Inspections, Compliance, Enforcement, and Criminal Investigations

Sandoz Inc. 12-Aug-08

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

August 12, 2008

VIA FEDERAL EXPRESS

Dr. Bernhard Hampl
President/Chief Executive Officer
Sandoz Inc.
506 Carnegie Center
Suite 400
Princeton, NJ 08540

WARNING LETTER
(08-ATL-13)

Dear Dr. Hampl:

On March 17 through March 31, 2008, the Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility located at 4700 Sandoz Drive, Wilson, North Carolina. The inspection revealed significant deviations from the Current Good Manufacturing Practice (CGMP) regulations (Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211) in the manufacturing of your drug products, which include Metoprolol Succinate ER tablets. These deviations 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)].

The violations include, but are not limited to, the following:

1. Failure to establish and follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess as required by 21 CFR § 211.100(a).

Specifically, you have failed to appropriately validate the manufacturing process for Metoprolol Succinate ER (25 and 50 mg) tablets prior to product distribution. For example:

a) Failures were noted in the process validation studies performed on the Metoprolol Succinate ER 50 mg tablets. Process validation lot MF001088 failed content uniformity at high speed compression, and process validation lot MF001089 failed dissolution at high hardness for the 4 hour time point. In response to these failures, your firm obtained additional samples from other commercial lots that were unrelated to the validation study.

Your firm therefore used one conforming validation lot and two unrelated commercial lots to deem the process acceptable. In addition, your firm failed to record tablet press speed and tablet hardness results in batch production records for both process validation and routine commercial lots.

b) Due to the variability noted in the Metoprolol ER pellet lots used in the production of the 25 and 50 mg tablets, your firm's current practice is to analyze pre-compression samples (cores) in an attempt to determine the appropriate hardness for each lot of tablets. The tablet cores are compressed at target hardness (**[redacted]** kp for 25 mg lots and **[redacted]** kp for 50 mg lots) and at a high hardness **[redacted]** kp for 25 mg lots and **[redacted]** kp for 50 mg lots) prior to tableting each batch, and then are tested for dissolution. Based on the dissolution testing results of the cores at this step of the process, a target hardness (no range was specified) was established for each lot. Your firm's process validation reports do not discuss this practice of pre-compression testing to determine hardness for each lot. This practice has been used for all commercial lots produced (over **[redacted]** lots) and represents a moving target of quality.

In your April 29, 2008 response to the FDA 483, you stated that your firm will continue releasing Metoprolol Succinate ER Tablets because routine product testing of manufactured lots is sufficient proof that the process is validated. We disagree with your assessment. Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce process variability: and successful process validation studies, in conjunction with product testing, provide assurance that the process will produce a product with the required quality characteristics. Your firm's validation efforts have revealed that you have not properly studied and established the relationships between compression forces, dissolution, and content uniformity. Also, it is not acceptable to disregard the findings in one of the lots by stating that another lot made under the same process had sample results that met the criteria. To the contrary, this is

an indication that you have not identified, and are unable to control, those factors that cause variability in the process. This also indicates that you lack a robust process design. Consequently, you do not have a high level of assurance that the process is in a state of control and is capable of consistently producing a product that meets specifications.

> 2. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed, and to extend the investigation to other batches that may have been associated with the specific failure or discrepancies as required by 21 CFR § 211.192.

Specifically, your firm has failed to conduct adequate investigations as per its SOP G-004, Guidelines for Investigations of Product Quality, which states that investigations are to be completed within 30 days. Numerous manufacturing investigations were not conducted and/or completed until after the initiation of the current inspection. According to SOP G-004, if an investigation requires more than 30 days for completion, an Investigation Interim Report must be prepared to explain the delay. Your firm's management stated that these reports, which require review and approval by Quality Assurance (QA), had not been completed for any of the investigations exceeding 30 days. Furthermore, investigations did not always include an evaluation of other lots or products potentially affected. For example:

