

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
NDA 50-778**

Correspondence

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Internet website: <http://www.fda.gov/orphan>

September 22, 1999

Pharmacia & Upjohn Company
7000 Portage Rd.
0634-298-113
Kalamazoo, MI 49001-0199

Attention: Denise S. Tindle
Regulatory Affairs Manager

Dear Ms. Tindle:

Reference is made to your orphan drug Ellence™ (epirubicin), which was designated an orphan drug pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 360bb) on September 14, 1999 (application #98-1214) for the treatment of breast cancer.

This letter is to inform you that as the first sponsor of Ellence™ to obtain marketing approval for this indication, you are entitled to seven years of exclusive marketing approval pursuant to Section 527 of the FFDCA (21 U.S.C. § 360cc) for the use of Ellence™ as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. The exclusive seven year approval period began on September 15, 1999, the date of approval of your new drug application (NDA 50-778).

Please note that holders of exclusivity for approved orphan drugs are required to assure the availability of sufficient quantities of an orphan drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drugs's exclusive approval [21 CFR 316.36(b)].

Thank you for your efforts in developing Ellence™ for the treatment of breast cancer. The whole premise of the Orphan Drug Act and program is based on the realization that the resources and commitment devoted to the development of drugs for "orphan" populations may not provide financial returns to their sponsors. It is with genuine gratitude that we recognize your efforts.

Sincerely yours,


Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

cc:

GCF-1/E.Dickinson

HFD-93/M.Holovac

HFD-94/F.Rowland

HFD-150/NDA 50-778/Div File

HFD-150/D.Spillman

HF-35/Chron File

HF-35/OPD File #98-1214

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service



Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane, Rm. B1
Rockville, MD 20855

OPD FAX COVER SHEET

DATE: 9/15/99

TO: Denise Tindle
ADDRESS: PO

+ Dianne Spillman
FDA

FAX NO: 616-833-0409

301-594

PHONE: _____

Pages to Follow: 2

FROM: _____

FAX: (301) 443-4915

PHONE: (301) 827-3666

message: _____

cc: NDA 50-778
HPD-150/DIV FILE
/D. Spillman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service



Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

September 14, 1999

Pharmacia & Upjohn
0634-298-113
7000 Portage Rd.
Kalamazoo, MI 49001-0199

Attention: Denise S. Tindle
Regulatory Affairs Manager

Dear Ms. Tindle:

Reference is made to your orphan designation application of December 11, 1998, submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of epirubicin as an orphan drug (application #98-1214). We also refer to your amendments dated June 15, 1999, July 12, 1999, and September 7, 1999.

We have completed the review of this application and have determined that epirubicin qualifies for orphan designation for the treatment of breast cancer. Please note that it is epirubicin and not its formulation that has received orphan designation.

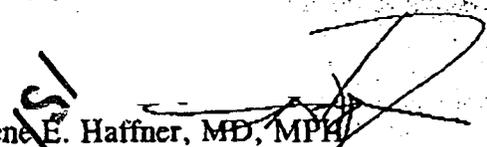
Please be advised that if epirubicin were approved for an indication broader than the orphan designation, your drug might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA. Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of epirubicin as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is

approved [21 CFR 316.30]. If you need further assistance in the development of your drug for marketing, please feel free to contact John McCormick, MD at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,


Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Redacted 6

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(b)(5)

information



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

August 30, 1999

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Amendment 028

**RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection**

Revised non-insert labeling proofs

Dear Sir/Madam:

Enclosed please find revised non-insert labeling proofs that incorporate the August 8, 1999 recommendations of the FDA chemistry reviewer.

The following revisions were made to the labeling:

- The size and prominence of the established name was increased;
- The term "For Intravenous Use" was changed to "For Intravenous Use Only";
- The storage statement was highlighted. (Please note that the highlighting will be more distinct in the final photographic image used for printing purposes.);
- The term "Caution-Cytotoxic Agent" was added to the carton label;
- The logo was removed.

Pharmacia and Upjohn would appreciate receiving FDA feedback regarding the acceptability of these revisions by September 7, 1999.

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script, appearing to read "Denise S. Tindle".

Denise S. Tindle
Regulatory Affairs Manager

DST:kmv

29 pages redacted from this section of
the approval package consisted of draft labeling

Electronic Mail Message

Date: 9/14/99 4:46:52 PM
From: Dianne Spillman (SPILLMAND)
To: Denise.S.Tindle (Denise.S.Tindle@am.pnu.com)
Subject: Epirubicin Insert

Denise -

Attached is the revised "marked-up" PI (ATT 1) and "clean" PI (ATT 2) which was sent back up to Dr. Temple this afternoon. A version of both will follow via fax.

As discussed, these versions have incorporated Dr. Temple's latest revisions to the labeling.

Please let me know if P&U finds these revisions acceptable.

Thanks.
Dianne

cc: NDA 50-778
HPD-ISO / DIV Files
~~D Spillman~~

45 pages redacted from this section of
the approval package consisted of draft labeling



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

September 10, 1999

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Amendment 029

**RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection**

Proposed Insert Labeling

Dear Sir/Madam:

Enclosed please find the proposed insert labeling for epirubicin hydrochloride injection. This submission includes:

- A strike-through/underline version of the proposed labeling containing explanations and references supporting changes;
- A clean copy of the proposed labeling;
- Attachment 1 providing NDA references;
- Attachment 2 provides an answer to FDA's question (FDA question from August 30, 1999 electronic mail transmission/rationale document) regarding studies of epirubicin in combination with paclitaxel and docetaxel.
- Diskettes containing electronic copies of the proposed labeling. These electronic copies have been scanned with Network Associates VirusScan NT software (v4.0.3a).

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Denise S. Tindle
Regulatory Affairs Manager

DST:kmv

Cc: Dianne Spillman

24 pages redacted from this section of
the approval package consisted of draft labeling

Electronic Mail Message

Date: 9/15/99 12:20:56 PM
From: Denise.S.Tindle (Denise.S.Tindle@am.pnu.com)
To: spillmand (spillmand@A1)
Subject: Epirubicin hydrochloride injection insert

Dear Diane,

Re: NDA 21-010 (50-778)

Attached please find a revision copy (925pi-m) and clean copy (915pi-c) of the proposed epirubicin insert. With these minor editorial changes included, we find the proposed labeling acceptable.

Also please note that Pharmacia & Upjohn would like to receive the approval letter for this application regardless of the status of our request for orphan drug designation.

With the provision of this information, I assume we will be in a position to receive an approval letter today. If this is an incorrect assumption, please let me know. We do not want to jeopardize our approval with these labeling changes.

Please note that on page 21 of the revision copy under Hepatic Dysfunction, the phrase, '_____ was deleted since it was defined previously that there were few patients with hepatic dysfunction in the studies.

If you have any questions regarding this information, please contact me at (616) 833-3825.

Sincerely,

Denise Tindle
Regulatory Manager
Pharmacia & Upjohn

cc NDA 50-778
HFD-100 / DW FLW
11

Electronic Mail Message

Date: 9/15/99 6:24:28 PM
From: Denise.S.Tindle (Denise.S.Tindle@am.pnu.com)
To: spillmand (spillmand@A1)
Subject: Epirubicin - agreement with proposal to change wording

Dear Dianne,

Re: NDA 21-010 (50-778)

This message is to indicate Pharmacia & Upjohn's agreement with the FDA proposal to use the following wording in the Dosing and Administration section under the subheading Hepatic Dysfunction:

"In patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions were recommended in the clinical trials, although few patients experienced hepatic impairment:
...."

