CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

CORRESPONDENCE

Adria
ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

May 11, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

5c-005/AC
NDA SUPPLEMENT

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

RE: **AADA 63-165/S-005**
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Amendment to Supplement

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting an amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of May 27, 1992.

As agreed during our telephone conversation of September 28, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson, we have prepared one bulk solution and filled it on our process line into 75 and 100 mg vials. It was agreed that the information on the 75 and 100 mg vials would be sufficient to qualify all six vial sizes, 10, 20, 50, 75, 100 and 200 mg for manufacture on the process line. The batch records for these lots have been included in the amendment filed to /S-003, /S-006 to the titled AADA (also being submitted today), and are referenced in this amendment. Similarly, the requested accelerated stability data generated through 3 months has been included in the amendment to /S-003, /S-006 and referenced in this amendment.

The requested filling process validation documentation was incorporated in the validation package submitted to the Agency June 11, 1991. We have been informed by the Agency that the package has been found to be acceptable.

ORIGINAL

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

F L Grab

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/ps
Enclosures

Containers & carton
PI satisfactory
for approval per
(ADRIAMYCIN @ app 5/3/89)
[signature] 5/20/93

Adria
ADRIA LABORATORIES

May 11, 1993

ADRIA LABORATORIES
Division of Erbamont, Inc.

P O. Box 16529
Columbus, Ohio 43216-6529

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

SC-003/AM
SL-006/AM

NDA SUPPL AMENDMENT

RECEIVED

MAY 14 1993

GENERIC DRUGS

FPL

See SC-005 for the Rev. date 5-11-93 → 5-14-93 in vol 5.1

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

RE: AADA 63-165/S-003, /S-006
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Amendment to Supplement

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting an amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of May 27, 1992.

As agreed during our telephone conversation of September 28, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson, we have prepared one bulk solution and filled it on our continuous process line into 75 and 100 mg vials. The batch records have been included in the amendment filed to /S-003, /S-006 to the titled AADA and referenced in the amendment to /S-005, which is also being submitted today. Similarly, the requested accelerated stability data generated through 3 months has been included in the amendment to /S-003, /S-006 and referenced in the amendment to /S-005.

As requested, our labeling pieces have been revised. Enclosed are twelve final printed copies of all of our labeling pieces effected.

ORIGINAL

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/ps
Enclosures

Note: NAI Mark Anderson 10/15/92

Adria®

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, OH 43216-6529

October 6, 1992

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RECEIVED
OCT 0 9 1992
GENERIC DRUGS

Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
Division of Generic Drugs
ATTENTION: DOCUMENT CONTROL ROOM 150
HFD 600
5600 Fishers Lane
Rockville, MD 20857

to SC-003
NEW CORRESP SL-006
SC-005

RE: AADA 63-165/S-003, /S-005 & /S-006
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)

Dear Sir/Madame:

This letter is being submitted to the supplements to the titled application to document what we believe was agreed to during our conference phone conversation of September 25, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson.

We had submitted a supplement March 28, 1991, assigned supplement numbers /S-003 and /S-006, to add two interim sizes, a 75 and 100 mg vial to the four sizes already approved. We also submitted a second supplement May 23, 1991, assigned supplement number /S-005, to qualify an automated line. FDA deficiency letters to both submissions requested a batch record and stability data.

It was agreed that accelerated stability data through 3 months generated on 75 and 100 mg vials prepared on the automated line would be satisfactory to support both supplements.

We would appreciate your confirming the correctness of our interpretation by signing and dating below.

