

Mail Stop 6010

May 1, 2007

Mr. Stanley N. Lapidus
President and Chief Executive Officer
Helicos BioSciences Corporation
One Kendall Square
Building 700
Cambridge, Massachusetts 02139

**Re: Helicos BioSciences Corporation
Amendment No. 2 to Registration Statement on Form S-1
Filed April 16, 2007
File No. 333-140973**

Dear Mr. Lapidus:

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 supplemental information so we may better understand your disclosure. After reviewing this information, we may or may not 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 on any other aspect of our review. Feel free to call us at the telephone numbers listed at the end of this letter.

Risk Factors, page 9

We have a history of operating losses, page 9

1. Please revise this risk factor to disclose the approximate time frame over which you expect to make the enumerated expenditures.

Use of Proceeds, page 28

2. We note that approximately 45% of the anticipated net proceeds are anticipated to be used for additional working capital and other general corporate purposes. To the extent possible, with respect to the proceeds to be used for “other general corporate purposes,” please furnish a brief outline of what these include, e.g. business development, administrative, etc.

Management’s Discussion and Analysis of Financial Condition and Results of Operations, page 35

Critical Accounting Policies and Significant Judgments and Estimates, page 43

Stock-based compensation, page 43

3. Please refer to your response to prior comment 37. Expand your disclosures to clarify the factors you considered in selecting “similar entities” for the purpose of determining expected volatility. Please refer to footnote 60 to paragraph A32 of SFAS 123R. Identify, on a supplemental basis, the specific entities considered in this calculation.
4. Please refer to your response to prior comment 38. Please provide the following information to assist us in evaluating your response. Note that we are deferring a final evaluation of stock compensation and other costs recognized until the estimated offering price is specified, and we may have further comment in this regard when the amendment containing that information is filed.
 - Tell us the assumptions and methodologies used to determine enterprise fair value in the retrospective valuations dated March 31, 2006 and October 31, 2006 and the method used to allocate enterprise fair value between preferred stock and common stock.
 - You identified “limited management team” as a factor in determining fair value during the period, January 1, 2006 to March 31, 2006 (\$0.40 per share). Explain to us why the Company’s Board of Directors concluded that only a ratable increase in the fair value of your common stock from April 1, 2006 (\$0.40 per share) to October 31, 2006 (\$1.97 per share) was appropriate considering the significant events that occurred during this time period, such as hiring a Chief Financial Officer and receiving your first government research grant.
 - Explain to us whether the Company’s Board of Directors considered any external events that may affect the price of your stock during the period from April 1, 2006 to February 28, 2007.

- Explain to us why only a ratable increase from \$1.97 per share to \$2.46 per share for November and December 2006 was appropriate considering the achievement of specific milestones during this time period.
 - Tell us how you determined the fair value of your common stock to be \$2.66 at February 28, 2007 and why only a ratable increase from January 19, 2007 to February 28, 2007 was appropriate.
5. Please expand your disclosure in response to prior comment 39 to include the following information, regarding your decision not to obtain a contemporaneous valuation performed by an unrelated valuation specialist in 2006.
- The significant factors, assumptions and methodologies used in determining fair value.
 - Why management chose not to obtain a contemporaneous valuation by an unrelated valuation specialist in 2006.

Business, page 49

General

6. We note your response to our prior comment 41 and reissue that comment. In your original Form S-1 you state that a proof-of-principle version of your instrument is currently in use in collaboration with the Institute for Systems Biology. Please provide us with an analysis as to why this collaboration is not material to your business and it not a material contract. Your analysis should provide support for your determination.

Industry Overview, page 51

7. We note your response to our prior comments 42 and 43 and your explanation that there are no standard criteria to measure the speed of genotyping and RNA expression analysis. In the table on page 53, however, you state that genotyping has “high throughput.” If the speed of genotyping can be measured by throughput, then it appears that you can compare the throughput of your method to the throughput of genotyping. Please revise your disclosure accordingly.

Intellectual Property, page 67

8. We note your response to our prior comment 45 and reissue that comment in part. Please describe the obligations/rights of each party to defend the technology that is the subject of the license.

Compensation, page 74

9. We note your statement that you analyze each of the primary elements of your compensation programs to ensure that your executives' total compensation is competitive with executive officers with similar positions at your peer group companies. Please revise to identify the companies that you consider your peer group companies.

Consolidated Financial Statements

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit), page F-6

10. Please revise the presentation in your EDGAR filing to separate redeemable convertible preferred stock from permanent equity with a solid line.

Notes to Consolidated Financial Statements

Note 8. Commitments and Contingencies

License agreements and patents, page F-15

11. Please expand your disclosure in response to prior comment 52 to include the termination provisions for each license agreement.

Note 10. Redeemable Convertible Preferred Stock, page F-19

12. Please refer to prior comment 54. We note your revisions to the pro forma presentations in the sections, summary consolidated financial data and the capitalization table. Please revise your pro forma disclosure of the redeemable convertible preferred stock issued in January 2007 to clarify, if true, that these shares are immediately convertible into common stock, resulting in no preferred stock discount. In the introduction to each section, you also discuss certain transactions "on a pro forma as adjusted basis." We do not understand the language, "conversion of the beneficial conversion feature from redeemable convertible preferred stock to additional paid-in capital," since it appears that additional paid-in capital has already been adjusted in the presentation "on a pro forma basis." Please revise your disclosure as appropriate or advise us further.

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As appropriate, please amend your filing 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 supplemental information. Detailed cover letters greatly facilitate our review. Please file your cover letter on EDGAR under the form type label CORRESP. Please understand that we may have additional comments after reviewing your amendment and responses to our comments.

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 Frank Wyman at (202) 551-3660 or Don Abbott at (202) 551-3608 if you have questions regarding comments on the financial statements and related matters. Please contact Sonia Barros at (202) 551-3655 or me at (202) 551-3715 with any other questions.

Sincerely,

Jeffrey P. Riedler
Assistant Director

cc: Lawrence S. Wittenberg, Esq.
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