This wording above replaces the following previous proposed wording:

Sincerely,

Denise Tindle
Regulatory Manager
Pharmacia & Upjohn

CC: NDA 50-778
HFD-USD / DIV FILCS
/ D. Spillman

48 pages redacted from this section of
the approval package consisted of draft labeling



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Denise S. Tindle	From: Dianne Spillman
Fax: (616) 833-0409	Fax: (301) 594-0499
Phone: (616) 833-3825	Phone: (301) 594-5746
Pages (including cover): 23	Date: August 27, 1999
Re: NDA 50-778: FDA Revised Package Insert	

Urgent For Review Please Comment Please Reply Please Recycle

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● **Comments:**

Denise –

As discussed, following is the revised package insert. An electronic copy of this document will be sent via e-mail along with the 3-column format of the labeling which provides justifications for some of the labeling revisions. Some of the changes to the package insert provided in the line-by-line format may not have been captured in the 3-column format, so please consider the former as the "official" version. Please note that changes to the clinical pharmacology section of the labeling may be made since I was not able to confirm all revisions with the reviewer at this time. It is also possible that Dr. Temple will make additional changes to the labeling overall.

I will send you the minutes from the August 16, 1999 meeting via fax as soon as I receive them from Patrick. We look forward to receiving the carton and container labeling next week.

Sincerely, /s/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 50-778
HFD-150 / Div File
/ D. Spillman

22 pages redacted from this section of
the approval package consisted of draft labeling

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Denise S. Tindle

From: Dianne Spillman

Fax: (616) 833-0409

Fax: (301) 594-0499

Phone: (616) 833-3825

Phone: (301) 594-5746

Pages (including cover): 31

Date: September 15, 1999

Re: NDA 50-778: Approval letter & labeling

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● **Comments:**

Denise –

Here is the approval letter, package insert, and carton/vial labeling for epirubicin. Please call me to confirm receipt of this fax. Thank you.

Sincerely /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

CC: NDA 50-778
HFD-150 / Div Files
/ D. Spillman.

MESSAGE CONFIRMATION

09/15/99 19:38
ID=ONCOLOGY/DOPDP/ODE-I/CDER/FDA

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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: Denise S. Tindle

From: Dianne Spillman

Fax: (616) 833-0409

Fax: (301) 594-0499

Phone: (616) 833-3825

Phone: (301) 594-5746

Pages (Including cover): 31

Date: September 15, 1999

Re: NDA 50-778: Approval letter & labeling

Urgent For Review Please Comment Please Reply Please Recycle

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• Comments:

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the approval package consisted of draft labeling

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**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: August 8, 1999

COMMENTS: Please refer to your NDA 50-778 regarding epirubicin hydrochloride for injection. Please see the attached Chemistry comments concerning your proposed carton and container labels.

Chemistry Comments:

1. The type size for "epirubicin hydrochloride" appears to be too small. According to 21 CFR 201.10(g)(2), "The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation....", therefore, the type size should be increased.
2. The term "For Intravenous Use" should be changed to "For Intravenous Use Only".
3. The storage statement in the labeling should be highlighted.
4. Addition of the term "Caution-Cytotoxic Agent" to the labeling for cartons is recommended.

Additional Comment:

- The logo  should be deleted from the labeling. In addition, the possibility of using it in advertisements would need to be discussed with DDMAC.

APPEARS THIS WAY
ON ORIGINAL

If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: August 8, 1999

COMMENTS: Please refer to your NDA 50-778 regarding epirubicin hydrochloride for injection. Please see the attached Chemistry comments concerning your proposed carton and container labels.

001 NO.159

08/09/99 15:20

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
08/09	00:40"	616 833 0409	CALLING	02	OK

08/09/99 15:21

MESSAGE CONFIRMATION

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: July 28, 1999

COMMENTS: Please refer to your NDA 50-778 regarding epirubicin hydrochloride for injection. Please see the attached Chemistry comments and information request.

*cc: Orig NDA 50-778
Dir File
SKim
PGuinn*

We are reviewing your submission and have identified the following comments and information requests:

Please respond to the following comments raised during the review of the amendments dated 5/27/99, 6/9/99 and 6/14/99:

1. Please provide information on the analytical method used for the reference standard, if the method is not provided in the original NDA application (see page 42, amendment of 6/14/99). The method should be identified by a specific code number, which was used in the original NDA application.
2. Concerning a specific identity test for the drug product, please refer to the ICH Q6A Guidance on "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" for further assistance. The guidance states that an identity test using only chromatographic retention times is not acceptable and a combination of tests into a single procedure, such as _____ may be acceptable. A specific identity test should be developed and included in the specifications for the drug product (e.g. IR) unless data are provided to justify difficulties in the development of a specific identity test. The provided comparative IR data suggests that an IR identity test could discriminate epirubicin from doxorubicin.
3. Bracketing usually includes the smallest and largest container sizes, based on container sizes proposed in NDA, regardless of sizes intended for marketing. The proposed bracketing commercial stability protocol at accelerated conditions appears to be inadequate due to the nature of the parenteral dosage form of the drug product packaged in different vial sizes. Different vial sizes could affect the stability of the drug product and must be validated with significant body of stability data. In addition, please note that a sterility test should be performed yearly during the stability studies. Please include the following commitments in the commercial stability protocol:
 - A sterility test will be performed yearly during the long-term stability studies.
 - The first three commercial batches of all different container sizes will be placed on accelerated stability conditions.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

... is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: July 28, 1999

COMMENTS: Please refer to your NDA 50-778 regarding epirubicin hydrochloride for injection. Please see the attached Chemistry comments and information request.

NO. 103 001

07/28/99 12:06

07/28 00:56" 616 833 0409 CALLING 02 OK 0000
DATE S,R-TIME DISTANT STATION ID MODE PAGES RESULT

07/28/99 12:08

MESSAGE CONFIRMATION

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindle (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: June 14, 1999

COMMENTS: Please refer to your NDA 50-778 (21-010) regarding epirubicin hydrochloride for injection. Please see the attached revision to a comment contained within the information request that was previously forwarded to you by facsimile transmission on May 14, 1999, and June 4, 1999.

*Orig NDA 50-778
Div File
P Guinn*

D) The following pertain to labeling:

2. Concerning labeling for vial, the term "Single dose vial" should be changed to " Single dose x ml vial". "x" represents 5ml, 10ml, 25ml, 75ml and 100ml depending on the presentation.

Should be revised as stated:

- Concerning labeling for carton and vial, the term " Single Dose Vial" should be changed to "Single Use X ml Vial". "X" represents 5 ml, 10ml, 25ml, 75ml and 100ml depending on the presentation.
- The term "Contains one X ml vial" in the carton labeling could be deleted.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
ON ORIGINAL**

DISCLOSURE UNDER THE PRIVACY ACT. If you are not the addressee, or a person authorized to receive this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindle (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: June 14, 1999

COMMENTS: Please refer to your NDA 50-778 (21-010) regarding epirubicin hydrochloride for injection. Please see the attached revision to a comment contained within the information request that was previously forwarded to you by facsimile transmission on May 14, 1999, and June 4, 1999.

