Sage Products Inc 7/17/17

Division of Pharmaceutical
Quality Operations III
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July 17, 2017

WARNING LETTER

Case# 520382

UPS NEXT DAY
SIGNATURE REQUIRED

Mr. Daniel Scott Brown
President
Sage Products, Inc.
3909 Three Oaks Road
Cary, IL 60013

Dear Mr. Brown:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility Sage Products Inc. at 3909 Three Oaks Road, Cary, Illinois, from June 2 to September 1, 2016.

The inspection revealed that your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, therefore making your drug products 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).

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21, Code of Federal Regulations (21 CFR, Part 210 and 211).

We reviewed your September 22, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165(e)).

You produce some bulk drug solutions at your facility (e.g., 2% chlorhexidine gluconate) and have entered into contract manufacturing arrangements for the production of other drugs (e.g., Sage Perox-A-Mint, manufactured for you byChemRite CoPac, Inc. ("ChemRite")). You use the **(b)(4)** method to screen for microbiological contamination in drugs produced entirely at your facility and those manufactured under contract. This **(b)(4)** screening method **(b)(4)** for microbiological examination of your liquid drug products is not adequate for its intended use. You attempted to validate your **(b)(4)** microbial detection method, but were not able to demonstrate that it could reliably and repeatedly determine whether objectionable microorganisms were present in your drugs.

You screened your Comfort Shield large three-pack product (lot 53957) for presence/absence of microbiological contamination in March, 2016, using the **(b)(4)** method. The **(b)(4)** test did not detect the presence of microbial contamination. You then released this lot for distribution.

After receiving three consumer complaints for discoloration of this product, you initiated testing of your retains using both the modified U.S. Pharmacopeia (USP) microbiological limits method and the **(b)(4)** method. Both analyses found microbial contamination. Notably, the USP modified method **(b)(4)** found an exceedingly high microbial count of over 57,000 CFU/ml, and also identified *Burkholderia cepacia,* an objectionable microorganism, in this product lot.

Your drugs are often used in hospital or clinical settings in which patients may have a higher vulnerability to infection with *B. cepacia* and other objectionable organisms. Detecting numbers and types of objectionable microorganisms in your products is critical to making appropriate batch disposition decisions, yet the microbiological screening method on which you rely to examine your products for the presence of microbiological contamination has not consistently and reliably detected the presence of *B. cepacia* in your drugs before you released them for distribution. For example, since 2006, your firm conducted at least four recalls for products associated with *B. cepacia* contamination, including:

Year	Product
2006	Comfort shield 3% dimethicone cloths
2008	2% chlorhexidine gluconate cloths
2014	Comfort Shield 3% dimethicone cloths
2016	3% dimethicone cloths 2% chlorhexidine gluconate cloths M-Care cleansing cloths Comfort Bath cleansing wash cloths

Had your firm been utilizing a screening method capable of consistently detecting *B. cepacia,* these products may not have been released in the first instance.

During a June 28, 2016, teleconference, FDA informed you that your **(b)(4)** method **(b)(4)** has not been adequately validated for detecting the presence of microorganisms, including the presence of *B. cepacia*. In a subsequent meeting on November 30, 2016, FDA advised you to use a verified compendial method for all bulk drug solutions and finished product microbiological testing until you could further assess the suitability of the **(b)(4)** method. In the November meeting, your firm's management agreed to continue efforts to assess the **(b)(4)** method, and if possible, validate it. However, you did not commit to using a compendial method until the **(b)(4)** method could be validated.

According to your firm's *Microbial Enumeration* QTP-079, "classical method testing should be performed for samples that do not have validated **(b)(4)** method testing to verify whether or not samples meet the microbial enumeration acceptance criteria." Your firm continues to lack a validated **(b)(4)** method. While your response indicates that you revised your SOP *Microbial Recovery Validation,* which references your attempted **(b)(4)** validation method, the SOP modifications did not address the method inadequacies or demonstrate equivalence or superiority to USP <61> *Microbial Examination of Nonsterile Products: Microbial Enumeration Tests* and USP <62> *Microbial Examination of Nonsterile Products: Tests for Specified Organisms* at detecting objectionable organisms such as *B. cepacia* and enumerating total microbial count levels.

Deficiencies in the **(b)(4)** method validation include the following.

- It specifies a **(b)(4)** dilution factor. USP <62> requires a 1:10 dilution factor. Your dilution factor is **(b)(4)** times greater than the USP method and provides insufficient detectability to rule out the presence of objectionable microorganisms and unacceptable total counts.
- It does not account for the enrichment step called for in USP <62>.
- It does not include the scraping step during sample preparation, which your submitted laboratory data indicates is required to validate organism recovery.
- It lacks evidence that small numbers of various microorganisms, including those that are injured and stressed, can be reliably recovered. Specifically, sample effect (defined by your firm as the inhibitory effect of a sample on the growth of various microorganisms) data for *B. cepacia* was collected using a fresh-grown culture, not a stressed organism.
- Microbial recovery results for each challenge organism are not fully described. The identity of recovered growth from organism challenge studies was not always verified.
- It does not establish potential sample interference factors (e.g., enhancing or quenching) for each product formulation.

In response to this letter, provide the following.

- A commitment to test retain samples for all drugs released to the U.S. market within expiry. Ensure that your retrospective testing protocol includes the use of compendial methods that have been verified to assure acceptable microbiological recovery.
- Your commitment to use a verified compendial method for microbial limits testing (i.e., total count and detection of *B. cepacia* and other objectionable microbes), including an appropriate enrichment step, for testing each lot of your drug products until you can validate a suitable alternative **(b)(4)** screening method.

