CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208647Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 121031

MEETING MINUTES

Sun Pharma Advanced Research Company (SPARC) Ltd.
Attention: Karin Kook, Ph.D.
Managing Director
4800 Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Dear Dr. Kook:

Please refer to your Pre-Investigational New Drug Application (PIND) file for submitted on behalf of SPARC Ltd. for rosuvastatin capsules.

We also refer to the telecon between representatives of your firm and the FDA on Monday, May 18, 2015. The purpose of the meeting was to discuss the format and content of your proposed marketing application.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Monday, May 18, 2015; 2:00 – 3:00 P.M.
Meeting Location: Teleconference

Application Number: PIND 121031
Product Name: rosuvastatin capsules
Sponsor/Applicant Name: Sun Pharma Advanced Research Company (SPARC) Ltd.

Meeting Chair: James P. Smith, M.D., M.S.
Meeting Recorder: Richard Whitehead, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

James P. Smith, M.D., M.S.	Deputy Director
Mary Roberts, M.D.	Clinical Reviewer
Stephanie Leuenroth-Quinn, Ph.D.	Nonclinical Reviewer
Pamela Lucarelli	Chief, Project Management Staff
Richard Whitehead, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Suong Tran, Ph.D.	Quality/CMC Lead
Tien-Mien Chen, Ph.D.	Biopharmaceutics Acting Team Leader
Mei Ou, Ph.D.	Biopharmaceutics Reviewer

Center for Devices and Radiological Health, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices

Ryan McGowan	Medical Device Reviewer

Office of Combination Products

Bindi Nikhar, M.D.	Associate Clinical Director

Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis

Mishale Mistry, Pharm.D.	Reviewer
Kishan Mistry, Pharm.D.	Reviewer
Vineeth Mair, Pharm.D.	Reviewer
Deveonne Hamilton-Stokes	Project Management Staff

Office of Scientific Investigations

Cynthia Kleppinger, M.D.	Medical Reviewer

SPONSOR ATTENDEES

Dr. Nitin Dharmadhikari	Senior Vice President – R & D (Formulation Development)
Dr. Yashoraj Zala	Vice President – R & D (Formulation Development)
Ms. Sangeeta Mirgal	General Manager – R & D (Analytical Development)
Mr. Pawan Mishra	Manager, R&D (Analytical Development)
Dr. Harry Ruan	Senior Director (Toxicology, Sun Pharma)
Dr. SuiLong Yao	Global Head (Clinical Development, Sun Pharma)
Dr. Ashwini Gadkari	Assistant Manager, R&D (Formulation Development)
Dr. Hitesh Thakkar	Project Manager
Mr. Sameer Kulkarni	Manager, Business Development
Dr. Karin Kook	Managing Director, Salamandra, LLC
Dr. Mona Zarifa	CMC Consultant, Salamandra LLC
Ms. Kaylee White	Project Manager, Salamandra LLC

1.0 BACKGROUND

Rosuvastatin calcium tablets were first approved in 2003 under NDA 021366. SPARC Ltd. is developing immediate-release rosuvastatin capsules that will be available in the same strengths and will have the same indications as the reference-listed (innovator) drug. Per the sponsor, the proposed product is a hard gelatin capsule that is filled with drug-containing (b) (4) designed for sprinkle application onto soft food or for nasogastric administration, or alternatively, for intact capsule ingestion when a sprinkle application is not required or desired.

FDA previously provided feedback via written responses to a pre-IND meeting request. These responses were issued on February 21, 2014.

The purpose of the current meeting is to discuss the format and content of SPARC Ltd.'s proposed marketing application, which will rely upon FDA's previous findings of safety and effectiveness for rosuvastatin under NDA 021366 via the 505(b)(2) regulatory pathway. The

briefing package was received on April 17, 2015, and preliminary meeting comments were sent to the sponsor on May 13, 2015. The sponsor provided an email containing "Questions for Clarification" on May 18, 2015, and meeting discussion was based on these questions.

2. DISCUSSION

The sponsor's questions are repeated below in *italics*, followed by the FDA preliminary response and meeting discussions (**bolded**). Note that as described in the sponsor's "Questions for Clarification" received on May 18, 2015 (included in Section 6), "Regarding Questions #5, 6, 7, 8, 10, 11, 12, 13, and 14, SPARC Ltd. accepts FDA's responses with no further discussion required," therefore nothing additional has been provided by FDA.