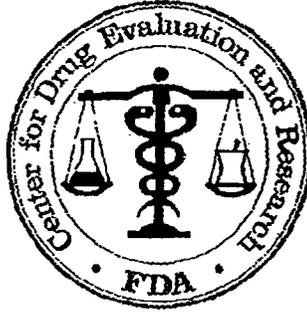
NO. 181 12:31 06/15/99

06/15 00:40 616 833 0409 CALLING 02 OK 0000
DATE S.R-TIME DISTANT STATION ID MODE PAGES RESULT

06/15/99 12:33

MESSAGE CONFIRMATION

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 15

Date: June 4, 1999

COMMENTS: Please refer to your NDA 50-778 (21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments and information request that were previously forwarded to you by facsimile transmission on May 14, 1999. This information is needed in order to complete the Chemistry review of your NDA. Please provide this information as soon as possible.

*cc: Orig NDA 50-778
Div File
SKim
[Signature]*

We are reviewing your submission and have identified the following comments and information requests:

A) The following concern manufacturing aspects of the drug substance:

- 1) It is stated that an identity test [redacted] will be performed at Pharmacia & Upjohn, Perth, Australia. Identity tests listed in the regulatory specifications should be performed at the Perth, Australia site [redacted].
- 2) Regarding specifications for Daunorubicin HCl, provided on page 220, v2.4, limits for total related substances should be included. In addition, please provide certificates of analysis for the recent representative batches for Daunorubicin HCl, which was used to manufacture Epirubicin HCl.
- 3) [redacted], please provide an acceptable yield range (expressed in percentage)
- 4) [redacted]
- 5) It is stated on page 214, v2.4 [redacted] obtained from 4-6 column runs. Do the 4-6 column runs mean 4-6 batch runs? What is the storage condition during the holding time? Do you observe any stability problems during the holding time? What are the acceptance criteria for the mixture [redacted] in order to proceed according to the b) process on page 214, v2.4?
- 6) Concerning [redacted] column, please define the rich eluate solution. What is the sieve size which was used in the manufacture of the drug substance? What is the typical particle size distribution of the drug substance? Was there any correlation between particle size of the drug substance and solubility? Please justify the absence of a control for particle size of the drug substance.
- 7) Concerning column [redacted] limits for rich fractions should be included in the in-process controls, based on the definition of rich fractions.
- 8) What is the acceptance criteria for reaction completion of the [redacted] (page 294, v2.4)?
- 9) The in-process control of NMT [redacted]% for [redacted] appears to be wide. Please justify the limit for this intermediate, based on manufacturing experience and analytical data.
- 10) Please justify specifications for [redacted]. Justifications should be based on available batch analysis data for the intermediate # 4 manufactured according to the NDA process.
- 11) Please describe any differences in physico-chemical properties, including spectral data, between the drug substance and doxorubicin HCl (e.g. melting point, NMR data, etc.).

B) The following comments should be addressed regarding the controls, analytical results, and stability of the drug substance:

- 1) Please provide specifications for the reference standard. Please note that a reference standard should have the highest purity reasonably attainable. Thus, the specifications for the reference standard should be tighter than that for the bulk drug substance.
- 2) It appears that the site for release testing of the bulk drug substance is different from that for acceptance testing. Please clarify.
- 3) The proposed limits for residual solvents appear to be acceptable, in accordance with the ICH Guidance Document on residual solvents. However, tightening of the limits is suggested to ensure consistency of quality and purity of the drug substance, when warranted by available batch data. Please justify the proposed high limits. —
- 4) Please list all identified related substances which belong to "each other unspecified" as a footnote in the specifications (see page 11, v2.4 and page 88, v2.5).
- 5) Limits for related substances should be tightened to ensure quality and purity of the drug substance, when warranted by batch data and stability data. —
- 6) Limits for residue on ignition and heavy metals should be included in the specifications, or justifications given for their absence.
- 7) It is stated that measurement of specific optical rotation of the drug substance was difficult due to a very deep red-orange color. Justification should be provided for not having data for the specific optical rotation. Justification should include any attempts to measure the specific optical rotation and results observed. In addition, explain why monitoring the specific optical rotation is not necessary in the specifications for the drug substance.
- 8) An identity test should be developed and added to specifications to discriminate the drug substance from doxorubicin HCl.
- 9) Please identify the manufacturing process (NDA process vs current process) for each drug substance which was used to manufacture the drug product presented on page 66-73, v2.5.
- 10) Please provide information on the supplier and/or the manufacturer of the glass bottle and polyethylene liner used for packaging the drug substance.
- 11) Primary stability data for the drug substance should be updated, when available. It is expected that at least 9 month data should be submitted for batches 8064FS41G, 8065FS41G, and 8066DS41G and 6 month data for batches 8112LS41G, 8113LS41G, and 8114LS41G by May, 1999.
- 12) Please discuss and provide information on major degradation products of Epirubicin HCl under stress conditions such as acidic, basic, oxidative, and thermal conditions.

C) We have the following comments concerning the drug product:

- 1) It is stated that labeling for the drug product may also take place in Phamacia & Upjohn, Kalamazoo, MI 49001. Identity tests for the drug product, as a minimum, should be performed before labeling at the Kalamazoo site.
- 2) It is noted that certain parameters and the format in the master batch records provided in v 2.6 are different from those in the executed batch records provided in v 2.7 (e.g. mixing time and speed, etc.). Please summarize any differences between two batch records and explain whether the differences are significant or not in terms of product quality, purity and stability. In addition, clarify which format for the batch record was used to manufacture primary stability batches. Please provide executed batch records for the primary stability batches (e.g. one typical executed batch record for each strength).
- 3) Limits for each known related substances should be established and included in the specifications for the drug product, if the identified related substance is known to be a degradant.
- 4) A specific identity test should be included. An additional identity test should be developed and added to discriminate stereochemistry of the OH group at C-4' in the drug substance from that in doxorubicin HCl.
- 5) Regarding the post-approval commitment provided on page 302, v2.6, a) the first three production batches packaged in each proposed container size should be placed on stability studies and the commitment should be revised accordingly (e.g. 5ml, 10ml, 25ml and 100ml vial sizes); b) in the Table G.10 should be revised to related substances which were known to be degradation products should be monitored.
- 6) Please update the primary stability data. Primary stability data should be updated to 9 months by the end of May, 1999.

D) The following pertain to labeling:

- 1)
- 2)
- 3)
- 4)

Draft

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
ON ORIGINAL**

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 85

Date: June 4, 1999

COMMENTS: Please refer to your NDA 50-778 (21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments and information request that were previously forwarded to you by facsimile transmission on May 14, 1999. This information is needed in order to complete the Chemistry review of your NDA. Please provide this information as soon as possible.

NO. 134 001

06/04/99 12:46

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	RESULT	PAGES	MODE	DISTANT STATION ID	S,R-TIME	DATE

06/04/99 12:49

MESSAGE CONFIRMATION

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Daniel G. Mannix, Ph.D. (616) 833-8095
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 4

Date: June 3, 1999

COMMENTS:

Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments regarding your DRAFT slides for presentation at the ODAC Meeting on June 7, 1999.

*2- Orig NDA 50-778
Div File
S Henig
D*

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Daniel G. Mannix, Ph.D. (616) 833-8095
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 4

Date: June 3, 1999

COMMENTS:

Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments regarding your DRAFT slides for presentation at the ODAC Meeting on June 7, 1999.

NO. 125 001

06/03/99 15:22

06/03 01:17 616 833 0409 CALLING 04 OK 0000

DATE S,R-TIME DISTANT STATION ID MODE PAGES RESULT

06/03/99 15:24

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 38

Date: June 3, 1999

COMMENTS:

Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached DRAFT slides for the FDA presentation at the June 7, 1999 ODAC Meeting.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 38

Date: June 3, 1999

COMMENTS:

Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached DRAFT slides for the FDA presentation at the June 7, 1999 ODAC Meeting.