John D. Harrison — 10/14/92
John Harrison (Branch Chief) — Date

E Duffy — 10/14/92
Eric Duffy (Chemistry Reviewer) — Date

ORIGINAL

We thank you for your assistance in this matter.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs
Generic Drugs

Desk Copy: Mark Anderson (Room 250 - Metro Park North II)

FLG/pss

ORIG

Adria®

ADRIA LABORATORIES

Mod labeling submitted
Prior will submit
when NFO-150 approves
labeling for NDAs.
Jessica 8/6/92

ADMINISTRATIVE OFFICES:

ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

AIRBORNE

July 20, 1992

RECEIVED

JUL 2 3 1992

GENERIC DRUGS

Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

S-003
S-006

ATTN: Michael G. Beatrice
Director, Chemistry II

Dear Mr. Beatrice:

Please refer to your letter dated May 27, 1992 regarding supplements S-003 and S-006 to AADA 63-165. These supplements provide for additional dosage strengths of 75 mg/vial and 100 mg/vial of Adriamycin PFS as well draft labeling for the new strengths.

The May 27, 1992 letter cites a number of deficiencies in the supplements and states they are not approvable. The deficiencies listed suggest that the supplements may not have contained sufficiently detailed explanations of the changes. The purpose of this letter is to provide that detail and to request that the supplements be reconsidered in light of this information.

The May 27, 1992 letter discusses the requirement for Drug Master File references for packaging components in general and specifically specification documentation and dimensional drawings for the proposed stoppers.

The supplement includes an Introduction Section that may have been overlooked that states the supplement specifies certain changes in the application and all other information in AADA 63-165 remains the same. The original application contains information about the container - closure system on pages 03-253 to 03-283. This information includes a reference to the glass (p.03-265), a DMF reference to the stopper (p.03-267), and diagrams of the stoppers (p.03-266). These remain the same for the 75 mg and 100 mg strengths. Components for these strengths are listed on pages 004 and 005 of the supplement. The additional sizes of the vials for these strengths are described on pages 014 to 017 of the supplement. Although the vial sizes changed, the vial neck size and the stoppers remain the same as described in AADA 63-165.

The May 27,1992 letter requests the submission of stability data and batch records from one lot of each proposed fill size (15%-20% of the maximum propose batch size).

AADA 63-165 for Adriamycin PFS manufactured at Adria-SP was approved on January 30, 1991. The original application provided for strengths of 10 mg, 20 mg, 50 mg, and 200 mg/vial. All four strengths were approved based upon stability for one lot of 10 mg and one lot of 200 mg only. Supplements S-003 and S-006 were submitted on March 28, 1991.

Supplements S-003 an S-006 also included by reference the batch records in the original AADA with the the addition of the specific pages in these records revised by the addition of the 75 mg/vial and 100 mg/vial strengths, pages 010 and 011 of the supplement.

The information submitted in supplement S-003 was based upon the experience with the original AADA that only the smallest and largest sizes must be placed on stability and on discussion with Division staff. Since the bulk drug substance, the formulation, the method of manufacture of the finished dosage form, and the concentration are identical for all strengths, it was reasonable to conclude that the two strengths provided for in the supplement would be encompassed by the stability data in the original application in the same manner as were the 20 mg and 50 mg strengths. In addition, please note that the supplement included a commitment to place commercial batches on stability and to recall any lots not meeting specifications. We are, therefore, dismayed to learn that new requirements are apparently being applied by the Division. Considerable time, effort and expense would be required to comply with this new requirement and would result in substantial delay in the approval of the supplement.

Adria respectfully requests that the Division rescind the request for new stability data on the 75 and 100 mg strengths included in Supplements S003 on the basis that stability of the 10 mg and 200 mg product has already been established.

2 (in A)

The May 17, 1992 letter requests the submission of revised final printed labeling.

Adria markets Adriamycin under two NDAs (50-629 and 50-467) and two AADAs (63-165 and 62-057). We have been working with the Division of Oncology/Pulmonary Drug Products to consolidate the inserts under these applications into one combined insert for all applications in order to maximize the uniformity and to avoid the potential for using the wrong insert in the various products. This activity is underway and a revised draft will be forwarded to the Division shortly. Please see the attached letter from the Office of Generic Drugs indicating that Adria should revise inserts in accord with the Divisions comments and submit final printed labeling to the two AADAs when that activity is complete and approval has been received from the Division. Therefore, in order to avoid the possibility of different inserts for the same product, please consider awaiting the approval of the revised insert before changing the insert for AADA 63-165.

