

November 19, 2007

Leslie K. Ball, M.D.  
Acting Division Director  
Division of Scientific Investigations, HFD-45  
Office of Compliance  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855

Ref: Warning Letter 07-HFD-45-1002

Dear Dr. Ball:

Sanofi-aventis respectfully submits this letter in response to the FDA Warning Letter received by certified mail on October 29, 2007. The Warning Letter identified issues in a study sponsored and conducted by Aventis, HMR3647A/3014 (Study 3014) entitled "Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin [Ketek®] and Amoxicillin-Clavulanic Acid [Augmentin] in Outpatients with Respiratory Tract Infections in Usual Care Settings". As was stated in your letter Study 3014 was conducted by Aventis prior to acquisition by Sanofi-Synthelabo.

Sanofi-aventis is and has been committed to conducting clinical studies that comply with Good Clinical Practice (GCP) in accordance with the US Code of Federal Regulations and other applicable regulations worldwide.

We recognize that our responsibilities are not diminished or altered by the unique design or type of study, or the particular circumstances in which a study is conducted. However, we believe that some of the unique aspects of Study 3014 contributed greatly to the problems that arose in the trial. Sanofi-aventis has critically reviewed the record of Study 3014 to assess the underlying causes of the issues that arose in the study and identified important lessons learned and has taken corrective action for ongoing and future clinical trials.

We acknowledge that deviations from GCP occurred during the conduct of Study 3014. We continue to take very seriously all issues raised by the Agency about the conduct of the study and performance of sponsor obligations, and we have and will participate in cooperation with FDA on inquiries and investigations relating to Study 3014.

Sanofi-aventis acknowledges our obligations, as a clinical trial sponsor, to the study subjects, to clinical trial investigators, and to the FDA and other Health Authorities. With respect to the issues raised in the Warning Letter, we are committed to enhancing our efforts in: (i) appropriately selecting and training investigators, (ii) ensuring proper monitoring, auditing and follow-up on identified issues, and (iii) fully investigating serious Good Clinical Practice (GCP) noncompliance or suspected scientific misconduct. We have already made changes to address

lessons learned in these areas, and we are aligning those efforts across the company through continuous improvement.

Our response below focuses on lessons learned in Study 3014, improved policies and procedures in International Clinical Development and our commitment to take all steps necessary to assure the Agency that ongoing and future clinical trials are designed, conducted, monitored and reported in a manner that complies with GCP.

#### Study 3014 Overview

Study 3014 was performed by Aventis in the US during the preapproval phase in response to FDA's request for additional safety data regarding adverse events of special interest (AESIs) in four areas: hepatic, visual, cardiovascular and vasculitis. Study 3014 was designed and implemented as a "usual care" study, seeking to evaluate safety (and secondarily effectiveness) of use of telithromycin in the typical physician's office/primary care setting, across a broad range of patients, including patients at an increased risk for potential drug-related toxicity and with multiple underlying diseases. The protocol included the use of a comparator control group, hepatic laboratory tests pre and post treatments, a defined follow-up period, and standard collection forms specific for each AESI.

Study 3014 enrolled approximately 24,000 adult outpatients at over 1,800 primary care sites across the United States (as compared to approximately 600 patients and 100 sites for a typical phase III safety and efficacy trial for anti-infectives), between October 2001 and January 2002, in one winter season. The collection and investigation of AESIs in a large population of patients in a usual care setting was the focus of this study. A large amount of the activity and resources of Pharmaceutical Product Development Inc. (PPD, a Contract Research Organization) and Aventis personnel involved in this study was directed to the tracking and assessment of AESIs, as well as follow-up of patients enrolled. By study design, the inclusion criteria and exclusion criteria were limited to mimic usual care clinical practice, and the collection forms were simplified. For example, the diagnosis of disease was based on the investigator's judgment and the protocol did not mandate specific tests to confirm diagnosis. In addition, the participating investigators had variable amounts of experience, and some had no prior direct experience in conducting clinical research trials.

