CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-344

Correspondence

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 4	**Date:** 4-22-02

Re: NDA 21-344 Faslodex.

COMMENTS:

Per the chemistry reviewer, on the following pages are comments that need to be addressed. We have requested that you respond to these comments in either an annual report or as a general correspondence/new correspondence to the NDA within 30 days of the approval of Faslodex. We ask that you commit to responding to these comments in the manner that we have requested (annual report or GC). You should provide this commitment via facsimile. Please note that these are not considered post-marketing commitments (phase 4), nor will they be noted in the approval letter. Please call should you have any questions.

Thank you,

Amy Baird

[Annual Report] = commitment to fulfill the agreement and report it in the next appropriate annual report.

[Now] = commitment to fulfill the agreement and report it as GC/NC as soon as feasible, but not more than 30 days post approval.

We have the following comments regarding fulvestrant drug substance:

1. **[Annual Report]** The proposed Assay specification for the [redacted] is [redacted]% w/w and the total organic impurities is [redacted]%. Please provide information regarding any additional impurities or degradants that may contribute to the remaining difference of [redacted]%.

2. **[Annual Report]** The proposed assay specification for [redacted] [redacted]% w/w and the total organic impurities is specified as [redacted]% w/w maximum. Please provide information regarding any impurities or degradants which contribute to the remaining [redacted]% w/w.

3. **[Annual Report]** The proposed assay specifications for [redacted] ranges from [redacted]% w/w. [redacted] is listed as an impurity at [redacted]% w/w maximum. Please provide information regarding any degradants or impurities that contribute to the remaining [redacted] %.

4. **[Annual Report]** The proposed Assay specification for [redacted] ranges from [redacted] This specification is rather broad it should be reevaluated after several commercial batch runs or one year after approval (via annual report) to better reflect actual batch data.

5. **[Annual Report]** The proposed Assay specification for [redacted] %. Please provide information regarding any degradants and impurities that contribute to the remaining [redacted] %.

6. **[Now]** Please revise the drug substance specification for water content, [redacted] specific optical rotation, microbial content, and endotoxins to reference appropriate USP/NF methods.

7. **[Annual Report]** [redacted] (limit NMT [redacted] %) was not detected in any batches. This limit should be reevaluated after several commercial batch runs or one year after approval to better reflect actual batch data.

8. Please submit documentation for the [redacted] bags, which indicates that it complies with 21 CFR **[now]**. Please describe further, the materials of construction for the [redacted] used for bulk packaging of fulvestrant drug substance and acceptance criteria, to support the use of these materials **[annual report]**.

9. **[Now]** Please provide a copy of the stability specification and tests for fulvestrant drug substance in the description of the stability protocol.

10. **[Now]** Please revise the specification for the IR Identification test to indicate that it is compared against that obtained from the Fulvestrant Reference Standard.

11. **[Now]** Please revise the Fulvestrant Reference Standard specification for water content, [redacted], specific optical rotation, microbial content, and endotoxins to reference appropriate USP/NF methods.

12. **[Now]** Please include your tests and limits for Total Organic Impurities in the Specifications for Fulvestrant Reference Standard.

13. **[Now]** Please provide a commitment that [redacted] will be performed without notification to the Agency.

We have the following comments for Faslodex Injection drug product:

1. **[FIO... No action required by the applicant.]** We have reviewed Drug Master File (DMF) [redacted] submitted by Vetter [redacted] GmbH & Co. KG [redacted] identified several comments. The nature of these comments will be communicated to the DMF holder separately. These comments to not affect your approvability.

2. **[Now]** Please include tests for optical clarity, viscosity, extractables [redacted] and free fatty acid content in the specifications for fulvestrant drug product as they are provided in the stability study of fulvestrant drug product.

3. **[Now]** Please provide the complete regulatory specifications for FASLODEX Injection in the body of the stability protocol description.

4. **[Annual Report]** Please provide the chemical resistance test and results for the Type I glass components (syringe barrel) as per current USP <661>.

5. **[Now]** Given the solvent power of the drug product vehicle, please provide results for a one-time characterization of extractables from the rubber container-closure components into the formulation.

6. **[Annual Report]** Please provide the test results for syringe barrel, rubber plunger and rubber tip-cap as per tests and specifications listed in Vol. 1.5, Container Closure Section of this application.

7. **[Annual Report]** Please submit certificate of analyses from the suppliers of container closure for batches of drug product submitted in this application.

8. **[Now]** Please provide a commitment that [redacted] of Faslodex Injection will be performed without notification to the Agency.

We recommend the following revisions to the Carton Label (2.5 mL and 5 mL) and Syringe Label:

1. **[Annual Report]** At your next available printing, please revise the list of inactive ingredients in the Carton Label and list as: Alcohol, USP; Benzyl Alcohol, NF; Benzyl Benzoate, USP; and Castor Oil, USP.

2. **[Annual Report]** At your next available printing, please include the following statement on the Syringe Label: RX only.

MESSAGE CONFIRMATION

04/22/02 16:00

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
04/22	01'29"	8862822	CALLING	04	OK	0000

04/22/02 15:58 NO.042 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
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Pages, including cover sheet: 4	**Date:** 4-22-02

Re: NDA 21-344 Faslodex.

