UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA	)	**Crim. No.**
	)	
v.	)	**Violation:**
	)	
SB PHARMCO PUERTO RICO, INC.	)	**21 U.S.C. §§ 331(a), 333(a)(2), and**
	)	**351(a)(2)(B) Interstate Shipment**
Defendant	)	**of Adulterated Drugs**
	)	

INFORMATION

The United States Attorney charges that:

I. GENERAL ALLEGATIONS

At all times material to this Information:

The Defendant

1. **SB PHARMCO PUERTO RICO, INC. ("SB PHARMCO")**, was a corporation organized under the laws of the Commonwealth of Puerto Rico with a principal place of business in Cidra, Puerto Rico. **SB PHARMCO** was an indirect subsidiary of GlaxoSmithKline, plc ("GSK"), a British corporation with a principal place of business in Brentford, Middlesex, England, with publicly traded shares on the London Stock Exchange (ticker symbol: GSK) and the New York Stock Exchange (ticker symbol: GSK).

2. **SB PHARMCO** was engaged in, among other things, the manufacture and interstate distribution of prescription drugs intended for human use throughout the United States, including the District of Massachusetts. **SB PHARMCO** owned and operated manufacturing and packaging facilities in Cidra, Puerto Rico.

3. **SB PHARMCO** was dissolved effective July 3, 2008, but continues to exist under operation of law for three years for purposes of litigation, prosecution, and settlement of its affairs.

The FDA and the FDCA

4. The United States Food and Drug Administration ("FDA") was the federal agency responsible for protecting the health and safety of the public by enforcing the Federal Food, Drug, and Cosmetic Act ("FDCA") and ensuring, among other things, that drugs intended for use in humans were safe and effective for their intended uses and that the labeling of such drugs bore true and accurate information. Pursuant to such responsibility, FDA published and administered regulations relating to the approval, manufacture, and distribution of drugs.

5. The FDCA defined drugs as, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man, and articles (other than food) intended to affect the structure of any function of the body of man. 21 U.S.C. §§ 321(g)(1)(B) and (C).

6. Prescription drugs under the FDCA were drugs intended for use in humans which, because of their toxicity or other potentiality for harmful effect, or the method of their use, or the collateral measures necessary to their use, were not safe for use except under the supervision of a practitioner licensed by law to administer such drugs, 21 U.S.C. § 353(b)(1)(A), or drugs limited by the terms of FDA approval to use under the professional supervision of a practitioner licensed by law to administer such drugs, 21 U.S.C. § 353(b)(1)(B).

7. The FDCA prohibited causing the introduction or delivery for introduction into interstate commerce of any drug that was adulterated. 21 U.S.C. § 331(a).

8. Under the FDCA, a drug was deemed adulterated if the methods used in, or the facilities or controls used for, its manufacturing, processing, packing or holding did not conform to or were not operated or administered in conformity with current good manufacturing practice ("cGMP") to assure that such drug met the requirements as to safety and had the identity and strength, and met the quality and purity characteristics, which it purported or was represented to possess. 21 U.S.C. § 351(a)(2)(B).

9. Implementing regulations under the FDCA further defined cGMP required for finished pharmaceuticals, and included, among other specific requirements, the following:

a. *Quality Control Unit.* Drug manufacturers were required to maintain a quality control unit with the responsibility and authority to approve or reject all components, drugs product containers, closures, in-process materials, packaging, material, labeling and drug products and the authority to review production records to assure that no errors had occurred or, if errors had occurred, that they were fully investigated. 21 C.F.R. § 211.22(a) (2003). The quality control unit was to have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product. 21 C.F.R. § 211.22(c) (2003).

b. *Contamination and Product Mix-ups.* Separate or defined areas or such other control systems were required for the firm's operations as necessary to prevent contamination or mixups during the course of packaging and aseptic processing. 21 C.F.R. §§ 211.42(c)(6) and (10) (2003). Packaging and labeling facilities were required to be inspected immediately before use to assure that all drug products were removed from previous operations,

and results of such inspections were required to be documented in the batch records. 21 C.F.R. § 211.130(e) (2003).