Aventis designed the monitoring plan for Study 3014 with PPD and the draft monitoring plan and protocol were submitted to the FDA prior to study initiation. According to the monitoring plan, 942 (52%) sites had an on-site monitoring visit, including 444 (approximately 99%) of 447 sites that enrolled more than 15 patients; approximately 93,000 monitoring telephone calls were made to investigator sites; and 9,376 (approximately 38%) of enrolled subjects had source document verification of study data performed by PPD monitors.

The recommended number of subjects per center was 4-50. Due in part to the simplified design and collection forms, some centers reached an enrollment of 50 subjects, at which point the company established an upper limit of 500 subjects, i.e. less than 3% of subjects by center. This, together with the continuing activation of study sites and a very large number of sites simultaneously enrolling and the sudden escalation in enrollment led to significant difficulties in the monitoring and auditing efforts.

During the monitoring, deviations from GCPs were noted at many sites, and in particular at high-enrolling sites. At the time, the overall impact of GCP issues was not considered by Aventis to compromise the validity of the study focus on AESIs. Nonetheless, Aventis undertook good faith efforts to address the complex problems that arose. Follow-up efforts were instituted by PPD as part of the Monitoring Plan, including documenting the deviations and working with investigators to institute corrective actions, in a manner that Aventis believed was consistent with regulations and applicable guidance. Given the sudden rapid enrollment and relatively short duration of treatment, and the study itself much of the auditing, monitoring and subsequent corrective actions were retrospective in nature, i.e., following enrollment and treatment of subjects at the site, thus reducing opportunities to correct GCP deviations on a "real-time" basis.

**Issues Raised In Warning Letter and Corrective Actions taken/to be taken by sanofi-aventis:**

**1. Failure to secure investigator compliance with the investigational plan and applicable FDA regulations [21 CFR 312.56(b)].**

With the benefit of hindsight and additional information obtained through extensive post-study review by Aventis and subsequent information made available from FDA's inspections, sanofi-aventis acknowledges that Aventis was unable to secure compliance with the investigational plan and applicable FDA regulations at a number of sites.

In retrospect, the use of a large number of investigators (over 1800) selected to reflect the usual care setting resulted in a pool of investigators with a variable understanding of GCP and regulatory requirements for conducting clinical trials. In addition, investigator training conducted in this study was not augmented by on-site initiation visits. These factors created risks of noncompliance that were not sufficiently addressed by investigator selection and training. In addition, the sudden rapid enrollment and short duration of treatment resulted in monitoring efforts and follow-up corrective activities that were insufficient to secure compliance by a number of sites prior to completion of the study.

Sanofi-aventis recognizes that securing investigator compliance requires appropriate procedures implemented in a number of key areas, including:

- Selection and training of investigators
- Timely and effective oversight of investigator conduct through appropriate monitoring, and
- Addressing all identified deficiencies, including serious GCP non-compliance/scientific misconduct.

Sanofi-aventis staff involved in clinical trials are trained in relevant SOPs in person or through e-learning modules. Training specific for clinical trials for company monitoring teams is performed and documented at the same time as investigator training ( [REDACTED] )<sup>1</sup>.

### Selection and training of investigators

Sanofi-aventis has enhanced procedures designed to ensure that clinical trial investigators have the training, experience and resources necessary to properly conduct a clinical trial.

Procedures for selection of investigators require verification of qualifications and experience through collection and review of documentation including curriculum vitae (CVs) and other supporting documentation such as adequate evidence of qualification (e.g. US medical licensing), performed as part of site selection assessment ( [REDACTED] )<sup>2</sup>. In addition, monitoring teams for International Clinical Development studies utilize a central database that manages information on clinical investigators ( [REDACTED] )<sup>3</sup>. This includes alert flags based upon publicly available information regarding debarment/disqualification/ restriction of healthcare practitioners, as well as information on the existence of disqualification proceedings or sanofi-aventis termination of investigator sites subject to serious GCP non-compliance or scientific misconduct ( [REDACTED] )<sup>4</sup>.

In addition to selection, current procedures require training of investigator site staff, including but not limited to the investigator, on all trial-related responsibilities, including specifics of the trial protocol, safety reporting requirements and adverse events, informed consent process and documentation requirements, management of investigational product and GCP principles. Training is performed before commencement of the study and is confirmed or reinforced during study site initiation and on an ongoing basis during routine monitoring efforts throughout the course of the trial ( [REDACTED] )<sup>5</sup>.