Adria believes the information provided in this letter is sufficient to provide for the reevaluation of the supplements and requests that they be approved. In the event that the Agency differs with our conclusions, we request a meeting to discuss the matter. I will call the week of August 3, 1992 to review this letter and our request.

Sincerely,

for

Angel Luis Canales
Director of Regulatory Affairs
Marketed Drugs and QC/QA

cc: Dr. R. Jerussi

Adria®
ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

AIRBORNE

July 20 1992

NEW CORRESP
SC-005

RECEIVED
JUL 2 3 1992
GENERIC DRUGS

Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ATTN: Michael G. Beatrice
Director, Chemistry II

Dear Mr. Beatrice:

Please refer to your letter dated May 27, 1992 regarding supplement S-005 of AADA 63-165. This supplement provided for alternate use of a continuous processing vial preparation, filling, capping and exterior vial rinsing line.

The referenced letter cites a number of deficiencies and, additionally indicates major portions of the supplement are missing. This letter suggests that the supplement may not have adequately explained the nature of the changes Adria is proposing. In addition, information submitted with respect to the manufacture may not have been properly brought to the attention of the reviewer. The purpose of this communication is to identify the areas of possible misunderstanding and to request a reevaluation of supplement S-005.

The process for the manufacture of Adriamycin PFS at Adria-SP by the process is the same as the process approved in the original AADA on January 30, 1991. The only change requested in S-005 is to replace several manual operations with automatic operations. The net result is decreased handling of the product and the reduction of the number of people required in the sterile room. The process more closely approximates the manufacture of Adriamycin at Farmitalia Carlo Erba, an affiliate of Adria, who produced the product for the US market prior to the approval of AADA 63-165. The use of the word verses "batch" in describing the change may have been a poor choice of words. Adriamycin is manufactured in batches by both methods. The supplement provides for the automation of a number of steps that are currently than being done manually. The attached schematic serves to compare the two operations and to identify the differences in a clearer manner.

A complete process validation package consisting of three volumes of information was submitted as a supplement on June 11, 1991. This timing was in accordance with an agreement with the FDA by letter dated 12/22/89 and agreed upon by Adria on 1/4/90. The agreement stipulated that the process validation should be submitted by six months after approval of the application. Approval was on January 30, 1991.

The submission includes validation information for both the batch and continuous process. We were unable to reference the validation package in supplement S-005 since its submission predated the June 11, 1991 supplement.

The letter of May 27,1992 requests revision of the Master Batch Record to incorporate the maximum batch size. Please see page 027 of the supplement for the statement of the batch size. It is stated as ____ Please note that this is not the maximum scale up of the batch in the original application, but represents the capacity of the largest compounding equipment currently avaialble at Adria-SP.

In response to a question in the May 27, 1992 letter, there were no revisions in the in-process controls.

Adria believes that the supplement S-005 is complete and reviewable as it stands. We therefore request that the review of this supplement proceed based upon the clarification provided in this letter. We apologize for any misunderstanding that may have occurred regarding the nature of the change and the data and information provided.

In the event that the Office disagrees with our conclusions and request, we would appreciate an opportunity to meet to discuss the matter. I will call the week of August 3, 1992 to discuss this letter and our request.

Sincerely

Angel Luis Canales
Director of Regulatory Affairs
Marketed Drugs and QC/QA

cc: Dr. R. Jerussi

AADA 63-165/S-005

MAY 27 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations dated May 23, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for alternate use of a continuous processing vial preparation, filling, capping and rinsing manufacturing line.

The supplemental application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

The application fails to contain major portions of required information, and therefore has not been comprehensively reviewed. We offer the following comments at the present time, and will offer comprehensive comment when all required information has been submitted.

1. Please provide a completed batch record, and stability data from a batch produced by the proposed alternate manufacturing process.