c. *Equipment.* Automatic, mechanical or electronic equipment or other types of equipment used in the manufacture, processing, packing or holding of a drug product was required to be of appropriate design to facilitate operations for its intended use. 21 C.F.R. § 211.63 (2003). Equipment was required to be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. 21 C.F.R. § 211.68(a) (2003).

d. *In-Process Testing.* In-process materials were required to be tested for identity, strength, quality and purity as appropriate, and approved or rejected by the quality control unit during the production process, e.g. at commencement or completion of significant phases or after storage for long periods. 21 C.F.R. § 211.110(c) (2003).

e. *Drug Product Testing.* Drug products failing to meet established standards or specifications and any other relevant quality control criteria were required to be rejected, unless satisfactorily reprocessed. 21 C.F.R. § 211.165(f) (2003).

f. *Production and control records.* Drug manufacturers were required to prepare drug product production and control records, and to have those records reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures, before a batch was released or distributed. 21 C.F.R. §§ 211.188 and 192 (2003). Any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications were required to be thoroughly investigated whether or not the batch was already distributed, and the investigation was required to extend to other batches of the same

drug product and other drug products that may have been associated with the specific failure or discrepancy. 21 C.F.R. § 211.192 (2003).

10. As part of its mission to enforce the FDCA and protect the public health, the FDA had the authority to enter and inspect, at reasonable times and within reasonable limits and in a reasonable manner, all establishments where drugs were manufactured, processed, packed or held for introduction into interstate commerce or after shipment in interstate commerce. 21 U.S.C. § 374(a)(1). Upon conclusion of the inspection, the FDA had various options, including among others:

a. *Form 483.* A "Form 483," otherwise known as a "Notice of Inspectional Observations," was issued by the FDA to summarize the cGMP deficiencies observed by the FDA inspectors during a particular inspection.

b. *Warning Letter.* A "Warning Letter" was issued by the FDA to document the agency's conclusion that certain manufactured products were adulterated, and to provide notice that unless sufficient corrective actions were implemented, further regulatory action would be taken without notice.

11. Drug manufacturers had certain duties and responsibilities to notify the FDA of information that might impact on the safety or efficacy of the drugs it manufactured, including among others, the following:

a. *Field Alert Reports.* The manufacturer of a drug subject to an approved new drug application was required to notify FDA in a "Field Alert Report" within three working days of receiving information if the information concerned 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 the drug product to meet the specification established for it under the drug's approved new drug application. 21 C.F.R. § 314.81(b)(1)(ii).

b. *Annual Reports*. The manufacturer of a drug subject to an approved new drug application was required to submit to FDA an annual report with the following information, among other information: (1) a brief summary of significant new information from the previous year that might effect safety, effectiveness or labeling of the drug product, 21 C.F.R. § 314.81(b)(2)(i) (2003); (2) reports of experiences, investigations, studies or tests involving chemical or physical properties, or any other properties of the drug that might affect the FDA's previous conclusions about the safety or effectiveness of the drug product, 21 C.F.R. § 314.81(b)(2)(iv)(a) (2003); and a full description of the manufacturing and controls changes not requiring a supplemental application, listed by date in the order in which they were implemented, 21 C.F.R. § 314.81(b)(2)(iv)(b) (2003).

The Cidra Manufacturing Facility

12. In or about January 2001, following the merger between Glaxo Wellcome and SmithKline Beecham pharmaceutical companies, the **SB PHARMCO** Cidra manufacturing site ("Cidra") became one of GSK's largest manufacturing facilities worldwide and a major supplier of prescription drugs to the United States market. Cidra was a SmithKline Beecham site prior to the merger. Cidra was responsible for making a complex portfolio of drugs, including pills, creams, ointments, and injectables. In addition, GSK designated Cidra to be a new product introduction site for solid dose form products, responsible for moving new compounds from development to commercial production, a technically challenging process.

