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U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Novartis International AG 11/18/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

November 18, 2011

VIA UPS

WL: 320-12-05

Joseph Jimenez
Chief Executive Officer
Novartis International AG
Forum 1, Novartis Campus
CH-4056 Basel, Switzerland

Dear Mr. Jimenez:

During our April 19 to May 6, 2011, June 6 to 22, 2011, and July 26 to August 4, 2011 inspections of your pharmaceutical manufacturing facilities, Sandoz Inc., located at 2555 W. Midway Blvd, Broomfield, Colorado; Sandoz Inc., located at 4700 Sandoz Dr., Wilson, North Carolina; and Sandoz Canada Inc., located at 145 Jules-Leger Street, Boucherville, Quebec, Canada, investigators from the Food and Drug Administration (FDA) identified significant violations of the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211. These violations cause your 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 manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

The August 2011 inspection also revealed that Sandoz Canada Inc. failed to submit NDA Field Alert Reports (FARs) to FDA in compliance with 21 CFR § 314.81(b)(1)(ii), as required by section 505(k) of the Act [21 U.S.C. § 355(k)]. An applicant is required to submit, within three working days of receipt, information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application.

We have reviewed your firm's responses of May 31, 2011, July 13, 2011, and August 25, 2011, and note that they lack sufficient corrective action.

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

CGMP Violations

A. Sandoz Canada Inc., Boucherville, Quebec, Canada

1. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures include validation of the sterilization process [21 CFR § 211.113(b)]. For example:

a) Your media fill studies were insufficient to establish that the aseptic process is in control. During media fill studies, you failed to establish appropriate criteria for reconciliation of filled vials (total units evaluated/incubated as compared to the total number of units filled) resulting in inconsistent and inaccurate media fill results. For six media fill lots manufactured from 2009 to 2011, the number of units filled did not match the number being evaluated/incubated. The number of units evaluated/incubated in some media fill runs was smaller than what had been filled, and in other media fill runs, the number of units evaluated/incubated was greater than what had been filled. Your firm lacked a justification for these discrepancies. For example:

i. Your media fill Lot# **(b)(4)** (filling end date August 20, 2009) shows that **(b)(4)** ampoules were received for incubation and **(b)(4)** ampoules were evaluated.

ii. Your media fill Lot# **(b)(4)** (filling end date October 30, 2009) shows that **(b)(4)** vials were received for incubation and **(b)(4)** vials were evaluated.

iii. Your media fill Lot# **(b)(4)** (filling end date July 1, 2010) shows that **(b)(4)** vials were filled and only **(b)(4)** vials were incubated. The number of media fill vials sent for manual visual inspection was also inconsistent with the number of units sent to the microbiology laboratory.

iv. Your media fill Lot# **(b)(4)** (filling end date November 18, 2010) shows that **(b)(4)** vials were received for incubation and only **(b)(4)** vials were evaluated.

v. Your media fill Lot# **(b)(4)** (filling end date December 14, 2010) shows that **(b)(4)** vials were received for incubation and only **(b)(4)** vials were evaluated.

b) You failed to follow your procedures for validation of aseptic processing. Your procedure, SOP P.200.136 (Media Fills), indicates that investigations will be initiated when there is a discrepancy between the units received by the laboratory and the units received for incubation. Your response indicated that an investigation was conducted for media fill lot# **(b)(4)** on July 23, 2010. As a result of this investigation, you proposed the following corrective actions: modify the sensor, improve documentation, and re-train personnel. However, two additional incidents (November 18, 2010 and December 14, 2010) occurred after the implementation of these corrective actions.

In your response to the FDA form 483 (Observation # 4a), you committed to update SOP P200.136 (Media Fills) to correct the reconciliation discrepancy at each step of the media fill: filling, visual inspection, receipt at the microbiology laboratory, mid-incubation, and final evaluation.

Please provide any data/documentation available from your investigations that establishes reconcilability of all media fill units. Total accountability of media fill units includes: units filled, rejected, received by microbiology department for incubation, removed for positive controls, and final inspection. Without this data, the acceptability of the above media fill runs and the capability of the process used to manufacture sterile drugs during this period is questionable. Please provide your firm's evaluation of the impact on products produced during this period.

