

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40263

CORRESPONDENCE



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

N/A

**Re: ANDA 40-263
Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved)
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 0301 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

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SEP 1

OFFICE OF DRUGS

OFFICE OF DRUGS



NOV 21 1997
FEDERAL BUREAU OF INVESTIGATION
U.S. DEPARTMENT OF JUSTICE

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

November 21, 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

ORIG AMENDMENT

N/A

Re: **ANDA 40-263**
Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved)
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

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NOV 24 1997

GENERIC DRUGS

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pages of trade

secret and/or

confidential

commercial

information

Chemistry

- a) Documentation related to raw material and packaging component lots which differ from those used to manufacture batch #970025 are provided under Attachment A.1.a. Nearly all the specific batches of raw materials and packaging components used to manufacture batch #970025 are the same as those described in the original application.
- b) A copy of the revised Master Batch Record for Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved) is provided under Attachment A.1.b.
- c) A copy of the executed batch record for batch #970025 is provided under Attachment A.1.c.
- d) Stability information is provided under Attachment A.1.d.
- e) Documentation related to the revised formula is provided under Attachment A.1.e.

2. Revision of SOP QC-595

The finished product test summary document provided on page 0368 of the original application includes an assay specification of _____ % of label claim for methotrexate. The acceptance criteria was to have been updated to _____ % of label claim, following the removal of a _____ % methotrexate overage from the formula. In addition, the osmolality acceptance criteria has been revised to accommodate the formula modification addressed under Item 1 of this correspondence. A revised copy of QC-595 is provided under Attachment A.2.

3. Revision of SOP CHM-095

The sample preparation section of SOP CHM-095: "Assay and Chromatographic Purity of Methotrexate Raw Material, Injection, and for Injection," has been modified so that the subject sample will now require fewer preparative steps prior to analysis. The revision will improve laboratory efficiency, enhance the accuracy of the analytical method as a result of the simplified preparation and reduce the amount of cytotoxic waste generated. The final sample concentration and diluent used for the product remains unchanged, obviating the need for additional method validation activity. The revised method is provided under Attachment A.3.

4. Revision of SOP CHM-060

The calculation section of SOP CHM-060: "Determination of Benzaldehyde in Benzyl Alcohol" was updated to clarify that the percentage of benzaldehyde is calculated on weight/volume (w/v) basis. In addition, an erroneous description of the _____ column has been corrected under the 'Materials and Equipment' section of the SOP. The correct column, which was used for all analysis, is now referenced. A revised copy of SOP CHM-060 is provided under Attachment A.4.

B. Sterility Assurance

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commercial

information

Sterility assurance

C. Labeling

1. *Revised Package Insert*

Revisions to Bigmar's package insert for Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved) 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*

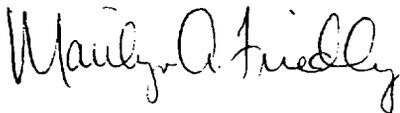
In recent unrelated applications, the agency has asked that Bigmar refer to Policy and Procedure Guide #30-91, section 3(D) and #41-95, section 3(B)(6) for guidance on ANDA tabulation and the establishment of a batch record summary table in future submissions. Bigmar shall incorporate these sections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

November 21, 1997
ANDA 40-263
Page 7 of 7

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,

A handwritten signature in cursive script that reads "Marilyn A. Friedly".

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures



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

NAT
6-1-98

December 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

ORIG AMENDMENT

N/AA

**Re: ANDA 40-263
Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved)
Gratuitous Amendment**

Dear Sir or Madam,

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

Bigmar's recent amendment, dated November 21, 1997, included a revised Master Batch Record for Methotrexate Sodium Injection USP, 25 mg (base)/mL (Preserved) and an additional stability batch (#970025). A comparison of the Master Batch Record and batch #970025 was inadvertently omitted in that amendment and is being provided under Attachment A.

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

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DEC 18 1997

GENERIC DRUGS



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

*To memo re,
madam - Friedly
6-1-98*

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

11/18

**Re: ANDA 40-263
Methotrexate Injection USP, 25 mg/mL (preserved)
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
Manager
Regulatory Affairs

Enclosures

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FEB 10 1998

GENERIC DRUGS



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

February 16, 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

N/AC

**Re: ANDA 40-263
Methotrexate Injection USP, 25 mg/mL (preserved)
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 February 02, 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.

Enhancements to the Master Batch Record have recently been added, following recommendations made during recent audits of Bigmar's batch record system. This amendment provides an opportunity to present those adopted recommendations. A copy of the current Master Batch Record, along with the highlighted changes, is provided under Attachment 11.

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, four (4) copies of draft 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.

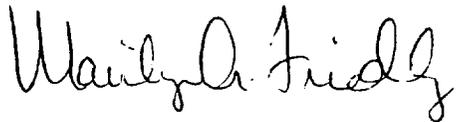
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GENERIC DRUGS

February 16, 1998

We believe that this correspondence provides a thorough response to the above referenced letter dated February 02, 1998. If you have any questions regarding this amendment, please contact me at the above address or at (614) 966-5800.

Sincerely,

A handwritten signature in cursive script that reads "Marilyn A. Friedly". The signature is written in black ink and is positioned above the typed name.