2. Validation documentation for the proposed aseptic filling process should be provided.

3. Please revise your exhibit Master Batch Record to incorporate the maximum batch size.

4. Please describe any revisions to in-process control procedures.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a major amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/27/92

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Draft for JDH
5/22/92

NOTED: JHannay 6/3/91

SE-005

Adria

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

May 23, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: AADA 63-165
Adriamycin PFS (Doxorubicin HCl Injection, USP)

Gentlemen:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are presenting a supplement to the referenced application.

The purpose of this supplement is to provide for a cess as an alternative to the currently approved process for the manufacture of Adriamycin PFS. The supplement includes a comparison of the and processes to demonstrate their comparability. The batch records have been reformatted to become specific and to incorporate previous forms into the batch records. The formulation and manufacturing procedure are the same as approved in the application.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
MAY 29 19

MAILING ADDRESS: PO Box 16529 Columbus OH 43216-6529

ORIGINAL

GENERIC DRUGS

SC-003

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:

ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

March 28, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA NO. 63-165 REF. NO. SC-003
NDA SUPPL FOR Pediatric Use

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Contains 3 carton
subfactory
PI - need revision
5/20/92

NDA NO 63-165 REF. NO. SC-006
NDA SUPPL FOR Controlled Rev

Re: AADA 63-165
Adriamycin PFS® (doxorubicin hydrochloride USP)
Injection

Dear Sir:

In accordance with the provisions of Paragraph 314.70(b) of Title 21 of the Code of Federal Regulations, we are submitting a supplement to the referenced application.

The purpose of the supplement is to provide for two additional vial sizes, 75mg and 100mg. These additional sizes are within the range covered by the approved application (10mg to 200mg).

Please note that the draft labeling reflects currently approved labeling. A separate supplement has been submitted containing the revisions requested by the Office of Generic Drugs. These changes, when approved, will be made for the sizes included in this supplement.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
APR 2 1991
GENERIC DRUGS

MAILING ADDRESS: P.O. Box 16529, Columbus OH 43216-6529

ORIGINAL

AADA 63-165/S-004

JUN - 1 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations dated April 2, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for optional use of the facilities at Albuquerque, New Mexico (Adria SP), or Columbus, Ohio (Adria Laboratories) for testing, packaging, and labeling of the product.

We have completed the review of this supplemental application and it is approved. Our letter of January 30, 1991 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/ 5/31/92

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Adria
ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

SC-0084

April 2, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: AADA 63-165
Adriamycin PFS™ (Doxorubicin HCI Injection, USP)

Gentlemen:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are presenting a supplement to the referenced application.

The purpose of this supplement is to provide for the option of conducting certain testing and packaging/labeling operations either at our facility at Albuquerque, New Mexico (Adria-SP) or in Columbus, Ohio (Adria Laboratories). The tests and procedures would not differ from those described in the approved application.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
APR 5

MAILING ADDRESS: P.O. Box 16529 Columbus OH 43216-6529

ORIGINAL

GENERIC DRUGS

AADA 63-165/S-003/S-006

MAY 27 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug applications submitted pursuant to Section 314.70 of the Regulations dated March 28, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP), 2 mg/mL.

The supplemental applications provide for additional dosage strengths of 75 mg/vial and 100 mg/vial (S-003) and draft labeling for the new fill sizes (S-006).

The supplemental applications are deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. Drug Master File references with accompanying authorization should be provided for all packaging components. Also included should be a listing of the components with the corresponding vendor commodity numbers and page references to the DMFs to permit access to technical information contained therein. The specification documentation should also be included for each packaging component. Dimensional drawings should be provided for the proposed stoppers as well as information on composition.

2. Please provide stability data and batch records from one lot of each proposed fill size (15 - 20% of the maximum proposed batch size).

3. Please revise and submit twelve final printed copies of your insert labeling based upon the following comments:

   Container: Satisfactory in draft for 75 mg and 100 mg, however we prefer "STERILE ISOTONIC SOLUTION" (rather than just "STERILE")

   Carton: Satisfactory in draft for 75 mg and 100 mg

Insert: Not Satisfactory

A. Title

Relocate "USP" to appear at the end of the established name: Doxorubicin Hydrochloride Injection USP.