This is a repeat observation from the July 2009 inspection at the Boucherville, Quebec facility.

2. 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 CFR § 211.192].

For example, the inspection revealed that your firm failed to conduct an adequate investigation of the crystallization of the solution in your finished product **(b)(4)** Injectable (**(b)(4)** mg/mL). Five out of eight lots (62.5%) of your finished product **(b)(4)** Injectable (**(b)(4)** mg/mL) reviewed during the inspection contained crystals in the vials as follows: 36% rejection of lot **(b)(4)** (**(b)(4)** mL in **(b)(4)** mL vials), 12% rejection of lot **(b)(4)** (**(b)(4)** mL vials), 29% rejection of lot **(b)(4)** (**(b)(4)** mL vials), 43% of lot **(b)(4)** (**(b)(4)** mL in a **(b)(4)** mL vial), and 25% of lot **(b)(4)** (**(b)(4)** mL in a **(b)(4)** mL vial). These lots were released for distribution to the United States. You submitted a field alert to FDA on August 05, 2011, after the conclusion of this inspection.

We are concerned that your firm lacks process understanding to consistently manufacture **(b)(4)** Injectable (**(b)(4)** mg/mL). Your response indicates that you had

no crystallization issues prior to 2009 and that there have been minor changes in the incoming materials and process parameters in the last two years. However, you failed to adequately determine the cause of this crystallization problem, including whether the significant frequency of crystallization in your current batches is due to the changes since 2009.

Your failure to implement appropriate corrective actions and prevent future recurrence is indicative of an ineffective quality system.

Please provide the summary report of your evaluation of finished product complaints regarding crystals, including investigations conducted to determine the root cause, any identified triggers that may cause the product to crystallize, and corrective actions implemented to optimize the process. In addition, please provide your revised procedure to ensure timely initiation of investigations when significant adverse trends are observed.

This is a repeat observation from the July 2009 inspection at the Boucherville, Quebec facility.

3. Your firm has not conducted at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 CFR § 211.84(d)(2)].

For example, your firm accepts and relies upon the Certificate of Analysis (CoA) from your stopper suppliers without conducting adequate vendor qualification. Notably, your firm does not routinely test for endotoxin on incoming stopper lots, and lacks justification for not conducting this testing. In your response, your firm commits to implement a new procedure for microbiological testing of stoppers for endotoxin content and to validate the reliability of the supplier's CoA. However, your response did not address the potential product quality impact of using stoppers that have not been properly evaluated for manufacturing sterile products.

This is a repeat observation from the July 2009 inspection at the Boucherville, Quebec facility.

B. Sandoz Inc., Broomfield, Colorado Facility

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR § 211.100(a)].

For example, you used two **(b)(4)** #8 and #15, interchangeably for the production of multiple drug products without validating the process using both pieces of equipment for each of the products. You conducted process validation for six of your drug products using only **(b)(4)** #15. When **(b)(4)** #15 was removed from service in 2007, you continued to manufacture these six drug products using **(b)(4)** #8. While **(b)(4)** #8 and #15 were identical in the construction of their external **(b)(4)**, they contained different internal configurations. Your firm did not validate the use of **(b)(4)** #8, and product manufactured in this **(b)(4)** had a slower dissolution rate than product manufactured in **(b)(4)** #15. The slower dissolution rate resulted in a recall of 16 lots of Triamterene Hydrochlorothiazide 50/25 mg manufactured in **(b)(4)** #8.

In your response, you state that there are controls in place to control variability in the process and in the final product. Your response, however, is inadequate because you do not adequately address the need to prospectively assess the adequacy of these controls through completion of successful process validation studies.

This is a repeat violation from the August 2008 Warning Letter issued to the Wilson, North Carolina facility.