13. Among other drugs manufactured at Cidra, **SB PHARMCO** made the following drugs for distribution to the United States, including in the District of Massachusetts: Kytril (a sterile injectable anti-nausea medication), Bactroban (a topical anti-infection ointment commonly used to treat skin infections in adults and children), Paxil CR (the controlled release formulation of the popular antidepressant drug, Paxil), and Avandamet (a combination Type II diabetes drug).

14. On or about April 1, 2003, GSK retained a new Site Director for Cidra. In or about July 2003, certain key managers at Cidra resigned as a result of the new Site Director's lack of leadership skills and poor management style. Those managers included, among others, a Quality Assurance Director, the Director of Solids Manufacturing and Packaging, a Manufacturing and Packaging Director, and the Human Resources Director.

15. From in or about April 2003 through September 2004, the Cidra Site Director interfered with the functioning of Cidra's Quality Unit by, for example: ordering all investigative results to be recorded in Spanish to make the results more difficult for GSK Corporate Quality Auditors to review, directing that no investigations into possible process deficiencies be opened without her prior approval, challenging the content of investigative reports prepared by the Quality Unit, and otherwise engaging in inappropriate actions to interfere with the Quality Unit at Cidra.

16. From in or about July 2003 through September 2004, additional managers and other employees at Cidra resigned as a result of the Site Director's interference and management style. Those managers and others employees included, among others, the Packaging Engineering Leader, Validation Manager, Laboratory Manager, Equipment Validation Scientists, Facilities

Validation Scientist, and Computer Validation Scientist. During this time frame, various managers and other employees also complained about the Site Director's interference and management style, including the Director of Quality Assurance and Quality Control, the Director of Compliance, a Quality Manager, and the Human Resource Director. In or about October 2004, the Site Director was removed.

Contaminants in Kytril

17. Kytril was a terminally sterilized injectable anti-nausea medication that was primarily used to treat cancer patients receiving chemotherapy or radiation, and post-surgical patients who experienced nausea. Kytril injection was manufactured at Cidra in the sterile suite. Kytril was manufactured in a Single Dose Vial of 1 ml, and a Multi Dose Vial of 4 ml from which four 1 ml doses could be extracted.

18. As part of the merger between SmithKline Beecham and Glaxo Wellcome, Kytril was divested to another pharmaceutical manufacturer. Under the divestiture agreement, **SB PHARMCO** was required to continue to manufacture Kytril at Cidra until an sNDA to transfer the product was approved.

19. **SB PHARMCO** manufactured Kytril until in or about December 2003, when production was transferred to the acquiring entity.

20. In or about January 2001, following the merger, GSK performed a compliance risk assessment of Cidra and found, among other "high priority" findings, that "[a]wareness needs to be heightened for current and future sterile expectations" and that "[a]septic filling areas had no barrier technology to protect components and point of fill" from contamination. One of the conclusions of the report was that "the aseptic filling area has not been updated with barrier

technology nor has the operation progressed technologically beyond its initial, dated design (circa 1980's)."

21. In or about December 2001, a GSK expert reviewed the Cidra sterile suite and informed **SB PHARMCO** and others that "[f]or the introduction of new or transferring sterile products, the current areas are not appropriate. Detailed improvements will be required which would require a capital project." The expert noted that "[p]resent areas and ways of working would not meet major regulators' (e.g. MCA [European regulators]/FDA) current expectations."

22. On or about July 1, 2002, the FDA issued a Warning Letter to **SB PHARMCO** stating that certain other drug products manufactured at Cidra were adulterated because, among other reasons, **SB PHARMCO** failed to "conduct investigations in a timely manner and to take corrective actions to prevent recurrence." FDA cited as examples delayed investigations involving the water sampling and media fill vials.

23. A follow-up FDA inspection was undertaken in the fall of 2002, and on or about October 9, 2002, the FDA issued a Form 483 observation to **SB PHARMCO** that: "[p]rocedures designed to prevent microbiological contamination of drug products purporting to be sterile were not followed. Specifically, the quality control unit did not assure that adequate systems and controls were in place to monitor sterile areas used to manufacture sterile drug products."