> a) Investigations were not conducted for 13 lots of Metoprolol Succinate ER 50 mg tablets and 5 lots of Metoprolol Succinate ER 25 mg tablets that were manufactured and rejected in 2007 (due to low dissolution results) until after the initiation of this inspection on March 17, 2008.
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> b) In March 2007, your firm initiated an investigation for Metoprolol Succinate ER pellets, lot MK070095, due to dissolution problems, but it was not completed until after the inspection began, approximately one year later.
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> c) Your firm initiated an investigation for Metoprolol Succinate ER tablets, lot MK072338, on December 21, 2007, due to low failing dissolution results, but you did not complete the investigation until March 26, 2008. No Investigation Interim Report was prepared (per your SOP G-004) to explain this delay.
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> d) In March 2007, your firm initiated an investigation of Orphenadrine Citrate ER 100 mg tablets, lot MK062041, which were rejected due to failing dissolution results. The investigation was completed one year later, after initiation of the current inspection. The investigation resulted in "operator retraining to minimize uneven application of the regulating

agent." Your firm did not evaluate other lots of this product to determine if they had been potentially impacted.

e) In addition, an investigation for Clarithromycin 500 mg ER Tablets, lots MK062164 and MK070178, which were rejected due to failing dissolution results, determined that the coater had been preheated for an extended period of time prior to the beginning of tablet coating. You failed to evaluate other lots of this product to determine if this incident had occurred before, and you had no documentation that operators were retrained to prevent a reoccurrence.

f) Additional studies that were to be performed to further evaluate the failures of content uniformity at high speed compression and dissolution at high hardness were not conducted. These failures occurred while conducting process validation studies of Metoprolol Succinate ER 50 mg Tablets (lots MF001088 and lot MF001089). These lots were released for distribution. Your firm's failure to complete these studies heightens our concerns about your Quality Control Unit's (QCU's) ability to implement corrective actions.

g) There were more than fifteen additional examples of products cited in the FDA 483 for which you failed to complete investigations within the timeframe established in your SOP. These products included Doxycycline Hyclate DR Capsules, Lisinopril Tablets, Alprazolam ER Tablets, Fentanyl Citrate Lozenges, Azithromycin for Oral Suspension, and Anagrelide HC1 Capsules. These investigations were only completed after this inspection was initiated. We consider this a significant failure of your QCU.

Additionally, it is important that you assess the impact of the investigational findings and take appropriate corrective actions for all of these products that were marketed prior to concluding the investigations. Your response should address this.

3. Failure to include in-process and laboratory control results in the batch record as required by 21 CFR § 211.188(b)(5).

For example, your firm did not have documentation in the batch record of all Metoprolol Succinate ER Tablets (25 mg and 50 mg) pre-compression sample hardness results, dissolution results, and hardness targets which are determined for each lot. These production and testing steps are part of current firm practice, and were instituted to define compression parameters due to variability in the Metoprolol ER pellet lots for the 25 and 50 mg tablets. During the inspection, you could not locate any documentation for some of these start-up hardness results, and this information was not included in the batch production records. Your firm failed to document these results for any Metoprolol 25 mg tablets lots manufactured in 2006. As a result, QA did not review pre-compression data when

reviewing the batch for release, in order to assure that the appropriate hardness was used throughout the manufacturing process.

Documentation for the pre-compression samples for the 25 and 50 mg lots was occasionally maintained by the compression supervisor, who decided what target hardness to provide to operators for use in a given lot. Notably, there was no range specified. This information was also not included in the batch production records. In your April 29, 2008 response to the FDA 483, you committed to amend your master batch records to include all pre-compression data, but you provided no explanation regarding the data that was missing at the time of the inspection.

> 4. Failure to include complete manufacturing and control instructions, sampling and testing procedures, specifications, and precautions to be followed in the master production and control records as required by 21 CFR § 211.186(b)(9).

For example, the master production records for Metoprolol Succinate ER tablets (25 and 50 mg) do not include the requirement for sampling and testing of pre-compression samples to determine target hardness for each lot. The master production records for the 50 mg tablets also do not reflect the changes made since November 11, 2007 to revise the inlet air temperature range and exhaust air temperature target and range for tablet coating. The master record also does not reflect the maximum spray rate of **[redacted]** mL/minute that was implemented several months ago. These changes were implemented in response to dissolution failures.

> 5. Failure to have laboratory controls to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity as required by 21 CFR § 211.160(b).

