INCELL Corporation LLC 10/28/16

Dallas District Office
4040 N. Central Expressway,
Suite 300
Dallas, Texas 75204

October 28, 2016

2017-DAL-WL-02

WARNING LETTER

UPS OVERNIGHT

Mary P. Moyer, Ph.D.
President & Chief Science Officer
INCELL Corporation, LLC
12734 Cimarron Path
San Antonio, Texas 78249-3424

Dear Dr. Moyer:

You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on May 29, 2015, and again on December 18, 2015. From August 18, 2015 to September 1, 2015, an FDA investigator inspected your facility, INCELL Corporation, 12734 Cimarron Path, San Antonio, Texas 78249-3424. During the inspection, the investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigator observed that your firm does not use sterile disinfectants to disinfect the production areas and does not monitor pressure differentials between the ISO 7 cleanroom and ISO 8 ante room. Furthermore, the FDA investigator found that your firm failed to demonstrate through appropriate studies that your **(b)(4)** was able to provide adequate protection of the ISO 5 area in which sterile products were produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

In addition, the investigator observed that you failed to meet the conditions under section 503B of the FDCA [21 U.S.C. § 353b] necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain requirements under the FDCA. FDA issued a FDA 483, Inspectional Observations, to your firm on September 1, 2015. FDA acknowledges receipt of your firm's responses, dated September 5, 2015, and September 8, 2015. FDA also acknowledges receipt of your correspondences, dated August 24, 2015, and August 28, 2015.

Based on this inspection, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013. Title I of the DQSA, the Compounding Quality Act (CQA), added a new section 503B to the FDCA [21 U.S.C. § 353b]. Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

The FDA investigator noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. Furthermore, the investigator observed significant CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)].

In addition, the investigator observed that your facility failed to meet the conditions of section 503B [21 U.S.C. §353b]. For example, during the inspection, the investigator noted the following:

1. Drugs compounded by your facility are not compounded by or under the direct supervision of a licensed pharmacist [Section 503B(a) of the FDCA [21 U.S.C. §353b(a)]].

2. Your facility's drug products do not include the following information on the product labels: the statement, "Office Use Only." In addition, neither the labels on the drug products nor the container labels list the inactive ingredients, identified by established name and the quantity or proportion of each ingredient [Section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]].

3. Your facility compounds a drug product that is sold by an entity other than your firm, the outsourcing facility that compounded such drug [Section 503B(a)(8) of the FDCA [21 U.S.C § 353b(a)(8)]].

Because your compounded drug products have not met all of the conditions in section 503B, they are not eligible for the exemptions under section 503B from the FDA approval requirements in section 505 of the FDCA [21 U.S.C. § 355], the requirement under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA [21 U.S.C. § 360eee-1].[2]

Furthermore, under section 301(ccc)(1) of the FDCA [21 U.S.C. §331(ccc)(1)], the resale of a compounded drug that is labeled "not for resale" in accordance with section 503B is a prohibited act.

Specific violations are described below.

Adulterated Drug Products

The FDA investigator noted that drug products compounded in your facility that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. For example, your firm does not use sterile disinfectants to disinfect the production areas and does not monitor pressure differentials between the ISO 7 cleanroom and the ISO 8 ante room.

Furthermore, FDA investigators found that your firm failed to demonstrate through appropriate studies that your **(b)(4)** was able to provide adequate protection of the ISO 5 area in which sterile products were processed.

The investigator also noted CGMP violations at your facility, causing your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, but are not limited to, the following:

1. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(iv))

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))

3. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions. (21 CFR 211.42(c)(10)(v))

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act* (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf). This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Misbranded Drug Products

You compound drug products that are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)], and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see, e.g.,* 21 CFR 201.115).

It is a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

C. Corrective Actions

In your September 5, 2015, and September 8, 2015, responses to the FDA 483 you described certain corrective actions taken in response to the observations. Although some of your proposed corrective actions appear adequate, others cannot be evaluated because of a lack of supporting information. For example, we acknowledge that you purchased sterile disinfectants; however, you did not provide an updated procedure that ensures adequate contact time with detailed instructions for use. Your response includes evidence that you hired a contractor to conduct dynamic smoke studies; however, the report does not include adequate details describing the dynamic conditions. In addition, your response does not include appropriate scientific

justification and supporting documentation regarding your alternative media fill testing referred to as “pilot test runs.”

Further, although the label revisions described in your FDA 483 response appear adequate to correct the labeling observation on the FDA 483, for your compounded drug products to qualify for the section 503B exemptions, including the exemption from the requirement that the label bear adequate directions for use (section 502(f)(1)), you should also address your firm’s failure to meet two conditions of section 503B as described above [503B(a) and 503B(a)(8)].

We also note that you compound using a bulk drug substance (dextrose anhydrous) that cannot be used in compounding under section 503B of the FDCA. Specifically, dextrose anhydrous is not on the list of bulk drug substances that can be used in compounding under section 503B of the FDCA, and the drug product you are compounding, **(b)(4)**, is not on the drug shortage list in effect under section 506E of the FDCA [21 U.S.C. §356e]. [Section 503B(a)(2) [21 U.S.C. §353b(a)(2)]].

On June 9, 2016, after FDA’s inspection of your facility, FDA issued a final guidance, *Guidance for Industry Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act,*[4] setting forth the Agency’s interim regulatory policy concerning outsourcing facilities that compound drug products using bulk drug substances that are not eligible for use in compounding under section 503B of the FDCA. Dextrose anhydrous is not eligible for the policy described in this guidance because it was not nominated for the 503B bulk drug substances list. In the future, you should only compound drug products using bulk drug substances that may be used in compounding under section 503B, or that are eligible for the interim regulatory policy described in this guidance.

FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation. You should fully implement necessary corrections in order to ensure that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations 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 ensure that your firm complies with all requirements of federal law, including FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. FDA intends to re-inspect your facility to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. If the corrective actions cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be completed. Your firm's response to this letter should be sent to: Dallas District Office, ATTN: Acting District Director, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204.

If you have any questions about the contents of this letter, please contact: John W. Diehl, Compliance Officer, at 214-253-5288.

Sincerely,
/S/
Karlton Watson
Acting Dallas District Director

CC:
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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] See, e.g., section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].

[3] In addition, the drug you are compounding, **(b)(4)**, may be essentially a copy of an approved drug. Compounded drug products that are essentially a copy of one or more approved drugs are not eligible for the exemptions under section 503B. Section 503B(a)(5) [21 U.S.C. §353b(a)(5)]. We note that there are approved drugs that contain the same active ingredient as your compounded **(b)(4)**. You should ensure that you do not compound any drug products that are essentially a copy of one or more approved drugs. On July 7, 2016, FDA issued a draft guidance, *Compounded Drug Products that are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and*

Cosmetic Act. This draft guidance proposes FDA's policies regarding section 503B(a)(5) of the FDCA. *See* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf.

[4] *See* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf.