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Review of Request for Orphan-Drug Designation

Date of request:	November 8, 2004
Date received by FDA:	November 9, 2004
Dates of Amendments:	January 19, February 22, May 24 and 25, June 8 and 10, 2005
Date review completed:	May 20, 2005
Designation request:	(b) (4)
Generic Name:	Raloxifene
Trade Name:	Evista®
Sponsor:	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285
Contact:	David R. McAvoy, J.D., M.S.E.S. Director Office of Scientific and Regulatory Affairs Lilly Research Laboratories Eli Lilly and Company Phone: 317-651-6058 (b) (4) FAX: 317-277-7778 E-mail Address: mcavoy_david_r@lilly.com
Alternate Contact:	David Ceryak, J.D. Associate General Counsel Global Regulatory Eli Lilly and Company Phone: 317-277-7263 FAX: 317-277-4055 E-Mail Address: dvceryak@lilly.com
Drug manufacturer:	Eli Lilly
Proposed designation:	Reduction of risk of breast cancer in postmenopausal women.

Regulatory status:

Evista is marketed for the prevention and treatment of osteoporosis in the U.S. (NDA 20-815), Europe, Canada, Japan, and 103 other countries. Evista is being developed for breast cancer risk reduction under (b) (4) (FDA Division of Oncology Drug

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Products). The IND was submitted to the FDA in October 1998. No supplemental NDA has been submitted to FDA for Evista for breast cancer risk reduction in postmenopausal women. Evista is not currently approved for breast cancer risk reduction in the U.S., but has recently been approved for reducing the risk of breast cancer in postmenopausal women with osteoporosis in Philippines, South Africa, Venezuela, and Argentina; for prevention of breast cancer in postmenopausal women with osteoporosis in Mexico, Russia, and Turkey; and for both reducing the risk and prevention of breast cancer in Lebanon.

1. Disease/Condition Background

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast and is the most common cause of cancer in women. Each year, 182,000 cases of breast cancer and 43,300 deaths occur in the United States. Risk factors include family history, nulliparity, early menarche, advanced age, and a personal history of breast cancer (in situ or invasive). The presence of certain genetic mutations has also been associated with breast cancer, including BRCA-1 and BRCA-2 mutations.

Various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy treatment options are currently employed in the treatment of breast cancer. In addition, much interest has emerged in the area of chemoprevention, using natural and synthetic compounds to intervene in the early stages of cancer (before invasive disease begins), with the intention to reverse, suppress, or prevent the progression of premalignant lesions to invasive carcinoma.

The Breast Cancer Prevention Trial (BCPT or the National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1 trial) demonstrated that, in women at high risk of breast cancer, tamoxifen citrate significantly reduced the risk of invasive breast cancer.[1] It is theorizes that raloxifene also may reduce the risk of invasive breast cancer and do so with a potentially more favorable risk profile than tamoxifen. Ongoing research is being conducted to demonstrate the efficacy and safety of Evista in such a chemoprevention context for the purpose of securing approval of a new indication.

While early detection with effective treatment has reduced mortality in some groups of women with breast cancer, efforts to control this disease by encouraging the development of primary prevention strategies continue. Currently, only tamoxifen is approved in the U.S. for the reduction of risk of breast cancer.

U.S. approval of the tamoxifen chemoprevention indication was based on the NSABP P-1 trial. The P-1 trial was a double-blind, randomized, placebo-controlled trial with the primary objective of determining whether 5 years of treatment with tamoxifen 20 mg/day would reduce the incidence of invasive breast cancer in women at high risk for the disease. The median duration of treatment at study termination was 3.5 years. After a total of 4.2 years of follow-up since enrollment, the relative risk for invasive breast cancer with tamoxifen treatment, compared with placebo for women 60 years of age or

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older, was 0.45 (95% Confidence Interval [CI] 0.27, 0.74). The absolute risk reduction for invasive breast cancer with tamoxifen therapy was 3.4%.[1]

Tamoxifen is registered in the U.S. for "reduction of the risk of breast cancer in women at high risk of the disease," where "high risk" is defined as a 5-year risk of invasive breast cancer greater than 1.7% (the average risk for a woman 60 years of age), based on the Gail Risk Evaluation.[2] Tamoxifen is a first-generation selective estrogen receptor modulator (SERM) that can have estrogen agonist effects on bone and uterine tissues, and can have estrogen antagonist effects on breast tissue.

