

Via Facsimile and U.S. Mail
Mail Stop 4720

December 15, 2009

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

**Re: Helicos BioSciences Corporation
Form 10-K for Fiscal Year Ended December 31, 2008
Form 10-Q for the quarterly period ended September 30, 2009
Schedule 14A Filed April 24, 2009
File No. 001-33484**

Dear Mr. Lowy:

We have reviewed your filings and have the following comments. In our comments, we ask you to provide us with information to better understand your disclosure. Where a comment requests you to revise disclosure, the information you provide should show us what the revised disclosure will look like and identify the annual or quarterly filings, as applicable, in which you intend to first include it. If you do not believe that revised disclosure is necessary, explain the reason in your response. After reviewing the information provided, we may raise additional comments and/or request that you amend your filings.

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 filings. 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.

Form 10-K for the Fiscal Year Ended December 31, 2008

Item 1. Business, page 3

Research and Development, page 14

1. We note the following statement on page 14: "In 2007, we substantially finished the assembly of five commercial grade Helicos Systems in advance of our first shipment of the Helicos System to our initial customer on March 5, 2008, which

was later returned.” Please revise your disclosure to name your “initial customer” and to provide details of why the first shipment was returned, including a quantification of any refunds issued.

Collaboration, page 16

2. We note your discussion of collaborations on page 16 of the filing. Please revise your disclosure to include information regarding each material collaboration arrangement that the company has entered into, including a discussion of the material terms of each arrangement. Your discussion should name the parties to each agreement, a summary of each party’s rights and obligations under the relevant agreement and the term and termination provisions thereof. This information should also be included for your agreement with Dr. Ambros at the University of Massachusetts Medical School. Also, please file copies of each agreement as exhibits to the extent you have not already done so.

Intellectual Property, page 18

3. Please provide proposed disclosure to be included in your next Form 10-K which includes a more robust discussion of your material patents, including which product groups they relate to and the expiration dates for each. See Item 101(c)(1)(iv) of Regulation S-K for guidance.
4. We note your discussion of the Roche License Agreement, AZTE License Agreement, Caltech License Agreement and the PerkinElmer License Agreement on pages 19 and 20. Please revise your disclosure to quantify the aggregate amount paid to date under each agreement, the aggregate potential milestone payments to be made under each agreement, as applicable, and to provide more information regarding the royalty rate provisions of each. We note that the company has been granted confidential treatment on the specific royalty rates themselves; therefore, either a range or a statement that the percentage is in the single digits, teens, etc. will be sufficient.

Signatures, page 99

5. Please note that Instruction D(2)(a) to Form 10-K requires that in addition to the signatures of the company’s CEO, CFO, PAO and board of directors, the filing must be signed by the registrant itself. Please confirm that your next Form 10-K will include a signature line for the company, to be signed on behalf of the company by the appropriate authorized officer.

Form 10-Q For The Quarterly Period Ended September 30, 2009

Exhibit 31.1 and 31.2

6. Please revise the certification, particularly with respect to paragraph 4, to include reference to internal controls pursuant to Item 601(b)(31) of Regulation S-K.

Schedule 14A filed April 24, 2009

Section 16(a) Beneficial Ownership Reporting Compliance, page 27

7. We note the following statement on page 27 of the filing: "To the best of our knowledge, based on a review of (i) Forms 3 and 4 and amendments thereto during the year ended December 31, 2008 and (ii) Forms 5 and amendments thereto furnished with respect to the year ended December 31, 2008, each director, executive officer, and 10% stockholder complied with all Section 16(a) filing requirements, except as described below." Your disclosure does not go on to describe any late Section 16(a) filings, as indicated in the quoted statement. Please provide an explanation as to why the information has not been included and confirm that in all future filings you will clearly include all information required by this section.

* * *

Please respond to these comments within 10 business days or tell us when you will provide us with a response. Please furnish a letter that keys your responses to our comments and provide the requested information. Detailed letters greatly facilitate our review. Please furnish the letter to us via EDGAR under the form type label CORRESP.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filings to be certain that the filings include all information required under the Securities Exchange Act of 1934 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.

In connection with responding to our comments, please provide, in your letter, a statement from the company acknowledging that:

- the company is responsible for the adequacy and accuracy of the disclosure in the filings;
- staff comments or changes to disclosure in response to staff comments do not foreclose the Commission from taking any action with respect to the filings; and

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- the company may not assert staff comments 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 our review of your filings or in response to our comments on your filings.

Please contact James Peklenk, Staff Accountant, at (202) 551-3661 or Mary Mast, Senior Accountant, at (202) 551-3613 if you have any questions regarding the processing of your response as well as any questions regarding comments on the financial statements and related matters. You may contact Laura Crotty, Staff Attorney, at (202) 551-3563 with questions on any of the other comments. In this regard, do not hesitate to contact me, at (202) 551-3679.

Sincerely,

Jim B. Rosenberg
Senior Assistant Chief
Accountant