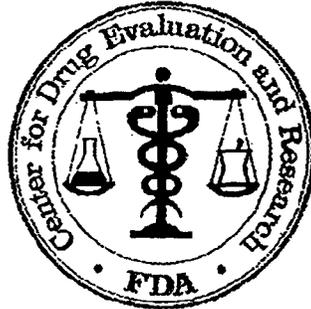
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06/03/99 17:33

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: June 1, 1999

COMMENTS: Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments and information regarding the status of your proposed Tradenames.

cc: orig NDA 50-778 (21-010)

Div File

[Redacted]

Upon further review of your proposed Tradename, it has been determined that the name ELLENCE is acceptable.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
ON ORIGINAL**

please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825

Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager

Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: June 1, 1999

COMMENTS: Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments and information regarding the status of your proposed Tradenames.

NO. 107 15:24 06/01/99

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DATE S,R-TIME DISTANT STATION ID MODE PAGES RESULT

06/01/99 15:25

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: May 28, 1999

COMMENTS: Please refer to your NDA 50-778 (previously 21-010) regarding epirubicin hydrochloride for injection. Please see the attached comments and information regarding the status of your proposed Tradenames.

cc = Orig NDA 50-778

Div File

Guinn

Upon review of your proposed Tradenames, your proposals for [REDACTED] Ellence were determined to be unacceptable for the following reasons:

[REDACTED] - This proposed name would be considered misleading and inaccurate because it is not a product active against all cancer.

[REDACTED] This proposed name would be considered misleading because "Epi" is often used to indicate a product contains epinephrine.

Ellence - We are still checking on the justification of finding this proposed name as unacceptable.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

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ON ORIGINAL

... immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: May 28, 1999

COMMENTS: Please refer to your NDA 50-778 (previously 21-010) regarding
epirubicin hydrochloride for injection. Please see the attached comments
and information regarding the status of your proposed Tradenames.

001 NO.086

05/28/99 09:47

DATE	S.R-TIME	DISTANT	STATION ID	MODE	PAGES	RESULT
05/28	00:39	616 833	0409	CALLING	02	OK

05/28/99 09:49

MESSAGE CONFIRMATION

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: May 21, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.
#10

*cc=orig NDA ~~24-010~~ 50-778
Div File
S Monig
P Guina*

We are reviewing your submission and have identified the following comments and information requests:

1. In study HEPI/010, one patient randomized to FEC 50 was taken off study after one cycle because of pregnancy. Please provide a narrative for this patient, including information about whether the pregnancy was carried to term and if so, the status of the baby.
2. What was the data lock date for study HEPI/010?

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
ON ORIGINAL**

please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: May 21, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

NO.062 11:32 05/21/99

05/21 00'43" 616 833 0409 CALLING 02 OK 0000
DATE S.R-TIME DISTANT STATION ID MODE PAGES RESULT

05/21/99 11:34

MESSAGE CONFIRMATION

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 11

Date: May 21, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information regarding the status of your application. Please also refer to the attachment (Guidance for Industry and Reviewers) regarding the Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act for additional information.

CC: Orig NDA 21-010 50-788
Div File
Guinn

Upon determining that your application NDA 21-010 is for an antibiotic, epirubicin, there are several changes that have occurred that directly affect your application. These changes are as follows:

1. The NDA reference number has been changed from 21-010 to 50-778.

Please refer to the explanation as provided in the attached guidance under:

III. POLICIES

B. Application Numbering Conventions

2. This application is considered a submission of an "old" antibiotic because an NDA for epirubicin was submitted on or before November 20, 1997.

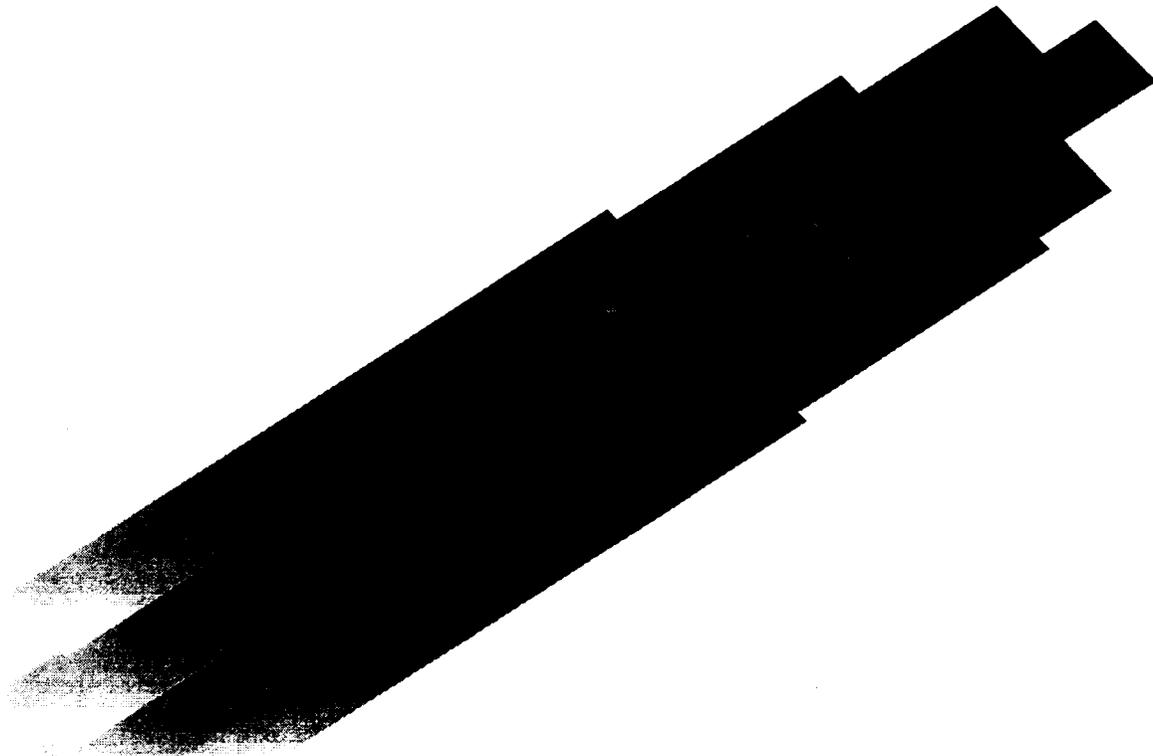
Please refer to the attached guidance, which should clarify how your application may be affected in other ways.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
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Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Procedural I**

Revised, May 1998

Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
The Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573

(Internet) <http://www.fda.gov/cder/guidance/index.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

Procedural 1

Revised, May 1998

Table of Contents

I. INTRODUCTION 1

II. SUMMARY OF SECTION 125 OF THE FDAMA 1

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GUIDANCE FOR INDUSTRY AND REVIEWERS¹

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

I. INTRODUCTION

Section 125 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law by President Clinton on November 21, 1997, repealed section 507 of the Federal Food, Drug, and Cosmetic Act (the Act). As a result of the repeal of section 507, which took effect immediately, several of the Agency's administrative processes for reviewing and approving antibiotic drug applications must be changed. This document is intended to clarify, on an interim basis, the administrative processes that will be followed in implementing section 125 of the Modernization Act. In the current revision, the Agency clarifies the procedures applicable to bulk drug substances for products previously regulated under section 507.