2. Population Estimate

To qualify raloxifene as an orphan drug, the sponsor contends that there is no reasonable expectation that costs of research and development of the drug for reduction of risk of breast cancer in postmenopausal women can be recovered by sales of the drug in the U.S. (b) (4) However, the sponsor states that they reserve the right to request orphan designation under the alternative standard of estimated patient population (21 CFR 316.20(b)(8)(i)), if necessary.

The sponsor states that the planned indication of raloxifene for breast cancer risk reduction in postmenopausal women represents a legitimate patient population. The sponsor notes that raloxifene is contraindicated for premenopausal women.

Reviewer Comment:

Raloxifene is classified as FDA pregnancy category X. It is contraindicated in women during pregnancy or in women who may become pregnant. Currently, raloxifene is not indicated for use in premenopausal females. Safety has not been established and its use is not recommended in this population. In addition, raloxifene should be avoided in women who are breast-feeding due to the potential risk to the newborn, although it is not known if the drug is excreted in human milk. Therefore, it remains reasonable for the sponsor to limit analyses included in this designation request to postmenopausal women.

3. Rationale for Use

Raloxifene is a selective estrogen receptor modulator (SERM) of the benzothiophene class. Raloxifene produces estrogen-like effects on bone and lipid metabolism, while antagonizing the effects of estrogen on the breast and uterus. The tissue-selective estrogen agonist and antagonist effects of raloxifene reside with the high affinity interaction for estrogen receptors. The ability of raloxifene to compete with estrogen for estrogen receptor binding is believed to account for the estrogen-antagonist effects in breast and uterus tissue, whereas the high affinity interaction of raloxifene with estrogen receptor in bone, vascular, and hepatic tissue is believed to produce estrogen-like effects of reduced resorption of bone, vasodilation, and lowered serum cholesterol.

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Large clinical trials examining the long-term effects of raloxifene include the Raloxifene Use for the Heart (RUTH) study, the Multiple Outcomes of Raloxifene Evaluation (MORE) that evaluates effectiveness for osteoporosis and the effect of raloxifene therapy on the risk of cardiovascular events and breast cancer in postmenopausal women up to 80 years of age, and the Study of Tamoxifen and Raloxifene (STAR) study that is designed to compare efficacy in the prevention of breast cancer. These studies include more than 35,000 women over almost a decade of research and will provide a substantial clinical experience from which to evaluate the effectiveness and safety of Evista for breast cancer risk reduction.

The Multiple Outcomes of Raloxifene Evaluation (MORE), a randomized, double-blind trial evaluated 7,705 postmenopausal women with osteoporosis. The effect on breast cancer incidence was a secondary endpoint. After a median follow-up of 47 months, the risk of invasive breast cancer decreased by 72%.[3] The incidence of all types of breast cancer (regardless of invasiveness) was reduced with raloxifene by 62%, corresponding to a relative risk of 0.38 (95% CI 0.24-0.58). This study also reported a 72% reduction in relative risk of invasive breast cancer with raloxifene (RR = 0.28, 95% CI 0.17-0.46). These data indicate that 93 osteoporotic women would need to be treated with raloxifene for 4 years to prevent one case of invasive breast cancer. As with tamoxifen, raloxifene appeared to reduce the risk of estrogen receptor-positive breast cancer but not estrogen receptor-negative breast cancer. Similar to tamoxifen, raloxifene is associated with an excess risk of hot flashes and thromboembolic events. The risk of venous thromboembolic disease (deep venous thrombosis or pulmonary embolism) was 2.4 times higher in women assigned to the raloxifene groups than to the placebo group. No excess risk of endometrial cancer was observed after 47 months of follow-up. Raloxifene did not increase the risk of endometrial hyperplasia. Subgroup analyses after 4 years of follow-up suggest that, among women who have osteoporosis, raloxifene reduces breast cancer incidence for both women at higher and lower risk of developing breast cancer. It is not known if women without osteoporosis would benefit in the same way.

4. Cost Recovery Analysis

The sponsor contends that there is no reasonable expectation that costs of research and development of the drug for reduction of risk of breast cancer in postmenopausal women can be recovered by sales of the drug in the U.S.

As stated in the sponsor's executive summary, costs and revenues were subjected to agreed-upon procedures by an independent certified public accountant (b) (4) as required by FDA regulations. Costs were calculated in accordance with Generally Accepted Accounting Principles (GAAP). Projected revenues attributable to the breast cancer risk reduction indication were based on primary market research with a sample of U.S. physicians most likely to prescribe Evista and who will be targeted by the company for marketing after the new indication is approved. Lilly calculated these revenues on an all-inclusive basis, which captures the total impact of the new indication on the U.S. sales of Evista.

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The financial analysis is set forth in a product contribution statement prepared by Lilly, entitled, "Statement of Historical and Projected Product Contribution Assuming Generic Entry Would Occur In 2012 Without Breast Cancer Risk Reduction Indication, Generic Entry Would Occur In 2010 With Breast Cancer Risk Reduction Indication and Incremental Net Sales of (b) (4) "

The following assumptions and allocations are contained in this product contribution statement:

Discounting

1) *Present value* was used to measure revenue and expenses. The product contribution each year was discounted to present value using the sponsor's weighted average cost of capital (WACC).

Costs

2) Research and Development (R&D) costs include both indication-specific costs and "common" costs.

    a) For indication-specific costs, preclinical and clinical development efforts associated with both breast cancer treatment and breast cancer risk reduction were included. In order to be included in the indication-specific cost estimate, clinical studies had to have a breast cancer-related primary endpoint.

    b) Common costs include discovery, clinical pharmacology, general safety studies, and formulation development and were allocated based on the number of indications taken into Phase 3 development at the time of the orphan drug application (b) (4)

3) The percentage of development costs incurred outside the U.S. was estimated using sampling. An expense was considered foreign if cash payment was made by a non-US affiliate. All expenses paid by the U.S. affiliate were considered domestic costs, although a portion of such payments may have been made for work done outside the United States.

4) Cost estimates for manufacturing, distribution, marketing, selling, and general and administrative expenses rely on the assumption that the sponsor's future sales to expense ratios will be consistent with past ratios. These costs were calculated as a percent of sales and applied to the sponsor's projected revenue for the breast cancer risk reduction indication.

Revenue

5) Revenue is calculated from the sale of the drug in the U.S. during its first 7 years of marketing for the orphan indication and assumes that orphan exclusivity has not been granted.

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6) Projected revenue includes sales driven by the breast cancer risk reduction indication as well as sales driven by a combination of the breast cancer risk reduction indication and existing osteoporosis indications.

7) The sponsor assumes Evista will face generic competition in 2010 if it adds a breast cancer risk reduction indication to its label in 2007, because it is very unlikely that Evista will have patent protection for this new use. Under this assumption, the only U.S. intellectual property protection for the breast cancer risk reduction indication would be data package exclusivity (also known as "Hatch-Waxman exclusivity") which will expire 3 years after approval of Evista by FDA for this new indication.

8) The current approved uses (prevention and treatment of osteoporosis) are protected by three use patents in the U.S., two that expire on July 28, 2012 and one that expires on March 2, 2014. The sponsor is assuming that only the 2012 use patents will be found valid and enforceable.