Your firm could not provide documentation or justification for the internal release specifications (4th hour dissolution) used for Metoprolol Succinate ER 25 and 50 mg tablets. This internal specification had been revised in an attempt to assure that the product would meet the dissolution specification throughout expiry of the product. An internal specification of not less than an average of **[redacted]** was used from October 2006 to January 2008. The specification of not less than an average of **[redacted]** has been used since that date. These specifications were reportedly based upon the current stability data. However, these changes were not part of a change control process. In addition, although firm officials indicated to our investigator that lots failing the internal specification were not to be distributed, five lots were released for distribution with results below the internal specification in 2007.

> 6. Failure to establish appropriate controls over computer or related

systems to assure that changes in master production and control records or other records are instituted only by authorized personnel as required by 21 CFR § 211.68 (b).

For example, the **[redacted]** data acquisition system for the **[redacted]** UV/Visible spectrophotometers allows your analysts to modify, overwrite, and delete original raw data files. The spectrophotometers are used for dissolution testing of finished product, stability samples, and process and method validation studies. All laboratory personnel were given roles as **[redacted]** Managers, which allowed them to modify, delete, and overwrite results files. This system also does not include an audit trail or any history of revisions that would record any modification or deletion of raw data or files. Your laboratory computer system lacks necessary controls to ensure that data is protected from tampering, and it also lacks audit trail capabilities to detect data that could be potentially compromised.

7. Failure to assure that the responsibilities and procedures applicable to the quality control unit are followed as required by 21 CFR § 211.22(d). For example,

a) Your firm's QCU failed to ensure that manufacturing investigations were initiated and completed according to your procedures.
b) Your firm's QCU failed to ensure that the manufacturing processes for the 25 and 50 mg Metoprolol Succinate ER tablets were adequately validated.
c) Your firm's QCU failed to review all raw data and test results for in-process tests and to incorporate manufacturing changes into master batch records.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and injunction.

We acknowledge that some corrections were initiated by your firm during the course of this inspection. We also acknowledge receipt of your initial response to the FDA 483, dated April 9, 2008, as well as your follow-up responses dated April 29, 2008 and June 27, 2008. In your responses, you committed to implementing a quality improvement plan for your facility after you complete your analysis of the existing quality system and the revision of all control records, which will be

completed by **[redacted]** and **[redacted]** respectively. You also agreed that the Metoprolol products were not validated, and you have committed to revalidate both strengths (25 and 50 mg). Our concerns with these responses were discussed with Sandoz representatives at the meeting held at the Atlanta District office on July 10. We are in receipt of a follow up response dated August 10 to that meeting. This latest response is currently under review.

You originally decided to temporarily suspend distribution of Metoprolol 25 and 50 mg tablets until the available pre-compression and dissolution data was reviewed. However, you have decided to resume distribution of these products based on your rationale that successful, routine, finished-product testing of manufactured lots is sufficient proof that the product is of acceptable quality. We question the continued distribution of this product until better process controls are implemented and process validation is completed. We are also concerned that the problems noted in the Metoprolol validations could be indicative of problems and poor decisions made with other product validations.

In addition to the deficiencies listed above, we are also concerned that you may not be utilizing a global approach to the implementation of manufacturing controls. For example, one proposed corrective action at the Wilson site is to implement an automated investigation management tracking system (**[redacted]**) which is already in use at other Sandoz sites. It is our expectation that all Sandoz sites intended to be used for the manufacture of drugs have a comprehensive evaluation to assure compliance with all laws and regulations governing the manufacture of drugs. We request that you provide documentation describing the specific steps you will take to perform these evaluations and to implement the necessary corrective actions at all Sandoz' sites.

Until FDA confirms correction of the deficiencies observed during the most recent inspection, this office can recommend disapproval of any pending New Drug Applications, Abbreviated New Drug Applications, or export certificate requests submitted by your firm. Federal agencies are advised of the issuance of all Warning Letters pertaining to drugs so that they may take this information into account when considering the award of contracts.

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. Your response should describe any specific actions, other than those already submitted, you will take, or have taken, to correct the violations described above, and include an explanation of how each action being taken will prevent recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for delay and the time within which corrections will be completed.

Sincerely yours,

/S/

Mary Woleske, Director
Atlanta District

cc: Bill Monteith, General Manager
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