DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Krathish Bopanna, Ph.D.
President & Chief Executive Officer
Semler Research Center Private Limited
75 A 15th Cross Road
Bangalore, India 560078

Dear Dr. Bopanna:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your firm between September 29, 2015 and October 9, 2015. Investigators Charles Bonapace, Pharm.D.; Arindam Dasgupta, Ph.D.; Dipesh K. Shah; and Daniel J. Roberts, representing the FDA, reviewed the conduct of the following studies:

Study # (b) (4), (b) (4) ” sponsored by (b) (4)

Study # (b) (4), “ (b) (4) ,” sponsored by (b) (4).

Studies # (b) (4) **and** (b) (4), (b) (4) sponsored by (b) (4)

This inspection is part of FDA's Bioresearch Monitoring (BIMO) Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

At the conclusion of the inspection, the FDA investigators presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 29, 2015, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, your October 29, 2015, written response to the Form FDA 483 observations, and your January 14, 2016, letter reporting the results of a retrospective investigative audit, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of bioequivalence studies. We wish to emphasize the following:

Your firm failed to demonstrate that the analytical method used in an *in vivo* bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, is accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body [21 CFR 320.29(a)].

During FDA's inspection of your firm, FDA found evidence documenting that you engaged in practices and processes that undermined the analytical methods used at your firm, which resulted in the submission of invalid study data to the FDA. As a result, FDA has significant concerns about the validity and reliability of bioequivalence and bioavailability data generated at your firm that is submitted to the FDA in support of Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs).

Specifically, you documented that for Study (b) (4), your firm replaced plasma samples from Subjects 41-60 with the plasma samples of different subjects that had already been analyzed. This substitution of samples undermines the reliability and validity of the analytical methods used at your firm and the study data produced by your firm.

For example, your server contained a spreadsheet showing that the following subjects' samples were substituted in Study (b) (4):

[redacted] ([redacted])	
Subjects	**Replaced (Substituted) Subjects**
41	10
42	16
43	23
44	9
45	28
46	14
47	11
48	8
49	4
50	26
51	3
52	25
53	29
54	31
55	32
56	21
57	1
58	20
59	36
60	17

During the inspection, we requested that you plot the [redacted] concentration-time profiles for the pairs of subjects that were documented as having their samples substituted (for example, Subjects 10 and 41), as is shown above, to compare the plasma drug profiles for those subjects. The resulting plots from your analysis showed almost identical concentration-time profiles for [redacted] for each pair of the subjects that you documented as having been substituted. During the inspection, you were unable to explain the similarity in concentration data from these pairs of subjects. You stated that your incurred sample reanalysis (ISR) could not have achieved these results and met the acceptance criteria (that is, the results of a reanalysis of a subset of subject samples are sufficiently consistent with the original results) if the subjects' samples had been substituted. However, FDA does not agree with your assessment, because the acceptance criteria

for the ISR would have been met if the same substituted samples were reanalyzed (for example, if two plasma samples from Subject 10, one of which was falsely labeled as Subject 41, were analyzed).

During the inspection, we also requested that you calculate the [(b) (4)] peak drug concentration (C_{max}) and area under the plasma concentration-time curve ($AUC_{0\text{-}inf}$) geometric mean ratios (GMRs) with their respective 90% confidence intervals (CI 90%) in three segments of the study population (n=53), to evaluate the impact of substituted plasma samples on the bioequivalence endpoints. As shown below, the calculations resulting from your analysis indicated that the [(b) (4)] GMRs data from the substituted subjects (Subjects 41-60) were distinct from the [(b) (4)] GMRs from subjects that were not documented as having been substituted (Subjects 1-40).

Study [(b) (4)] ([(b) (4)] Bioequivalence Endpoints)			
Subjects	***Parameter***	***GMR Point Estimate (%)***	***90% CI***
1-20 (n=16)	C_{max}	137.69	109.81-172.66
	$AUC_{0\text{-}inf}$	113.62	90.46-142.67
21-40 (n=18)	C_{max}	128.95	101.41-163.96
	$AUC_{0\text{-}inf}$	100.51	86.97-116.17
Substituted 41-60 (n=19)	C_{max}	62.18	51.51-75.06
	$AUC_{0\text{-}inf}$	85.93	71.89-102.70
Reported to FDA (n=53)	C_{max}	101.43	87.82-117.15
	$AUC_{0\text{-}inf}$	98.50	89.07-108.92

We note that you indicated during the inspection that the study results were correct, and that the unusual trends with the [(b) (4)] GMRs were a product of physiological conditions and the intrinsic properties of the molecule, [(b) (4)]'s high intrasubject pharmacokinetic (PK) variability in particular. However, FDA does not agree with this explanation because it fails to explain the inconsistencies in the study data adequately. Specifically, high intrasubject PK variability would not produce almost identical [(b) (4)] concentration-time profiles in study subjects. In addition, PK variability would occur randomly across study subjects, not in distinct subject segments. You also failed to explain why the PK data (the C_{max} and $AUC_{0\text{-}inf}$ GMRs) for subjects with substituted samples are inconsistent with PK data for subjects that were not documented as substituted.

The invalid PK data discussed above for Study (b) (4) were submitted to the FDA in support of an NDA for (b) (4) capsules.

We also note that your server contained documentation indicating the substitution, and the possible manipulation or dilution, of subject samples for Studies (b) (4) ((b) (4)) and (b) (4) ((b) (4)), which were submitted to FDA in support of drug applications. In your October 29, 2015, written response, you acknowledge that your firm's server contained a spreadsheet that documented the substitution and manipulation of subject samples for certain bioequivalence studies conducted at your firm, including (b) (4), (b) (4), and (b) (4). You explained that you could not determine who created the document or its impact on the study endpoints, but that your firm would begin random reviews of subject concentration data and/or PK data for all studies submitted to FDA.

In your January 14, 2016, letter, you submitted a report that summarizes the findings of a retrospective investigation into the possible switching or substitution of subject samples. You indicated that an independent team of external consultants audited the clinical, bioanalytical, and PK aspects of the studies mentioned above. You also acknowledged the spreadsheet on your server and its implications on the integrity of the data from your firm. The audit report showed that the clinical portions of the studies had minor transcription errors and discrepancies in time stamps. The audit report also showed that the bioanalytical phase of the studies had issues with sample storage, flaws in the handwritten sample-processing system, and poor documentation practices for instrument stabilization. You concluded that, although the audit did not reveal any direct evidence of sample switching or substitution, the audit did observe the same concerning data trends for the studies noted above, but that it was not possible to explain the data trends on a physiological basis.

Your responses are inadequate because you failed to address (1) why your firm had documentation indicating that subject samples were substituted or manipulated in order for studies to meet the bioequivalence criteria; (2) if any other bioequivalence or bioavailability studies conducted at your firm had subject samples substituted or manipulated; (3) what impact the sample substitution and manipulation had on Studies (b) (4), (b) (4), and (b) (4), respectively; and (4) how each of these studies could have multiple instances of overlapping subject sample concentrations.

This letter is not intended to be an all-inclusive list of deficiencies with your bioequivalence studies. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will comply with FDA regulations.

We remind you that it is your firm's responsibility to ensure the integrity of all data generated at your firm that is submitted to the FDA in ANDAs or NDAs. The manner in which Semler conducted the studies noted above causes FDA to have significant concerns with the reliability and validity of all bioequivalence data generated by Semler.

Within thirty (30) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will take to correct the violations noted in this letter and to prevent similar violations in the future.

We appreciate the cooperation shown to FDA investigators Bonapace, Dasgupta, Shah, and Roberts during the inspection. Should you have any questions regarding this letter or the inspection, please call Dr. Chrissy J. Cochran, Division Director, at +1-301-796-5633, Fax +1-301-847-8748, or write to her at this address:

Chrissy J. Cochran, Ph.D.
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5364
10903 New Hampshire Avenue
Silver Spring, MD 20993
U.S.A.

Sincerely yours,

{See appended electronic signature page}

David Burrow, Pharm.D., J.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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

/s/

DAVID C BURROW
04/19/2016