9) Market research was performed using (b) (4) to survey (b) U.S. physicians (primary care and obstetrician-gynecologist physicians) who will be the target of the sponsor's marketing efforts.

10) Market research assumed a (b) invasive breast cancer risk reduction in postmenopausal women versus placebo, and identical safety profile to the current Evista label.

11) Year-on-year market uptake projections were based on the rate observed with the weekly formulation of Actonel (risedronate) as well as the uptake rate observed with Zyprexa for bipolar mania. Decay rate was based on the rate of decline observed when generic competition for Prozac entered the U.S. market.

12) Market research results were combined with Lilly projections about the size of the U.S. osteoporosis market, expected entrants to the U.S. market, and market share distribution to generate an incremental prescription (and ultimately sales) impact of the breast cancer risk reduction indication for Evista.

    a) The sponsor developed a 7-year prescription projection for Evista with a breast cancer risk reduction indication using the (b) (4) research (see item 9 above) and uptake and decay rates (see item 11 above). The projection was compared to a projection of Evista prescriptions without a breast cancer risk reduction indication, but with the longer period of market exclusivity that Evista would maintain absent that indication (2012 versus 2010, see items 7 and 8 above), to calculate the total incremental prescriptions associated with the breast cancer risk reduction indication.

    b) The sponsor assumes that Evista is competing in the osteoporosis market, which was selected given (b) (4) data that indicated that the breast cancer risk reduction indication incremental prescriptions are principally attributable

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to osteoporosis. Market size projection is based on extrapolation of historical market growth, assuming that the growth rate for this maturing market will slow in the future.

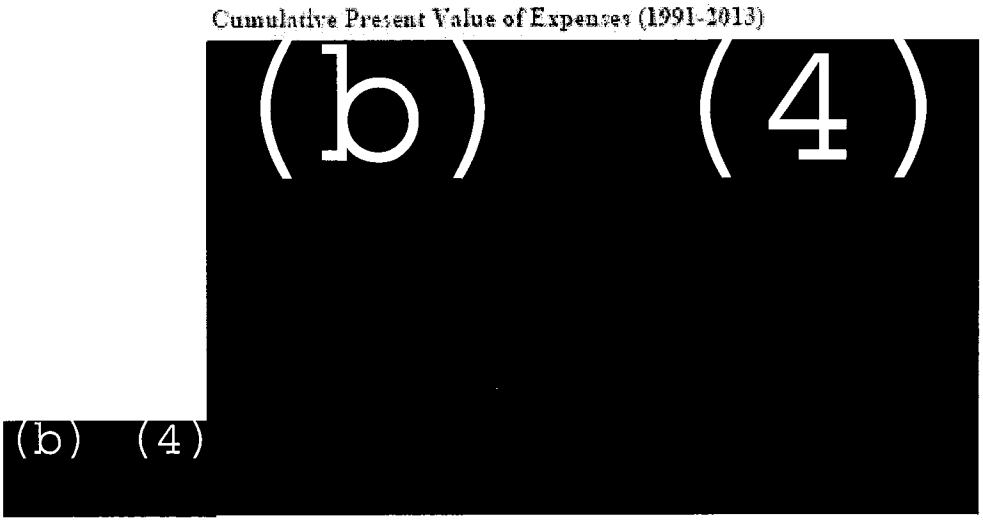
c) Evista's market share is projected to decline in the osteoporosis market. Five new product launches for osteoporosis between now and 2007 were modeled for this projection. The sponsor projects that the launch of the breast cancer risk reduction indication in 2007 will moderately grow Evista's U.S. market share from the 2006 level.

13) The sponsor assumes an average (b) net price growth from 2003 until 2006, with less than (b) price growth after 2006 as new osteoporosis products enter the market. The price is the same with or without the breast cancer risk reduction indication.