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Pages, including cover sheet: 2	**Date:** 4-18-02

Re: NDA 21-344 Faslodex. Phase 4 Commitment Requests.

COMMENTS:

Attached is the latest version of three Phase 4 commitments the Division will be requesting of AstraZeneca. These commitments are still considered DRAFT. You do not need to reply to this facsimile. Call me should you have any questions.

Thank you,

Amy Baird

MESSAGE CONFIRMATION

04/18/02 12:49

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
04/18	00'49"	8862822	CALLING	02	OK	0000

04/18/02 12:47 NO.027 001

FAX

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Center for Drug Evaluation and Research, HFD-150
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Re: NDA 21-344 Faslodex. Phase 4 Commitment Requests.

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 4-5-02

Re: NDA 21-344 Faslodex. Phase 4 Commitment Requests.

COMMENTS:

Attached is a DRAFT version of three Phase 4 commitments the Division will be requesting of AstraZeneca. You do not need to reply to this facsimile. Call me should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

04/05/02 09:27

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
04/05	00'46"	8862822	CALLING	02	OK	0000

04/05/02 09:25 NO.130 P01

FAX

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To: E. Jane Valas, Ph.D. **From:** Amy Baird, CSO

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Phone: 302-886-2122 **Phone:** (301) 594-5771

Pages, including cover sheet: 2 **Date:** 4-5-02

Re: NDA 21-344 Faslodex. Phase 4 Commitment Requests.

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Pages, including cover sheet: 2	**Date:** 3-22-02

Re: NDA 21-344 Faslodex. Proposed announcement for ASCO.

COMMENTS:

Attached is the proposed announcement that we will send to ASCO membership the day that Faslodex is approved. Please review and comment.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

03/22/02 11:00

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
03/22	00'50"	8862822	CALLING	02	OK	0000

3/22/02 10:59 NO.070 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 3-22-02

Re: NDA 21-344 Faslodex. Proposed announcement for ASCO.

FAX

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Pages, including cover sheet: 6	**Date:** 2-21-02

Re: NDA 21-344 Faslodex. Carcinogenicity Review.

COMMENTS:

Attached are the official minutes from the Carcinogenicity Committee review meeting on Faslodex. Please call should you have any questions.

Thank you,

/S/

Amy Baird

Executive CAC
Date of Meeting; December 4, 2001
Rat Carcinogenicity Study

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Timothy McGovern, Ph.D., HFD-170, Alternate Member
David Morse, Ph.D. Supervisory Pharmacologist, HFD-150
Lilliam Rosario, Ph.D., Pharm-Tox Reviewer, HFD-150

Author of Draft: Lilliam Rosario, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21,344
Drug Name: Faslodex (Fulvestrant; ICI 182,780
Sponsor: Astra Zeneca Pharmaceuticals

Mouse Carcinogenicity Study: Not conducted

Background
This 2-year carcinogenicity study in rats was submitted to NDA 21,344. This NDA proposes the use of ICI 182,780 (fulvestrant) for the Draft

The recommended dose of Faslodex is 250 mg to be administered intramuscularly (IM) monthly.

The Sponsor indicates fulvestrant is an antiestrogenic agent, which acts by downregulation of the estrogen receptor (ER). Fulvestrant binds ER in a competitive manner with a high affinity comparable to estradiol. Further, the Sponsor suggests that Fulvestrant is a non-agonist antiestrogen which blocks the uterotrophic action of estradiol in mice, rats and monkeys without itself having any partial agonist estrogen- like activity.

Genotoxicity
The mutagenic and clastogenic potential of ICI 182,780 has been studied in bacterial mutation assays in strains of *Salmonella typhimurium* and *Escherischia coli*, an *in vitro* cytogenetics assay in cultured human lymphocytes, a mouse lymphoma mutation assay, and an *in vivo* rat micronucleus test. ICI 182,780 has shown no evidence of genotoxic/clastogenic potential in this battery of tests.

Rat Carcinogenicity Study:

Study Design:

- Dose concurrence was obtained on July 28, 1998.
- The Sponsor selected the high dose level to represent the maximum possible dose by the IM route (maximum feasible dose).
- There were 6 groups (50 sex/group); Sprague Dawley rats [redacted]

Control-1 (C1):	Vehicle/15 days
Control-2 (C2):	Vehicle/30 days
Control-3 (C3):	Saline/15 days
Low Dose (LD):	15 mg/kg/30 days
Middle Dose (MD):	10 mg/rat/30 days
High Dose- (HD):	10 mg/rat/15 days

The following table shows the ~ actual dose (mg/kg) administered to Groups V (10 mg/rat/30days) and Group VI (10 mg/rat/15 days). For comparison purposes, these values have also been normalized for frequency of administration (from every 15 days to every 30 days)

		Group V 10 mg/rat/30 days		**Group VI 10 mg/rat/15 days**		
Sex	**Week**	**Body weight (g)**	**mg/kg/ 30 days**	**Body weight (g)**	**mg/kg/ 15 days**	**mg/kg/30 days**
Male	1	262.9	38	257.8	39	78
	96	793	13	781.5	13	26
Female	1	184.7	54	185.7	54	108
	96	580.3	17	574.4	17	34

