Mail Stop 6010 March 27, 2007

Mr. Christoph Westphal
Chief Executive Officer
Sirtris Pharmaceuticals, Inc.
790 Memorial Drive
Cambridge, Massachusetts 02139

Re: Sirtris Pharmaceuticals, Inc.
Registration Statement on Form S-1
Filed March 1, 2007
File No. 333-140979

Dear Mr. Westphal:

We have reviewed your filing and have the following comments. Where indicated, we think you should revise your document in response to these comments. If you disagree, we will consider your explanation as to why our comment is inapplicable or a revision is unnecessary. Please be as detailed as necessary in your explanation. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure. After reviewing this information, we may raise additional comments.

Please understand that the purpose of our review process is to assist you in your compliance with the applicable disclosure requirements and to enhance the overall disclosure in your filing. We look forward to working with you in these respects. We welcome any questions you may have about our comments or any other aspect of our review. Feel free to call us at the telephone numbers listed at the end of this letter.

FORM S-1

General

1. Please provide us proofs of all graphic, visual, or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary prospectus. Please note we may have comments regarding these materials.

2. Please note that when you file a pre-effective amendment containing pricing-related information, we may have additional comments. As you are likely aware, you must file this amendment prior to circulating the prospectus.

3. Please note that when you file a pre-effective amendment that includes your price range, it must be bona fide. We interpret this to mean your range may not exceed $2 if you price below $20 and 10% if you price above $20.

4. Please note that where we provide examples to illustrate what we mean by our comments, they are examples and not complete lists. If our comments are applicable to portions of the filing that we have not cited as examples, please make the appropriate changes in accordance with our comments.

5. In the event you file a request for confidential treatment related to this filing, please be advised that we will not be in a position to consider a request for acceleration of effectiveness of the registration statement until we resolve all issues concerning the confidential treatment request.

Prospectus Summary, page 1

6. Please expand the discussion to briefly indicate that you have no products approved for commercial sale and you have not generated any revenues from commercial sales.

7. While you have included a discussion of your positive opinions and beliefs regarding your proposed products, you have not balanced the discussion with a discussion of the negative aspects of your business, and have not clearly indicated that positive results are not assured. The discussion of the negative aspects of your business should be disclosed as prominently as the positive aspects.

8. Please define the term "Orphan Drug status."

Risk Factors, page 9

9. Please delete the statement that there are additional risks and uncertainties. It is not appropriate to reference risks that are not discussed.

"Our results to date provide no basis for predicting whether any of our product candidates will be safe or effective….", page 9

10. Please expand the discussion to indicate the nature of any material adverse side effects observed in your previous trials.

"Our current product candidates are SIRT1 activators. Resveratrol, a SIRT1 activator, is marketed by other companies as a dietary supplement. As a result, any products we successfully develop may be subject to substitution and competition." Page 11

11. Please provide the basis for your belief that your product candidates will have a superior therapeutic profile to resveratrol.

"We may not be able to manufacture our product candidates in clinical or commercial quantities….", page 11

12. Please identify the third parties you substantially rely upon for the manufacture and packaging of your drug candidates. You should also file the agreements as exhibits to the registration statement and include a discussion of the material terms of these agreements in the "Business" section. If you believe you are not substantially dependent on these parties, please provide us with an analysis supporting this determination, including a discussion of the number of manufacturers capable of producing your product. If there are a limited number, discuss the potential adverse impact this could have on your future operations.

"We may not be able to obtain and maintain the third party relationships that are necessary….", page 11

13. If applicable, please identify the third parties you substantially rely upon for conducting your clinical trials. Also, to the extent you have any agreements with such parties, please so indicate and describe in your business section the material terms of the agreement(s). You should also file the agreements as exhibits to the registration statement. If you have determined that you are not substantially dependent on these parties, please provide us with an analysis supporting this determination and disclose the number of parties you engage to conduct your clinical trials.