II. SUMMARY OF SECTION 125 OF THE FDAMA

Prior to the enactment of the Modernization Act, the Agency approved antibiotic drug marketing applications under section 507 of the Act. In addition, section 507 required the Agency to publish regulations (antibiotic monographs) that set forth standards of identity, strength, quality, and purity for each marketed antibiotic drug.

As a result of the repeal of section 507, the Agency's legal obligation to publish antibiotic monographs has been eliminated from the Act. Moreover, all antibiotic drug applications will now be filed, reviewed, and approved under section 505 of the Act, as are all other new drugs.

Section 125 of the Modernization Act specifically provides that:

1. All full applications approved under section 507 on or before November 20, 1997, are now deemed to have been submitted and filed under section 505(b) and approved for safety and effectiveness under section 505(c).
2. All abbreviated applications approved under section 507 on or before November 20, 1997, are now deemed to have been filed and approved under section 505(j). (The status of antibiotic bulk drug applications that were submitted or approved under former section

¹This guidance has been prepared by the Antibiotic Working Group of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the implementation of the repeal of section 507 of the Federal Food, Drug, and Cosmetic Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

507 is discussed in section III.F., below.)

3. All applications for drugs that contain an antibiotic that was the subject of any marketing application *received by the Secretary* on or before November 20, 1997, (hereafter referred to as an "old" antibiotic) are exempt from the patent listing, patent certification, and exclusivity provisions in section 505. (See section III.C, below.) The effects of this exemption provision include the following:
 - a. Antibiotic drug marketing applications that were pending in FDA on or before November 20, 1997, need not be updated with the patent information required under section 505(b)(1) and would not be eligible to claim exclusivity under sections 505(c) or 505(j).
 - b. Already approved antibiotic drug marketing applications need not be updated with patent information and cannot seek exclusivity under sections 505(c) or 505(j).
 - c. New applications (those received on or after November 21, 1997) under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information and are not eligible for exclusivity under sections 505(c) or 505(j).
 - d. An application received on or after November 21, 1997, that does not contain an "old" antibiotic would be required to file patent information and could seek exclusivity, as appropriate, under sections 505(c) or 505(j).
 - e. An abbreviated application under section 505(j) or an application under section 505(b)(2) that refers to a drug that does not contain an "old" antibiotic would be required to include appropriate patent certifications and may be subject to the exclusivity provisions in sections 505(c) or (j), as appropriate.
4. Finally, section 125 preserves for all products containing an antibiotic drug the special export status that has been allowed over the years for antibiotic drugs.

III. POLICIES

A. Definitions

For purposes of section 125 of the Modernization Act, the "date of the enactment of this Act" is November 21, 1997. *Before the date of the enactment of this Act* means on or before November 20, 1997.

B. Application Numbering Conventions

Because of the exemptions that apply to *old* antibiotics, we will continue to maintain our numbering system for new drug applications to allow us to distinguish between applications that contain *old* antibiotics and all other applications. Beginning November 21, 1997, we will apply our NDA numbering system as follows:

1. All applications (except bulk drug applications) assigned a series 50,000 or series 60,000 NDA number on or before November 20, 1997, will keep that number. As discussed above, the exemption provisions in section 125 that exempt applications for drugs that contain "old" antibiotic drugs from the patent listing, patent certification, and exclusivity provisions in section 505 of the Act apply to these applications. For bulk drug applications assigned series 60,000 numbers on or before November 20, 1997, see section III.F, below.
2. Series 50,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions apply.
3. Series 60,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions apply.
4. Series 20,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions do not apply.
5. Series 70,000 or 40,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions do not apply.

Example. The marketing application (NDA) for azithromycin was submitted to FDA (i.e., the Secretary) before November 21, 1997. If, on or after November 21, 1997, another NDA is submitted for a new dosage form or a new indication for azithromycin, this newly submitted NDA would be assigned a series 50,000 number because the drug (i.e., azithromycin) that is the subject of the new NDA was originally received by the Secretary (see section C.2., below) prior to November 21, 1997.

C. Applications Subject to Section 125 Exemptions

Section 125 of the Modernization Act exempts from the patent listing, patent certification, and sections 505(c) and (j) marketing exclusivity provisions, marketing applications for drugs that contain *old* antibiotics. (See section 125(d)(2) of the Modernization Act for a list of the specific provisions in section 505 of the Act that do not apply to applications that contain *old* antibiotics.) For purposes of implementing this provision, consider these

points in deciding whether an application is subject to the exemption.

1. The drug that is the subject of the application must contain (in whole or as part of a combination) an *antibiotic drug*. As was the case prior to the repeal of section 507, an *antibiotic drug* is:

any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance) or any derivative thereof. (See new section 201(jj) of the Act.)

2. The antibiotic drug that is contained in the application must have been the subject of a marketing application that was *received by the Secretary* on or before November 20, 1997. For purposes of section 125 of the Modernization Act, this would include any antibiotic application (including an old Form 5 or Form 6 application) that was:
 - a. Received by FDA (as evidenced by an Agency date stamp) on or before November 20, 1997.
 - b. Filed or approved on or before November 20, 1997.
 - c. Received on or before November 20, 1997, and is presently under review.
 - d. The subject of an action letter on or before November 20, 1997 (e.g., AE, NA, or WD), and is now *back with the company*.
 - e. Received on or before November 20, 1997, filed, reviewed, approved, and then withdrawn from the market (either for safety or other reasons).
 - f. Received on or before November 20, 1997, and then withdrawn prior to filing and has not been further submitted.
 - g. Received on or before November 20, 1997, and subsequently refused filing and has not been further submitted.
 - h. Received on or before November 20, 1997, and was unacceptable for filing under PDUFA for failure to submit the appropriate user fee and has not been further submitted.

For purposes of section 125 of the Modernization Act *received by the Secretary* does *not* mean (1) canceled applications (i.e., administrative errors) or (2)

applications for which only a *presubmission* was received without a full submission ever having been received subsequently by the Agency. (See also 21 CFR 314.101(d).)

3. Other factors, such as the extent to which derivatives of the active moiety of an *old* antibiotic are also considered to be *old* antibiotics, are beyond the scope of this administrative guidance and may be addressed as part of an Agency rulemaking proceeding.²

D. Action Letters

Beginning November 21, 1997, the action letter templates for 507 drugs will no longer be used. Section 507 no longer provides a statutory basis for approval of a drug product. All action letters must use the 505(b) or 505(j) templates, even for drugs that originally were submitted under section 507, but are the subject of Agency action on or after November 21, 1997.

For action letters on marketing applications to which the section 125 exemptions apply,² the following sentence should be added after the initial reference to section 505: "We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997."

E. Monographs

On and after November 21, 1997, FDA will no longer publish or maintain antibiotic monographs in the Code of Federal Regulations (CFR). Products approved under section 505 do not require such monographs. The Agency recently published a direct final rule to remove the antibiotic monographs from the CFR (63 FR 26066, May 12, 1998).

F. Bulk Drug Applications (Pending and Approved)

Prior to the repeal, the Agency consistently read section 507 to require that bulk antibiotic drug substances must be either batch certified or exempted from batch certification through the approval of an antibiotic drug application. Applications for bulk antibiotic drugs were previously assigned 60,000 application numbers. The Agency, however, has not required the filing or approval of such an application under section 505 for bulk drug substances used in the manufacture of non-antibiotic new drug products. Rather, in accordance with 21 CFR 314.420, information about drug substances, drug substance intermediates, and materials used in their preparation or in the preparation of new drug

² Section 125 of the Modernization Act also authorizes the Secretary to publish the established name of each antibiotic drug that is subject to the section 125 exemption (i.e., each "old" antibiotic drug). The Agency has not yet decided how it will implement this authority.

products may be filed and maintained as Type II Drug Master Files (DMFs). Alternatively, drug substance information may be filed as part of the marketing application for the finished dosage form of the drug.