B. DESCRIPTION

1. paragraph 1, second sentence, revise to read:

Doxorubicin consists of a napthacenequinone...

2. paragraph 3, add:

37.5 mL (75 mg) and 50 mL (100 mg) single dose

3. The requirements of 21 CFR 201.57(a)(1)(ii) and (iv) must be met. We believe the route should be more specific than "parenteral".

C. CLINICAL PHARMACOLOGY, paragraph 2

We prefer (to rather than hyphen)

40% to 50%
4% to 5%

D. WARNINGS

1. paragraph 1, fourth sentence, revise to read:

...into account previous or... (delete "a")

2. paragraph 4, first sentence - we prefer:

...10 to 14 days...

E. PRECAUTIONS, paragraph 3 - we prefer:

...1 to 2 days...

F. ADVERSE REACTIONS, Gastrointestinal, first and second sentences revise to read:

...5 to 10 days..

The dosage regimen consisting...

G. DOSAGE AND ADMINISTRATION

1. Paragraph 2

a) first sentence - revise to read:

The most commonly used dosage schedule is 60 to 75 mg/m^2...

b) third sentence - revise to read:

An alternative dosage schedule is...

c) fourth sentence - revise to read:

Thirty (30) mg/m^2...

d) final sentence - we prefer:

... 1.2 to 3.0 mg/dL...

2. paragraph 4 - revise to read:

...with heparin or fluorouracil... (delete 5)

3. Add as paragraph 3:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

H. HOW SUPPLIED

1. single dose vials, storage statement, revise to read:

2°-8°C (36°-46°F). Protect from light...

2. single dose vials.

Move "Discard" statement to the next line.

3. multiple dose vials, storage statement, revise to read:

2°-8°C (36°-48°F). Protect from light and retain in carton until contents are used.

I. REFERENCES

Update reference #7 to read:

...Am J Hosp. Pharm. 1990; 47:1033-1049.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a minor amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 12/6/02

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

SUPPLEMENT NOT APPROVABLE

AADA 63-165/S-007

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

MAY 19 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated November 3, 1992, submitted pursuant to 21 CFR 314.70 of the Regulations, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

Reference is also made to your amendment dated April 29, 1993.

The supplemental application provides for a manufacturing rework procedure.

We have completed the review of this supplemental application and it is approved.

Please note and acknowledge the following request:

> Please submit microbiological monitoring results from personnel in the rework area for the first production rework lot of the subject drug product. Samples should include fingertips and sleeves of gowns.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/

5/19/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

April 29, 1993

AIRBORNE

SC-007 \ Am
NDA SUPPL AMENDMENT

RECEIVED

APR 3 0 1993

GENERIC DRUGS

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

RE: **AADA 63-165/S-007**
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Minor Amendment to Supplement

MINOR AMENDMENT

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting a minor amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of March 30, 1993.

In response to various questions, a revised Master Batch Record (MBR) is included herein.

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

F L Grab

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/pss
Enclosures

ORIGINAL

AADA 63-165/S-007

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

MAR 30 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated November 3, 1992, submitted pursuant to 21 CFR 314.70 of the Regulations, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for a manufacturing rework procedure.

The supplemental application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. The sterile operating area should be specified (i.e., class 100, sterile core # X, etc.). For filling, the approved filling line for this product should be specified.

2. The environmental microbial monitoring of the designated rework area should be described, in particular as it relates to personnel. Provide data from such monitoring.

3. Use of should be specified as is required for the approved manufacturing process.

4. Adjustment of for subpotent rework lots should not be provided for unless a means for ontent determination is established.

5. Time limits for production should be established per 21 CFR 211.111. In particular, for lots proposed for rework due to sterility assurance failure and pH limits being exceeded, where the stability of the product has not been determined, the proposed limits should be suitably short. Time limits for bulk solution holding prior to fill should also be established.