Sanofi-aventis recognizes the importance of obtaining appropriate and timely informed consent from study subjects, and this is reflected in training provided to the investigator site staff ( [REDACTED] )<sup>6</sup>. Monitoring oversight includes assessment of the informed consent process and associated documentation as well as 100% source document verification on all informed consent forms for all subjects to confirm that the subject exists by checking against investigator or hospital files during the monitoring process ( [REDACTED] )<sup>7</sup>.

Sanofi-aventis believes that a simplified large scale clinical study in the usual care setting for registration purposes is possible with additional measures implemented, including adapting the monitoring capacity to the number of enrolling sites, enhancing GCP training particularly for investigators with limited experience, providing tighter controls on the rate and extent of enrollment, and improving the timing of on-site monitoring to assess compliance and allow for timely corrective action, as needed. We believe that this level of control can be achieved with application of standards consistent with current SOPs and our ongoing continuous improvement.

Timely and effective oversight of investigator conduct through appropriate monitoring

Sanofi-aventis has in place comprehensive procedures governing all aspects of monitoring clinical trial conduct, including site initiation, routine monitoring and site closing ( [REDACTED]

[REDACTED]<sup>8</sup>. Monitoring teams are trained to, and monitor, investigating sites in line with company procedures. Sanofi-aventis procedures require that there be a final written monitoring plan available prior to study start for every clinical trial ( [REDACTED]<sup>9</sup>). It is implemented to address the specific requirements of the clinical trial for monitoring activities and the roles and responsibilities of sanofi-aventis departments involved (and any Contract Research Organization (CRO) to whom monitoring has been transferred by the sponsor). The nature and extent of the source documentation verification and the periodicity of monitoring visits are defined in the monitoring plan to allow for standardized implementation at clinical study sites. The monitoring plan together with the protocol is a core document for the management and oversight of the study. Monitoring plans may be revised periodically to address issues throughout the conduct of the study, and SOPs are in place to address and document these revisions. An example of a monitoring plan will be presented at the upcoming meeting with the Agency.

Following site initiation, an on-site monitoring visit is to be performed as specified in the Monitoring Plan, shortly after the first subjects have been enrolled, in order to ensure Protocol adherence and to detect potential problems and/or to decide upon action(s) needed to be taken, if any ( [REDACTED]<sup>10</sup>). The frequency of the routine monitoring visits is specified in the Monitoring Plan and depends on the nature of the clinical trial, the total number of expected subjects, the progress of subject enrollment and any other specific Protocol requirement(s).

Deviations from the Protocol, SOPs, GCP, or applicable regulatory requirements are to be reported in the monitoring reporting system/forms for the purpose of follow-up and resolution. Significant deviations are to be additionally communicated in writing to the investigator ( [REDACTED]<sup>11</sup>).

The quality management process implemented by sanofi-aventis is comprised of two components: clinical monitoring as a means of quality control of all clinical trials, and quality auditing as an independent function/oversight to verify the adequacy and compliance of clinical monitoring to good clinical practices and to regulations ( [REDACTED]<sup>12</sup>).

Routine audits are conducted throughout clinical programs to provide information to the clinical development organization as well as management. Two of the major objectives of these audits are (1) to detect non-compliance issues so that they can be addressed and the appropriate action taken, and (2) to analyze the sources and root causes of such non-compliances and thus develop corrective/preventative methods for assuring future compliance. In addition to routine audits, for cause audits are conducted to address cases

indicative of potential misconduct, upon the decision of Clinical Quality and Compliance management.

Addressing all identified deficiencies, including serious and persistent non-compliance

Deviations from the Protocol, GCP, or applicable regulatory requirements observed during a monitoring visit are to be directly reviewed with the investigating site while at the site, and communicated in writing to the Investigator. The Investigator is responsible for implementing corrective action to prevent recurrence of the deviations. The monitoring team is to ensure that all issues and all corrective actions have been followed up to resolution with appropriate documentation. It is the responsibility of all individuals involved in monitoring, auditing or handling data from any sanofi-aventis sponsored clinical trial, to be alert to the possibility of scientific misconduct or serious GCP non-compliance ( )<sup>13</sup>.