2.1. Chemistry, Manufacturing, and Controls

Question 1: *Are the proposed drug product specifications adequate in support of the NDA?*

FDA Response to Question 1: Add a test method and propose acceptance criteria for the particle size attribute of the drug product, given that the product will be labeled as (b) (4) for sprinkle as well as for administration via nasogastric tube. The drug product specification will be finalized as part of our review of the complete NDA and based on all available information in the application.

In reference to Dissolution: Based on the information of in vitro dissolution in your meeting package, your proposed dissolution method development looks acceptable. Dissolution method has appropriate discriminating ability. However, you did not provide full dissolution method validation. The typical dissolution method validation should include these main characteristics: Specificity, Linearity, Accuracy, Precision, Range, Quantitation limit, Detection limit, Precision, Robustness, etc. Please refer the "Guidance for Industry Analytical Procedures and Method Validation for Drugs and Biologics."

Your proposed specification is too lenient. We recommend the following data driven specification: NLT (b) (4)% (Q) label time at 20 minutes by using your proposed Dissolution Testing Conditions (Medium: pH 6.6, 0.05 M sodium citrate buffer, Volume: 900mL, Apparatus: USP Apparatus II (Paddle), Agitation speed: 50 rpm, Sampling time: 5, 10, 15, 20, 30 and 45min).

The dissolution method development report, method validation and the specification will be reevaluated in the context of your full NDA submission.

Sponsor Meeting Discussion: **The Division asked SPARC Ltd. to include a particle size test and specification for the finished drug product. The (b) (4) range in size between (b) (4) to (b) (4) µm (b) (4) SPARC Ltd. would like to clarify that particle size is controlled**

(b) (4)

Sponsor Request for Clarification: ***Does this approach to control of particle size address the Division's concerns?***

> ***FDA Meeting Discussion*:** **We acknowledge your agreement to implement controls for the particle size attribute of the drug product. The proposed specifications will be evaluated as part of our NDA review.**

Sponsor Meeting Discussion: **In reference to the validation of the dissolution method, SPARC Ltd. will ensure that the Division's recommendations are taken into consideration. Dissolution testing in the ongoing stability protocols has been only at the (b) (4) minute time point; at present, data are available for the registration batches stored for 9 months. SPARC Ltd. will amend the protocol so that at the 12-month time point, which is scheduled for later in May, and subsequent time points, dissolution testing will include both the 20- (b) (4) minute time points. SPARC Ltd. is willing to accept an interim specification of NLT (b) (4) % (Q) label claim at 20 minutes, contingent on the outcome of continued testing.**

Sponsor Request for Clarification: ***Is this approach acceptable to the Division?***

> ***FDA Meeting Discussion*:** **This approach looks acceptable for dissolution section for testing stability batches (9 and 12 months), however, we recommend obtaining a complete dissolution profile for stability batches and using the proposed dissolution QC methods. Further evaluation on the totality of the dissolution data will be conducted upon NDA submission.**

Question 2: *Are the in-use studies on soft food (apple sauce) adequate?*

FDA Response to Question 2: We strongly recommend that you provide in-use studies with different kinds of soft food over a pH range in order to allow for flexibility in the dosing instructions in the label. The proposed dosing instructions will need to be based on data demonstrating the stability of your product in the food vehicle(s) you studied over the proposed storage period. Even if label instructions call for administration immediately after mixing, at least one hour of stability data will need to be submitted. Stability data should include dissolution profiles using the registered method. For dissolution testing of the drug/food mixture, you should follow the dissolution method approved for drug release testing and compare the dissolution profile with that of the intact drug product. For these dissolution studies we recommend a sample size of $n \geq 6$ per each time point/food vehicle, to allow for meaningful statistical comparisons (i.e., mean ± standard deviation).

Sponsor Meeting Discussion: **SPARC Ltd. has performed dissolution, assay, and related substance testing of drug product 15 minutes after addition to apple sauce. In response to the Division's request, stability data, including dissolution profiles (10, 20, and 30 minutes), will be generated 60 minutes after product has been added to apple sauce. These experiments will be performed in the R&D laboratory using 6 units each of the lowest and highest strength capsules (b) (4) . These results will be included in the Product Development Report in the NDA.**

SPARC Ltd. will also evaluate the feasibility of administering the drug product sprinkled in other soft foods. Once two additional suitable foods of differing pH are identified, in-use studies will be performed. These data are anticipated to be available by the time of the 120-Day Safety Update. These experiments will be performed in the R&D laboratory using 6 units each of the lowest and highest strength capsules (b) (4) These results will be included as an addendum to the Product Development Report.

