UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

DIVISION OF
CORPORATION FINANCE

May 10, 2013

Via E-Mail
Jason Rhodes
Executive Vice President and Chief Financial Officer
Epizyme, Inc.
400 Technology Square
Cambridge, MA 02139

**Re: Epizyme, Inc.**
**Amendment No. 1 to Registration Statement on Form S-1**
**Filed April 26, 2013**
**File No. 333-187982**

Dear Mr. Rhodes:

We have reviewed your registration statement and have the following comments. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure.

Please respond to this letter by amending your registration statement and providing the requested information. If you do not believe our comments apply to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing any amendment to your registration statement and the information you provide in response to these comments, we may have additional comments.

Our lead product candidates, page 3

1. Please define your use of the terms "biological effect" and "clinical effect," and disclose how and why these effects are distinguishable from one another. In particular, please specifically address why a biologic effect, such as partial inhibition, does not demonstrate a clinical effect of your product candidate.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Stock-Based Compensation, page 53

2. Please refer to your response to our comment 13. It is unclear how you have sufficiently addressed the quantitative or qualitative components in our initial comment regarding the discussion of each significant factor contributing to the difference between each valuation and the estimated IPO price considering the 539% increase in the fair value from the

June 7, 2012 price to the midpoint of your price range. Please revise your proposed disclosure to provide this information from the June 7, 2012 grant to the latest grant.

Phase 1 Clinical Trial, page 77

3. We note your statement that there were no adverse events greater than Grade 2, moderate, in relation to your Phase I trial for EPZ-5676. Please revise your disclosure to identify the specific adverse events that were experienced and the number of patients that experienced such adverse effects.

Director Compensation, page 122

4. We note your disclosure that your board approved a director compensation program in April 2013. Please file a copy of this compensatory plan as an exhibit to your registration statement as required under Item 601(b)(10)(iii)(A) of Regulation S-K. To the extent it is not set forth in any formal document, a written description the director compensation plan should be filed as an exhibit.

Notes to Consolidated Financial Statements
9. Collaborations, page F-21

5. Please refer to your response to our comment 29. For your research, development, and regulatory milestones, please quantify those that you determined were substantive and those that you determined were not substantive for the Eisai and GlaxoSmithKline agreements. For your research, development, and regulatory milestones that you determined were substantive please provide further disaggregation. Consider disaggregation by categories such as preclinical, phase 1, phase 2, regulatory, etc.

6. Please refer to your response to our comment 33. We are still evaluating how you determined the option exercise fee included in the total allocable arrangement consideration is fixed and determinable. You state "the Company has estimated the number of available targets that it believes are reasonably likely to be selected by Celgene during the option period, based on information available to management at the time the agreement was executed." Please clarify the additional information available to management, and whether this number represents the minimum number of targets available.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that the filing includes the information the Securities Act of 1933 and all applicable Securities Act rules require. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

Please refer to Rules 460 and 461 regarding requests for acceleration. We will consider a written request for acceleration of the effective date of the registration statement as confirmation

of the fact that those requesting acceleration are aware of their respective responsibilities under the Securities Act of 1933 and the Securities Exchange Act of 1934 as they relate to the proposed public offering of the securities specified in the above registration statement. Please allow adequate time for us to review any amendment prior to the requested effective date of the registration statement.

You may contact Tabatha Akins at (202) 551-3658 or Joel Parker at (202) 551-3651 if you have questions regarding comments on the financial statements and related matters. Please contact Amy Reischauer at (202) 551-3793, Bryan Pitko at (202) 551-3203, or me at (202) 551-3715 with any other questions.

Sincerely,

/s/ Daniel Greenspan for

Jeffrey P. Riedler
Assistant Director\

cc: Via E-Mail
Rosemary Reilly
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109