

# 浙江华海药业股份有限公司

## 关于 FDA 警告信的翻译文件

警告信：320-19-04

2018 年 11 月 29 日

杜军先生  
执行副总裁  
浙江华海药业股份有限公司  
中国浙江台州临海沿海工业园东海第五大道 9 号川南分厂  
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尊敬的杜先生：

FDA 于 2018 年 7 月 23 日至 8 月 3 日对公司位于中国浙江台州临海沿海工业园东海第五大道 9 号的川南分厂进行了检查。

本警告信对相关 API cGMP 重大不符合项进行了汇总。

鉴于公司用于生产、加工、包装或存放的方法、设施或控制不符合 cGMP 要求，按照美国法典 351(a)(2)(B)，联邦食品药品化妆品法 501(a)(2)(B) 章规定，公司的 API 被判定为掺假药品。

我们仔细审核了公司于 2018 年 8 月 26 日递交的回复，并收到了公司后续的通信。

检查期间，我们的调查人员发现的具体问题包括但不限于以下内容：

### 1. 质量部门未能保证质量相关投诉的调查和解决

#### 缬沙坦 API

在川南生产的缬沙坦 API 残留溶剂检测中发现一未知峰后，公司于 2018 年 6 月 6 日收到了一起客户投诉。该未知峰被鉴定为潜在的人类致癌物二甲基亚硝胺（NDMA）。公司调查(DC<sub>e</sub>-18001)后发现 NDMA 的产生需同时满足三个工艺条件，其中使用二甲基甲酰胺(DMF)作为溶剂是条件之一。公司该调查认为只有缬沙坦的一条工艺（调查中称为氯化锌工艺）有 NDMA 存在。

但 FDA 分析公司的 API 样品以及用公司 API 生产的制剂产品后，在其他工艺生产的多个批次中检出了 NDMA，即三乙胺工艺，该工艺没有使用 DMF 作为溶剂。这些数据表明公司的调查不充分、没能控制和解决已销售给客户的缬沙坦中的 NDMA 问题。此外，调查还存在以下问题：

- 未能包含其他可能影响 NDMA 产生的因素。例如，调查中缺乏所有工艺中使用原料的

详尽评估，包括饮用水。

- 未评估可能的 API 交叉污染因素，包括混批、溶剂回收套用、共线生产和清洁程序。
- 未评估公司产品中存在其他基毒杂质的可能性

检察官还发现了公司色谱未知峰调查不充分的其他例子。例如，缬沙坦中间体（C20213-17-339 和 C20213-17-340）未知单杂超标，两批结果均为 0.56%，标准为 $\leq 0.5\%$ 。作为调查的一部分，公司计划采取措施对该杂质进行鉴定，但公司实际未能鉴定出来。此外，公司未能明确该杂质产生的根本原因。公司称两批中间体进行了返工并用于后续生产。

公司在回复中称 NDMA 很难被发现。但如果公司在当时进行更深入的调查的话，也许可以在残留溶剂图谱中发现迹象警示 NDMA 的存在。例如，公司告知检查官说公司知道缬沙坦残留溶剂图谱中甲苯峰之后有一个峰，该出峰位置疑似 NDMA 的出峰。在检测时，公司认为该未知峰是基线噪音而没有进一步调查。此外，使用 DMF 作为溶剂的缬沙坦氯化锌工艺 2012 验证批（C5355-12-001, C5355-12-002, C5355-12-003）的残留溶剂分析图谱显示甲苯峰后 NDMA 疑似出峰区域内至少有一个未知峰。

公司还回复称缬沙坦 API 中存在 NDMA 的并不只有华海一家。FDA 通过检测样品发现华海缬沙坦 API 中的 NDMA 比其他公司缬沙坦中的 NDMA 高得多。对于川南分厂生产的所有 API 和中间体中是否有潜在的基因毒性杂质，FDA 表示严重关切，因为缬沙坦 API 多个工艺中均发现了该杂质，且公司的调查存在严重不足。

回复此信时请：

- 提交川南场地生产的所有 API 和中间体的潜在基因毒性杂质风险评估。
- 提交针对华海所有 API 中 NDMA 和其他潜在基因毒性杂质的调查和 CAPA 更新情况
- 提交充分且独立的针对公司偏差、不符合、OOS 结果、投诉和其他异常调查体系的评估。此外，请提供公司对尚在有效期内的所有已销售批次的回顾性审核，确认公司是否放行了不符合既定标准或适当生产标准的批次。
- 提供所有血管紧张素受体 II 阻断剂（ARBs）类产品及中间体的 NDMA、NDEA 和其他潜在基因毒性杂质检测结果。

### 左乙拉西坦 API

2016 年 9 月 13 日公司收到一起客户投诉，左乙拉西坦 API 批次（C5152-16-243 和 C5152-16-254）超出氨基甲酸乙酯 $\leq 0.24$  ppm 的质量标准。氨基甲酸乙酯是潜在的人类致癌物。客户的氨基甲酸乙酯检测结果与公司的不符，公司放行检测结果显示这两批合格。公司投诉调查（CC-16008）未发现明显实验室错误，相应批次生产也未发现异常。公司该调查中未对其他左乙拉西坦 API 批次进行评估以确认是否有氨基甲酸乙酯超标的不良趋势。例如，左乙拉西坦批次 C5152-16-244、C5152-16-250 和 C5152-16-251 由于生产原因导致氨基甲酸乙酯超标，但在投诉调查中未进行讨论。

公司在回复中称左乙拉西坦 API 批次 C5152-16-243 和 C5152-16-254 已经退货并进行返工，之后放行提供给客户，这些客户是非美国市场的。

公司在回复中还称 2017 年 8 月氨基甲酸乙酯执行了新的检测方法，采用三重四极杆 LC-MS/MS 检测方法代替了单四级杆 LC-MS 方法，后者证明容易产生假阳性结果。公司未

能核实所有左乙拉西坦 API 批次（包括 C5152-16-254 批）原先放行时采用单四级杆 LC-MS 方法获得的氨基甲酸乙酯检测结果的可靠性，因公司称单四级杆方法不如更新后的方法。

回复此信时请：

- 提交针对效期内的所有左乙拉西坦 API 批次的风险评估报告。
- 提交修订后的投诉管理程序，以及川南分厂为保证所有投诉均被充分记录和调查所进一步采取的具体控制措施
- 退货产品接收和返工程序
- 放行到美国市场的所有左乙拉西坦 API 批次用三重四极杆 LC-MS/MS 方法所测得的氨基甲酸乙酯结果

## 2. 未能评估工艺变更对 API 质量的潜在影响

2011 年 11 月公司批准了使用 DMF 作为溶剂的缬沙坦 API 工艺变更（PCRC-11025）。目的是为了改进工艺，提高收率和降低生产成本。但是执行新工艺时公司未能充分评估潜在的基因毒性杂质产生的可能性。具体地，公司没有考虑到 DMF 降解物可能导致基因毒性或其他有毒杂质的产生，包括 DMF 主要降解产物二甲胺。根据公司正在进行的调查，二甲胺是缬沙坦 API 生产工艺中形成人类潜在致癌物 NDMA 所需要的。公司川南分厂生产的缬沙坦 API 中发现了 NDMA。

批准工艺变更前，公司也未评估是否需要增加检测来确保能够恰当地检出和控制缬沙坦 API 中的非预期杂质。工艺开发和变更时，公司有责任开发和使用适当的方法来检测杂质。如果发现新杂质或杂质含量升高，公司应该对杂质进行全面评估并采取措施保证药品对患者的安全性。

公司在回复中称，预测缬沙坦生产工艺中 NDMA 的形成需要有超出当前工业界行业规范的额外考量维度，称公司的工艺开发研究是充分的。FDA 不同意此观点。FDA 提醒公司工业界业内普遍的做法可能并不总是符合 cGMP 要求，公司对所生产的药品质量负有责任。

公司在回复中未写明充分的整改措施来确保公司变更管理程序的充分性：1) 彻底评估 API 生产工艺，包括工艺变更；2) 检测任何不安全的杂质，包括潜在基因毒性杂质。FDA 目前对潜在基毒杂质控制的想法参见 FDA 指南文件 M7 (R1) 限制潜在癌症风险的药品 DNA 活性（突变性）杂质控制和评估；FDA 认为适当的基毒杂质的评估措施参见 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347724.pdf>。