24. On or about April 2, 2003, GSK Global Quality Assurance ("GQA") reviewed regulatory risks at Cidra and identified nine areas of risk required to be controlled to avoid future regulatory enforcement activities. One of the identified risk areas was "sterile manufacturing facility activities and documentation including Kytril Injection." Another identified risk area was

"isolation of objectionable organisms in the water system" and "out of specification events for environmental monitoring of clean equipment."

25. On or about June 13, 2003, **SB PHARMCO** concluded a trend investigation regarding microbial growth in bulk solution in 15 of the 19 Kytril lots manufactured in the first campaign of 2003 at Cidra. The cause was determined to be a bottom outlet flange assembly of glass lined holding tanks that was not disassembled and cleaned, causing microbial growth "TNTC" (too numerous to count). The types of microbial growth included *bacillus cereus, staphylococcus sp., burkholderia cepacia, comamonas testosterone, and stenotrophomonas maltophilia.*

26. From on or about June 23, 2003 until on or about June 27, 2003, GSK GQA audited Cidra against its Quality Management System ("QMS") and found a major deficiency in the sterile manufacturing of Kytril injectable, noting that "[o]perations do not comply with current QMS expectations and a recent campaign has resulted in rejected batches due to high bioburden of bulk solution." QMS auditors concluded that "[c]apital expenditure is necessary to improve current conditions or sterile operations should be discontinued with a sense of urgency."

27. Between in or about April 29, 2003 and May 28, 2003, **SB PHARMCO** released to the company that acquired Kytril for distribution in interstate commerce, including in the District of Massachusetts, certain lots of Kytril that were deemed adulterated because the manufacturing processes and laboratory testing were insufficient to assure the Kytril was of the quality and purity that Kytril was represented to possess.

Contaminants in Bactroban

28. Bactroban was a topical antibiotic primarily used to treat skin infections such as impetigo, in adults and children. Bactroban was manufactured at Cidra both as an ointment and a cream.

29. On or about June 1, 2001, **SB PHARMCO** released Bactroban Ointment Lot 50-1B25 for distribution in interstate commerce even though it was contaminated with *"pseudomonas fluorescens."*

30. On or about November 1, 2001, **SB PHARMCO** issued a Field Alert Report to notify the FDA of the release of the contaminated Bactroban Ointment Lot 50-1B25.

31. On or about February 27, 2002, after additional communications with the FDA regarding the possible health risks of the contaminated Bactroban, **SB PHARMCO** conducted a voluntary recall for Lot 50-1B25.

32. From on or about February 7, 2002 through on or about April 10, 2002, the FDA inspected Cidra.

33. On or about April 10, 2002, the FDA issued a Form 483 to **SB PHARMCO** that noted, among other deficiencies, the following:

> Your Quality Control Unit (QCU) failed to reject drug products not meeting established specifications and quality control criteria. Specifically, your QCU failed to properly review batch records and laboratory analysis reports for Bactroban Ointment lot 50-1B25. Consequently, this batch that was contaminated with *Pseudomonas fluorescens*, an objectionable organism, was released into the market on June 1, 2001. . . .
>
> This oversight was not noticed until Investigation 01-207 was initiated six months later in November 2001 to investigate continuous problems with microbial contamination in Bactroban lots. . . .

> Your firm failed to recognize and evaluate the possible risk of this contamination in a product used to treat impetigo in small children. Your firm did not recall this lot until this issue was brought up during the inspection and a conference call was held with CDER [Center for Drug Evaluation and Research at the FDA].
>
> Your firm failed to investigate and evaluate the reason for recurrent contamination with the organism CDC Group IV c-2 (*Ralstonia paticula*) in Bactroban Ointment and its impact that it might have on the safety and efficacy of Bactroban Ointment. Lots 2901B25, 62-1B25, 84-1B25, 94-1B25 and 105-1B25 were contaminated with this organism and were released and distributed in the market. . . .
>
> Your procedures and actions designed to prevent objectionable microorganisms in drug products not required to be sterile were not effective. . . .