Statistical Methods:

- All tests for tumor incidence were one-sided looking for an increase in response/incidence.
- The Haseman (1983) principle of statistical significance was adopted; a rare tumor (<1% spontaneous incidence) will be deemed statistically significant if $p<0.05$, and a common tumor shall be deemed significant if $p<0.01$.
- The statistical comparisons of interest were implemented using Peto's survival-adjusted trend test.
- Note that the significance values used by the Sponsor are in accordance with those employed by CDER when only a single carcinogenicity study is conducted. The probability levels for determining significance of tumor incidence has not been adjusted for multiple statistical comparisons as would be appropriate to maintain a constant error rate over multiple studies.

RAT TUMOR FINDINGS:

It appears that the IM administration of ICI 182,780 (fulvestrant) for 24 months increased the incidence of ovarian granulosa cell tumors and testicular Leydig cell tumors in female and male rats, respectively.

Ovaries:

- A 14% increase in the incidence of a rare ovarian granulosa cell tumors in the high dose female animals (7/50 rats at 10 mg/rat/15d; p=0.01887).
- Spontaneous incidence of granulosa cell tumors for this strain of rat is 0.06% (n=1729) (Giknis and Clifford, 2001
- The conducting laboratory reports background instances varying from 0/120 to 1/120 (0.2%).
- Another study (n=4493) with the same strain and source reports 0.3% (Gregson and Abbott, 1984).

Testes:

- There was increase incidence (2-12%) of interstitial Leydig cell tumors (adenomas-common) in drug-treated animals.
- These tumors were present at a low incidence (4%) in the saline control group and absent in the vehicle control groups. The incidence in the high dose group was similar to controls (2%) while slightly increased (8-12%) in the two low dose groups.
- In Group 4 (15 mg/kg/30 days), interstitial cell tumors were increased significantly (p=0.01922)
- Spontaneous incidence for this strain of rat is 2.35%

The reviewer proposed 3 questions for the EXEC CAC committee:

1. Are the survival rates observed in control and drug-treated groups adequate to determine the carcinogenic potential of ICI 182,780 (fulvestrant)?
   - Even though survival rates appear lower than expected for control males, the Committee agreed that the rate of mortality is adequate to determine the carcinogenic potential of ICI 182,780.

2. Does the Committee agree that administration of ICI 182,780 increases the incidence of granulosa cell tumors and interstitial Leydig cell tumors?

   The Committee
   - agreed that administration of ICI 182,780 increases the incidence of both granulosa cell tumors and interstitial Leydig cell tumors, in females and males, respectively.
   - recommended the statistical evaluation of these results take into consideration that only one carcinogenicity study was submitted.
   - recommended to carefully examine the pharmacological data submitted to support the claim that ICI 182,780 is a "non-agonist" antiestrogen. The increase incidence of interstitial Leydig cell tumors in males may suggest a drug-induced estrogenic effect.
   - noted that while the carcinogenicity study was acceptable, the Sponsor did not perform the defining studies for an anti-estrogen to determine if the compound is non-genotoxic.

The Committee suggested that a ^{32}P post labeling study to determine whether ICI 182,780 induces DNA adducts.

3. Does the Committee agree that these findings should be included in the product labeling for ICI 182,780 (fulvestrant)?
   The Committee agreed that the increase incidence of both granulosa cell tumors and interstitial Leydig cell tumors, in females and males, respectively be included in the product labeling for ICI 182,780 (fulvestrant).

Additional comments from the Committee:

The Committee

- pointed out that, unlike tamoxifen, the incidence of liver tumors was not changed in ICI 182,780-treated rats.
- suggested that, since male rats in the high dose group lost weight, the mid-dose male group should also be considered in evaluation of carcinogenic response.

Executive CAC Recommendations and Conclusions:

1) Fulvestrant increases the incidence of ovarian granulosa cell tumors in female rats, and the incidence of interstitial Leydig cell tumors in male rats.
2) The increase incidence of granulosa and Leydig cell tumors should be included in the product labeling for fulvestrant.
3) The Committee recommended that the Sponsor be asked to perform ^{32}P post-labeling study to determine if fulvestrant and/or its' metabolites may form adducts with cellular DNA.

/S/

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-150
/David Morse, Ph.D. Supervisory Pharmacologist, HFD-150
/Lilliam Rosario, Ph.D., Pharm-Tox Reviewer, HFD-150
/Amy Baird, HFD-150
/Adele Seifried, HFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph DeGeorge
12/11/01 08:31:08 AM

MESSAGE CONFIRMATION

02/21/02 09:32

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/21	01'56"	8862822	CALLING	06	OK	0000

02/21/02 09:29 NO.021 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 6	**Date:** 2-21-02

Re: NDA 21-344 Faslodex. Carcinogenicity Review.

FAX

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Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 2-15-02

Re: NDA 21-344 Faslodex. Repro tox labeling issue.

COMMENTS:

On the following page is a statement from the pharmacology review team regarding Warnings section of the labeling. Please call should you have any questions.