Sponsor Request for Clarification: ***Please confirm whether this approach and the planned timing of submissions would be acceptable?***

FDA Meeting Discussion: **We do not agree with the planned timing of the in-use studies. All quality information should be included in the initial NDA submission. We expect you to submit a complete NDA for filing and we do not commit to reviewing additional data submitted during the review cycle such as this information that you propose to submit by the time of the 120-Day Safety Update. If apple sauce remains the only soft food studied by the time of the original NDA submission, labeling may be explicitly restrictive.**

We also recommend using Bio-Batch or Clinical Batch for you proposed two strengths (5, 40 mg). The proposed sampling time for in-use studies on soft food is acceptable as 10, 20, 30, and 60 minutes for recovery testing (for stability in soft food). We recommend comparing the % dissolution (as recovery) with that of intact drug product (b) (4) Further evaluation on the totality of the in-use study data will be conducted upon NDA submission.

Question 3: *Are the nasogastric in-use studies adequate?*

FDA Response to Question 3: You have not clearly stated the manner in which you desire to indicate or label your drug for delivery via a nasogastric tube. Please provide the Agency with the specific indication statement, or instructions for use, that you intend to include within the future NDA submission. Clearly state if you intend to label your proposed drug for general administration through any nasogastric tube, for administration with specific nasogastric tubes, or if you will limit the type of nasogastric tubes which may be used through descriptive characteristics.

Provide the in-use studies on nasogastric tubing and dissolution studies at multiple time points other than only at 30 minutes (i.e. 15, 30, 45, 60, 90 min after your drug product dissolved and remained in syringe). Also, conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference/control products at each time point. The comparative data should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the reference product, and the measurements should be done in triplicate for each lot tested. Provide the complete dissolution data (*i.e., individual, mean, and standard deviation at each time point*) and mean dissolution profiles for your products. Acceptance criteria for in-use studies on nasogastric tubing will be determined upon review of your full NDA submission.

Conduct sedimentation, particle size, acid resistance and recovery testing. Include details about the tube and syringe used (e.g. material, brand, size etc.), holding positions of the tube, shaking method, analytical site and testing dates for each of the studies.

Submit individual data, mean values, standard deviations, and coefficient of variation (%CV) for each study in an Excel file. The photographs should be submitted to support your observations and results. Also provide the standard operating procedures, pre-study and within-study, wherever applicable, for each of these tests.

Sponsor Meeting Discussion: **The tentative labeling language addressing drug delivery *via* nasogastric tube would be as follows:**

"For patients who have a nasogastric tube in place, rosuvastatin capsules can be opened and the intact (b) (4) emptied into a 60-mL syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The (b) (4) in rosuvastatin capsules may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16 french) and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the pellets, the nasogastric tube should be flushed with additional water. USE IN OTHER LIQUIDS (b) (4) IS (b) (4) NOT RECOMMENDED."

As requested, SPARC Ltd. will perform additional dissolution testing at multiple time points; which will include (b) (4) nasogastric tubes. SPARC Ltd. will then perform testing on 6 units with one batch of the highest and lowest strength (b) (4) at time points 15, 30, 45, 60, 90 minutes after adding the (b) (4) to the syringe. SPARC Ltd. will also conduct the requested studies of sedimentation, particle size, and recovery testing. The experiments will be performed in the R&D facility following a pre-specified protocol; the requested details will be included in the addendum to the Product Development Report which is expected to be available at the time of the 120-Day Safety Update. (b) (4)

Crestor, the listed drug to be referenced in the NDA, is a tablet dosage form that should not be crushed and must be swallowed whole according to the approved labeling. Since this product would not be given *via* nasogastric tubing, SPARC Ltd. believes that comparative testing is not warranted.