34. In early April 2002, GSK performed a recall investigation at **SB PHARMCO** to determine the root cause of the improper release of the contaminated Bactroban Lot 50-1B25 to market. The audit found that "the final portion of batches were filled as manufacturing operators opened the tank and hand scraped the tank and hopper walls facilitating the filling of the final portion but potentially introducing objectionable organisms as a result of this human intervention," and that a likely cause of the contamination of the Bactroban was that manufacturing operators "could inadvertently introduce the contaminated water into the end of the batch while performing the tank/hopper scrape down." The audit noted that "the practices of disconnecting the chilled water hose from the tank and scraping the tank have been discontinued."

35. On April 23, 2002, GSK responded to the FDA's Form 483 observations and represented in part that **SB PHARMCO** had discontinued "human intervention with holding tanks during filling; the practice of manually scraping the holding tanks during filling; and the practice of disconnecting the hoses supplying the water to the jacket of the holding tanks."

36. In May 2002, as a result of further communications with the FDA, **SB PHARMCO** extended the voluntary recall to five additional lots of Bactroban Ointment that were contaminated with gram-positive organisms that were potentially objectionable.

37. On or about July 1, 2002, the FDA issued a Warning Letter to **SB PHARMCO** stating that certain drug products, including Bactroban Ointment, were adulterated because of the following cGMP violations, among others: (a) failure of the quality control unit to exert its responsibility and authority as required by 21 C.F.R. § 211.22 to reject all drug product that failed to meet the established specifications; and (b) failure to have in place procedures to prevent microbial contamination of products as required by 21 C.F.R. § 211.113, that resulted in release of certain lots of Bactroban to market contaminated with *Pseudomonas fluorescens* and questionable gram-positive organisms.

38. After a new Cidra Site Director was appointed in April 2003, the practice of manually scraping the Bactroban tanks was re-instituted to increase yield of Bactroban ointment, with projected 2003 cost savings of $128,074.

39. In June 2003, the Cidra Site Director's new Director of Manufacturing congratulated the "Semisolids Unit" for salvaging Bactroban that was "being wasted" by the failure to scrape the tanks and hopper, resulting in a reduction of waste from 84 kg to 1.25 kg per lot, an increase in production of 3,343 units, and an increase in output from 88% to 97.7%.

40. On or about October 24, 2003, **SB PHARMCO** released Lot 71-3B25 of Bactroban Ointment for distribution in interstate commerce, including in the District of Massachusetts, despite the fact that the potentially objectionable gram positive organism "*staph spp. not aureus or intermedius*" was identified on equipment used to manufacture the lot.

41. Lot 71-3B25 of Bactroban Ointment was deemed adulterated because the manufacturing processes and laboratory testing procedures were insufficient to assure that the Bactroban was of the strength, identity, quality, and purity that was represented to possess.

Split Tablets in Paxil CR

42. Paxil was a drug used to treat depression, anxiety, and pre-menstrual dysphoric disorder. The controlled release formulation of the drug, Paxil CR, controlled the rate of dissolution and absorption of the active ingredient, Paroxetine, in the body. **SB PHARMCO** manufactured Paxil CR in varying strengths including 12.5 mg, 25 mg, and 37.5 mg strengths.

43. Paxil CR had two layers, one containing the active ingredient ("active layer"), and one containing no active ingredient ("barrier layer").

44. During the manufacturing process, first the active layer was compressed and then the barrier layer was added to the active layer for compression into the final bi-layer tablet. In development at GSK's Crawley plant in the United Kingdom, GSK used a triple-layer press machine to perform these functions.

45. In or about February 2002, **SB PHARMCO** began commercial manufacture of the Paxil CR tablet, the first and only bi-layer tablet manufactured at Cidra. Cidra used three modified single-layer Hata press machines to perform the compression function. The three Hata compression machines used by Cidra were less sensitive in their ability to measure the compression force than the triple-layer press machine GSK used in development.