In light of the repeal of section 507 and the Agency's longstanding regulatory approach to handling bulk drug substances under section 505, the Agency intends to administratively convert all antibiotic bulk drug substance applications ("bulk applications") into DMFs.

Action — After August 31, 1998, all unapproved bulk applications that were pending in CDER as of November 21, 1997, will be administratively converted into DMFs. Likewise, after August 31, 1998, FDA will begin administratively converting all approved bulk applications into DMFs. Any bulk application received by CDER after November 21, 1997, will be returned to the applicant. The agency has not approved any bulk applications since the repeal of section 507 went into effect on November 21, 1997.

Following issuance of this revised guidance, the Agency will provide written notice to each sponsor of a bulk application of the Agency's intention to convert the application into a DMF. Following the conversion of each application, the Agency will notify the sponsor of the newly assigned DMF reference number.

The Agency does not intend at this time to require sponsors of converted bulk applications to submit new letters of authorization for each of the dosage form manufacturers who may reference the DMF. Similarly, the Agency does not expect to require dosage form manufacturers to amend their marketing applications to reference the newly assigned DMF number. However, following conversion of a bulk application, any new letters of authorization or other correspondence relating to the bulk substance will be expected to reference the new DMF number, in accordance with 21 CFR 314.420(b).

Sponsors of bulk applications need not take any action for their applications to be converted. The Agency expects most, if not all, bulk applications will be handled under this process. However, if a sponsor does not wish to maintain a DMF for a particular bulk drug substance, the information in the bulk application may be merged into one or more dosage form applications, or the Agency may cancel and retire the application in accordance with Agency record keeping practices. The Agency also would consider requests for more expeditious conversion of bulk applications to DMFs from sponsors who would like their applications converted before August 31, 1998. Sponsors interested in one of these alternatives should contact Jerry Phillips, Director, Division of Labeling and Program Support, CDER, at 301-827-5846, before August 31, 1998.

please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 11

Date: May 21, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information regarding the status of your application. Please also refer to the attachment (Guidance for Industry and Reviewers) regarding the Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act for additional information.

NO. 065 01

05/21/99 15:16

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
05/21	03:15	616 833 0409	CALLING	09	OK

05/21/99 15:20

MESSAGE CONFIRMATION

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: May 14, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*cc: orig NDA 21-010
Div File
SKim
PGuinn*

DUPLICATE

We are reviewing your submission and have identified the following comments and information requests:

A) The following concern manufacturing aspects of the drug substance:

- 1) It is stated that an identity test [redacted] will be performed at Pharmacia & Upjohn, Perth, Australia. Identity tests listed in the regulatory specifications should be performed at the Perth, Australia site [redacted].
- 2) Regarding specifications for Daunorubicin HCl, provided on page 220, v2.4, limits for total related substances should be included. In addition, please provide certificates of analysis for the recent representative batches for Daunorubicin HCl, which was used to manufacture Epirubicin HCl.
- 3) [redacted] please provide an acceptable yield range (expressed in percentage) for each synthetic step.
- 4) [redacted]
- 5) It is stated on page 214, v2.4 that [redacted] are obtained from 4-6 column runs. Do the 4-6 column runs mean 4-6 batch runs? What is the storage condition during the holding time? Do you observe any stability problems during the holding time? What are the acceptance criteria for the mixture [redacted] in order to proceed according to the b) process on page 214, v2.4?
- 6) Concerning [redacted] column, please define the rich eluate solution. What is the sieve size which was used in the manufacture of the drug substance? What is the typical particle size distribution of the drug substance? Was there any correlation between particle size of the drug substance and solubility? Please justify the absence of a control for particle size of the drug substance.
- 7) Concerning column [redacted] limits for rich fractions should be included in the in-process controls, based on the definition of rich fractions.
- 8) What is the acceptance criteria for reaction completion of [redacted] (page 294, v2.4)?
- 9) The in-process control of NMT [redacted] % for [redacted] appears to be wide. Please justify the limit for this intermediate, based on manufacturing experience and analytical data.
- 10) Please justify specifications for intermediate [redacted]. Justifications should be based on available batch analysis data for the intermediate # 4 manufactured according to the NDA process.
- 11) Please describe any differences in physico-chemical properties, including spectral data, between the drug substance and doxorubicin HCl (e.g. melting point, NMR data, etc.).

B) The following comments should be addressed regarding the controls, analytical results, and stability of the drug substance:

- 1) Please provide specifications for the reference standard. Please note that a reference standard should have the highest purity reasonably attainable. Thus, the specifications for the reference standard should be tighter than that for the bulk drug substance.
- 2) It appears that the site for release testing of the bulk drug substance is different from that for acceptance testing. Please clarify.
- 3) The proposed limits for residual solvents appear to be acceptable, in accordance with the ICH Guidance Document on residual solvents. However, tightening of the limits is suggested to ensure consistency of quality and purity of the drug substance, when warranted by available batch data. Please justify the proposed high limits for _____
- 4) Please list all identified related substances which belong to "each other unspecified" as a footnote in the specifications (see page 11, v2.4 and page 88, v2.5).
- 5) Limits for related substances should be tightened to ensure quality and purity of the drug substance, when warranted by batch data and stability data. _____
- 6) Limits for residue on ignition and heavy metals should be included in the specifications, or justifications given for their absence.
- 7) It is stated that measurement of specific optical rotation of the drug substance was difficult due to a very deep red-orange color. Justification should be provided for not having data for the specific optical rotation. Justification should include any attempts to measure the specific optical rotation and results observed. In addition, explain why monitoring the specific optical rotation is not necessary in the specifications for the drug substance.
- 8) An identity test should be developed and added to specifications to discriminate the drug substance from doxorubicin HCl.
- 9) Please identify the manufacturing process (NDA process vs current process) for each drug substance which was used to manufacture the drug product presented on page 66-73, v2.5.
- 10) Please provide information on the supplier and/or the manufacturer of the glass bottle and polyethylene liner used for packaging the drug substance.
- 11) Primary stability data for the drug substance should be updated, when available. It is expected that at least 9 month data should be submitted for batches 8064FS41G, 8065FS41G, and 8066DS41G and 6 month data for batches 8112LS41G, 8113LS41G, and 8114LS41G by May, 1999.
- 12) Please discuss and provide information on major degradation products of Epirubicin HCl under stress conditions such as acidic, basic, oxidative, and thermal conditions.