Thank you,

Amy Baird

We agree that in this study, the percentage incidence of fetuses and litter with an extra 13th rib, in both the control and the high dose group, was high possibly indicating a normal variation within this strain of rabbits. However, there is a significantly increased fetal incidence of backwards displacement of the pelvic girdle in animals treated with 0.25 mg/kg/d fulvestrant [24 out of 102 fetuses (23.5%) in fulvestrant-treated rabbits compared to 16 out of 152 fetuses (10.1%) in the control animals showing a doubling in fetal incidence]. Similarly, there was a significantly increased fetal incidence of 27 pre-sacral vertebrae [24 out of 102 fetuses (23.5%) in fulvestrant-treated rabbits compared to 19 out of 152 fetuses (12%) in the control animals]. The possibility that these results may represent a random effect on variations cannot be examined since you did not conduct a full histomorphological assessment of all the doses tested in this study. Thus, the increased incidence of the above-mentioned variations should be included in the product label.

Point of clarification, this study in rabbits was considered inadequate to fully define the possible adverse effects on fetal development because administration of fulvestrant (up to 0.25 mg/kg/d) to pregnant rabbits did not result in any maternal toxicity and you did not evaluate the skeletons of fetuses from the lower two dose groups.

Please refer to the Warning section of the label. In the following sentence

Proposed Labeling

We agree that the skeletal effects seen in the drug treated rabbits should be described as in 'increased incidence of skeletal variations.

MESSAGE CONFIRMATION

02/15/02 11:01

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/15	00'49"	8862822	CALLING	02	OK	0000

02/15/02 11:00 NO.020 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
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Pages, including cover sheet: 2	**Date:** 2-15-02

Re: NDA 21-344 Faslodex. Repro tox labeling issue.

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 17	**Date:** 1-29-02

Re: NDA 21-344 Faslodex. Division of Medication Errors and Technical Support (DMET) reviews.

COMMENTS:

Regarding the proposed trademark name Faslodex (fulvestrant injection), attached are the DMET reviews. If you wish DMET to reconsider the acceptability of the name Faslodex, you should respond to the concerns expressed in the attached reviews with information that shows the improbability of misadministration. Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

01/30/02 15:38

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
01/30	05'50"	8862822	CALLING	17	OK	0000

01/30/02 15:29 NO.006 P01

FAX

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Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 17	**Date:** 1-29-02

Re: NDA 21-344 Faslodex. Division of Medication Errors and Technical Support (DMET) reviews.

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Pages, including cover sheet: 2	**Date:** 1-25-02

Re: NDA 21-344 Faslodex. Labeling.

COMMENTS:

The first sentence of the DESCRIPTION section of the labeling reads as follows:

"FASLODEX (fulvestrant) Injection for intramuscular administration is a [redacted]

FDA Comment: We are not yet convinced that there is sufficient information to prove that the mechanism of action of Faslodex is truly novel. Although Faslodex may represent a more selective estrogen antagonist, Tamoxifen also causes a decrease in ER expression.

The INDICATIONS AND USAGE section currently reads as follows:

[redacted]

FDA Comment: Please provide information concerning how many women in the trial had undergone hysterectomies in the clinical studies 20 and 21, if you want us to consider putting in [redacted] any where in the labeling. We believe this information was recorded in the CRF's but we did not see it in the trial reports. Also, please provide any information on follow-up for uterine abnormalities in women who had not undergone hysterectomies, i.e., the incidence of dysfunctional uterine bleeding, uterine pathology, uterine ultrasounds, hysterectomies while on study, etc., in both treatment groups, if this information is available.

Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

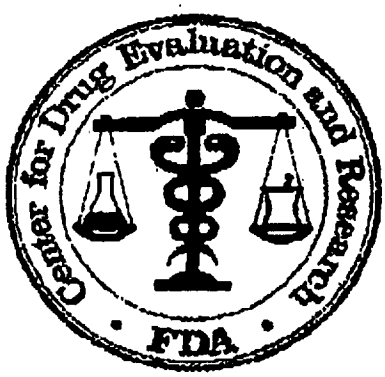
01/25/02 17:55

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
01/25	00'42"	8862822	CALLING	02	OK	0000

01/25/02 17:53 NO.093 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857



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Pages, including cover sheet: 2 **Date:** 1-25-02

Re: NDA 21-344 Faslodex. Labeling.

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Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 1-25-02

Re: NDA 21-344 Faslodex. Request for PK Information.

COMMENTS:

Per Dr. Gene Williams, please provide the following:

1. Is there any data describing the ability of CYP 1B1 or 1A1 to metabolize fulvestrant?
2. What is your assessment of the potential for drug interactions where:

    a. fulvestrant inhibits CYP 1B1 or 1A1 substrates?
    b. CYP 1B1 or 1A1 inhibitors inhibit the metabolism of fulvestrant?
    c. fulvestrant induces CYP 1B1 or 1A1 thus increasing the metabolism of CYP 1B1 or 1A1 substrates?
    d. CYP 1B1 or 1A1 inducers induce CYP 1B1 or 1A1 thus increasing the metabolism of fulvestrant.

Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

01/25/02 13:36

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
01/25	00'31"	8862822	CALLING	01	OK	0000

01/25/02 13:35 NO.090 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D. **From:** Amy Baird, CSO

Fax: 302-886-2822 **Fax:** (301) 594-0498

Phone: 302-886-2122 **Phone:** (301) 594-5771

Pages, including cover sheet: 1 **Date:** 1-25-02

Re: NDA 21-344 Faslodex. Request for PK Information.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 12-21-01

Re: NDA 21-344 Faslodex. PK information.

COMMENTS:

Per the biopharm reviewer, please see the attached and respond. Please call should you have any questions.

Thank you,

/S/

Amy Baird

This NDA provides the following evidence that fulvestrant concentrations will not be altered by CYP 3A4 inhibitors:

1. Sulfation occurs.
2. Rifampicin pre-treatment did not alter fulvestrant concentrations in an *in vivo* study.

Currently, we find this evidence less than compelling because:

1. The relative roles of sulfation and CYP 3A4-mediated metabolism have not been determined quantitatively *in vivo*.
2. Rifampicin pre-treatment is not as rigorous a test of the ability of CYP 3A4 to mediate fulvestrant metabolism as in an *in vivo* study measuring the ability of a strong inhibitor to alter fulvestrant concentrations (e.g., a study of the effect of ketoconazole treatment on the pharmacokinetics of fulvestrant).

Based on the above, [redacted]

MESSAGE CONFIRMATION

12/21/01 11:02

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
12/21	00'40"	8862822	CALLING	02	OK	0000

12/21/01 11:01 NO.021 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 12-21-01

Re: NDA 21-344 Faslodex. PK information.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 12-6-01

Re: NDA 21-344 Faslodex. Carcinogenicity Data.

COMMENTS:

Apparently in the carcinogenicity data you submitted on 10-29-01, tissues not showing tumors were categorized as "tissue not examined". Specifically, the 'ORGANEXM' variable is always coded as '3' when there was no tumor in the tissue. ORGANEXM should be '1' if the tissue was examined whether or not a tumor was found. Please examine the data and re-code as necessary and re-submit ASAP.

Please call me should you have questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

12/06/01 16:32

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
12/06	00'29"	8862822	CALLING	01	OK	0000

12/06/01 16:31 NO.039 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D. **From:** Amy Baird, CSO

Fax: 302-886-2822 **Fax:** (301) 594-0498

Phone: 302-886-2122 **Phone:** (301) 594-5771

Pages, including cover sheet: 1 **Date:** 12-6-01

Re: NDA 21-344 Faslodex. Carcinogenicity Data.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 11-19-01

Re: NDA 21-344 Faslodex.

COMMENTS:

The microbiology review of your application has been completed, please respond to the attached list of deficiencies and comments as soon as possible. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

Several subjects relevant to process product quality microbiology and sterile process validation were not found in the submission. These are itemized below. Information relative to these subjects may be found in FDA's "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products." which is available on the world wide web at, http://www.fda.gov/cder/guidance/index.htm. Please refer to this guidance when addressing the following questions.

1. Process flow descriptions did not indicate which fill line was used and could not be linked to specific rooms or processing areas. Please identify the building and rooms where the [redacted] is done. The [redacted] line should be described so it can be associated with the lines that are validated in the process simulations (media fill [redacted]

2. Please summarize methods and acceptance criteria for environmental microbiology tests conducted in the [redacted] facility. Emphasis should be placed on the critical [redacted] fill) area. File and support rooms should be identified.

3. Container and closure integrity testing was not noted. Please summarize the initial studies on the container and closure system that demonstrate the system's barrier to microbial ingress.

4. Validation of the [redacted] system was not noted, including retention or determination of the integrity test acceptance criteria. Please summarize the validation experiments for the [redacted] used in product manufacture. The [redacted] should be identifiable and its relationship to the experimental [redacted] (including lot numbers) should be established.

5. Summaries of the sterilization processes validation studies were not found. Processing equipment should be identified and the items processed by those pieces of equipment should be shown as part of the validated loads. Test results for the validations should be summarized including physical and biological results.

6. Methods and acceptance criteria for process simulation studies (media fills) that validate the [redacted] filling were not found. The fill line and media fill results should be summarized. Media fill acceptance criteria and the frequency of retesting should be presented.

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

11/19/01 16:27
ID=FDA-DODP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/19	00'51"	8862822	CALLING	02	OK	0000

11/19/01 16:25 FDA-DODP → 913028862822 NO.048 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 11-19-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 11-9-01

Re: NDA 21-344 Faslodex.

COMMENTS:

Per Dr. Gene Williams, please address the following:

Is apheresis essential for IV administration?

Please call me should you have questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

11/09/01 13:27

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/09	00'27"	8862822	CALLING	01	OK	0000

11/09/01 13:26 NO.030 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 11-9-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 11-9-01

Re: NDA 21-344 Faslodex.

COMMENTS:

Per Dr. Rosario, please address the following:

Please state the ICI 182,780 formulation used in study TCR/2683 "A 2 YEAR INTRAMUSCULAR CARCINOGENICITY STUDY OF ICI 182,780 IN THE ALBINO RAT". Please indicate the identity and amount of each component in the formulation. Please also clarify whether the same formulation was used in batches P/1465/22A (ADM 62181D99) and P/1359/4 (ADM 39454G97).