14) The sponsor assumes that Evista marketing and selling effort is comparable to 2003 Evista marketing and selling effort in the U.S., with the addition of direct-to-consumer advertising.

The sponsor estimates the development and marketing present value costs for the new indication at (b) (4) (non-discounted price (b) (4)). Lilly projects total revenue attributable to this indication in the U.S. of $(b) (4) for the 7-year post-approval period required for an orphan designation analysis. The result is that the sponsor's expected loss is more than (b) (4) (all amounts in 2004 present value). Without factoring in the time value of money, Lilly's expected loss on this indication totals more than (b) (4) if an orphan designation is not granted.

The following pie chart shows distribution of the cumulative present values of expenses:



The sponsor attempts to validate this projected loss with the results of five separate sensitivity analyses, conducted to assess the impact of changing key assumptions that

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underlie the revenue projection. The sponsor contends that data from these analyses support their cost recovery analysis findings even if: 1) the expected price of Evista is increased to levels that could not be justified in today's competitive market; 2) the expected approval date for the new indication is delayed or accelerated by several years; 3) the expected period of market exclusivity based on existing patents is modified; 4) the expected market size is increased beyond what historical experience would suggest is feasible; or 5) the incremental prescription projection for Evista is increased by an amount that represents the largest variance between projected and actual prescribing based on the historical accuracy of the market research firm utilized by the sponsor to conduct that research.

The January 19, 2005 amendment provides additional information regarding the cost recovery analysis:

1) New competition sensitivity analysis.

Holding all other factors constant, the sponsor was unable to identify any future competitive environment that enables the company to break even on its breast cancer risk reduction investment. The sponsor modeled scenarios ranging from no new competition to new competition completely dominating the market. As discussed in the application, the sales attributable to the breast cancer risk reduction indication are calculated based on the difference between Evista sales with and without this indication. In the absence of new competition, sales of Evista without the breast cancer risk reduction indication would be substantially greater and the difference in sales between the "with" and "without" scenarios would be decreased. As a result, the sales attributable to the breast cancer risk reduction indication would be decreased, and Lilly's net loss on its breast cancer risk reduction investment would be increased. In a more competitive environment, Lilly's loss on the breast cancer risk reduction indication would be reduced but not eliminated. In this case, sales of Evista in 2006 would be smaller, thus providing a smaller base from which to grow with the new indication.

In the case of no new competition, the present value of sales attributable to the breast cancer risk reduction indication is less than (b) (4) Using the base case (as presented in the original designation), with five new entrants, the present value of sales attributable to the breast cancer risk reduction indication sales is (b) (4) Lilly views this case as the most likely. In the case that new competition dominates the market, the present value of sales attributable to the indication is (b) (4)

(b) (4)

2) Market Research

The sponsor provided additional information regarding the market research conducted by (b) (4) Table 1 presents the results of this research:

Table 1. Expected Year 1 Prescriptions (millions)

	Control Physicians	BrCa Physicians	
	Base Evista Rx'ing (Year 1 Rx MM)	Evista Rx'ing without Product X	Evista Rx'ing with Product X
Total PCPs	(b) (4)	(b) (4)	(b) (4)
for Osteoporosis			
for Breast Cancer Prevention Only			
Total Ob/Gyns			
for Osteoporosis			
for Breast Cancer Prevention Only			
Total All MDs			
for Osteoporosis			
for Breast Cancer Prevention Only			
DTC Driven		(b) (4)	

All responses indicate Rx's in year 1 (millions)

Sample Physicians	Control	BrCa without Prod X	BrCa with Prod X
PCPs	(b) (4)		
OB Gs			

Control Physicians see only the current Evista message
BrCa Physicians without Prod X see only Evista + BrCa Risk Reduction message
BrCa Physicians with Prod X see both Evista + BrCa RR and Product X message

Abbreviations: BrCa = breast cancer, DTC = direct-to-consumer, MDs = doctors, MM = millions, Ob/Gyns = obstetrician/gynecologists, PCPs = primary care physicians, Rx = prescription.