46. In or about late March and early April 2002, shortly after commercial production began, **SB PHARMCO** observed during packaging that some of the Paxil CR tablets separated between the active layer and the barrier layer. Split tablets contained either only the active layer,

which was absorbed in the body more quickly because of the absence of the controlled release function provided by the barrier layer, or only the barrier layer, which had no active ingredient and no therapeutic benefit for the patient.

47. **SB PHARMCO** classified the split tablet as a "critical defect" which was defined by **SB PHARMCO** as a defect with "a high probability of causing adverse consequences to the patient or consumer, [or] may result in significant deviations in the safety, identity, strength or purity of the product. . . ."

48. On or about April 5, 2002, **SB PHARMCO** completed an investigation of split tablets observed in five different lots of Paxil CR 25 mg and concluded that the most probable cause of the splits was that the compression forces on the active layer in commercial production were slightly higher than the compression forces applied during validation, which could result in the barrier layer not adhering to the active layer. After concluding the investigation, **SB PHARMCO** performed 100 percent visual inspection in an attempt to remove the split tablets, and distributed the five lots.

49. In or about April 2002, **SB PHARMCO** implemented 100 percent visual inspection of all Paxil CR tablets in an attempt to remove split tablets prior to packaging and release of the product to market. As **SB PHARMCO** knew, visual inspection of millions of tablets by human operators was subject to error as a result of the quality of the operator's depth perception, speed of the conveyor belt, and other environmental and human conditions.

50. From in or about December 2002 to February 2003, **SB PHARMCO** conducted a Design of Experiment ("DOE") to determine the cause of the split tablets. The DOE report concluded that "the splitting of CR tablets occurred because the active layer in side A was

compressed using a high pressure, which did not allow a good adhesion of the active layer to the barrier layer." The DOE report recommended, among other things, that **SB PHARMCO** "use lower pressures in the active layer compression process, combined with a load cell that could read those pressures." A load cell was a pressure sensor that detected variations in compression force, and the DOE report concluded that a "load cell of 50 KGF is required to allow the Hata [to] read the low pressures required to control the split situation."

51. Despite its own classification of the split tablet defect as a critical defect, **SB PHARMCO** failed to report the defect or findings of the DOE to the FDA in its 2003 Annual Report, instead informing the FDA that "[n]o significant new information was obtained during this reporting period that might affect the safety, effectiveness, or labeling of Paxil (paroxetine hydrochloride) CR."

52. In or about February 2004, following a series of studies, **SB PHARMCO** instituted manufacturing changes to lower the compression force and to monitor tablet weight, thickness, and hardness during production of the active layer of the 12.5 mg and 25 mg Paxil CR. **SB PHARMCO** did not install the more sensitive load cells on the Hata tablet presses that were necessary to allow the Hata presses to read the lower pressures.

53. After instituting the manufacturing changes, **SB PHARMCO** eliminated visual inspection of the coated 12.5 mg and 25 mg Paxil CR tablets for splits, and substituted statistical inspection. The 37.5 mg tablets continued to undergo 100 percent visual inspection. Statistical inspection involved examination of a sample of 1000 tablets in a batch of approximately 1.5 to 2 million tablets. If no split tablets were found in the sample, the lot was released for packaging and distribution; if splits were found, the lot was 100 percent visually inspected.

54. The change from 100 percent visual to statistical inspection of Paxil CR was a significant change in the manufacturing process, requiring progression and documentation through **SB PHARMCO's** change control process, which included approval by Cidra's Quality Unit. **SB PHARMCO** did not follow the change control process for the implementation of the statistical inspection protocol.

55. Following the change from visual to statistical inspection, **SB PHARMCO** continued to find split tablets of Paxil CR 12.5 mg and 25 mg during packaging, both at Cidra and at GSK's packaging facility in Zebulon, North Carolina, which also packaged Paxil CR for Cidra. Five separate investigations of eight different lots were initiated between April and August 2004 relating to the occurrence of splits in 12.5 and 25 mg tablets after compression. **SB PHARMCO** performed 100 percent visual inspection in an attempt to remove the split tablets and distributed these lots

56. From on or about September 7, 2004 through on or about November 5, 2004, the FDA conducted another inspection of Cidra. The FDA issued a Form 483 to **SB PHARMCO** with the following observation:

> Your firm failed to take adequate corrective and preventive actions to prevent the split tablet defect, classified by your firm as critical defect, in distributed Paxil CR product. Although your process controls include an inspection after the coating process to detect the defect, the defect has been found during the packaging operation of Paxil CR 12.5 tablets and Paxil CR 25 tablets, in approximately 12% and 25% of the batches manufactured/packaged during 2004.
>
> Furthermore, this defect has been found in distributed products and non-distributed products outside GSK-Cidra premises . . . . [providing five examples].