We share a common concern with FDA to identify investigators who commit serious GCP non-compliance/scientific misconduct and preclude them from participation in clinical trials. Subsequent to concerns raised by Study 3014, sanofi-aventis revised and enhanced its policy to address suspected scientific misconduct and serious GCP non-compliance ( )<sup>14</sup>. This policy specifies the course of action to be followed if there are any allegations or suspicions during the course of a clinical trial that involve scientific misconduct or serious GCP non-compliance. This ensures that all cases are investigated, documented and reported appropriately. The policy specifically includes appropriate reporting to FDA, other Health Authorities, and IRB of investigators terminated for failure to secure investigator compliance as per 21 CFR § 312.56(b), or any case involving substantiated scientific misconduct or fraud.

The monitoring team is to promptly notify clinical management, as well as Clinical Quality and Compliance in the event of any suspicion of scientific misconduct or serious GCP non-compliance ( )<sup>15</sup>. Any case of suspected scientific misconduct or serious GCP non-compliance is subject to prompt review and follow-up by designated investigation panels. While issues of scientific misconduct or serious GCP non-compliance at an investigator site are being investigated, prompt consideration is to be given to temporary suspension of recruitment and or subject treatment or follow-up. Upon completion of the investigation, results are reviewed and decisions are made by the Investigation Panel and communicated to appropriate functional area senior management. These may include site termination, notification to the FDA and other Health Authorities, IRB notification and potential exclusion of data from the analysis in the clinical study report ( )<sup>16</sup>. The centralized database on investigators which captures regulatory and quality flags is to be updated as appropriate ( )<sup>17</sup>. This process will be described in more detail at the upcoming Agency meeting.

To enhance the ability of sanofi-aventis to recognize potential significant regulatory non-compliance and possible fraud detection in the conduct of clinical studies, the company has and will continue to provide standard training.

Since sanofi-aventis acquired Aventis, Clinical Quality and Compliance has enhanced its policy on Scientific Misconduct and Serious GCP Non-Compliance as described above, and reflected this in the monitoring SOP to which members of monitoring teams have been and are trained. In July 2007 sanofi-aventis US staff involved in the monitoring or auditing of clinical trials received additional consolidated training regarding detection of fraud and misconduct in clinical trials.

An e-learning module to address misconduct in line with the Clinical Quality & Compliance policy on scientific misconduct and serious GCP non-compliance has been prepared. It is available on an internal learning management system and will be added to the staff training plan as this system is deployed in the organization. In addition, further training sessions on the Scientific Misconduct and Serious GCP Non-Compliance policy are scheduled for delivery on a global basis in 2008.

**2. Failure to ensure proper monitoring of the clinical investigation [21 CFR 312.50].**

One of the lessons learned from Study 3014 is that monitoring a study is particularly challenging in cases of rapid recruitment, and controls should prospectively limit the rate and extent of recruitment at a given investigator site. This allows for more timely monitoring and the ability to implement prompt corrective actions as needed to ensure compliance with GCP.

Other procedures and actions that relate to ensuring proper monitoring of the clinical investigation are discussed in the response to observation 1 above.

To prevent the recurrence of these problems, the maximum number of subjects at each investigational site is now specified in the study documentation/contract with each investigator ( )<sup>18</sup>. In addition the maximum number of overall subjects is included in the protocol. If the maximum number of patients in the protocol is changed, an amendment is provided to investigators who are to submit it to the IRB for approval, and this is verified by the monitoring team. Changes have also been implemented to monitoring plan templates for International Clinical Development trials to include details to cover both the maximum number of subjects and the rate of recruitment at individual sites ( )<sup>19</sup>. Any recruitment of additional subjects beyond the pre-defined threshold for a site is to be approved by the sanofi-aventis Study Director for the concerned study, based upon the findings from a recent monitoring visit that confirms that the site is compliant with the investigational plan, and continues to have adequate resources and capability to execute the study protocol in compliance with GCP and regulations ( )<sup>20</sup>. Additional information regarding this will be presented at the upcoming meeting with the Agency.