3) Research and Development costs

The sponsor provided additional information regarding the studies (both indication-specific and common) included in the research and development costs.

4) Third Party Grants

The sponsor defines a third party grant as a payment by the company to an individual researcher or research organization for clinical work related to the studies. The sponsor states that the research and development expenses included in the orphan drug financial analysis include only Lilly expenses. Expenses incurred or funded by government entities or other third parties are not included.

(b) (4)

5) Financials

The sponsor provides additional information on Product Cost Schedule, Manufacturing Variance Schedule, Distribution Cost Schedule, Research and Development Cost Schedule, General and Administrative Expense Schedule, and Selling and Marketing Expense Schedule supporting the product contribution statement provided in the initial application. Also included is the (b) (4) report detailing the derivation of Lilly's historical weighted average cost of capital (WACC) and the (b) (4) eport providing Lilly's current WACC.

The February 22, 2005 amendment provides additional information regarding the cost recovery analysis:

1) The sponsor provided additional information regarding: the methodology involved in calculating the (b) increase in first year prescriptions; The (b) (4) Marketing Research database; and the capture of any tamoxifen market.

2) The sponsor states that the reason for the difference between the survey results and actual prescription numbers available in the (b) database is due to the fact that this estimate is projected to 2006.

3) Regarding overstatement of prescription patterns, (b) (4) relies on "proprietary techniques" that are not discussed in detail. (b) (4) uses a calibrated model to provide a forecast for expected sales given a dual indication Evista. The stated accuracy of this model to evaluate changes to established brands is within (b) (versus (b) for new product models). (b) (4) states that this design is standard for this type of research within the industry.

4) PCPs/OB-GYNs make up (b) of the osteoporosis market. Doctors in decile 3 to 10 (i.e., 3+ decile) include (b) of the prescription writing universe. This is standard (b) (4) sampling.

5) (b) (4) was unable to differentiate between prevention and treatment for tamoxifen. In response, Lilly decided to use (b) (4) to estimate usage in primary prevention, which found that (b) of tamoxifen was for prevention ((b) (4)).

6) The doctor survey collected data on:

- Current prescription behavior
- Expected prescription behavior post the new indication
- Attribute ratings versus other treatment offerings
- Likelihood of increasing prescription activity post the new introduction
- Open-ended likes/dislikes/confusion
- Closed-ended uniqueness and believability
- Writing behavior vis-à-vis indication (osteoporosis, cancer prevention)
- Perceptual changes due to new indication

(b) (4)

7) Consumer survey collected data on:

- Current category experience
- Classification (e.g., is the respondent 'at risk'?)
- Consumer likelihood to take action on the DTC message
- Types of action consumer would take
- Expected speed of action
- Open-ended likes/dislikes/confusion
- Closed-ended uniqueness and believability
- Other diagnostics

5. Evaluation and Recommendation

The sponsor requests orphan-drug designation for raloxifene (Evista®) for reduction of risk of breast cancer in postmenopausal women. Based on the information presented, the sponsor has provided sufficient evidence to support the scientific rationale for the use of raloxifene in this patient population. However, concerns remain regarding the cost recovery analysis intended to support the sponsor's contention that there is no reasonable expectation that costs of research and development of the drug can be recovered by sales of the drug in the U.S.

To assist in the review of the economic and market research components of this complex cost recovery analysis, OOPD consulted with FDA's Office of Economics Staff (John Goldsmith, Ph.D.) and with a Special Government Employee working with FDA's Division of Drug Marketing, Advertising, and Communications (Jack Swasy, Professor of Marketing at American University). These consult reviews are included in the file.