Marilyn A. Friedly
Manager
Regulatory Affairs

Enclosures



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

ANDA CIRC AMENDMENT
N/As

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 40-263
Methotrexate Injection, 25mg/mL (preserved)
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,

A handwritten signature in black ink, appearing to read "Peter Stoelzle", written over a horizontal line.

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

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JUN 03 1998

GENERIC DRUGS



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

ANDA 40-263
N/AA

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

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JUN 12 1998

Re: **ANDA 40-263**
Methotrexate Injection, 25 mg/mL (preserved)
Gratuitous Amendment

GENERIC DRUGS

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 _____ 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.

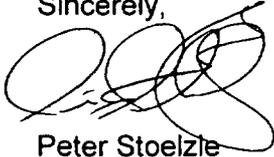
The "Stability Program / Policy " SOP has been revised to reference testing of samples stored in the upright position. The revised document replaces the SOP found on pages 1816 – 1820 of the original application and is located under Attachment A. 2.

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.

**ANDA 40-263
June 11, 1998
Page 2 of 2**

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

Sincerely,

A handwritten signature in black ink, appearing to read "Peter Stoelzie", written over a horizontal line.

Peter Stoelzie
Executive Vice President
Bigmar Incorporated

enclosure



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

September 05, 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

NEW CORRESP
N C b
Fix

**Re: ANDA 40-263
Methotrexate Injection USP (preserved), 25 mg/mL, 2mL and 10mL fills
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 06, 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 06, 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

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SEP 09 1998

enclosure

GENERIC DRUGS



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

September 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

IPL
ANDA 40-263 FACSIMILE AMENDMENT
N/A

**RE: ANDA 40-263
Methotrexate Injection, 25mg/mL (preserved)
Facsimile Amendment Response to 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 September 16, 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 September 16, 1998. If you have any questions or comments concerning this amendment, please contact me at the above address or at (740) 966-5800.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure



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

702
FA
October 29, 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

RE: ANDA 40-263
Methotrexate Injection, 25 mg/mL, Contains Preservative
Facsimile Amendment 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 October 7, 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.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Peter Stoelzle", written over a horizontal line.

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

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OCT 30 1998

GENERIC DRUGS



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 40-263
Methotrexate Injection USP (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,

A handwritten signature in black ink, appearing to read "Peter Stoelzie", is written over a large, stylized circular scribble.

Peter Stoelzie
Executive Vice President
Bigmar Incorporated

enclosure

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NOV 23 1998



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

November 30, 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

EPL
NDA 40-263 AMENDMENT
FA

**RE: ANDA 40-263
Methotrexate Injection USP (preserved) 25 mg/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 18, 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.

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

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

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DEC 04 1998

GENERIC DRUGS



FA

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

January 08, 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 40-263
Methotrexate Injection USP (preserved), 25 mg/mL, 2mL 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,

A handwritten signature in black ink, appearing to read "Peter Stoelzle", written over a horizontal line.

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

RECEIVED

JAN 11 1999

GENERIC DRUGS



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

Handwritten: NC to Fax

RE: ANDA 40-263
Methotrexate Injection USP (preserved) 25mg/mL, 2mL and 10mL fills
Gratuitous Amendment: Microbiology Deficiencies

Dear Sir or Madam:

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

Bigmar, Inc., has received directives from the Agency's James McVey, Ph.D. following his most recent review of ANDA 40-265. The requested information, submitted in an amendment dated January 27, 1999, would also apply to ANDA 40-263.

Dr. McVey asked that Bigmar provide a copy

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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 , 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.

Stamp: RECEIVED

Stamp: JAN 27 1999

Stamp: GENERIC DRUGS

January 27, 1999
ANDA # 40-263
Page 2 of 2

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



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 40-263
Methotrexate Injection USP (preserved), 25 mg/mL, 2mL and 10mL fills
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 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.

The above referenced deficiency letter included a request for labeling revisions. The recommended changes were identical to those received via facsimile on November 18, 1998. Bigmar's response, which included the submission of final printed labeling, was submitted on November 30, 1998 and received by the Agency on December 01, 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.

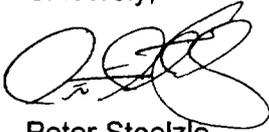
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JAN 22 1999

REGISTRATION DIVISION

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,

A handwritten signature in black ink, appearing to read 'Peter Stoelze', with a stylized flourish at the end.

Peter Stoelze
Executive Vice President
Bigmar Incorporated

enclosure



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

**RE: Methotrexate Sodium Injection,
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, equivalent to Methotrexate, 25 mg/mL. This product is indicated for the treatment of various neoplastic diseases as well as 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.

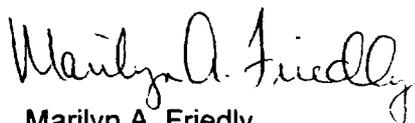
An analytical methods validation package, which includes three (3) additional copies of non-compendial assay procedures and their corresponding validation studies, is provided under separate cover.

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, 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,

A handwritten signature in cursive script that reads "Marilyn A. Friedly". The signature is written in black ink and is positioned above the printed name and title.

Marilyn A. Friedly
Manager, Regulatory Affairs