

Mail Stop 6010

February 2, 2009

Ronald A. Lowy  
Chief Executive Officer  
Helicos BioSciences Corporation  
One Kendall Square  
Building 700  
Cambridge, Massachusetts 02139

**Re: Helicos BioSciences Corporation  
Registration Statement on Form S-3  
Filed January 22, 2009  
File No. 333-156885**

Dear Mr. Lowy:

We have limited our review of your filing to the issues we have addressed in our 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.

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.

General

1. We note that you are registering the resale of up to 68,406,202 shares of common stock, including 25,652,333 shares of common stock issuable upon the exercise of warrants. Given the size of the offering relative to the number of shares outstanding held by non-affiliates, the nature of the offering and the selling stockholders, it appears that the offering may be a primary offering. Because you do not appear to be eligible to conduct a primary offering on Form S-3 you do not appear to be eligible to conduct a primary at-the-market offering under Rule 415(a)(4).

Please tell us your basis for determining that the transaction is appropriately characterized as a transaction that is eligible to be made under Rule 415(a)(1)(i). In your analysis, please address the following among any other relevant factors:

- the length of time the selling stockholders have held the shares;
- the relationship of each selling stockholder with the company, including an analysis of whether the selling stockholder is an affiliate of the company;
- any relationships among the selling stockholders; and
- whether or not any of the selling stockholders is in the business of buying and selling securities.

Please include in this analysis your basis for determining that each affiliated selling stockholder is not an underwriter. Please provide a separate analysis for each affiliated selling stockholder.

Selling Stockholders, page 20

2. Please revise your selling stockholder table to clearly identify the number of shares beneficially owned by each selling stockholder prior to this public offering, which should include all shares offered in this public offering and all shares beneficially owned but not offered in this public offering. Also, please revise the selling stockholder table to clearly disclose the aggregate number of shares to be offered by each selling stockholder in this public offering.
3. Please revise your selling stockholder table to identify the natural persons that have sole or shared voting or investment power over Vision Opportunity Master Fund, Ltd.

Signatures, page II-6

4. Please revise your signature page to include the signature of your controller or principal accounting officer. If your principal financial officer or one of the other officers who signed the filing also serves as your controller or principal accounting officer, please revise the signature page to clarify that fact.

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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 response 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.

Ronald A. Lowy  
Helicos BioSciences Corporation  
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Please contact Sebastian Gomez Abero at (202) 551-3578 or me at (202) 551-3715 with any questions.

Sincerely,

Jeffrey P. Riedler  
Assistant Director

cc: Stuart M. Cable, Esq.  
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