U.S. Department of Health & Human Services

U.S. Food & Drug Administration

## Inspections, Compliance, Enforcement, and Criminal Investigations



### Merck KGaA 12/15/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

**Warning Letter**

**VIA UPS MAIL**

**WL: 320-12-06**

December 15, 2011

Dr. Karl-Ludwig Kley
Chairman of the Executive Board and General Partner
Merck KGaA,
Frankfurter Str. 250
64293 Darmstadt
Germany

Dear Dr. Kley:

The U.S. Food and Drug Administration (FDA) conducted inspections of Merck Serono S.A. Corsier-sur-Vevey (hereinafter referred to as MS-Corsier-sur-Vevey), located at Zone Industrielle B, CH-1809, Fenil-sur-Corsier, Switzerland; Merck Serono S.A. (hereinafter referred to as MS-Aubonne), located at Zone Industrielle de l'Ouriettaz, CH-1170, Aubonne, Switzerland; and Merck Serono S.p.A. (hereinafter referred to as MS-Tiburtina), located at Via Luigi Einaudi 11, 00012 Guidonia Montecelio, Rome, Italy.

The inspection of MS-Corsier-sur-Vevey, an Active Pharmaceutical Ingredient (API) manufacturing facility, was conducted during June 1 to 9, 2011. The inspection of MS-Aubonne, a finished drug manufacturing facility, was conducted during June 10 to 16, 2011; and the inspection of MS-Tiburtina, a pharmaceutical site responsible for the testing of US products, was conducted during June 27 to July 1, 2011.

During our June 1 to 9, 2011 inspection of your MS-Corsier-sur-Vevey facility, an investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs and significant violations to 21 C.F.R. § 601.12 requirements regarding reporting changes to an approved application.

During our June 10 to 16, 2011 and June 27 to July 1, 2011 inspections of your pharmaceutical facilities, MS-Aubonne and MS-Tiburtina, investigators from the FDA identified significant violations of CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (C.F.R.), Parts 210 and 211 and 21 C.F.R. § 600.14(c) requirements regarding the submission of Biological Product Deviation Report (BDPR) to FDA and 21 C.F.R. § 601.12 requirements regarding reporting changes to an approved application.

These violations cause your APIs and finished drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)], in that the methods used in, or the facilities or controls used for, their Merck KGaA, Darmstadt, Germany manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We reviewed your firm's responses of June 28, 2011 , July 8, 2011, and July 20, 2011 , and note that they lack sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

**MS-Corsier-sur-Vevey**

1. Changes to a product, production process, quality controls, equipment or facilities were not reported to FDA through a supplement, CBE-30 report to FDA or an annual report [21 C.F.R. § 601.12].

For example, the approval of the **(b)(4)** API[1] included the commitment to use dedicated equipment for all surfaces in direct contact with the API solution. The **(b)(4)** API is manufactured in Suite **(b)(4).** Since licensure, your firm added the **(b)(4)** API[2] process to Suite **(b)(4)**. Your firm failed to report to FDA this change to the process.

Your response stated that you will send all of the process changes to the FDA by September 2011 and that you revised the procedure for Change Management Control to be consistent with criteria defined in the Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Product. However, your response is inadequate because it did not include the specific changes to the SOP that will prevent recurrence.

In addition, you stated in your response that none of the changes made should have an adverse effect on the approved and licensed **(b)(4)** API. However, you provided no scientific rationale for this conclusion. In response to this letter, please provide your revised procedure and your scientific rationale to conclude that the changes did not impact drug quality.

**MS-Aubonne**

1. Your firm has not established or followed appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21 C.F.R. § 211.113 (b)].

For example, the media fill program does not include all major contamination risk factors in your aseptic process and consequently does not sufficiently demonstrate the state of process control. There is no assurance that your media fill studies are sufficient to establish that the aseptic process is in control. Specifically, your current media fill procedure is deficient in that:

a. Not all personnel involved in the aseptic manufacturing and filling of sterile drug products have participated in a media fill. Please note that media fill is a critical evaluation of the process uses ability of aseptic processing personnel to perform aseptic interventions, and their participation is essential.

b. Your firm lacks records to establish that aseptic processing personnel performed interventions that are representative of the operation.

For example, during the inspection, the investigator noted that your firm's media fill, conducted February 24, 2011 on Line, **(b)(4)** failed to require

performance of interventions, document these interventions, or document when the individuals performing aseptic processing operations entered and exited the room.