"If we choose to commercialize SRT501 as a dietary supplement, we may not be able to successfully market SRT501 as a therapy for disease, if approved, and our results may be affected." Page 12

14. Under what circumstances will you commercialize SRT501 as a dietary supplement?

"If we are not able to retain our current senior management…", page 13

15. Please discuss the extent to which you have employment agreements with these individuals.

16. Please briefly describe the material term and termination provisions of your employment contracts, if any, with key executives.

17. To the extent you have experienced problems attracting and retaining key executives and scientists in the recent past, please revise the discussion to describe these problems. Additionally, if any key employee has plans to retire or leave your company in the near future, please revise the discussion to disclose this information.

"We have a history of operating losses…", page 14

18. Please expand the discussion to indicate the amount of losses you experienced for each of the past two years.

"The regulatory approval process is costly and lengthy and we may not be able to successfully obtain all required regulatory approvals." Page 16

19. Please revise the last paragraph of this discussion to include a discussion of the consequences of another company receiving FDA approval for a drug for MELAS before you obtain FDA approval for SRT501.

"We may have significant product liability exposure…", page 23

20. Please expand the discussion to quantify the extent of your product liability coverage. Similarly, revise "We use and generate materials that my expose us to material liability."

Use of proceeds," page 30

21. Please clarify what stage of development you expect to achieve for each indication for your product candidates using the proceeds from the offering.

Dilution, page 34

22. Please revise to start your narrative discussion with your historical net tangible book value.

Management's Discussion and Analysis of Financial Condition and Results of Operations

Liquidity and capital resources

Contractual obligations and commitments, page 42

23. It appears that you have several license agreements with minimum annual royalty and maintenance payments that are not reflected in the table of contractual obligations. Please include these commitments in the table or expand your disclosure in footnote one of the table to disclose the terms of each significant arrangement disclosed in Footnote 10 to your consolidated financial statements.

Critical accounting policies and estimates

Accrued expenses, page 44

24. Please disclose the amount of the change in this estimate for each period presented. Include a sensitivity analysis showing the effect that reasonable likely changes in the estimate as of December 31, 2006 may have on financial position and results of operations.

Stock based compensation, page 44

25. We note your analysis of how you determined the fair value of the underlying common stock and any related stock-based compensation for each equity issuance. Once an estimate IPO price is determined, please disclose the significant factors contributing to the difference between the fair value as of the date of each grant and the estimated IPO price.

26. We note throughout your filing you reference an independent third-party valuation specialist. The reference to an independent valuation firm equates to the use of a valuation expert. Please name the independent appraiser under "Experts" and provide the consent of the appraiser in the registration statement.

27. Clarify why you believe the peers used in the market approach were comparable companies and what specific factors and assumptions you considered in determining that they were comparable companies. Tell us why you believe the median valuation of the peer group is an appropriate measure. Explain to us why the financial statement metrics discussed in paragraph 50 of the practice aid were not used.

28. Disclose the key factors and assumptions used in the market approach. Refer to paragraphs 60, 61, and 182 of the practice aid.

29. You state that you are using the market approach, but you also appear to be using other factors outside of the market approach in valuing your stock, such as valuation in preferred stock issuances and your proposed public offering. Tell us how the other factors are considered in your market approach and why you believe your methodology is appropriate. We do not believe that using the underwriters' enterprise value is appropriate in determining your enterprise value. Also, if you

are using preferred stock issuances to related parties, we do not believe those issuances are representative of the fair value of your stock.

30. Please tell us why it is appropriate under the probability-weighted expected return method to deduct the liquidation preference from the enterprise value in determining the fair value of your common stock under the dissolution and sale scenarios. Please revise your methodology or tell us why your method is consistent with the methodology described in paragraph I22-I29 of the practice aid.

31. Please tell us why you believe a risk-adjusted discount rate of 35% is appropriate for your IPO scenario. The discount rate should be based on your company and should not be based on rates disclosed in the Practice Aid.