- A global CAPA plan that describes tangible improvements to the design and control of your manufacturing operations to prevent recurrence of microbiological quality problems.

  If you intend to attempt to validate the **(b)(4)** method for its intended use, also include the following.
- Provide updated validation protocols and final reports for each product that include specificity, limit of detection, robustness, ruggedness, repeatability, and equivalence of your method to the USP compendial method.
- Comprehensively evaluate your method and fully address its inadequacies, including those cited in this letter. Once this full evaluation is complete, provide all findings and deviations encountered in assessing whether the revised method is equivalent or superior to the USP compendial method.

2. Your firm failed to establish scientifically sound and appropriate sampling plans and test procedures designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your written procedures for microbial enumeration are insufficient to ensure that each batch is acceptable for distribution. In particular, your method lacks adequate provisions for performing **(b)(4)** testing when a positive result is obtained to ensure recovery and further evaluation of the microbiological contamination.

An original sample found to be contaminated using the **(b)(4)** test is not further analyzed. Instead, a small additional sample is tested using a modified USP method **(b)(4)**. If no growth is detected in this small sample, you require no further testing. You lack scientific justification that this **(b)(4)** sample is representative of the batch, and allows for proper evaluation of the positive result in **(b)(4).** As a result, the **(b)(4)** test is effectively used as a "confirmatory test," rather than using it to evaluate and investigate the extent and type of contamination in the batch.

In your response, you also describe the **(b)(4)** test as destructive, which you contend "makes the processed **(b)(4)** preparations unsuitable for recovery and further testing." Your response is inadequate. Your protocol for assuring subsequent enumeration and identification when a positive result is obtained by the **(b)(4)** method screening test **(b)(4)** lacks sufficient detail. Among other things, your protocol does not ensure that **(b)(4)** testing adequately evaluates the extent and type of contamination present in the given batch, or that it employs a representative sample of the batch. Furthermore, the protocol does not assure that appropriate investigations of any objectionable batch contamination are performed, including when a preservative might have some efficacy against the given microbe. Lastly, the protocol does not provide for potential speciation of the detected microbial contamination in the **(b)(4)** initial screening test.

In response to this letter, provide the following.

- An improved sampling plan, which includes sufficiently representative samples for each product lot so that you can evaluate intra-batch variation and prevent distribution of lots contaminated with objectionable organisms. This sampling plan should improve detection of microbiological contamination, which is generally non-uniformly distributed throughout a lot, to improve the capacity of your quality control tests to identify objectionable contamination before products are released for use by patients.

- Commit to discontinue any provisions that allow an initial positive **(b)(4)** screening result to be invalidated by a negative **(b)(4)** finding.
- Expand your testing and sampling regimen for further **(b)(4)** evaluation of any positive **(b)(4)** screening **(b)(4)** method result.
- Summarize your global CAPA for the review of specifications, procedures, and standards for all products (e.g., oral, topical) manufactured by your firm.

3. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

Your acceptance criteria included in your bioburden analysis report *(Analysis of In-Process Bioburden/Cleaning Surveillance for* **(b)(4)** *Line* **(b)(4)***)* failed to include *B. cepacia* on the list of objectionable organisms. This is despite the fact that your facility has a history of recurring *B. cepacia* contamination issues and that a 2016 root cause investigation conducted in your facility revealed a biofilm had become established within the Clean-in-Place (CIP) system servicing **(b)(4)** lines **(b)(4)**. Your firm cultured and identified *B. cepacia* within these cleaning samples from the CIP system. This root cause analysis was conducted following the recall of product contaminated with *B. cepacia.*

In response to this letter, provide the following.

- Reassess the adequacy of objectionable organism (including *B. cepacia)* acceptance criteria.
- Comprehensively evaluate the adequacy of cleaning and sanitization processes. Include a CAPA to address any deficiencies observed.

Objectionable Organisms

For further information regarding the significance of *B. cepacia*https://www.fda.gov/Drugs/DrugSafety/ucm559508.htm. and other objectionable contamination of liquid drug products, see FDA's advisory notice posted on May 22, 2017, at

Drugs Made for You by ChemRite

You have engaged ChemRite to manufacture Sage Perox-A-Mint, **(b)(4)**. These products, which you test using the **(b)(4)** method discussed above, are adulterated as enumerated in the preceding violations. They are also adulterated for the reasons set forth in Warning Letter 515029, issued by FDA to ChemRite on June 29, 2017. Among other things, ChemRite manufactured your oral solution drugs using the same equipment in which ChemRite manufactured toxic industrial-grade car washes and waxes. You are responsible for ensuring that all of your products are manufactured in accordance with CGMP, including oversight of the manufacturing operations conducted by your contractor, ChemRite, on your behalf. Contractors are extensions of the manufacturer, and you are required to ensure that your drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements,*

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf.

Consultant

We strongly recommend engaging a consultant to 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.

Conclusion

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

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within fifteen (15) working days. Specify what you have done since our inspection to correct your violations 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.

Please address your reply to:

Russell Riley, Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III
Chicago Office
550 W. Jackson Blvd., Suite 1500
Chicago, IL 60661

Refer to the Unique Identification Number (Case# 520382) when replying. If you have questions regarding the contents of this letter, please contact Russell Riley by phone at (312) 596-4219 or by email at Russell.Riley@fda.hhs.gov.

Sincerely,
/S/
Art O. Czabaniuk
Division Director
Division of Pharmaceutical Operations
III

cc:
Mr. Brad Saar, President
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Stryker Global Headquarters
2825 Airview Boulevard
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