**3. Failure to select qualified investigators and provide investigators with the information needed to conduct the study properly [21 CFR 312.50].**

As discussed in the response to observation 1, procedures have been implemented to select and train qualified investigators. One of the remaining challenges in this area,

however, relates to healthcare practitioner licenses on probation by a state board. During the site selection and initiation process for US investigators documentation is obtained to verify that the investigator is medically qualified. This includes verification of a current license to practice medicine in the state where the clinical site is located ( )<sup>21</sup>.

Sanofi-aventis intends to modify its clinical investigator contract templates by the 1<sup>st</sup> Quarter in 2008 to provide that investigators disclose and commit to disclose to sanofi-aventis if they are restricted in their practice as medical doctors by a competent court, board, or similar authority, unless such disclosure is prohibited under privacy standards or otherwise under applicable law or regulations.

**4. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND [21 CFR 312.50].**

Among the lessons learned from Study 3014 was that the protocol must be written clearly to define study criteria; investigator training must adequately underscore protocol requirements; and study monitoring must sufficiently assess the documentation of protocol compliance.

The use of waivers, including subject selection criteria, is prohibited by International Clinical Development. Failure to follow the investigational plan results in a protocol deviation/GCP violation, which must be properly followed-up with appropriate corrective actions, including retraining of investigator site staff. Important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment are to be described in the Clinical Study Report. According to sanofi-aventis policy, if changes to protocol criteria are necessary, they must be addressed through appropriate protocol amendments reviewed and approved by the IRB and relevant Health Authorities as required, prior to implementation. This currently appears in a ( )<sup>22</sup> which is part of the Quality Document system and will also be reflected in a SOP by 1<sup>st</sup> quarter 2008.

Other procedures and actions that relate to ensuring compliance with the protocol, investigational plan, GCPs and regulatory requirements or terminating the site and reporting the investigator are discussed in the response to observation I above.

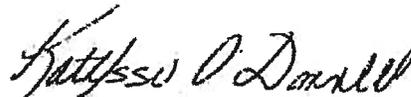
In conclusion, sanofi-aventis assures the Agency that we take our responsibilities as a sponsor of clinical research seriously. We have taken the events surrounding Study 3014 seriously and have improved policies and procedures to identify and correct the issues identified in the Warning Letter in currently ongoing and future clinical trials. We are committed to continuous enhancement, standardization and alignment of our study policies and procedures to be compliant with good clinical practices.

We remain responsive to your concerns, and request a meeting with the Agency to discuss these actions and procedures in greater detail. This letter will serve as the Briefing Package for this meeting.

Sanofi-aventis understands that Agency policy is not to make responses to Warning Letters public unless requested by the recipient of the letter, and that any response posted is redacted to the extent permitted under the Freedom of Information Act (FOIA). Sanofi-aventis respectfully requests that prior to any posting or disclosure of this response, we be provided with an opportunity to redact information that is exempt from disclosure under the FOIA.

As requested in your letter, we have identified Kathleen O'Donnell, Regulatory Development (telephone 908-304-6332, facsimile 908-304-6549, or secured electronic mail ([kathleen.odonnell@sanofi-aventis.com](mailto:kathleen.odonnell@sanofi-aventis.com))), as the point of contact for the expected meeting. In addition we will provide the list of appropriate individuals from sanofi-aventis to participate in that meeting directly to Leslie Vaccari, Division of Scientific Investigations.

Sincerely,



Richard Gural, Ph.D.  
Vice President  
Corporate Regulatory Affairs

Reference List [REDACTED]

Reference	[REDACTED]	[REDACTED]
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]
4	[REDACTED]	[REDACTED]
5	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
6	[REDACTED]	[REDACTED]
7	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
8	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
9	[REDACTED]	[REDACTED]
10	[REDACTED]	[REDACTED]

	[REDACTED]	[REDACTED]
11	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
12	[REDACTED]	[REDACTED]
13	[REDACTED]	[REDACTED]
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22	[REDACTED]	[REDACTED]