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

DIVISION OF
CORPORATION FINANCE

September 22, 2017

Ankit Mahadevia
President and Chief Executive Officer
Spero Therapeutics, Inc.
675 Massachusetts Avenue, 14th Floor
Cambridge, MA 02139

Re: Spero Therapeutics, Inc.
Draft Registration Statement on Form S-1
Submitted August 25, 2017
CIK No. 0001701108

Dear Dr. Mahadevia:

We have reviewed your draft 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 providing the requested information and either submitting an amended draft registration statement or publicly filing your registration statement on EDGAR. 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 the information you provide in response to these comments and your amended draft registration statement or filed registration statement, we may have additional comments.

Draft Registration Statement on Form S-1

Prospectus Summary, page 1

1. In this section you state your belief that SPR994 will have an accelerated timeline and the QIDP designation potentially provides priority review for SPR994. Please state specifically whether you have received any designation from the FDA that would permit your drug candidates to progress on an accelerated basis. If not, please include disclosure to indicate that an accelerated review process is not assured and the impact on your development timeline if SPR994 is not reviewed on an accelerated basis.

2. Please include disclosure that the FDA has not made a determination as to whether Phase

2 clinical trials of SPR994 will be required, why the FDA may not agree that SPR994 can enter Phase 3 testing following successful completion of Phase 1 and the impact on your timeline if the FDA requires Phase 2 testing of SPR994.

3. Please revise the second paragraph on page 2 to clarify the potential addressable market for SPR994, given that you will be seeking approval to treat a particular type of infection that appears to be a subset of the market you describe.

4. We note your statement on page 3 that previous attempts by others to develop agents that interact with the outer membrane of Gram-negative bacteria have failed in pre-clinical testing and Phase 1 clinical trials due to safety concerns. Please balance this statement with disclosure about the competition that you face for SPR741 because it does not appear from disclosure on page 122 that all previous attempts have failed.

5. We note your statement in the first paragraph on page 3 that data from your Phase 1 dosing trial demonstrate that SPR741 was "well tolerated with a favorable safety profile and favorable pharmacokinetics." Statements regarding efficacy and safety are determinations that only the FDA and foreign government equivalent regulations have the authority to make. Please revise your disclosure to eliminate any suggestion that your product candidates have been or will ultimately be determined to be effective or to have demonstrated efficacy for purposes of granting marketing approval by the FDA or comparable agency.

6. The pipeline chart on page 4 seems to suggest that the various milestones represented in the table will be met and that each candidate will complete the phases of development portrayed in the chart, even though they are dependent on the achievement of successful trial results within the anticipated time frames. Please revise the chart to avoid giving the impression that these milestones will definitively be achieved within the time frames presented.

7. Please tell us if you expect there to be any limitations to using the Phase 1 trial information for SPR994 for approval by the FDA since this trial is being conducted outside of the United States.

Implications of Being an Emerging Growth Company, page 9

8. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications.

Use of Proceeds, page 60

9. It appears from your disclosure that the proceeds from the offering will not be sufficient to fund development of your product candidates through regulatory approval and commercialization. Please revise to make this clear and disclose the sources of other funds needed to reach regulatory approval and commercialization for each product

candidate. Refer to Instruction 3 to Item 504 of Regulation S-K.

10. Please amend your disclosure to indicate how far you expect to advance SPR206 and SPR720 based on the allocation of the proceeds from the offering.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Critical Accounting Policies and Significant Judgments and Estimates
Stock Based Compensation
Determination of the Fair Value of Common Units and Common Stock, page 88

11. We may have additional comments on your accounting for equity issuances including stock compensation and beneficial conversion features. Once you have an estimated offering price, please provide us an analysis explaining the reasons for the differences between recent valuations of your common stock leading up to the IPO and the estimated offering price.

Collaboration and License Agreements, page 117

12. Please expand the descriptions of your collaboration and license agreements to describe the term of each agreement and the termination provisions.

Government Awards, page 119

13. Please file the government contracts described in this section as exhibits to the registration statement or tell us the basis for your conclusion that it is not required to file these agreements.

General

14. We note that you have requested confidential treatment for several agreements that will be filed as exhibits to the registration statement. We will send any comments on your application for confidential treatment under separate cover.

15. Please provide us proofs of all graphics, visual, or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary prospectus. Please note that we may have comments regarding this material.

You may contact Christine Torney at 202-551-3652 or Sharon Blume at 202-551-3474 if you have questions regarding comments on the financial statements and related matters. Please contact Chris Edwards at 202-551-6761 or Mary Beth Breslin at 202-551-3625 with any other questions.

Division of Corporation Finance
Office of Healthcare & Insurance

cc: Matthew Gardella