Your response indicates corrective actions by November 2011 including training and revision of standard operating procedures (SOPs) to include specific instructions for operations in the aseptic areas. Your response was inadequate because it did not address the following issues:

- major interventions
- instituting **(b)(4)** plate monitoring of the aseptic line personnel who participate in a media fill
- total number of personnel and their activities (only three technicians were mentioned)
- a risk assessment for previously manufactured products
- an interim plan for manufacturing on an appropriately qualified line

In your response to this letter, describe how you will address the issues listed above as part of your corrective actions.

2. Your firm has not established or followed appropriate written procedures for the handling of complaint records to determine if an investigation is required [21 C.F.R. § 211.198].

For example, your investigation regarding complaints of bent needles was inadequate. Your investigation failed to assess whether the 75 complaints received between January 2009 and August 2010 represented a serious defect in your product. Your supplier, **(b)(4)**, notified you in December 2008 that 18 lots of syringes delivered to you were manufactured with the wrong specifications, resulting in the bent needle defect. You did not perform an evaluation of the product lots that may have been impacted by this defect or implement appropriate corrective action to ensure that the testing of incoming container closure components was capable of detecting this defect. In addition, your complaint handling procedure, SOP #LSA1000007, does not detail how to conduct a complaint investigation. We also noted that this procedure provides no information on how you inform the complainant of the outcome of your investigation.

In your response you stated that a retrospective investigation will be conducted and that the complaint handling procedure SOP #LSA1000007 would be revised by August 2011. It also stated that **(b)(4)** was responsible for the defect and therefore, the defect was not related to your local operations.

Your response is inadequate because it did not include a detailed description of the changes you intend to implement to prevent recurrence of the problem. Secondly, the defective syringes were used for the production of **(b)(4)** pre-filled syringes, completed at your facility, and therefore you are responsible for the quality of the materials received and used during the operation. Finally, your response stated that the defect did not affect container closure integrity and hence did not represent any risk to patients.

In your response to this letter, please provide data to support your conclusion that the defect did not affect the integrity of the container closure system and ultimately compromise the sterility of the product. In addition, provide a copy of the investigation report into this incident and the revised complaint handling procedure.

3. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 C.F.R. § 211.160(b)).

For example, the reference standard used for the identity testing of incoming **(b)(4)** API and for release testing of **(b)(4)** pre-filled syringe lots is inadequate. Specifically, your firm uses a reference standard manufactured using the unapproved **(b)(4)** process to test API and drug product manufactured via the **(b)(4)** process.

Your response stated that the scientific rationale used to justify the adequacy of the **(b)(4)** reference standard for the testing of **(b)(4)** batches, and to support that there is no impact on the purity, potency and quality of the released batches, is provided as the "Position paper: scientific rationale on the suitability of the **(b)(4)** physico-chemical reference standard." However, the paper did not contain sufficient information to support the use of a reference standard derived from an unapproved, **(b)(4)** manufacturing process. In addition, some of the analytical data submitted was limited in scope and the raw data is of poor photographic quality (e.g., glycoform analysis). Furthermore, your response did not include the comparability study (Report 10563/P580) or the co-calibration of **(b)(4)** Reference Standard lot # **(b)(4)** against the **(b)(4)** reference standard (Report IMP26875) mentioned in your response.

Also, the identity test currently used can not distinguish between the **(b)(4)** and **(b)(4)** APIs. An identity test must be able to distinguish a material from any other material processed in your manufacturing facility. Your response is inadequate because it does not address the issue of a unique identity test.

The use of an inadequate standard for the identity and release testing of **(b)(4)** API and the stability testing of the **(b)(4)** API and drug product was also noted during the inspection of your MS-Corsier-sur-Vevey API facility and your MS-Tiburtina control testing laboratory facility.

4. Your firm failed to submit a Biological Product Deviation Report (BDPR) to FDA in a timely manner as required by 21 C.F.R. § 600.14(c) for your licensed biological product approved under section 351(a) of the Public Health Service Act (PHS Act) [42 U.S.C. § 262(a)].

Manufacturers who hold a biological product license are required to submit a biological product deviation report to the agency as soon as possible, but in no later than 45 calendar days from the date the manufacturer, its agent, or another person who performs a manufacturing, holding, or distribution step, acquires information reasonably suggesting that a reportable event has occurred. In December 2008 **(b)(4)**notified your firm that you had received 18 lots of out-of-specification syringes. The firm distributed all of the **(b)(4)** finished product lots produced with defective syringes to the U.S. Your firm submitted a BDPR to the FDA on July 15, 2011, three years after you were notified by your supplier.

Your response stated that the requirements for submitting a BPDR, currently contained in SOP #LSA1001511, "The Regulatory and Periodic Review of Complaints," will be incorporated into the revised complaint handling SOP #LSA1 000007. Your response also stated that the bent needles pose no risk to patients and that these lots expired before August 2010. Your response is inadequate because it does not describe the specific changes made to the SOP that will prevent recurrence. Also you did not perform a retrospective review of all of your deviations to ensure the Agency has been notified of other reportable events.