2. 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. You failed to extend investigations to other batches of the same product and other products that may have been associated with the failure, and your firm's written investigation records failed to include your conclusions and follow-up [21 CFR § 211.192]. For example:

a. Fourteen out of 79 (18%) laboratory investigations lacked documentation of either an investigation into other associated batches or products, or a corrective action.

b. In-process specification for **(b)(4)** uniformity was not met for three validated processes including: **(b)(4)** mg capsules (lots **(b)(4)**, **(b)(4)**), **(b)(4)** mg/**(b)(4)** mg **(b)(4)** tablets (lots **(b)(4)** and **(b)(4)**) and **(b)(4)** mg tablets (lots **(b)(4)** and **(b)(4)**). For the lots that were distributed, the root cause of the failure was identified as sample bias. However, your firm failed to conduct an adequate follow-up to correct this problem. For the lots that were destroyed, you failed to extend your investigation into other associated batches or establish a root cause.

In your response, you reiterated that these specification failures were attributed to sample bias, and that you conducted further studies to correct for this sampling bias. However, your response is inadequate because you had released product to the market based on stratified sampling without adequate scientific justification. It is important that your firm's investigation procedures ensure that a full investigation, including all associated lots and root cause identification, is performed prior to distribution. We will verify the implementation of your revised investigation procedures during a future inspection.

3. Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product [21 CFR § 211.67(a)].

For example, investigators observed that several pieces of equipment, including your, **(b)(4)** were still dirty after cleaning had been completed and verified by a supervisor.

In your response, you state these were isolated instances and that there is no impact to product. However, this is a repeated violation from the August 2008 Warning Letter issued to the Wilson, North Carolina facility. We are concerned that your firm has been cited for inadequate cleaning during a number of previous inspections, and that you have promised corrective actions but our
inspections continue to reveal problems in this area of CGMP.

C. Sandoz Inc., Wilson, North Carolina Facility

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR § 211.100(a)].

For example, process validation for several drug products (e.g.,**(b)(4)** mg; **(b)(4)** mg; **(b)(4)** mg; and **(b)(4)** mg) was not adequate. During the inspection, our investigator identified at least four products for which process validation was performed using a **(b)(4)** ; however, these four tablet products were also being manufactured using the **(b)(4)**. Using a **(b)(4)** when products were validated on a **(b)(4)** was not in your approved validation procedure, and you had no data to demonstrate equivalence of the different **(b)(4)**.

In your response, you state that there are controls in place to control variability in the process and in the final product. These controls and variability should have been prospectively assessed through completion of successful process validation studies. In addition, you reference the Cpk values for processes using a **(b)(4)** versus the processes using the **(b)(4)**. Your response is inadequate because a Cpk value alone is not an appropriate metric to demonstrate statistical equivalence. Cpk analysis requires a normal underlying distribution and a demonstrated state of statistical process control (ASTM E2281). Statistical equivalence between the **(b)(4)** and **(b)(4)** could be demonstrated using either parametric or non-parametric (based on distribution analysis) approaches (comparing means and variances). Your response to Observation #1 does not utilize either of these approaches, and lacks the proper analysis to support your conclusion that no significant differences existed between the two **(b)(4)** processes.

Further, your response attempts to demonstrate equivalence of the **(b)(4)** and **(b)(4)** processes through uniformity and dissolution data, although you did not provide any data regarding **(b)(4)** or **(b)(4)** parameters. Also, in Attachment VI of your response, you attempt to demonstrate the equivalence of the **(b)(4)** processes by providing data obtained through your "SAS" system that contains projected expiry information. However, the data you present for the "projected expiry" of **(b)(4)** mg does not confirm that the two processes are equivalent; instead, this data demonstrates the variability in your process and the expected failure of lot **(b)(4)**, asset #**(b)(4)**, produced using the **(b)(4)**. Therefore, we find your response inadequate to address our concerns regarding your failure to validate the above-noted products on the **(b)(4)** equipment.

This is a repeat violation from the August 2008 Warning Letter issued to the Wilson, North Carolina facility.

Field Alert Report (FAR) Violation

Sandoz Canada Inc., Boucherville, Quebec, Canada

Your firm failed to submit a Field Alert Report (FAR) concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application within three working days [21 CFR § 314.81(b)(1)(ii) and §
505(k) of the Act [21 U.S.C. § 355(k)]].