57. During the FDA inspection, on or about September 15, 2004, **SB PHARMCO** re-instituted 100 percent visual inspection of 12.5 and 25 mg Paxil CR tablets.

58. In or about November 2004, **SB PHARMCO** purchased sorting machines to conduct 100 percent automated inspection of the thickness of Paxil CR tablets.

59. Between on or about February 20, 2004 and September 15, 2004, **SB PHARMCO** released certain lots of Paxil CR 12.5 mg and 25 mg tablets for distribution in interstate commerce, including in the District of Massachusetts, that were deemed adulterated because the equipment on which Paxil CR was manufactured was insufficient to ensure that the proper compression force was used on the active layer, and the process controls could not assure that Paxil CR released to market was of the strength, identity, quality and purity that the drug was represented to possess.

Content Uniformity Failures in Avandamet

60. Avandamet was a drug used to treat diabetes. Avandamet was a tablet comprised of two substances blended together in specific amounts. Those substances were rosiglitazone and metformin. Avandamet was made of a small amount of rosiglitazone and a large amount of metformin (e.g. one strength of Avandamet was 1 mg of rosiglitazone and 500 mg of metformin, known as the "1/500 mg" strength).

61. To properly manufacture Avandamet, a homogenous blend of rosiglitazone and metformin was required to ensure all tablets were comprised of the proper blend of the two substances, referred to as "content uniformity." To achieve content uniformity, the rosiglitazone and the metformin were subjected to a granulation process (much like sifting flour to make a cake). Cidra used a wet granulation process that involved adding liquid solution to the powders to achieve the correct density so that a homogenous blend of the two drug substances could be obtained.

62. Commercial production of the 1/500 mg, 2/500 mg and 4/500 mg strengths of Avandamet commenced at Cidra in October 2002. Avandamet was manufactured, in part, in granulation areas known as the Niro 200 suite and the Niro 300 suite at Cidra.

63. In the first few months of production, certain batches of Avandamet failed content uniformity tests. A failed content uniformity test related to rosiglitazone meant that the batch was out-of-specification ("OOS") and contained sub-potent or super-potent tablets.

64. In or about February 2003, one of the GSK GQA auditors commented in connection with a proposed internal mock pre-approval inspection for production of the 2/1000 and 4/1000 mg strengths of Avandamet that "there are many investigations now for content of the 1/500 mg tablet."

65. In or about April 2003, GSK GQA performed the mock pre-approval inspection for the 2/1000 and 4/1000 mg tablets and observed one "Priority 1" finding, which was a finding that "may result in the regulatory agency not having sufficient confidence in process/facility/quality systems/people to allow them to approve the facility as a manufacturer." The Priority 1 finding was "[t]he Niro Fluid Bed Dryer malfunctioned allowing inconsistent drying of the granulation used in Avandamet 1-gram qualification batch, commercial Avandamet 500 mg tablets and commercial Avandia tablets."

66. In or about November 2003, **SB PHARMCO's** sister site in Aranda, Spain complained of defects in tablets received from Cidra, including out-of-specification [i.e. content uniformity failures] tablets.