Please call me should you have questions.

Thank you.

/S/

Amy Baird

MESSAGE CONFIRMATION

11/09/01 12:48

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/09	00'30"	8862822	CALLING	01	OK	0000

11/09/01 12:47 NO.029 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 11-9-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 10-18-01

Re: NDA 21-344 Faslodex.

COMMENTS:

Per Dr. Gene Williams (biopharmaceutical reviewer), please address the following:

[redacted] This method of calculating the ratios seems inappropriate (discontinuity of units) to the reviewer. Is someone from the biopharmaceutical team at AstraZeneca available to discuss this issue with Dr. Williams? Dr. Williams' phone number is 301-594-0488.

Please call me should you have questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

10/18/01 13:16

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/18	00'30"	8862822	CALLING	01	OK	0000

10/18/01 13:14 NO.160 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 10-18-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 4	**Date:** 10-15-01

Re: NDA 21-344 Faslodex. Specifically, your fax of 10-11-01 regarding information on response assigned and treatment reassignments and your fax of 10-12-01 requesting clarification to FDA responses sent on 10-9-01.

COMMENTS:

Per the clinical reviewer, see the attached. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

Regarding your fax of 10-11-01:

You are correct regarding the 2 patient ID #'s:

FDA Response reassignments

Study 21				
Pt ID # submitted	Corrected Pt #	Sponsor response	FDA response	Max % change
0026005	00260005	PR	SD	60%

Treatment Reassignments

Study 20	Pt ID # submitted	Corrected Pt #	TRTSEQ	TRTREC
	00830004	00830002	2	1

We understand that the protocol specified that for the responses used in your analysis, the investigator's response designation could supercede the response algorithm.

We re-analyzed the data for pts with measurable disease using a simplified response algorithm, and found that this had no appreciable effect on overall efficacy results.

Regarding your fax of 10-12-01:

"Safety data from Trial 0025 and rat carcinogenicity data are being prepared for submission. Clarification is sought on whether both items should be submitted to IND [redacted] or to the NDA."

FDA Response: Please submit it to the NDA.

Question 3: Has FDA identified any deficiencies during the review of the NDA thus far (e.g., non-inferiority)?

FDA Response: Safety review is ongoing, but thus far no significant deficiencies have been identified. There were minor discrepancies found in response categorization of a few patients, which have not affected the overall conclusions. With a non-inferiority margin of 10% the FDA preliminary analysis agrees with the sponsor that fulvestrant 250 mg was non-inferior to anastrozole with respect to best objective response rate in Trials # 0020 and #0021. With a non-inferiority margin of 25%, the FDA preliminary analysis agrees with the sponsor that fulvestrant 250 mg was non-inferior to anastrozole with respect to time to progression in Trials # 0020 and #0021.

"AstraZeneca understands that reviews for clinical safety and other review disciplines are ongoing, and that deficiencies in NDA 21-344 may yet be identified. In minutes from FDA's Pre-Meeting on data from Trials 0020 and 0021 (Pre-NDA, November 9, 2000), FDA noted that, even in the absence of demonstration of superiority in TTP for the pivotal trials, the review focus would be on non-inferiority of response rate.

Clarification is sought on FDA's view of whether the non-inferiority margins shown in FDA's preliminary analysis for fulvestrant 250 mg for best objective response rate and time to progression are acceptable non-inferiority margins (margin of 10% for best objective response rate: margin of 25% for time to progression). Can FDA comment?"

FDA Response: In general, non inferiority margins should be pre-specified. We have decided to accept the 10% margin for best objective response and 25% for time to progression, based on previous applications.

Question 4: What are the potential questions regarding fulvestrant to be presented for discussion before the Oncology Drugs Advisory Committee (ODAC)?

FDA Response: We are considering taking action on this NDA without presenting the application to the ODAC.

"Can FDA clarify the date when AstraZeneca will know whether fulvestrant 250 mg will be presented to ODAC, given that the redacted sponsor briefing document is due to Dr. Timpleton-Somers of FDA on October 31, 2001?"

FDA Response: We do not anticipate any significant questions for the ODAC, the issues are fairly straightforward, therefore, we plan to take action on this application without consulting the ODAC.

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

10/15/01 12:13
ID=FDA-DODP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/15	01'15"	8862822	CALLING	04	OK	0000

10/15/01 12:11 FDA-DODP → 913028862822 NO.146 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 4	**Date:** 10-15-01

Re: NDA 21-344 Faslodex. Specifically, your fax of 10-11-01 regarding information on response assigned and treatment reassignments and your fax of 10-12-01 requesting clarification to FDA responses sent on 10-9-01.

10/15/01
Drs. Williams, Bross, Morse, Rosario, Chen + Yang. Please comment ASAP.