At issue with the cost recovery analysis are the numerous assumptions which the sponsor relies upon to justify the proposed financial loss without orphan-drug designation. While some of these assumptions appear appropriate, several others remain quite speculative. These remaining concerns and questions include:

1. The sponsor is actively litigating patent infringement cases (both primary and secondary patents). If successful, generic entry could be delayed until 2017, regardless of indication. This assumption is critical to the sponsor's current analysis. As stated in the original application (page 29, footnote 16) the sponsor has assumed for the purpose of this request that one or more generic companies may ultimately circumvent these other patents. This assumption is grounded on the Federal Trade Commission's statistical analysis of generic patent challenges and is not based upon the sponsor's assessment of the possible outcomes of the existing challenge to its Evista Orange Book patents. The sponsor has taken the position in connection with existing generic drug litigation involving Evista Orange Book patents that these other patents are infringed and validly enforceable beyond 2012, as evidenced by the following statements in their 2003 Annual Report filed with the Securities and Exchange Commission:

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"In October 2002, we were notified that Barr Laboratories, Inc. (Barr), had submitted an ANDA to the U.S. FDA seeking permission to market a generic version of Evista several years prior to the expiration of our U.S. patents covering the product, alleging that the patents are invalid or not infringed. On November 26, 2002, we filed suit against Barr in federal district court in Indianapolis seeking a ruling that Barr's challenges to our patents claiming the method of use and pharmaceutical form (expiring from 2012 to 2017) are without merit. In June 2003, Barr added a challenge to one of our additional patents (expiring in 2017), claiming a component in the pharmaceutical form of Evista. This patent has now been added to the lawsuit. The trial is tentatively scheduled to begin in August 2005. While we believe that Barr's claims are without merit and expect to prevail, it is not possible to predict or determine the outcome of the litigation. Therefore, we can provide no assurance that we will prevail. An unfavorable outcome could have a material adverse impact on our consolidated results of operations, liquidity, and financial position."[4]

2. How accurate and robust is the market research performed by (b) (4)?

3. How accurate are the uptake/decay rates?

4. How might "marketing and selling effort" affect the analysis? The level of marketing expense assumes the same level as in 2003 plus direct to consumer spending. This issue is further explained in Jack Swasy's consult review.

5. Is it appropriate to assume the price is not likely to increase significantly?

6. How accurate is the market size/share estimate?

7. Is the "summary of significant projection assumptions" (SSPA) reasonable and accurate?

8. Is the assumption of "5 new product launches between now and July 2007" provided in the SSPA accurate?

9. Is price growth rate appropriate as described in the SSPA?

10. The doctor and consumer surveys use "Product X," a SERM with better bone efficacy, an additional indication for female sexual arousal disorder, but no breast cancer risk reduction. This product profile was selected based on 3 SERMS in late stage development. However, it is unclear that this comparator is the most appropriate approach at estimating the impact of a new indication which could potentially differentiate Evista from all other products on the market or in clinical development.

11. It remains unclear whether (b) (4) "normalization" procedure based on historical trends applies to this specific example. No detailed explanation is given for how this

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normalization is validated for Evista's particular situation, given the addition of a second indication.

Because these issues raise questions about the cost recovery analysis, it has been difficult to determine whether these assumptions meet the threshold for presenting a reasonably likely scenario for purposes of orphan-drug designation. However, after considering all the information presented in this request, it is this reviewer's opinion that the sponsor has presented available documentation that supports their contention that there is no reasonable expectation that costs of research and development can be recovered by sales in the U.S., as required under 21 CFR 316.21(c). However, before a recommendation to grant this request can be proposed, it is recommended that the sponsor be required to provide written commitments which detail the sponsor's understanding regarding reporting requirements intended to substantiate the assumptions and hypotheses presented in this request. This information should be presented in subsequent annual reports, as required under 21 CFR 316.30, as well as prior to marketing approval, and after a certain period of postmarketing experience is available (to be negotiated). At each of these time points, OOPD will need to determine if the designation and/or marketing exclusivity should remain in place or whether the designation and/or exclusivity should be revoked as permitted under 21 CFR 316.29.

