CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING

Amendment to Supplement

FPL

DATE OF REVIEW: May 26, 1993

ANDA #: 63-165/S-006

NAME OF FIRM: Adria

NAME OF DRUG: Trade: Adriamycin PFS®

Generic: Doxorubicin Hydrochloride Injection USP, 75 mg and 100 mg single dose vials.

DATE OF SUBMISSION: May 11, 1993

COMMENTS:

Container - For 75 mg and 100 mg: Satisfactory in FPL.

Carton - For 75 mg and 100 mg: Satisfactory in FPL.

Insert: Satisfactory in FPL.

However, at the time of next printing revise your package insert as described below. Revised labeling may be submitted with an annual report provided you describe the changes.

A. INDICATIONS AND USAGE, first sentence, revise to read -

ADRIAMYCIN PFS® (Doxorubicin HCl Injection USP) has been used...

B. WARNINGS

1. paragraph 2, third sentence -

cumulative [spelling]

2. paragraph 4, third sentence -

...1000/mm^3... [add "/"]

3. paragraph 8, first sentence -

On intravenous administration of doxorubicin, extravasation...
[delete "HCl" and add comma]

C. REFERENCES

1. Revise reference #4 to read -

   National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

2. Revise reference #7 to read -

   American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990:47:1033-1049.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. For the Record

   a. In a 5/15/92 conversation, Dr Williams (HFD-150) confirmed the 75 mg vial was acceptable.

   b. The last sentence in the first paragraph of the WARNINGS section was found to be acceptable in a 6/22/92 NA letter to the firm. The wording was confirmed by Ellen Cutler (HFD-150) in a 5/27/93 memo.

John Grace

6/1/93
6/1/93

//

REVIEW OF PROFESSIONAL LABELING

Supplement

DRAFT - FPL

DATE OF REVIEW: 5/14/92

AADA #: 63-165/S-00~~5~~ S-006

NAME OF FIRM: Adria

NAME OF DRUG: Trade:

Generic: Adriamycin PFS® (Doxorubicin Hydrochloride Injection USP) 75 mg and 100 mg single dose vials

DATE OF SUBMISSION: 3/28/91

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.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels, and carton and insert labeling, then prepare and submit final printed labels and labeling.

John Kenan 5/19/92

Div. of slogg
See record of phone conversation
5/19/92

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 1992

FROM: Mark Anderson, CSO, Branch 5

SUBJECT: AADA 63-165/S-003 and S-005

TO: The record

John Harrison, Eric Duffy, Ph.D. and I spoke with Fred Grab in follow-up to the 9/21/92 conversation I had with Mr. Grab. After discussion, it was clarified that in order to gain approval of S-003 and S-005 Adria will need to prepare a test batch of at least 10% of the proposed maximum batch size which may be split filled into 75 mg and 100 mg vials. Ninety day accelerated stability data gathered prior to submission of the amendments to S-003 and S-005 will also be required.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 21, 1992

FROM: Mark Anderson, CSO

SUBJECT: AADA 63-165/S-003 and S-005 Requests by Adria to reconsider our 5/27/92 NA letters

TO: The record

I called Fred Grab, Adria Labs [(614) 764-8128] about his pending requests dated July 20, 1992 for meetings to discuss the not approvable letters Adria received for S-003 (which provides for additional dosage strengths of 75 and 100 mg/vial of Adriamycin PFS) and S-005 (which provides for use of a continuous processing vial preparation, filling, capping and exterior vial rinsing line to replace the manual line now in use). The Adria letters take exception to our reasons for not approving the supplements and request the above mentioned meetings if we do not agree with their proposals.

I told Mr. Grab that after internal discussion, we did not feel a meeting(s) would serve a useful purpose. However it was suggested that we instead have a conference call with Mr. Harrison, Dr. Duffy and Adria to clarify our position.

Mr. Grab said Adria is still especially concerned with the need to submit stability data and batch records for the 75 mg and 100 mg strengths prior to approval due to the expense of the raw materials and the possibility the products may expire prior to approval. He referred to discussions which he said were held between Mr. Harrison (and possibly others) and Mr. Warren Myers of Adria in November 1988 which was prior to submission of Adria's AADA 63-165 in January of 1989. It was and is Adria's understanding from that meeting that agreement was reached to permit intermediate fill sizes to be manufactured based on stability data generated on the largest and smallest fill sizes.

After checking, I told Mr. Grab I was unable to locate any November 1988 meeting minutes but that even if agreement was reached at that time that our policies are subject to change and that, as Dr. Duffy had previously explained (refer to 9/2/92 T. Con.), manufacture of one batch of each strength is necessary prior to approval. This is a policy we apply to all applicants.

Mr. Grab then asked if it would be possible to review other aspects of the supplements and resolve deficiencies such that they could be found approvable except for submission of stability data and batch records for the 75 and 100 mg fill sizes as a means of minimizing the possibility of product expiring before approval. I said I would relay this request to Mr. Harrison.