5. Changes to a product, production process, quality controls, equipment or facilities were not reported to FDA through a supplement, CBE-30 report or an annual report [21 C.F.R. § 601.12].

For example, the application approved by the agency for **(b)(4)** pre-filled syringes, **(b)(4)** described the use of dedicated equipment for product contact surfaces and indicated that the drug product was to be manufactured in Line **(b)(4)** filling suite. Since licensure, your firm added three products to the Line **(b)(4)** filling suite:1) **(b)(4)** in February 2006; (2) **(b)(4)** in July 2007; and (3) in **(b)(4)** December 2008. You distributed these products, as well as the **(b)(4)**, in the U.S. without reporting this change to the Agency.

Additionally, according to the terms of your license, the **(b)(4)** process reference standard used for testing product identity and purity was prepared from **(b)(4)** in **(b)(4)** medium (**(b)(4)** process). Your firm replaced this reference standard in 2007 with material derived from **(b)(4)** from **(b)(4)** in **(b)(4)** medium (an unapproved **(b)(4)** process).

Your response stated that you would file a CBE-30 for the equipment change and a PAS for the reference change by August 2011 and that you would revise SOP MS-GMP-Q-ST, "Change Control Management" to be consistent with criteria defined in the Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Biotechnology and Specified Synthetic Biological Product. The Agency has received your CBE-30 for the changes to Line **(b)(4)** as well as the prior approval supplement for the change in reference standard. However, your response is inadequate because it did not provide the specific changes to your change management SOP that are intended to prevent recurrence. In addition, you did not perform a retrospective review of all the changes introduced at your facility since the approval of your **(b)(4)** application to ensure that you provided proper notification to FDA wherever it was appropriate to do so.

**MS-Tiburtina**

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example, the inspection documented that OOS investigations 270605 (Batch **(b)(4)**) and 263873 (Batch **(b)(4)**) involved the stability failure of **(b)(4)** API for Specific Activity after 36 months at -20 °C. The specification was **(b)(4)/**mg and the results were **(b)(4)** and **(b)(4)**/mg for batches **(b)(4)** and **(b)(4)**, respectively. Both investigations concluded that the root cause of the failure was " .. .likely due to the combined

inherent variability of the two assays generating the final results ... ". However, your firm did not include a scientific rationale for this conclusion. In addition, no corrective or preventive actions were included in the investigations.

Your response indicated that your firm revised SOP I-QA-DC-09-F, "Handling of out of Specification Results," to include a timeframe for the closure of analytical investigations. The response is inadequate because your firm did not initiate corrective or preventive actions for the failures or perform a study to demonstrate the inherent variability of the assay. In your response to this letter, please include documentation to demonstrate that you implemented adequate corrective and preventive actions.

We note that some of the CGMP violations listed in this letter impacted all three Merck KGaA facilities. We remind you that you are responsible for ensuring that your firm's drug manufacturing operations comply with all applicable requirements, including the CGMP regulations. FDA expects Merck KGaA to undertake a comprehensive and global assessment of your manufacturing operations in all your facilities to ensure global, adequate, and timely resolution of the issues, including making needed improvements to your quality system.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facilities. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

The lack of compliance with CGMPs may lead to production problems and adversely impact the availability of critical medically necessary products that meet required quality standards. Any interruption in production may lead to its unavailability for those patients who rely on such treatments. To help ensure an ongoing supply, we request that you notify FDA as soon as possible, if you are considering any changes to your production plans that may adversely impact supply. We also request that you develop a proactive plan to ensure a continued supply in the event there is a significant production delay.

Until all corrections are completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission into the United States of articles manufactured at MS-Aubonne, MS-Tiburtina, and MS-Corsier-sur-Vevey. The articles may be subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S. C. § 381(a)(3)],in that, the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S. C. § 351(a)(2)(B)].

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen (15) working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI # 3003131678 (MS-Corsier-sur-Vevey), FEI # 3002807447 (MS-Aubonne), and FEI # 3002807252 (MS-Tiburtina).

If you have questions or concerns regarding this letter, contact Allison A. Aldridge, Ph.D., Compliance Officer, or Maan S. Abduldayem, Compliance Officer, at the below address and telephone numbers.

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Sincerely,

/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

[1]The **(b)(4)** process uses **(b)(4)** and contains **(b)(4)**
[2]The **(b)(4)** process uses **(b)(4)** and its is a **(b)(4)** process

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