6. Bioburden limits for the compounded bulk solution should be established.

7. Filled vial accountability limits should be established.

8. With respect to this rework procedure being applicable to lots where there you have not specified which would qualify a lot for rework and provided data that indicate that product degradation does not occur. In the absence of these data, or a demonstration batch the proposed rework procedure is not considered appropriate for rework due to

9. Please provide any stability data available to date.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/29/93

C.Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Note: request denied
Request denied
review in turn 11/12/92
Mark Anderson

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont Inc

P.O. Box 16529
Columbus, OH 43216-6529

November 3, 1992

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
Division of Generic Drugs
ATTENTION: DOCUMENT CONTROL ROOM 150
HFD 600
5600 Fishers Lane
Rockville, MD 20857

NDA NO. _____ REF. NO. 3C-002

NDA SUPPL FOR Manufacturing Chan
3C-002 AR

RECEIVED
NOV 0 6 1992
GENERIC DRUGS

RE: AADA 63-165
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
SUPPLEMENT

SUPPLEMENT - EXPEDITED REVIEW REQUESTED

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are submitting a supplement to the referenced application.

The purpose of this supplement is to qualify a rework procedure. The supplement includes certificates of analysis for a batch which was subsequently reworked. The certificates demonstrate their comparability.

The formulation, packaging materials, specifications and analytical methods for the reworked material are identical to those approved in the AADA. Other than for those activities involved in the rework, the manufacturing process is also unchanged.

We are requesting an expedited review because the batch that was reworked was a full commercial batch of an expensive material. We would appreciate a prompt review and approval so that the majority of the reworked batch can be placed into commerce at a time sufficiently before its expiration date of September 1993. Our not being able to do so would impose an extraordinary hardship on us. We would be willing to do whatever is needed to assist in expediting the review and approval of this supplement.

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs
Generic Drugs

FLG/ps

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

June 23, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

to SC-007
NEW CORRESP

RE: AADA 63-165/S-007
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Acknowledgement Letter

Dear Sir/Madame:

We are submitting this document in response to an Agency request in their letter of May 19, 1993 approving the titled supplement.

We have noted and acknowledge the following:

> "Please submit microbiological monitoring results from personnel in the rework area for the first production rework lot of the subject drug product. Samples should include fingertips and sleeves of gowns."

At the time our approved rework procedure is next carried out, it is our intention to perform the microbiological monitoring requested by the FDA. The results of such monitoring will then be submitted to the Agency.

Should any clarification be desired, please call me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

RECEIVED
JUN 25 1993
GENERIC DRUGS

FLG/pss

AADA 63-165/S-008

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

OCT 12 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated July 27, 1993, submitted pursuant to 21 CFR 314.70, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for a change in the manufacturing process which calls for addition of Doxorubicin Hydrochloride USP to water for more ready dissolution.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated antibiotic application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 10/8/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Noted:
To Mr. Harrison
Mark Anderson
7/30/93

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

July 27, 1993

AIRBORNE

NDA NO. _____ REF NO. SCI-008
NDA SUPPL FOR Manufacturing Rev.

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

RECEIVED
JUL 28 1993
GENERIC DRUGS

RE: AADA 63-165
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP) 2 mg/mL

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

cK J. Harrison 7/30/93

Dear Sir/Madame:

In accordance with the provisions of 314.70(c)(1) of Title 21 of the Code of Federal Regulations, we are submitting a Special Supplement - Changes Being Effected to the referenced application.

The purpose of this submission is to reverse the order of two steps involved in the compounding of the initial, concentrated solution. Attached is a copy of the revised page (5B) from our Master Batch Record where Steps C and D have been reversed. The currently

[illegible] of the vessel during the [illegible]

Since the change in the order of addition should not have a negative affect on the product, we are implementing this change August 9.

Should any clarification be desired, please call me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: Mark Anderson

FLG/pss