Business - General, page 51

32. Please expand the discussion to clarify the size of the market for the indications for which your products are designed to treat.

Preclinical data for diabetes, page 56

33. Please expand the discussion to explain the term "DIO model."

Clinical progress for diabetes, page 56

34. Please discuss the significance of not meeting primary endpoints.

35. Please explain the meaning of the term "naïve to other treatments."

36. Explain the significance of the p value.

Patents and other proprietary rights, page 59

37. Please expand your existing discussion or include a section describing, as applicable, your material collaboration, commercial and license agreements, and grants. The discussion of each agreement should include the material terms of each, including, but not limited to, the aggregate amounts of any milestone payments, termination provisions, minimum royalty payments, financial commitments, aggregate amounts paid to date, and any other material terms.

38. You should also file these agreements as exhibits. If you have determined that these agreements are not material and that you are not substantially dependent upon them, please provide us with an analysis supporting this determination.

Compensation Discussion and Analysis, page 66

39. Please expand this section to discuss how each compensation element and the company's decisions regarding that element affect decisions regarding other elements. See Item 402(b)(1)(vi) of Regulation S-K.

40. Please expand this section to specifically discuss how corporate performance and individual performance are taken into account in making compensation decisions. You should discuss what specific items of corporate performance are taken into account in making compensation decisions and how specific forms of compensation are structured and implemented to reflect these items of the company's performance. Further, you should also discuss how specific forms of compensation are structured and implemented to reflect the executive officer's individual performance and/or individual contribution, describing the elements of individual performance and/or contribution that are taken into account. See Item 402(b)(2) of Regulation S-K.

Notes to consolidated financial statements, page F-8

41. Please revise the notes to the financial statements as appropriate for the above comments.

Note 6. Redeemable convertible preferred stock, page F-24

42. Please tell us why no beneficial conversion feature was recorded for your issuance of preferred stock in accordance with EITF 00-27 and EITF 98-5.

* * *

As appropriate, please amend your registration statement in response to these comments. You may wish to provide us with marked copies of the amendment to expedite our review. Please furnish a cover letter with your amendment that keys your responses to our comments and provides any requested information. Detailed cover letters greatly facilitate our review. Please understand that we may have additional comments after reviewing your amendment and responses to our comments.

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 all information required under the Securities Act of 1933 and that they have provided all information investors require for an informed investment decision. 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.

Notwithstanding our comments, in the event the company requests acceleration of the effective date of the pending registration statement, it should furnish a letter, at the time of such request, acknowledging that:

- should the Commission or the staff, acting pursuant to delegated authority, declare the filing effective, it does not foreclose the Commission from taking any action with respect to the filing;

- the action of the Commission or the staff, acting pursuant to delegated authority, in declaring the filing effective, does not relieve the company from its full responsibility for the adequacy and accuracy of the disclosure in the filing; and

- the company may not assert staff comments and the declaration of effectiveness as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

In addition, please be advised that the Division of Enforcement has access to all information you provide to the staff of the Division of Corporation Finance in connection with our review of your filing or in response to our comments on your filing.

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. We will act on the request and, pursuant to delegated authority, grant acceleration of the effective date.

We direct your attention to Rules 460 and 461 regarding requesting acceleration of a registration statement. Please allow adequate time after the filing of any amendment for further review before submitting a request for acceleration. Please provide this request at least two business days in advance of the requested effective date.

You may contact Dana Hartz at (202) 551-3648 or Mary Mast at (202) 551-3613 if you have questions regarding comments on the financial statements and related matters. Please contact John Krug at (202) 551-3862, Suzanne Hayes, Branch Chief, at (202) 551- 3675, or me at (202) 551-3715 with any other questions.

Sincerely,

Jeffrey Riedler
Assistant Director

cc: Marc Rubenstein, Esq.
Richard D. Truesdell, Jr., Esq.