Thanks,
Amy

ASTRAZENECA PHARMACEUTICALS

Regulatory Affairs Department

Wilmington, DE 19850

RAPIFAX RAPIFAX RAPIFAX

Date: OCT 12 2001

Pages to follow this lead sheet: 4

Rapifax message for: Ms. Amy Baird

Rapifax message from: Jane Valas

Please make copies for:

Please confirm rapifax to 1-302-886-2822- Thank You

AstraZeneca

Date: OCT 12 2001

Richard Pazdur, M.D.
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 150, Room No. 2055
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852-1448

Re: NDA 21-344
FASLODEX® (fulvestrant) Injection
NDA Review Status Meeting: Request for Clarification to Responses

Dear Dr. Pazdur:

Reference is made to the facsimile received October 9, 2001 providing FDA's responses to AstraZeneca Pharmaceuticals LP's (AstraZeneca) questions to be discussed at the NDA Review Status meeting scheduled for October 16, 2001.

AstraZeneca is in agreement with responses provided for Questions 1, 2, and the issue on Duration of Response. Safety data from Trial 0025 and rat carcinogenicity data are being prepared for submission.

- **Clarification is sought on whether both items should be submitted to IND [redacted] or to the NDA.**

AstraZeneca requests clarification on FDA's responses to Questions 3 and 4. Text from the October 9, 2001 facsimile from FDA is provided for ease of response.

Question 3: Has FDA identified any deficiencies during the review of the NDA thus far (e.g., non-inferiority)?

FDA Response: Safety review is ongoing, but thus far no significant deficiencies have been identified. There were minor discrepancies found in response categorization of a few patients, which have not affected the overall conclusions. With a non-inferiority margin of 10% the FDA preliminary analysis agrees with the sponsor that fulvestrant 250 mg was non-inferior to anastrozole with respect to best objective response rate in Trials #0020 and #0021. With a non-inferiority margin of 25%, the FDA preliminary analysis agrees with the sponsor that fulvestrant 250 mg was non-inferior to anastrozole with respect to time to progression in Trials #0020 and #0021.

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-344: FASLODEX® (fulvestrant) Injection

Question 3 Clarification: AstraZeneca understands that reviews for clinical safety and other review disciplines are ongoing, and that deficiencies in NDA 21-344 may yet be identified. In minutes from FDA's Pre-Meeting on data from Trials 0020 and 0021 (Pre-NDA, November 9, 2000), FDA noted that, even in the absence of demonstration of superiority in TTP for the pivotal trials, the review focus would be on non-inferiority of response rate.

Clarification is sought on FDA's view of whether the non-inferiority margins shown in FDA's preliminary analysis for fulvestrant 250 mg for best objective response rate and time to progression are acceptable non-inferiority margins (margin of 10% for best objective response rate; margin of 25% for time to progression).

- **Can FDA comment?**

Question 4: What are the potential questions regarding fulvestrant to be presented for discussion before the Oncology Drugs Advisory Committee (ODAC)?

FDA Response: We are considering taking action on this NDA without presenting the application to the ODAC.

Question 4 Clarification: Given FDA's response to question 4, above,

- **Can FDA clarify the date when AstraZeneca will know whether fulvestrant 250 mg will be presented to ODAC, given that the redacted sponsor briefing document is due to Dr. Templeton-Somers of FDA on October 31, 2001?**

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Please direct any questions or requests for additional information to me, or in my absence, to Dr. Kathleen Gans-Brangs at (302) 886-2440.

Sincerely,

E. Jane Valas, Ph.D.

E. Jane Valas, Ph.D.
Associate Director
Regulatory Affairs
Telephone: (302) 886-2122
Fax: (302) 886-2822

EJV/rak

Desk Copy : Ms. Amy Baird, HFD No. 150, Room 2106 (Cover Letter Only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
IPR Pharmaceuticals, Inc.

DATE OF SUBMISSION OCT 12 2001

TELEPHONE NO. *(Include Area Code)*
(600) 456-3669

FACSIMILE (FAX) Number *(Include Area Code)*
(302) 886-2822

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE:
AstraZeneca Pharmaceuticals LP
Kathleen R. Gans-Brangs, Ph.D.
Regulatory Affairs Director
1800 Concord Pike P.O. Box 8355
Wilmington, DE 19803-8355
(302) 886-2440
(302) 886-2822

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-344

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Fulvestrant

PROPRIETARY NAME *(trade name)* IF ANY
Faslodex® Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
7 α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5-(10)-triene-3,17 β diol

CODE NAME *(If any)*

DOSAGE FORM:
Solution for injection

STRENGTHS:
250 mg/5 mL

ROUTE OF ADMINISTRATION
Intramuscular injection

(PROPOSED) INDICATION(S) FOR USE:
[redacted] Draft

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Follow-up for Clarification to NDA Review Status Meeting Responses

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS: ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND — DMF — DMF — DMF — DMF —

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. Use Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
K L Gans-Brangs	Kathleen R. Gans-Brangs, Ph.D. Regulatory Affairs Director	OCT 12 2001
ADDRESS *(Street, City, State, and ZIP Code)* 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355		Telephone Number (302) 886-2440

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/00)

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 10-2-01

Re: NDA 21-344 Faslodex.