C) We have the following comments concerning the drug product:

- 1) It is stated that labeling for the drug product may also take place in Pharmacia & Upjohn, Kalamazoo, MI 49001. Identity tests for the drug product, as a minimum, should be performed before labeling at the Kalamazoo site.
- 2) It is noted that certain parameters and the format in the master batch records provided in v 2.6 are different from those in the executed batch records provided in v 2.7 (e.g. mixing time and speed, etc.). Please summarize any differences between two batch records and explain whether the differences are significant or not in terms of product quality, purity and stability. In addition, clarify which format for the batch record was used to manufacture primary stability batches. Please provide executed batch records for the primary stability batches (e.g. one typical executed batch record for each strength).
- 3) Limits for each known related substances should be established and included in the specifications for the drug product, if the identified related substance is known to be a degradant.
- 4) A specific identity test should be included. An additional identity test should be developed and added to discriminate stereochemistry of the OH group at C-4' in the drug substance from that in doxorubicin HCl.
- 5) Regarding the post-approval commitment provided on page 302, v2.6, a) the first three production batches packaged in each proposed container size should be placed on stability studies and the commitment should be revised accordingly (e.g. 5ml, 10ml, 25ml and 100ml vial sizes); b) _____ in the Table G.10 should be revised to _____ c) related substances which were known to be degradation products should be monitored.
- 6) Please update the primary stability data. Primary stability data should be updated to 9 months by the end of May, 1999.

D) The following pertain to labeling:

- 1) Concerning the proposed package insert, the proposed chemical name _____ should be changed to "(8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride".
- 2) Concerning labeling for vial, the term "Single dose vial" should be changed to "Single dose x ml vial". "x" represents 5ml, 10ml, 25ml, 75ml and 100ml depending on the presentation.
- 3) Please submit a draft layout of labeling for the vial and carton.
- 4) Proposed trademarks, _____ ELLENCE were found to be unacceptable. However, _____ was adequate as proposed.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: May 14, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

NO. 026 001

15:55

05/14/99

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
05/14	01:53	616 833 0409	CALLING	05	OK

05/14/99 15:58

MESSAGE CONFIRMATION

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

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Rockville, Maryland 20857

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: May 7, 1999

COMMENTS: #9 Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

cc = Orig NDA 21-010
Div File
Stonig
P Guinn

We are reviewing your submission and have identified the following comments and information requests:

1. For future applications, please enter dates in date format, not as text. Similarly, please do not enter tumor measurements as text; instead, please enter as numbers. It requires additional time and manipulations on the part of the reviewer to transform these data points into a format that can be used to recalculate and verify your reported results.
2. Please also use unique tumor identifiers in future database designs. In study HEPI013, all lesions in the liver, for example, were given a designation of "site 1". It was necessary for the reviewer to create a unique tumor ID from the site number ("1"), the organ ("lymph nodes", and the description ("left supraclavicular", "right cervical") in order to begin to verify time to progression results.
3. In reviewing the table "Lesion" for advanced breast cancer, it does not appear that measurements for new lesions not present at baseline were entered into the database. Is this interpretation correct?
4. In reviewing changes in LVEF for study HEPI013, it appears that all 5 patients accrued at site 70 entered with baseline LVEF values of 30-35%. These patients were placed at significant risk for cardiac events, if the database entries are correct. Have you discussed these violations with the principal investigator at that site?
5. Have the results of HEPI013 been published? If so, please provide the reference if it is not included in the NDA.
6. The study report for HEPI 010 (volume 2.44, page 8/35/028) lists definitions of measurability of lesions. These definitions were not included in the protocol document. Did analysts at P&U apply these definitions retrospectively? If so, how did this affect the numbers of patients deemed to be measurable versus evaluable? Did it change the calculated response rate or TTP?
7. On study HEPI 010, 214 patients were randomized to FEC 100 and 242 were randomized to FEC 50. Is this imbalance due to the 4 strata and need to balance by center?
8. Thank you for your comments about the randomization process for study GFEA05. Within each center, how big were the randomization blocks? (For example, frequently randomization lists are generated for blocks of 4).

Please respond to these and the other outstanding questions as soon as possible.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is

finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
ON ORIGINAL**

MESSAGE CONFIRMATION

05/07/99 10:50

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
05/07	01'01"	616 833 0409	CALLING	03	OK 0000

05/07/99 10:48

NO. 039 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: May 7, 1999

Total number of pages, including cover sheet 3

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301) 594-2473 FAX: (301) 594-0498

... us of telephone and return it to us at the above address by mail. Thank you.

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 6

Date: May 6, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. We remind you that we are still awaiting a response to the comments and information requests that were sent via facsimile transmission on March 25 and April 15, 1999. I have attached those comments and information requests that have not been addressed for your convenience. If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

*cc: Orig NDA 21-010
Div File
S Monig*

FAX sent March 25, 1999 (Questions 2, 4, 5, 6, 8 and 9 have not been addressed)

1. In volume 2.29, page 8/20/317, the first narrative refers to the drug "isoprenaline." Please clarify the nature of this drug--it is not listed/manufactured in the United States. Is it isuprel?
2. In protocol MA-5, one of the sites was Hospital St. Luc. Was _____ one of the associate investigators at this site? Did he enter any patients on the trial?
3. In protocol MA-5, premenopausal women were analyzed separately from perimenopausal women as exploratory subset analyses. What definitions were used to distinguish pre- and perimenopausal status?
4. Did you include the investigator's term for adverse events in the database? For example, in study MA-5, I am trying to locate the actual description by the investigator that corresponds to the cardiovascular AE categories of "function", "pain", "dysrhythmia", "edema", and "venous."
5. According to the MA-5 protocol, MUGA scans were used to determine cardiac function, but ECHO could be used if the center did not have nuclear medicine capabilities. From the FDA.CARVAS database, it appears that all centers used MUGA scans throughout the study, and no one was tested for LVEF with an ECHO. Is this statement correct?
6. According to the MA-5 protocol, patients with clinical T1-3 were eligible. Patients with pathologic evidence of dermal lymphatic invasion were still eligible, provided that there was no clinical evidence of inflammatory breast cancer prior to surgery. How many patients had dermal lymphatic invasion seen at path? This information is not included in the database.
7. Please provide electronically the number of involved nodes found for each patient in studies MA-5 and GFEA-5. This information was not coded in the database.
8. How many patients entered study MA-5 with bilateral breast cancer? How many had unilateral versus bilateral axillary node dissections? What was the pathologic staging for each cancer in these patients? This information is not provided in the electronic database.
9. In MA-5, how many women had positive margins after lumpectomy and did not undergo re-excision? This information is not in the database.
10. Please identify the 6 patients on MA-5 who received concurrent radiation therapy and chemotherapy. From my database queries, I think the patients on the CEF arm are patients MG2 and PN1.

For CMF, all of the following patients appear to have overlapped radiation and chemotherapy treatments:

CENTER	PATID
GS	3

HO 6
KG 2
LM 77
MN 21
MN 27
MP 3
MP 9
MV 4
SA 2
SS 27

Which patients were considered to have received concurrent treatment in your analysis? Were some patients excluded because they started radiation during the second half of C6 (i.e., before the official end of therapy, but after all drugs were administered on days 1-14)?

Is this correct? Please provide the reasons for dose reductions in these patients.

Second FAX sent March 25, 1999 (Questions 1, 2, and 3 have not been addressed)
In addition, we provided a clarification of a question sent to you on March 5, 1999 which has not been addressed.

1. Investigative groups have attempted to define a set of anthracycline doses that are "equivalent" to certain doses of doxorubicin. Do you have a defined "equivalence set" for epirubicin and doxorubicin? For example, what dose of epirubicin do you feel is comparable to doxorubicin doses of 300 mg/m² and 450 mg/m²?

2. Were serotonin receptor antagonist drugs, such as ondansetron and granisetron, used in HEPI013?

3. I previously asked a question about randomization in study GFEA-05 (FDA fax 2/26/99). In your response dated 3/5/99, you stated for question 4 that "...the randomization was not stratified, at variance with what was stated in the protocol." Does this mean that randomization was not stratified by center, was not stratified by nodal status, or was not stratified in any way? Please clarify this statement, and explain why stratification did not occur.