***Sponsor Request for Clarification*:**

a. ***Is the general approach to performing the in-use testing of SPARC Ltd.'s product acceptable?***

b. ***Does the Division agree that comparative testing with the listed drug is not required?***

c. ***Please confirm that the plan to include the protocol with the final study report addresses the following request: "Also provide the standard operating procedures, pre-study and within-study, wherever applicable, for each of these tests?"***

d. ***Please confirm whether the planned timing of submissions would be acceptable?***

FDA Meeting Discussion:

a. **It is acceptable.**
b. **We agree that the comparative testing of Crestor for nasogastric administration is not necessary because Crestor is not labeled for nasogastric administration. The proposed sampling times of 15, 30, 45, 60, and 90 minutes are acceptable pending on the length of infusion, however, the % dissolution as recovery for your proposed drug product after infusion with nasogastric tubes should compare with that of intact drug product (b) (4) using dissolution QC method.**
c. **It is acceptable.**
d. **We do not agree with the planned timing of the in-use studies. All quality information should be included in the initial NDA submission. We expect you to submit a complete NDA for filing and we do not commit to reviewing additional data submitted during the review cycle such as this information that you propose to submit by the time of the 120-Day Safety Update.**

In reference to nasogastric tubes it is important to stratify responses for the in-use study from the ability to label your product for use with nasogastric tubes. The assumption appears to be that completing the in-use study would allow you to market their device as noted in the clarifying questions document, "For patients who have a nasogastric tube in place, rosuvastatin capsules can be opened and the intact (b) (4) emptied into a 60-mL syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The (b) (4) in rosuvastatin capsules may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16 french) and deliver the contents of the syringe through the nasogastric tube into the stomach.

After administering the (b) (4) **the nasogastric tube should be flushed with additional water."**

The Agency notes that claims related to delivery of your drug product via nasogastric tubes will be assessed within your future NDA submission. You should consider the range of device characteristics and materials available within legally marketed nasogastric tubes.

The Agency's publically available 510(k) and product classification database are available to assist you in determining indications for use and basic descriptions of individual nasogastric tubes which have received clearance from the Center for Devices and Radiological Health; however these resources will likely not be of assistance in the identification of nasogastric tube materials or designs.

510(k) Database:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

CDRH Device Classification Database:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

The sponsor asked if they explored a range and found that some nasogastric tubes would not be acceptable, could labeling be more restrictive? The Agency answered that this is the correct concept; this will be a review issue. What may or may not be allowed in labeling will depend on the data provided and the sponsor's accompanying justification.

Question 4: *SPARC Ltd. seeks advice from the Division as to any additional information that would be needed to support the possible use of* (b) (4)

(b) (4)

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(b) (4)

2.2. Nonclinical

Question 5: *Can the Division confirm that the 30-day GLP bridging toxicity study is adequate to support the NDA and that no additional nonclinical studies are needed?*

FDA Response to Question 5: A nonclinical comparative 30-Day GLP bridging toxicology study with a U.S. approved product in a relevant species is appropriate to support a 505(b)(2) application. Pending review of your product impurity profile, in vitro genetic toxicology studies may be required to qualify any new impurities and degradants. Final acceptability of

any nonclinical study report including study design, toxicity, toxicokinetics and comparability to the listed drug will be a review issue.

Question 6: *Is the plan to submit the study reports in Module 4 and prepare only the Nonclinical Overview (Section 2.4), Nonclinical Introduction (Section 2.6.1), and Nonclinical Toxicology Summaries (Sections 2.6.6 and 2.6.7) in the eventual NDA acceptable?*

FDA Response to Question 6: Your NDA will need to provide any required Pharmacology/ Toxicology final study reports as well as your summaries noted above.

2.3. Biopharmaceutics and Clinical Pharmacology

Question 7: *Does the Division agree that the studies performed adequately demonstrate the relative bioavailability of the new product and listed drug?*

FDA Response to Question 7: The adequacy of the studies conducted will be evaluated during the NDA review.

Question 8: *Does the Division agree that the studies are also sufficient for the purposes of supporting dosing recommendations, i.e., that SPARC Ltd.'s rosuvastatin (calcium) capsules can be administered with or without meals and ingested either intact or sprinkled on applesauce?*

FDA Response to Question 8: The adequacy of data to support the proposed dosing recommendation will be evaluated during the NDA review.

Question 9: *Is the plan to request a waiver of the need to do in vivo biopharmaceutics studies for the lower strength capsules (5, 10, and 20 mg) acceptable?*

FDA Response to Question 9: At this time, your provided information is not considered sufficient to demonstrate that your proposed drug product is eligible for a biowaiver. However, you can request a waiver for your lower strengths capsules (5, 10, and 20 mg) based on (i) acceptable in vivo bioavailability (BA) / bioequivalence (BE) studies on the 40 mg strength, (ii) proportional similarity across all strengths, and (iii) acceptable complete dissolution testing of all strengths. We will review the formulation composition, in vitro dissolution data and profile, and in vivo BA/BE studies during the NDA review.