回复此信时请：

- 提交详细的修订后的变更管理程序，描述公司后续将如何评估和控制场地中生产的 API 和中间体中的所有杂质，包括基因毒性杂质。
- 提交详细的描述如何建立公司生产的产品杂质谱的程序。这些程序需要包括如何与注册申报中杂质谱、或历史数据进行定期比对的说明，以便发现原料、设备操作参数或生产工艺改变后导致的 API 变化。
- 公司生产的其他 API 和中间体的回顾性分析，确认之前是否对预期和非预期杂质进行了

充分的评估，包括潜在基因毒性杂质。

### **cGMP 顾问建议**

鉴于 FDA 在公司所发现的偏差的性质，FDA 强烈建议公司聘用一位有资质的顾问来评估公司的运行并协助公司符合 cGMP 要求。使用顾问并未解除公司符合 cGMP 的义务。公司的高级管理层仍对解决所有缺陷、确保持续符合 cGMP 负有义务。

### **质量体系指南**

公司的质量体系是不足的。关于如何建立和遵循 cGMP 质量体系的指南，参见 <http://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf> 中的“Q8(R2)Pharmaceutical Development”；

<http://www.fda.gov/downloads/drugs/guidances/ucm073511.pdf> 中的“Q9 Quality Risk Management”；

<http://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf> 中的“Q10 Pharmaceutical Quality System”；

### **其他的 API cGMP 指南**

在决定 API 的生产是否符合 cGMP 时，FDA 考虑了 ICH Q7 的内容。参见 <http://www.fda.gov/downloads/drugs/.../guidances/ucm073497.pdf> 中的 FDA API cGMP 指南文件“Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients”。

### **结论**

本警告信中列出的缺陷并不是包括一切的。公司有责任去调查这些缺陷，找出原因，防止再次发生，以及预防其他缺陷。

如果公司计划采取的行动可能会影响药品供应，FDA 要求公司联系 CDER 药物短缺负责人员，[drugshortage@fda.hhs.gov](mailto:drugshortage@fda.hhs.gov)，以便 FDA 可以用最有效的方式协助公司使之符合 cGMP。联系 CDER 药物短缺负责人员可让公司符合按照 21 U.S.C. 356C(b)报告药品中断/终止的义务，使 FDA 可以考虑采取何种行动来避免出现药品短缺，和保护需要该产品的病患健康。

FDA 在 2018 年 9 月 28 日将公司列入了进口禁令 66-40。

FDA 可能会暂停批准所有将公司作为药品生产商的任何新申请或补充申请，直至公司完全整改了所有的缺陷，并由 FDA 确认了 cGMP 符合性。

如不能对这些缺陷进行整改，FDA 会继续根据 FD&C Act, 21 U.S.C. 381(a)(3)中的 section 801(a)(3)拒绝华海药业位于中国浙江台州临海沿海工业园东海第五大道 9 号的川南一分厂所生产的产品进入美国市场。同样的，生产的工艺和控制看上去不符合美国法典 351(a)(2)(B)，联邦食品药品化妆品法 501(a)(2)(B) cGMP 要求的产品也可能被拒绝进入美国市场。

收到此信后，请在 15 个工作日内回复至本办公室。在回复中说明检查后公司做了哪些工作来纠正你们的偏差、防止其再次发生，如果无法在 15 个工作日内完成纠正措施，请说明延迟的原因及完成计划。

请以电子方式回复至 [CDER-OC-OMQ-Communications@fda.hhs.gov](mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) 或将回复邮寄至：

Rory K. Geyer

Compliance Officer  
U.S. Food and Drug Administration  
White Oak Building 51, Room 4235  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
USA

回复时请注明 FEI 号 3003885745.

Francis Godwin  
Acting Director  
Office of Manufacturing Quality  
Office of Compliance  
Center for Drug Evaluation and Research



U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

**Via UPS  
Return Receipt Requested**

**Warning Letter: 320-19-04**

November 29, 2018

Mr. Jun Du  
Executive Vice President  
Zhejiang Huahai Pharmaceutical Co., Ltd.  
Coastal Industrial Zone, Chuannan No. 1 Branch No. 9  
Donghai Fifth Avenue, Linhai, Taizhou Zhejiang 317016  
CHINA

Dear Mr. Du:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, from July 23 to August 3, 2018.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your August 26, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

**1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.**

*Valsartan API*

Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DC<sub>E</sub>-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing

process (referred to as the ZnCl<sub>2</sub> process in your investigation) was impacted by the presence of NDMA.