COMMENTS:

Per the biopharmaceutical reviewer, there is an inconsistency in the electronic Population Pharmacokinetics submission (CD submitted 3-29-01). File "6.prn" contains 24 columns. However, the "$INPUT" record for file "6.for" contains only 12 items. Would you please explain this and, as needed, provide me with a revised 6.prn, 6.for, or both?

The reviewer has not checked files other than 6.*, so a similar problem may exist between other "#.prn" and corresponding "#.for" files. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

10/02/01 15:44

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/02	00'29"	8862822	CALLING	01	OK	0000

10/02/01 15:42 NO.111 001

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 10-2-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Kathleen R. Gans-Brangs, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2440	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 9-6-01

Re: NDA 21-344 Faslodex.

COMMENTS:

Per the statistical reviewer, please provide the results of the interim analysis for both trials. In particular, for each trial, we would like to know:

1. The actual data (for response & TTP) used for the interim analysis.
2. Data cut-off date.
3. The nominal alpha level used for response and TTP.

Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

09/06/01 13:22

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
09/06	00'28"	8862822	CALLING	01	OK	0000

09/06/01 13:21 NO.002 P01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Kathleen R. Gans-Brangs, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2440	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 9-6-01

Re: NDA 21-344 Faslodex.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Kathleen R. Gans-Brangs, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2440	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 5-11-01

Re: NDA 21-344 Faslodex. Electronic NDA Presentation.

COMMENTS:

The electronic submission presentation for Faslodex has been scheduled, see the attached. Please do not hesitate to call should you have any questions.

Thank you,

Amy Baird

Date: 5-30-01

Time: 10:00am (scheduled for 1 hour only)

Place: Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20854
Conf. Room A.

FDA Attendees:

Peter Bross, M.D., Clinical Reviewer, HFD-150
Josephine Jee, Chemistry Reviewer, DNDC1
Lilliam Rosario, Ph.D., Pharmacology Reviewer, HFD-150
Peiling Yang, Ph.D., Statistical Reviewer, HFD-150
Gene Williams, Ph.D., Biopharmaceutical Reviewer, HFD-150
Amy Baird, Project Manager, HFD-150

FDA Attendees Invited Only:

Grant Williams, M.D., Clinical Team Leader, HFD-150
Eric Duffy, Ph.D., Chemistry Team Leader, DNDC1
Dave Morse, Ph.D., Pharmacology Team Leader, HFD-150
Gang Chen, Ph.D., Statistical Team Leader, HFD-150
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, HFD-150

MESSAGE CONFIRMATION

05/11/01 11:45

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/11	00'40"	8862822	CALLING	02	OK	0000

05/11/01 11:43 NO.023 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Kathleen R. Gans-Brangs, Ph.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2440	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 5-11-01

Re: NDA 21-344 Faslodex. Electronic NDA Presentation.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 4-24-01

Re: NDA 21-344 Faslodex.

COMMENTS:

NDA presentation scheduled for 4-26-01 at 10:00am. Please do not hesitate to call should you have any questions.

Thank you,

Amy Baird

FDA Expected Attendees:

The following are the review team assigned to Faslodex.

Richard Pazdur, M.D., Director, HFD-150
Grant Williams, M.D., Clinical Team Leader, HFD-150
Peter Bross, M.D., Clinical Reviewer, HFD-150
David Morse, Ph.D., Pharmacology Team Leader, HFD-150
Lilliam Rosario, Ph.D., Pharmacology Reviewer, HFD-150
Eric Duffy, Ph.D., Chemistry Team Leader, DNDC1
Josephine Jee, Chemistry Reviewer, DNDC1
Gang Chen, Ph.D., Statistical Team Leader, HFD-150
Peiling Yang, Ph.D., Statistical Reviewer, HFD-150
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, HFD-150
Gene Williams, Ph.D., Biopharmaceutical Reviewer, HFD-150

The following are the remainder of the team leaders that are with the Division. They will not be involved in the review of Faslodex, but nonetheless I have scheduled this presentation on their calendars.

Alison Martin, M.D., Clinical Team Leader, HFD-150
Donna Griebel, M.D., Clinical Team Leader, HFD-150
John Leighton, Ph.D., Pharmacology Team Leader, HFD-150
Rebecca Wood, Ph.D., Chemistry Team Leader, HFD-150

The remainder of the Division has also been invited to the presentation. The number of people who will be attending is unknown as I only invited them via email and did not schedule this on their calendars.

MESSAGE CONFIRMATION

04/24/01 16:19

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
04/24	00'43"	8862822	CALLING	02	OK	0000

04/24/01 16:17 NO.024 D01

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: E. Jane Valas	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-2122	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 4-24-01

Re: NDA 21-344 Faslodex.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-344

AstraZeneca Pharmaceuticals
Attention: Anthony Rogers
Vice President, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Rogers:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: FASLODEX® (fulvestrant) Injection

Review Priority Classification: Standard (S)

Date of Application: March 28, 2001

Date of Receipt: March 28, 2001

Our Reference Number: NDA 21-344

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 26, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 28, 2002 and the secondary user fee goal date will be March 28, 2002.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Amy Baird, Project Manager, at (301) 594-5771.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Baird
5/11/01 01:11:31 PM
For Dotti Pease