As per 21 CFR 320.21, you are required to include in your NDA submission, either evidence of measuring the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product that is the subject of the NDA or information to permit FDA to waive the submission of evidence measuring in vivo BA or BE. To satisfy the CFR's BA/BE evidence requirement, you may include in your NDA:

a. The drug product specific BA/BE study; or

b. Pharmacokinetic literature data, in lieu of the drug product specific BA studies. However, FDA's acceptance of the provided literature information/data as evidence of satisfying the BA requirement is contingent on the appropriateness of the scientific bridge between the formulation used in the literature studies using the oral route of administration and your proposed formulation; or

c. Information supporting a BE waiver request. For the biowaiver you should demonstrate that your proposed drug product contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug.

The adequacy of the submitted information to support BA/BE, clinical, and, labeling decisions is a review issue under the NDA.

Sponsor Meeting Discussion: **SPARC Ltd. will include the information necessary to support the request for a waiver. With respect to the dissolution testing, this will include multi-media dissolution profiles for one batch of each of the four strengths of rosuvastatin capsules and the corresponding listed drugs (12 units each). A report of the results will be included in the NDA.**

Sponsor Request for Clarification: ***Please confirm that the above plan is adequate to address the requirement for complete dissolution testing of all strengths.***

FDA Meeting Discussion: **It is acceptable. Further evaluation on the totality of the dissolution profile data will be conducted upon NDA submission. You need to submit your biowaiver request and justification with comparative dissolution profile data of all three lower strengths vs. the highest strength including f2 calculation to support the biowaiver.**

Question 10: *SPARC Ltd. requests confirmation that no additional biopharmaceutics or clinical pharmacology studies will be needed.*

FDA Response to Question 10: If BA/BE is established on the highest strength and a biowaiver is granted for the other lower strengths, and there is no safety concern on the excipients from nonclinical, additional biopharmaceutics studies may not be needed. However, in vitro dissolution testing is required for all of your proposed strengths from a quality control perspective. Please see response to Question 9.

No additional clinical pharmacology studies are needed for your NDA submission.

Question 11: *Is the plan for preparing the NDA sections acceptable?*

FDA Response to Question 11: Your plan seems acceptable.

2.4. Clinical

Question 12: *Does the Division agree that no clinical studies are required given that the two products have been demonstrated to be bioequivalent?*

FDA Response to Question 12: We agree that additional clinical studies will not be required for submission and review of the NDA; however, determination of bioequivalence and any need for further studies to support approval are review issues.

Question 13: *Does the Division agree with the plans for the content of the clinical sections of the NDA?*

FDA Response to Question 13: We have the following comments for the clinical sections of the NDA:

a. Safety information should be reported for the individual studies in addition to the ISS;

b. Narratives of deaths, serious adverse events, or discontinuations due to adverse events must be provided;

c. It is unclear from the tabular listing of patients with elevations in liver enzymes (Table 6:13) when the events occurred relative to administration of study drug. For patients with abnormalities in liver enzymes, provide a narrative and graphical patient profile displaying all relevant laboratory values (ALT, AST, bilirubin), study period, study day, time of dosing and formulation, and adverse events to better characterize these events. Please provide updated follow-up information on patients with elevated liver enzymes at the end of the study.

Question 14: *Is the proposed plan for summarizing the efficacy information identified in the literature acceptable, specifically, the plan to summarize the Cochrane reviews in text and to only provide tabular summaries of the additional publications identified in the literature search?*

FDA Response to Question 14: This is acceptable.

Additional Biopharmaceutics Comments:

Address the following items for your proposed drug products in your NDA:

a. Dissolution Testing: Include the dissolution method development report supporting the selection of the proposed test, including the following information:

i. Solubility data for the drug substance covering the pH range.

ii. Detailed description of the dissolution method being proposed for the evaluation of your products and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a (b) (4) is used, include the data supporting the selection of the type and amount of (b) (4) Clearly specify the testing conditions used for each test, including the formulation and batch information (*i.e., batch No., batch size, strength, site, date of manufacture/testing, age when tested*). The dissolution profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., *no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve dosage units each of all strengths of the test and reference products per testing variable.

iii. Provide the complete dissolution data (*i.e., individual, mean, and standard deviation at each time point*) and mean dissolution profiles for your products. Report the dissolution data as the cumulative percentage of drug released/dissolved with time (*the percentage is based on the product's label claim*).

iv. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (*i.e.*, ± (b) (4) *% change to the specification-ranges of these variables*).

v. Supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*i.e., precision, accuracy, linearity, stability, etc.*).

b. Dissolution Acceptance Criteria: Provide the complete dissolution profile data from the pivotal clinical and stability registration batches supporting the selection of the dissolution acceptance criteria (*i.e., specification-sampling time points and specification values*). For the setting of the drug dissolution acceptance criteria, consider the following points:

i. The in vitro dissolution specifications should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.

ii. Data from the lots used in the clinical trials and primary stability studies must be used.

iii. The dissolution acceptance criteria (Q) should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

iv. The selection of the specification time point should be at least, where Q= (b)(4)% dissolution occurs for immediate release products.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA review stage. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review, based on the totality of the provided dissolution data.

Additional Clinical Comments:

a. We remind you of the need to remove any information related to indications that are protected by patents or exclusivity in the most updated version of the label of the listed drug.

b. With your NDA, provide a side-by-side comparison of the differences between the listed drug's label and your proposed label. Include notations justifying any differences between the two labels.

c. All literature references must be submitted with the NDA.

2. OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the ***PLR Requirements for Prescribing Information*** and ***PLLR Requirements for Prescribing Information*** websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

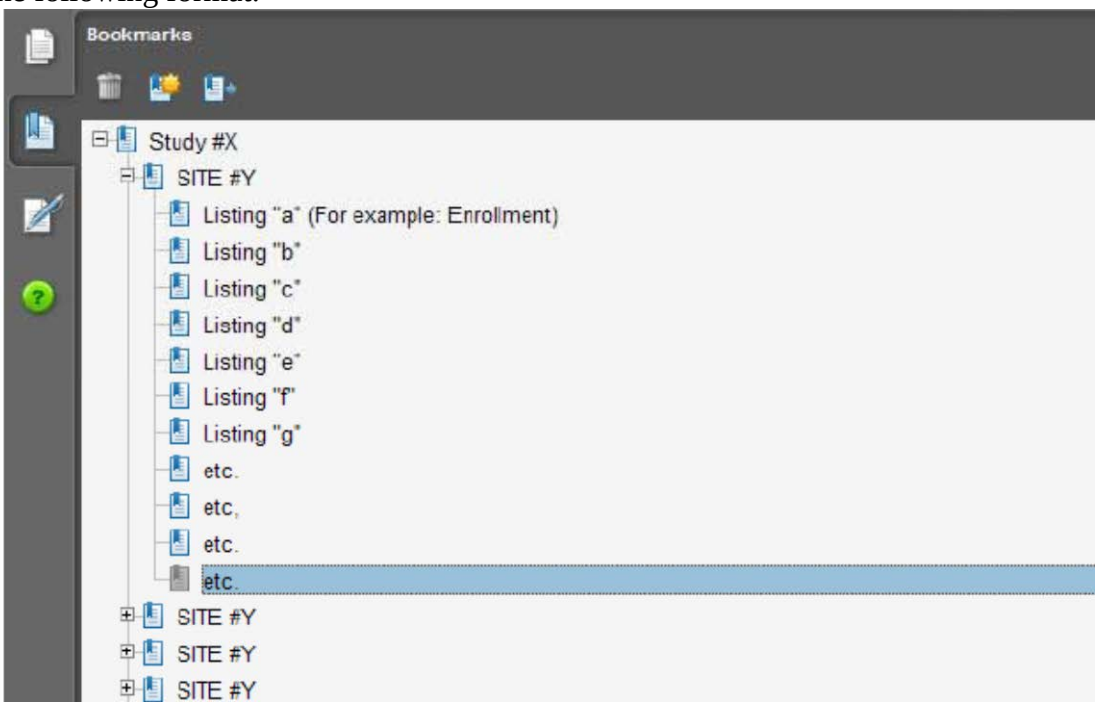
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1 to Section 3.3

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

3. ATTACHMENTS AND HANDOUTS

"Questions for Clarification" emailed to Richard Whitehead, M.S., Regulatory Health Project Manager, on May 18, 2015. The "Questions for Clarification" are imbedded in the Section 2. *Discussion* with FDA responses.

Rosuvastatin (Calcium) Capsules Pre-NDA Meeting
PIND 121031
Questions for Clarification

Regarding Questions #5, 6, 7, 8, 10, 11, 12, 13, and 14, SPARC Ltd. accepts FDA's responses with no further discussion required.

(b) (4)

SPARC Ltd. seeks clarification from the Division as follows for Questions 1 through 3 (CMC) and Question 9 (Biopharmaceutics and Clinical Pharmacology).

Question 1: Are the proposed drug product specifications adequate in support of the NDA?

The Division asked SPARC Ltd. to include a particle size test and specification for the finished drug product. The (b) (4) range in size between (b) (4) to (b) (4) µm (b) (4)

SPARC Ltd. would like to clarify that (b) (4)

(b) (4)

(b) (4)

SPARC Ltd. request for clarification: ***Is this approach acceptable to the Division?***

Question 2: Are the in-use studies on soft food (apple sauce) adequate?

SPARC Ltd. has performed dissolution, assay, and related substance testing of drug product 15 minutes after addition to apple sauce. In response to the Division's request, stability data, including dissolution profiles (10, 20, and 30 minutes), will be generated 60 minutes after product has been added to apple sauce. These experiments will be performed in the R&D laboratory using 6 units each of the lowest and highest strength capsules (b) (4) These results will be included in the Product Development Report in the NDA.

SPARC Ltd. will also evaluate the feasibility of administering the drug product sprinkled in other soft foods. Once two additional suitable foods of differing pH are identified, in-use studies will be performed. These data are anticipated to be available by the time of the 120-Day Safety Update. These experiments will be performed in the R&D laboratory using 6 units each of the lowest and highest strength capsules (b) (4) These results will be included as an addendum to the Product Development Report.

***SPARC Ltd. request for clarification**: Please confirm whether this approach and the planned timing of submissions would be acceptable?*

Question 3: Are the nasogastric in-use studies adequate?

The tentative labeling language addressing drug delivery *via* nasogastric tube would be as follows:

> "For patients who have a nasogastric tube in place, Rosuvastatin Capsules can be opened and the intact (b) (4) emptied into a 60-mL syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The (b) (4) in Rosuvastatin Capsules may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16 french) and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the pellets, the nasogastric tube should be flushed with additional water. USE IN OTHER LIQUIDS (b) (4) IS (b) (4) NOT RECOMMENDED."

As requested, SPARC Ltd. will perform additional dissolution testing at multiple time points; which will include (b) (4) nasogastric tubes. SPARC Ltd. will then perform testing on 6 units with one batch of the highest and lowest strength (b) (4) at time points 15, 30, 45, 60, 90 minutes after adding the (b) (4) to the syringe. SPARC Ltd. will also conduct the requested studies of sedimentation, particle size, and recovery testing. The experiments will be performed in the R&D facility following a pre-specified protocol; the requested details will be included in the addendum to the Product Development Report which is expected to be available at

the time of the 120-Day Safety Update. (b) (4)

Crestor®, the listed drug to be referenced in the NDA, is a tablet dosage form that should not be crushed and must be swallowed whole according to the approved labeling. Since this product would not be given *via* nasogastric tubing, SPARC Ltd. believes that comparative testing is not warranted.

SPARC Ltd. request for clarification:
Is the general approach to performing the in-use testing of SPARC Ltd.'s product acceptable?

Does the Division agree that comparative testing with the listed drug is not required?

Please confirm that the plan to include the protocol with the final study report addresses the following request: "Also provide the standard operating procedures, pre-study and within-study, wherever applicable, for each of these tests"?

Please confirm whether the planned timing of submissions would be acceptable?

Question 9: Is the plan to request a waiver of the need to do in vivo biopharmaceutics studies for the lower strength capsules (5, 10, and 20 mg) acceptable?

SPARC Ltd. will include the information necessary to support the request for a waiver. With respect to the dissolution testing, this will include multi-media dissolution profiles for one batch of each of the four strengths of Rosuvastatin Capsules and the corresponding listed drugs (12 units each). A report of the results will be included in the NDA.

SPARC Ltd. request for clarification: ***Please confirm that the above plan is adequate to address the requirement for complete dissolution testing of all strengths.***

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
06/15/2015