This recommendation appears to be supported by the following regulations:

1. 21 CFR 316.21(d): A sponsor that is requesting orphan drug designation for a drug designed to treat a disease or condition that affects 200,000 or more persons shall, at FDA's request, allow FDA or FDA designated personnel to examine at reasonable times and in a reasonable manner all relevant financial records and sales data of the sponsor and manufacturer.

2. 21 CFR 316.29 (Revocation of orphan drug designation):

> (a) FDA may revoke orphan drug designation for any drug if the agency finds that:
>
> > (1) The request for designation contained an untrue statement of material fact; or
> >
> > (2) The request for designation omitted material information required by this part; or
> >
> > (3) FDA subsequently finds that the drug in fact had not been eligible for orphan drug designation at the time of submission of the request therefor.
>
> (b) For an approved drug, revocation of orphan drug designation also suspends or withdraws the sponsor's exclusive marketing rights for that drug but not the approval of the drug's marketing application.

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3. 21 CFR 316.30(c): A brief discussion of any changes that may affect the orphan-drug status of the product.

It is recommended that this review and recommendation, as well as any subsequent written responses from the sponsor on this issue, be forwarded to FDA's Office of General Counsel before a final decision on this request is made.

In addition, the sponsor has stated their intention to respond to four issues raised in Jack Swasy's review (dated May 18, 2005), and submit this response as an amendment to the request. This information should be forwarded to Prof. Swasy for his consideration.

Also, the (b) (4) report will need to be finalized and submitted as an amendment. This report should be provided to John Goldsmith for his consideration and approval.

Assuming these outstanding issues are adequately addressed, it is recommended that the following letter comments (in addition to boiler-plate language) be used as a template when drafting a designation letter to be issued to the sponsor (these comments should be edited based on pending sponsor commitments and other agreements):

> Reference is made to your request for orphan-drug designation dated November 8, 2004, for raloxifene (Evista®) for breast cancer risk reduction in postmenopausal women. We also refer to our acknowledgement letter of November 10, 2004, and to your submissions dated January 19, February 22, May 24 and 25, June 8 and June 10, 2005.
>
> Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of raloxifene (trade name Evista®) is granted for reduction of the risk of breast cancer in postmenopausal women. Specifically, orphan-drug designation is being granted on the basis that there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States for seven years after approval of a marketing application [21 CFR 316.20(8)(ii)].
>
> We acknowledge your agreement to provide additional information as described in your commitment letter of June 10, 2005, and as outlined below.
>
> 1. Provide updated information related to the assumptions on patent status reflected in section 8.4.2 of your Application. This includes information on any new patents or other significant intellectual property rights that would impact Evista for the orphan indication.
>
> 2. Provide information identifying new competitor product launches since the date of application (section 8.4.5.2).
>
> 3. Provide a current and projected net price for the next 12-month period for Evista.

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4. Provide updated estimates for projected marketing investment for the orphan indication as reflected in section 3.2, Supplement #1 of the Application.

5. Provide a description of Evista's prescription growth for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.

6. Provide Evista's net revenue for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.

As agreed to in your June 10, 2005 letter, the above information will be submitted within 90 days following the first full year of marketing Evista for the orphan indication in the United States, and thereafter annually for an additional two years.

It should be noted that this Office reserves the right to revoke the orphan drug designation of Evista, and exclusive marketing rights if approved, as stipulated under 21 CFR 316.29.

If you have any questions, please contact Jeff Fritsch, R.Ph., in this Office at (301) 827-3666.

Bradley J. Glasscock, Pharm.D.
Reviewing Pharmacist
OOPD/FDA/HF-35

Concurrence:

Date: 17 June 2005

Marlene E. Haffner, MD, MPH
RADM, USPHS
Director, Office of Orphan Products Development

cc:

HF-35/Designation file (b) (4)
HF-35/Chron file
HF-35/Glasscock

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