



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

DIVISION OF
CORPORATION FINANCE

September 29, 2010

Hugh C. Martin
Chief Executive Officer
Pacific Biosciences of California, Inc.
1380 Willow Road
Menlo Park, California 94025

**Re: Pacific Biosciences of California, Inc.
Registration Statement on Form S-1
Amended September 20, 2010
File No. 333-168858**

Dear Mr. Martin:

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.

1. We may have further comments after you complete the blanks in your document and file remaining exhibits.

Graphics

2. We understand from your counsel that you plan to make further changes to the graphics on the front cover. We will continue to evaluate your response to prior comment 3 after we have reviewed these changes.

Our Solution, page 2

3. We note your response to prior comment 17. Please revise to clarify that you compensated Scientia Advisors for providing the market opportunity data cited in your prospectus and file their consent as an exhibit.

SMRT Sequencing Advantages, page 3

Ability to observe and capture kinetic information, page 4

4. We note your response to prior comment 21. It remains unclear from your disclosure how your technology allows for structural variation analysis, such as methylation analysis, to be conducted at the same time as sequencing analysis, and why first and second generation sequencers are unable to accomplish structural variation analysis. We do note, however, that the article you provided us from *Nature Methods* entitled “Direct detection of DNA methylation during single-molecule, real-time sequencing” indicates that this ability is a product of your SMRT technology being able to measure the duration of the fluorescence pulses and the interval between successive pulses and from this information you are able to determine the methylation status of certain nucleotides. If true, please explain your system works in identifying structural variation in clear, everyday terms. Also make clear why first and second generation sequencers are unable to acquire this information.

Risk Factors, page 10

We may encounter difficulties in managing our growth..., page 14

5. We note your response to prior comment 28. Please tell us how you have determined “that all seven limited production release customers [are expected to] accept such instruments after testing is completed and will ultimately accept the commercial release version.”

Dilution, page 32

6. We note that you have added the disclosure as to how the percentage of shares owned by existing and new investors would be affected if the over-allotment option is exercised in full. Please continue to expand your disclosure in the paragraph that follows the table at the bottom of page 32 to address how the numbers, amounts and average price per share information would change if the over-allotment option is exercised in full as requested by prior comment 40.

Management’s Discussion and Analysis of Financial Condition..., page 36

Results of Operations, page 46

7. We note that you have included the loss from operations and net losses in each table that precedes your discussion of each of the periods presented. Please also include separately captioned paragraphs which discuss and analyze your loss from operations and net losses for each of the periods presented.

Backlog, page 66

8. We note your response to prior comment 58. Please revise to clarify the reason why you do not expect to recognize revenue on any orders prior to the end of your fiscal year.

Intellectual Property, page 68

9. Regarding your response to prior comment 60, please revise your disclosure in this section to clarify that the terms of the government march-in rights are not exclusive to your license with Cornell University.

Peer Group, page 80

10. We reissue prior comment 65, as it remains unclear from your revised disclosure the extent to which compensation paid for each component and in the aggregate deviates from the applicable compensation benchmark. Specifically, we note your disclosure in the penultimate paragraph on page 81, which indicates that “[y]our total cash compensation generally compares near or below the competitive range, both in aggregate compensation and relative to the individual compensation elements.” Please revise your disclosure to indicate clearly whether each component (cash and non-cash) of compensation paid to each named executive officer, as reported in the summary compensation table, fell within the targeted benchmark, and if not, clarify the reasons why.

Components of Our Executive Compensation Program, page 81

11. We reissue prior comment 66 in part. It is unclear from your revised disclosure what “individual skills” and “performance contributions” by your named executive officers other than Mr. Phillips were considered in determining base salaries. If your determination of base salary instead is based solely on a review of comparative salary and benchmarking information, please revise your disclosure to clarify.

Certain Relationships and Related Party Transactions, page 98

12. Please expand your disclosure in response to prior comment 69 to provide all information required by Regulation S-K Item 404(a), including the basis upon which Gen-Probe Incorporated is a related party and the approximate dollar amount involved in the transaction.

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.

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Notwithstanding our comments, in the event you request acceleration of the effective date of the pending registration statement please provide a written statement from the company 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.

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 David Burton at (202) 551-3626 or Kevin Vaughn, Accounting Branch Chief, at (202) 551-3643 if you have questions regarding comments on the financial statements and related matters. Please contact Celia Soehner at (202) 551-3463 or Tim Buchmiller, Senior Attorney, at (202) 551-3635 with any other questions.

Sincerely,

Russell Mancuso
Branch Chief

cc (via facsimile): Larry W. Sonsini, Esq. — Wilson Sonsini Goodrich & Rosati P.C.
Donna M. Petkanics, Esq. — Wilson Sonsini Goodrich & Rosati P.C.