Our investigation revealed that you did not submit FARs within three days regarding trends of complaints for **(b)(4)** Injectable that could signal chemical, physical, or other changes or deterioration in the distributed batches of that product. For example, from January to June 2011, you received 33 complaints for crystallization/cloudy solution of this product. Your firm should have submitted these FARs concerning the continuing crystallization complaints within three working days.

In addition, you did not file FARs within three working days for two lots of **(b)(4)** Injectable, **(b)(4)** mg/mL (lot **(b)(4)** and lot **(b)(4)**) that failed particulate

characterization at the initial and twelve month stability stations. You did not file FARs for these two specification failures for approximately three months and after the investigation closed. The intent of the 21 CFR § 314.81(b)(1) regulation is to establish an early warning system so that significant problems are brought to the Agency's attention by applicant holders in order to prevent potential safety hazards from drug products already in distribution.

Sandoz Canada Inc., must develop and implement an SOP and appropriate training of all relevant employees detailing the process and responsibilities for handling FARs. We will verify the implementation and effectiveness of this corrective action during a future inspection of your facility.

We note that CGMP violations listed in this letter include multiple repeated violations from those cited in the August 2008 Warning Letter issued to Sandoz Inc.'s Wilson, North Carolina facility and repeated observations from previous inspections at your Sandoz Canada Inc. facility in Boucherville, Quebec, Canada. It is apparent that Novartis International AG (Novartis) is not implementing global and sustainable corrective actions. We remind you that you are responsible for ensuring that your firm's drug manufacturing operations comply with applicable requirements, including the CGMP regulations. FDA expects Novartis to undertake a comprehensive and global assessment of your manufacturing operations to ensure that drug products conform to FDA requirements. Finally, the Agency is concerned about the response of Novartis to this matter. Corporate management has the responsibility to ensure the quality, safety, and integrity of its products. Neither upper management at Novartis nor at Sandoz Inc., nor at Sandoz Canada Inc., ensured global, adequate, or timely resolution of the issues at these sites.

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, and for assuring compliance with all requirements of federal law and FDA regulations. If you wish to continue to ship your products from Sandoz Canada Inc., to the United States, it is the responsibility of your firm to ensure compliance with all United States standards for CGMP and all applicable United States laws and regulations.

Until all corrections have been 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 of articles manufactured at Sandoz Canada Inc., 145 Jules-Leger Street, Boucherville, Quebec, Canada into the United States. The articles are 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 CGMP within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations at the Broomfield, Colorado, and Wilson, North Carolina facilities may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. A re-inspection may be necessary at the Broomfield, Colorado, and Wilson, North Carolina, and Boucherville, Quebec facilities.

Within fifteen 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 working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production. Please identify your response with appropriate FEI # for each location.

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or bulk drug substances produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Please contact the CDER's Office of Manufacturing and Product Quality (OMPQ) within five days of receipt of this letter to schedule a regulatory meeting to discuss your proposed corrective actions and time frames, as well as your plan for ensuring timely and meaningful involvement of corporate senior executive management from Novartis, Sandoz Inc., and Sandoz Canada Inc. in addressing significant issues in the future. Please contact Keith Olin, Project Management Officer, OMPQ, at (301) 796-0962 or keith.olin@fda.hhs.gov, to schedule a meeting at CDER headquarters.

Your reply to the Warning Letter concerning Broomfield, Colorado and Wilson, North Carolina facilities should be sent to the Food & Drug Administration, Denver District Office, Building 20-Denver Federal Center, P.O. Box 25087, 6th Avenue & Kipling Street, Denver, Colorado 80225-0087, to the attention of Nancy G. Schmidt, Compliance Officer. In addition, your reply to the Warning Letter concerning Sandoz Canada, Inc. Boucherville, Quebec facility should be sent to the Food & Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, Office of Manufacturing and Product Quality, Division of International Drug Quality, White Oak Building 51, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, to the attention of Maan Abduldayem, Compliance Officer.

Sincerely,

/Steven Lynn/
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Cc:

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