REVIEW OF PROFESSIONAL LABELING

Amendment to Supplement

NO LABELING SUBMITTED

DATE OF REVIEW: August 6, 1992

AADA #: 63-165/S-006 (New Correspondence)

NAME OF FIRM: Adira

NAME OF DRUG: Trade: Adriamycin PFS
Generic: Doxorubicin Hydrochloride Injection, USP

DATE OF SUBMISSION: July 20, 1992

COMMENTS:

We acknowledge the firm's commitment to submit final printed labeling as soon as the Division of Oncology/Pulmonary Drug Products approves the two NDA's associated with this product.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

J.Grace

FINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	[redacted]
☒ Original ☐ Follow-Up ☐ FUR	5/24/93	295-8360	

REQUESTOR'S NAME	DIVISION	MAIL CODE
Eric Duffy/Jena Weber	OGD	HFD- 635

APPLICATION AND SUPPLEMENT NUMBER
63-165/S-005

BRAND NAME	ESTABLISHED NAME
Adriamycin PFS	Doxorubicin HCl Injectinn, USP

DOSAGE AND STRENGTH	STERILE
10, 20, 50, 200 mg/vial	☒ YES ☐ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
SVS	

APPLICANT'S NAME
Adria Laboratories

ADDRESS
7001 Post Road
Dublin, OH

COMMENTS

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. Adria SP, Inc. 2272 Balloon Park Rd. Alburquerque, NM 87109	Manufacturing, Testing		[redacted]	
2. Continuous process full line Room 274			[redacted]	
3.			[redacted]	
4.			[redacted]	
5.			[redacted]	

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 5/15/92

NDA NUMBER: 63-165

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☐ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Adriamycin PFS

FIRM NAME: Adria

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr Williams - FDA Oncology Medical Officer for this drug; Ellen Cutler - CSO for Oncology Drugs

TELEPHONE NO.: 443-5197

I spoke with Dr Williams about the acceptability of a 75 mg single dose vial. He indicated it is ok:

1) reasonable as single dose
2) already have 50mg & 100mg

I spoke with Ellen Cutler about the 3/27/91 submission to NDA's 50-467 & 50-629. These submissions provide for combined inserts & we can't approve the supplements we have until they approve theirs. Ellen said still not received. I confirmed that she had received a copy of the review we sent over.

SIGNATURE: Yana Mille

DIVISION: Office of Generic Drugs

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service — 2-96c

Memorandum

te May 20, 1992

From Division of Generic Drugs — HFD- 632

Requestor's Name Eric Duffy/Dave Doleski — Phone 295-8360

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product X — Non Sterile Product _____

Application and Supplement No. 63-165/S-004

Brand Name *(if any)* ADRIAMYCIN PFS

Establishment Name, Dosage Form and Strength Doxorubicin Hydrochloride Injection USP

_____ Profile Class Code: SVP

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Adria Laboratories

Address: 7001 Post Rd., Dublin, OH 43017

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) — **For HFD 320 Use** Status & Date of Inspection:

1. ADRIA Adria SP 4272 Balloon Park Rd. Alburquerque, NM — AC- 2/21/92
   ~~QC testing, labeling packaging~~
2. ASTA Adria SP 3700 Osuna Drive Suite 715 Albuquerque, NM — AC- 2/21/92
   QC testing, labeling, packaging
3. _____
4. _____
5. _____

Other Information or Special Requests: _____

****

For HFD-320 Use Only: Date Received: 5/21/92

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: _____ Date Completed: 5/22/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90) — ★U.S.GPO:1991-0-281-805/41633

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 12, 1992

FROM: Mark Anderson, CSO, Branch 5

SUBJECT: AADA 63-165/S-007 for Doxorubicin HCl Inj. by Adria
Request for Expedited Review

TO: The Record

I called Mr. Fred Grab, Regulatory Affairs at Adria [6140 764-8128] and informed him that his request for expedited review for the supplement dated November 3, 1992 has been denied. I explained that economic hardship, other than that caused by events outside the applicant's control, was not a grounds for granting expedited review.

Mr. Grab thanked me for the information and, although not in agreement, said he was not surprised as to our decision. He asked for an estimate as to how long it might be before the supplement was reviewed. I said, based on current workloads, it appeared the supplement would be reviewed within about 4 months - though I offered no assurance of this.

The conversation ended cordially.

11/12/92 called firm re relay decision See memo M. Anderson

OFFICE OF GENERIC DRUGS

EXPEDITED REVIEW REQUESTED

ANDA/AADA SUPPLEMENT #: 63-185 SC-007 APPLICANT: Adria Laboratories

DRUG: Doxorubicin HCl Injecton

DATE OF SUBMISSION: 11/3/92

The Office of Generic Drugs Policy and Procedure Guide #18-90 as revised on January 22, 1992 lists the following criteria for granting expedited review status to a supplemental new drug application. At least one of the criteria must be met.

1. **PUBLIC HEALTH NEED.** Events that affect the availability of a drug for which there is no alternative.

2. **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a. Catastrophic events such as explosion, fire, storm damage.

   b. Events that could not have been reasonably foreseen, and for which the applicant could not plan. Examples include:

      ▲ abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and

      ▲ relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a.).

3. **AGENCY NEED.**

   a. Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.

   b. Federal or state legal/regulatory actions, including mandated formulation changes or labeling changes if it is in the Agency's best interest.

   c. Expiration-date extension or packaging change when the drug product is the subject of a government contract award.

RECOMMENDATIONS:

Branch CSO/Chemist	Grant/Deny	Mark Anderson 11/9/92 Signatures & Dates
Supervisory Chemist	Grant/Deny	E. Duffy 11/10/92 Signature & Date
Division Director	Grant/Deny	C. Greg Fry 11/10/92 Signature & Date

Although it is an extraordinary hardship, it doesn't meet a #6 of the policy.

COMMENTS: While there may be economic hardships involved our Policy + Procedure Guide # 18-90 does not "fit" this type of situation and applicant has not claimed a public health need.

CC: ANDA/S#, Division File, Doc. Room log, R.Pollock, CSO.