFR Part 314.96(b), Bigmar Inc. certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

We believe this amendment provides a thorough response to the Agency's request dated December 09, 1998. Please contact me at the above address or at (740) 966-5800 if you have any questions regarding this correspondence.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

January 21, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 40-265
Methotrexate Injection USP (non-preserved)
25 mg/mL (2mL, 4mL, 8mL and 10mL fill volumes)
Facsimile Amendment Response to Chemistry and Microbiology Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated December 24, 1998. The Agency indicated that Bigmar's response should be submitted as a facsimile amendment.

To facilitate your review, each observation and corresponding response is provided as an attachment to this amendment. Necessary supportive documentation is also provided for each response.

In accordance with 21 CFR Part 314.96(b), Bigmar Inc. certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

We believe this amendment provides a thorough response to the Agency's letter dated December 24, 1998. Please contact me at the above address or at (740) 966-5800 if you have any questions regarding this correspondence.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

January 27, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA CORRESP

NC

RE: ANDA 40-265
Methotrexate Injection USP (non-preserved)
25mg/mL (2mL, 4mL, 8mL and 10mL fill volumes)
Telephone Amendment Response to Microbiology Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to provide information requested by the Agency's James McVey, Ph.D., following discussions with Bigmar representatives on January 26, 1999.

Dr. McVey asked that Bigmar provide a copy of

which summarize the cycle parameters followed for the sterilization of dry goods. Dr. McVey also asked that a summary comparison of sterilization cycle parameters utilized during ongoing production and those followed during validation be provided. A copy of SOP MFG-200, including English translation, is provided under Attachment I of this correspondence. A side-by-side sterilization cycle comparison table is provided under Attachment II. Computer printouts of the corresponding production and validation cycle parameters are provided under Attachment III.

Bigmar reviews the sterilization cycle records for each sterilization load immediately following cycle completion and again at the time of batch record review. In the event that cycle parameters do not meet the validated criteria, processing equipment would be resterilized. Rubber closures would be discarded, however, and fresh stoppers prepared.

We believe this amendment provides a thorough response to the Agency's telephone request from January 26, 1999. Please contact me at the above address or at (740) 966-5800 if you have any questions or comments concerning this amendment.

RECEIVED

JAN 1) 1999

GENERIC DRUGS

In accordance with 21 CFR, Part 314.96(b), Bigmar, Inc, certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

Sincerely,

Heather L. Munsell FOR:

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure