DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Kenneth Collins
President & CEO
Replidyne, Inc.
1450 Infinite Drive
Louisville, CO 80027

Ref: 08-HFD-45-0117

Dear Mr. Collins:

This Warning Letter is to inform you of objectionable conditions found during the U.S. Food and Drug Administration's (FDA) investigations into Replidyne, Inc.'s (hereafter referred to as Replidyne) role as the applicant [21 CFR 314.3(b)] who submitted a marketing application in support of the approval of [ ]. The FDA notes that the following clinical studies were submitted in support of the New Drug Application (NDA)[ ]

Protocol[ ]"Prospective, randomized, double-blind, three-armed, multi-center comparative trial to evaluate the efficacy and safety of [ ] BID for 7 days vs. [ ] BID for 10 days vs. [ ] BID for 10 days in the treatment of [ ]

Protocol[ ]"Prospective, randomized, double-blind, study comparing [ ] BID for 10 days with [ ] BID for 14 days in the treatment of patients with [ ]

Protocol[ ]"Prospective, randomized, double-blind study comparing [ ] BID for 5 days with [ ] for 5 days [ ] in the treatment of patients with [ ]

Protocol[ ]"Prospective, randomized, double-blind, multi-center, comparative trial to evaluate the efficacy and safety of [ ] BID for 7 days vs. [ ] BID for 7 days in the treatment of [ ]

This investigation is a part of FDA's Bioresearch Monitoring Program which is designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Another objective of the program is to ensure that data submitted in support of New Drug Applications are scientifically valid and accurate.

The FDA notes that the above mentioned studies of the investigational drug [ ] were sponsored by [ ] (hereafter referred to as [ ] under IND [ ] and the studies were performed between 2000 and 2003. We note further that these studies were originally monitored by [ ] or [ ] agents. The rights for the product were subsequently transferred from [ ] to [ ] and in 2004 Replidyne obtained ownership of the product from [ ] In February 2005, the US Adopted Names Council assigned the new name [ ] for this product. On December 20, 2005, Replidyne prepared and submitted a marketing application to FDA for [ ] (i.e. NDA [ ]

We note that FDA investigators visited Replidyne between July 19, 2006 and August 8, 2006 for an initial inspection, and between September 11, 2006 and October 17, 2006 for a second inspection. At the conclusion of each inspection, FDA personnel presented and discussed with you and your staff the Form FDA 483, Inspectional Observations. We have reviewed Replidyne's written responses dated September 11, 2006, and February 8, 2007 to the items listed on the Form FDA 483 dated August 8, 2006 and October 17, 2006, respectively.

From our review of the establishment inspection reports (EIRs), the documents submitted with that report, your written responses dated September 11, 2006 and February 8, 2007 to the inspectional observations, and the EIR and documents for the clinical investigators that were inspected for NDA [ ] we conclude that Replidyne did not adhere to the applicable statutory requirements and regulations governing an applicant's responsibilities concerning submission of data and information to the FDA. We wish to emphasize the following deficiencies with respect to the above-referenced clinical investigations submitted in support of NDA [ ]

1. **FAILURE TO MAKE AVAILABLE THE UNDERLYING RAW DATA FROM THE INVESTIGATION FOR FDA'S AUDIT [21 CFR 314.3(b)].**

   The FDA notes that Replidyne acquired the *right of reference or use* [21 CFR 314.3(b)] of the clinical investigations originally conducted by [ ] and subsequently submitted a marketing application to the FDA. Thus as the applicant who acquired the *right of reference or use*, Replidyne was required to make available the underlying raw data from the above clinical investigations for FDA audit. We note that you failed to provide all of the underlying raw data for FDA's audit. For example,

a. During the FDA audit, when FDA investigators asked for information regarding the training of individuals involved in the studies, Replidyne reportedly stated that [ ] refused to provide Replidyne with a copy of the standard operating procedures (SOPs) used for the conduct and monitoring of studies that were submitted in support of NDA [ ]

b. For Protocol [ ] Clinical Site #36 (Dr. [ ] the monitoring visit report for 12 December 2001 was not available for FDA inspection.

c. The FDA had requested information from Replidyne concerning audits that were to take place for 4 international clinical investigators that conducted studies under NDA [ ] We note that in a letter dated September 24, 2007, you noted that you were unable to locate Dr. [ ] and Dr. [ ] and that you also did not have access to the records for these two investigators.

We wish to emphasize that it was the responsibility of Replidyne, as the applicant [21 CFR 314.3(b)], to ensure that prior to submission of the application, all of the underlying raw data from all of the clinical investigations conducted to support the application was to be made available to the FDA for possible auditing.

2. FAILURE TO PROVIDE THE FDA ADEQUATE DESCRIPTIONS AND ANALYSES OF ANY OTHER DATA OR INFORMATION RELEVANT TO THE EVALUATION OF THE SAFETY AND EFFECTIVENESS OF THE DRUG PRODUCT OBTAINED OR OTHERWISE RECEIVED BY THE APPLICANT FROM ANY SOURCE, FOREIGN OR DOMESTIC INCLUDING INFORMATION DERIVED FROM CLINICAL INVESTIGATIONS [21 CFR 314.50(d)(5)(iv)].

The FDA notes that as the applicant, Replidyne was required to provide within the application to the FDA, a description and analysis of any other data or information relevant to the evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations [21 CFR 314.50(d)(5)(iv)] to permit the FDA to make a knowledgeable judgment about whether or not the application should be approved. The FDA notes that Replidyne failed to provide sufficient information at the time of submission of the application.

a. The FDA notes that Replidyne submitted data from several clinical investigative research sites in support of NDA [ ] but did not adequately verify the integrity of the data at those sites, prior to the submission to the FDA. For example,

   i. FDA's investigation of Dr. [ ] for Protocol [ ] revealed that Dr. [ ] did not personally meet with at least two of his sub-investigators who conducted the study, nor did he review the research or clinic records regarding the subjects they enrolled. Dr. [ ] informed FDA investigators that he was not aware that all the screening x-rays obtained by the two sub-investigators were re-interpreted by a second radiologist at the

end of the study and that he was not aware that only the results from the second radiologist were reported to the study-sponsor. Dr.[ ]also stated that he did not review the inclusion criteria, treatment outcomes, protocol deviations, or adverse event documentation for the subjects enrolled by these sub-investigators. FDA's inspection concluded that the data generated from the site were unreliable and issued Dr.[ ]a Warning Letter.

ii. FDA's investigation of Dr.[ ]for Protocols[ ] revealed that numerous subjects were not randomized in accordance with the investigational plan. FDA notes that the problems with randomization were so broad and numerous that the FDA was unable to verify the integrity of the data at this site.

iii. FDA's investigation of Dr.[ ]for Protocol[ ]found that he failed to retain research records in accordance with 21 CFR 312.62(c). Thus the FDA was unable to verify the integrity of the data submitted by Replidyne to the FDA from this site.

b. The FDA notes that during the course of both inspections that occurred at your facility, FDA investigators were unable to locate all of the monitoring reports from several clinical investigative sites (e.g. protocol[ ]site #27, Dr.[ ] protocol[ ] site #23, Dr.[ ] site #34, Dr.[ ] and site #48, Dr. [ ]protocol[ ]site #36, Dr.[ ]We note that you only obtained possession of these monitoring reports either during the FDA audits or after the FDA audit and in response to the Form FDA 483 that was issued.

The FDA notes that as you did not have all of the monitoring reports within your possession prior to submission of the NDA to the agency, we cannot assess how you could have properly ensured the integrity of the data that was submitted to the FDA from the clinical investigators sites and have subsequently provided the FDA with an adequate description and analysis of any other data or information relevant to the evaluation of the safety and effectiveness of the drug product.

This letter is not intended to be an all-inclusive list of deficiencies with the submission of a marketing application to the FDA. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Dr. Tejashri Purohit-Sheth at (240) 276-8840; FAX (240) 276-8811. Your written response and any pertinent documentation should be addressed to Dr. Leslie Ball at the address below.

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Division Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research
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Rockville, MD 20855

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/s/

Leslie Ball
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