However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the triethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:

- To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including potable water.
- To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending, solvent recovery and re-use, shared production lines, and cleaning procedures.
- To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates (C20213-17-339 and C20213-17-340) failed testing for an unknown impurity (specification ≤ 0.5%) with results of 0.56% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your ZnCl<sub>2</sub> process, with DMF in 2012 (C5355-12-001, C5355-12-002, and C5355-12-003) show at least one unidentified peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

In response to this letter:

- Submit risk assessments for all APIs and intermediates manufactured at your facility for the potential presence of mutagenic impurities.
- Provide an update on investigations and CAPA plans initiated to address the presence of NDMA and other potential mutagenic impurities in all APIs manufactured at your firm.
- Provide a thorough, independent assessment of your overall system for investigating deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications or appropriate manufacturing standards.
- Provide test results for all angiotensin II receptor blockers (ARBs) and intermediates for the presence of NDMA, N-Nitrosodiethylamine (NDEA), and other potentially mutagenic impurities.

#### Levetiracetam API

Your firm received a customer complaint on September 13, 2016, concerning levetiracetam API batches (C5152-16-243 and C5152-16-254) that exceeded the specification for ethyl carbamate ( $\leq 0.24$  ppm). Ethyl carbamate has been classified as a probable human carcinogen. Your customer's test results conflicted with your ethyl carbamate test results, which showed the two batches meeting the specification upon release. Your complaint investigation (CC-16008) identified no clear laboratory error, and no anomalies were detected during the production of the batches. Your investigation failed to evaluate other levetiracetam API batches to determine if the presence of excess ethyl carbamate was an adverse trend. For example, levetiracetam batches C5152-16-244, C5152-16-250, and C5152-16-251 were OOS for ethyl carbamate because of production errors; however, they were not discussed in your complaint investigation.

Your response states that levetiracetam API batches C5152-16-243 and C5152-16-254 were returned, reprocessed, and released to customers in non-U.S. markets.

Your response also states that in August 2017 you implemented a new ethyl carbamate test method that uses a triple quadrupole LC-MS/MS method, to replace the single quadrupole LC-MS method that was prone to erroneous OOS results. You failed to verify the reliability of the ethyl carbamate results for all levetiracetam API batches (including levetiracetam batch C5152-16-254) originally released using your single quadrupole LC-MS method, which you indicated was inferior to your updated method.

In response to this letter, provide:

- A risk assessment for all levetiracetam API batches manufactured within expiry.
- A revised complaint handling procedure and details of any further controls your facility has implemented to ensure that all complaints are adequately documented and thoroughly investigated.



- Procedures for accepting and reprocessing returned drugs.
- Results of ethyl carbamate testing of all levetiracetam API batches released to the U.S. market using your updated triple quadrupole LC-MS/MS ethyl carbamate test method.

**2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.**

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.

Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* for approaches that FDA considers appropriate for evaluating mutagenic impurities, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>.

In response to this letter, provide:

- Detailed revised change management procedures describing how your firm will assess and control all impurities, including mutagenic impurities, in API and intermediates manufactured at your facility.

- Detailed procedures describing how your firm establishes impurity profiles for products manufactured at your firm. These procedures should contain instructions for comparing at appropriate intervals against the impurity profile in the regulatory submission, or for comparing against historical data, to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- A retrospective analysis of other API and intermediates manufactured at your firm to determine if they were adequately evaluated for anticipated and unanticipated impurities, including potentially mutagenic impurities.

#### **CGMP consultant recommended**

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

#### **Quality Systems Guidance**

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf>; *Q9 Quality Risk Management*, at <https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>; and *Q10 Pharmaceutical Quality System*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf>.

#### **Additional API CGMP guidance**

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API, at <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>.

#### **Conclusion**

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov), so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what

actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

FDA placed your firm on Import Alert 66-40 on September 28, 2018.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to [CDER-OC-OMQ-Communications@fda.hhs.gov](mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Rory K. Geyer  
Compliance Officer  
U.S. Food and Drug Administration  
White Oak Building 51, Room 4235  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
USA

Please identify your response with FEI 3003885745.

Sincerely,



Francis Godwin  
Acting Director  
Office of Manufacturing Quality  
Office of Compliance  
Center for Drug Evaluation and Research