4. What is the data lock date for protocol HEPI 013?

5. Where is the analysis of quality of life for HEPI 013?

In response to the submission dated 3/22/99 from Pharmacia & Upjohn:

In the FDA fax dated 3/5/99, question 5 states "In studies MA-5 and GFEA-055, was CT treatment planning used at all investigative sites when irradiating left sided lesions?"

➤ Yes, CT stands for computerized tomography. My question concerns any possible contribution of radiation therapy as part of the local treatment for a left-sided breast cancer to

observed cardiotoxicity. If CT treatment planning is used, a minimal amount of heart is included in the field. If CT scans are not used, cardiac exposure to radiation increases and can increase the risk for cardiomyopathy. Please do not re-examine each case individually. A general feeling for whether or not CT planning was used by most radiation oncologists at most centers will suffice. We would appreciate your prompt written response so we can continue our evaluation of your NDA.

FAX sent April 15, 1999 (Questions 1-10 have not been addressed)

1. In study HEPI 013, you calculated relative dose-intensity. Please describe this calculation in detail, since patients could have received from 6-9 cycles per protocol.
2. For study HEPI 013, volume 2.33, page 8/24/048 indicates that 223 patients on FEC and 231 on CMF were included in the analysis of TTF. Figure 3, page 8/24/132 shows that the total patients included in the Kaplan-Meier curve were 220 and 231 respectively. There is a small discrepancy between the numbers of patients included in the survival curve also. Are these differences due to early drop-out? Please explain the discrepancies.
3. Review of the line listings for cardiac toxicity (volume 2.37, listing 8.2) for study HEPI 013 showed symptoms in 2 patients on CMF and 8 patients on FEC that could be consistent with cardiac dysfunction:

FEC:

Patient 5-62 AR: Paroxysmal nocturnal dyspnea and tachycardia; occurred after treatment was discontinued

Patient 11-29 IT: Tachycardia, dyspnea after C1

Patient 13-1 GR: Angina after C3

Patient 24-62 IT: DOE after C2

Patient 26-13 DD: DOE and tachycardia at C3

Patient 34-13 URSS: Peripheral edema, tachycardia at C5

Patient 52-3 CS: Shortness of breath, DOE, edema, and tachycardia after C4

Patient 56-21 PL: SOB, DOE, cough, tachycardia after C4

CMF:

Patient 26-2: DOE, nocturia, tachycardia after C1

Patient 49-11: Peripheral edema

Did these patients have other reasons for these symptoms? Please explain why they were not included in the discussions of cardiac toxicity.

4. Queries of the electronic database showed 4 patients with CHF on FEC who were not discussed in the study report. These patients are:

5-29

13-5

23-11

58-24

Please supply narratives for these patients.

5. In the electronic database for HEPI013, data on survival was entered for 429 patients, not for the 460 randomized patients (Table FOLSTAT). Why were 31 patients excluded from this table? Please supply the date of death and the censor date for all patients. (Censor status is available from table EFFICACY).
6. Please define how TTP was censored. Did you use the last date the patient was seen, the last date the patient was fully evaluated, or the last date there was any contact with the patient (i.e., by phone), or some other method?
7. In study HEPI 013, it is not clear to me how many patients were observed without further therapy, for how long, and whether progression occurred on or off treatment. Please indicate how many patients received all 6 cycles, and how many at that point were responders (CR +PR) and how many had no change. Of the patients with no change, how many were observed? Average length of observation? Did progression occur off therapy? Any difference between treatment arms? Please provide the same information for responders-- how many received 3 additional cycles of treatment, how many were observed instead, average length of observation, progression on or off chemotherapy, differences between treatment arms.
8. In study HEPI 013, "pain on injection" was recorded in the database table "AES" but no grades are recorded. "Extravasation" is treated the same way, yet at least one patient, according to the narratives (patient on FEC listed as "thrombophlebitis"). How many patients experienced these problems? Were other extravasations recorded, and what medical intervention did they require?
9. Febrile neutropenia is listed as a symptom in the AE database table for advanced breast cancer, but no grades are listed. Please supply documentation of which patients experienced febrile neutropenia.
10. For study HEPI 013, you reported grade 3-4 neutropenia in 171 patients on FEC and in 156 patients on CMF. A database query for neutrophils less than 1000 reports 187 patients on FEC and 189 on CMF with grade 3-4 neutropenia. Did you use different grading criteria?

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is

NDA 21-010

Page 6

finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

Please provide responses to the issues identified above as soon as possible. We remind you that the ODAC meeting is scheduled for June 7 and 8, 1999 and the User Fee date for this application is June 15, 1999.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

**APPEARS THIS WAY
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action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 6

Date: May 6, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. We remind you that we are still awaiting a response to the comments and information requests that were sent via facsimile transmission on March 25 and April 15, 1999. I have attached those comments and information requests that have not been addressed for your convenience. If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

NO. 037 001

05/06/99 15:23

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MESSAGE CONFIRMATION

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: April 29, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments regarding your proposed trademarks.

*cc Orig NDA 21-010
Div File
Skim
~~Guinn~~*

According to recent recommendations from the CDER Labeling Committee, the proposed trademarks, ██████████ ELLENCE, submitted in the pending NDA 21-010 were found to be unacceptable. However, please note that ██████████ was accepted as proposed.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

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MESSAGE CONFIRMATION

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NO. 005

001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments regarding your proposed trademarks.

Date: April 29, 1999

Total number of pages, including cover sheet 2

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301) 594-2473 FAX: (301) 594-0498

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FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 4

Date: April 28, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. We remind you that we are still awaiting a response to the comments and information requests that were sent via facsimile transmission on March 25, 1999 and April 15, 1999. I have attached those comments and information requests for your convenience. If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

*c: Orig NDA 21-010
Div File
S Honig
P Guinn*

March 25, 1999

We are reviewing your submission and have identified the following comments and information requests:

1. Investigative groups have attempted to define a set of anthracycline doses that are "equivalent" to certain doses of doxorubicin. Do you have a defined "equivalence set" for epirubicin and doxorubicin? For example, what dose of epirubicin do you feel is comparable to doxorubicin doses of 300 mg/m² and 450 mg/m²?
2. Were serotonin receptor antagonist drugs, such as ondansetron and granisetron, used in HEPI013?
3. I previously asked a question about randomization in study GFEA-05 (FDA fax 2/26/99). In your response dated 3/5/99, you stated for question 4 that "...the randomization was not stratified, at variance with what was stated in the protocol." Does this mean that randomization was not stratified by center, was not stratified by nodal status, or was not stratified in any way? Please clarify this statement, and explain why stratification did not occur.
4. What is the data lock date for protocol HEPI 013?
5. Where is the analysis of quality of life for HEPI 013?

In response to the submission dated 3/22/99 from Pharmacia & Upjohn:

In the FDA fax dated 3/5/99, question 5 states "In studies MA-5 and GFEA-055, was CT treatment planning used at all investigative sites when irradiating left sided lesions?"

- Yes, CT stands for computerized tomography. My question concerns any possible contribution of radiation therapy as part of the local treatment for a left-sided breast cancer to observed cardiotoxicity. If CT treatment planning is used, a minimal amount of heart is included in the field. If CT scans are not used, cardiac exposure to radiation increases and can increase the risk for cardiomyopathy. Please do not re-examine each case individually. A general feeling for whether or not CT planning was used by most radiation oncologists at most centers will suffice. We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.