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

DIVISION OF
CORPORATION FINANCE

Mail Stop 4720

December 21, 2015

Via E-mail
Nancy Simonian, M.D.
President and Chief Executive Officer
Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, Massachusetts 02139

Re: Syros Pharmaceuticals, Inc.
Draft Registration Statement on Form S-1
Submitted November 20, 2015
CIK No. 0001556263

Dear Dr. Simonian:

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.

Prospectus Summary

1. Please briefly explain the terms “transcription factors “transcriptional kinases, “proprietary assays” and “agonist.”

2. Please explain here, and wherever else relevant in your filing, the reason(s) you are initiating clinical testing of SY-1425 with a Phase 2 trial, and not a Phase 1 trial designed to assess safety and tolerability, and indicate whether you have communicated with the Food and Drug Administration about the clinical pathway you intend to follow.

Risks Associated with Our Business, page 5

3. Please include a bullet point summarizing the risk factor on pages 17-18 that relates to the possible failure of clinical trials for your product candidates to demonstrate safety and efficacy and cite the failure of tamibarotene to achieve its primary endpoint in trials conducted by a third-party. Please also cite this failed clinical trial in your disclosure on pages 104-105.

4. In your last bullet point, please note that you do not have composition of matter patent protection for SY-1425 and also state this in your Intellectual Property discussion on page 112.

Risk Factors
Risks Related to the Discovery, Development and Commercialization of Product Candidates
"Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates . . .," page 18

5. Please amend this risk factor to note the adverse effects and the serious adverse event identified from the use of SY-1425 as a treatment for APL cited on page 103.

6. Please amend this risk factor to provide examples of the retinoids similar to SY-1425 that cause birth defects.

7. Please include a bullet point summarizing this risk factor in your prospectus summary and cite the propensity of retinoids to cause birth defects in it.

Use of Proceeds, page 63

8. To the extent practicable, please separate the amount of offering proceeds you intend to allocate toward the development of SY-1425 for the AML indication from that to be allocated for the MDS indication.

9. To the extent practicable, please separate the amount of offering proceeds you intend to allocate toward development of SY-1425 for additional indications from that to be allocated toward the CDK7 inhibitor program for other indications.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Critical Accounting Policies and Estimates
Stock-Based Compensation, page 77

10. 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.

Business, page 90

11. We note your intention to use proceeds of the offering for companion diagnostic development; your references to the need to successfully validate, develop and obtain regulatory approval for companion diagnostics; and your dependence on third party collaborators to develop companion diagnostics. Please describe your agreements with these collaborators and describe these agreements. Additionally, either files the agreements as exhibits to the registration statement or provide your analysis supporting your determination that you are not substantially dependent on these agreements.

Our Clinical Programs, page 101

12. In your discussion of the preclinical data relating to the SY-1075 compound on page 108, please revise your description of its biochemical and cellular potency and selectivity to express the results in layman's language.

Intellectual Property, page 111

13. With respect to issued patents that you license from third parties, please disclose when they expire.

Other Comments

14. 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.

15. Please confirm that the graphics included in your registration statement are the only graphics you will use in your prospectus. If those are not the only graphics, please provide any additional graphics prior to their use for our review.

You may contact Bonnie Baynes at (202) 551-4924 or Joel Parker at (202) 551-3651 if you have questions regarding comments on the financial statements and related matters. Please contact Scot Foley at (202) 551-3383 or me at (202) 551-3675 with any other questions.

Sincerely,

/s/ Suzanne Hayes

Suzanne Hayes
Assistant Director
Office of Healthcare and Insurance

cc: Steven D. Singer
Cynthia T. Mazareas
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109