67. From in or about October 2003 to December 2003, the FDA conducted an inspection of Cidra, and issued Form 483 findings to **SB PHARMCO** that observed the following deficiencies, among others:

a. *Failure to question process.* "The following investigations related to OOS (assay/content uniformity and/or dissolution) obtained for Avandamet have not been questioned in terms of the adequacy of the process for Avandamet tablets . . ."

b. *Failure to take corrective action:* "Failure to take appropriate action against all lots that may be affected by a conclusion included as the assignable cause of a failing result . . . . Although your conclusion assigns as the most probable cause the use of common Rosiglitazone concentrate . . . not all lots using this same granulation concentration were rejected . . . . Furthermore, no action has been taken against any batch that may have been released to the market for distribution."

c. *Inadequate investigations:* "Your 2003 OOS manufacturing investigations related to assay, content uniformity and/or dissolution OOS, obtained for batches of Avandamet . . . are inadequate in that none of these investigations have questioned the adequacy of the process validation used to determine that your manufacturing process is robust and reproducible. Furthermore, your investigations related to these and other failures are not completed in a timely manner . . . ."

68. The FDA conducted another inspection of Cidra from on or about September 7, 2004 through November 15, 2004, and observed continuing deficiencies regarding the Avandamet manufacturing process:

> Since July 2004, your firm has obtained about nine (9) out-of-specification (OOS) results in the content uniformity test for Avandamet as follows [listing lots]. As of November 5, 2004, your firm had not determined the root cause for the failures; if all the OOS results were related to each other; and how to correct the problem. . . . The impact in other lots that used the same in-process materials and obtained passing finished testing results has not been determined. . . .
>
> Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product. Specifically, lot #323-4A67 was recommended for rejection on 9/28/04 due to OOS results for content uniformity test for the Rosiglitazone

> active ingredient. At the closing of the investigation, your firm had not determined the assignable cause for the failure. Twenty seven (27) other lots of Avandamet were manufactured using one or more of this lot's granulations and blends. . . . These lots were not included in the investigation and twenty six (26) of them were released and distributed. There is no assurance that the other lots manufactured under the same manufacturing conditions of the failing lots will have the strength, quality and purity they represent to possess.

69. In early 2005, GSK sent above-site experts to Cidra to determine the root cause of the content uniformity failures regarding Avandamet. Those experts concluded that: (a) a humidity sensor in a Fluid Bed Dryer in the Niro 300 suite had been improperly calibrated for an unknown amount of time, resulting in inappropriate drying times and a shift in granulation moisture content that resulted in poor blending of the metformin; and (b) a spacer or washer had been inserted in the milling machine in the Niro 200 suite that was used to produce rosiglitazone granules, resulting in some over-sized granules of rosiglitazone being used in the final product.

70. Between in or about March 2003 and October 2004, **SB PHARMCO** released certain lots of Avandamet for distribution in interstate commerce, including in the District of Massachusetts, that were deemed adulterated because the manufacturing processes and laboratory testing procedures were insufficient to assure that the Avandamet was of the strength, identity, quality and purity that Avandamet was represented to possess.

Product Mix-Ups

71. During 2002, eight Field Alert Reports were filed with the FDA regarding complaints of product commingling from patients, pharmacies, and hospitals, and nine internal investigations were initiated based on line clearance problems that raised concerns of possible product mix-ups at Cidra.

72. On or about April 2, 2003, a GSK GQA auditor summarized the compliance risks at Cidra against QMS and informed **SB PHARMCO** and others that one of the areas of high risk was product mix-ups and commingling of product.

73. On or about December 2, 2003, the FDA informed **SB PHARMCO** in Form 483 observations:

> Your firm fails to have appropriate procedures and controls in place to prevent mix-ups and/or adverse effects to product from occurring during the manufacturing/packaging process. Furthermore, batches are released by your Quality Unit for distribution although you are aware of findings of mix-ups prior to these batches being released to market.
>
> Product mix-up incidents have been repeatedly occurred [sic] since year 2001 through 2003. Products mentioned in the above examples were approved and released for distribution. Furthermore, complaints related to product mix-ups have been received since year 2001-2003 (period covered during the EI). Nevertheless, you have informed the FDA through FARs [Field Alert Reports] and previous and the current inspection that all incidents are isolated and not related to your manufacturing operation.

74. From in or about at least January 2004 until in or about October 2004, the Cidra Site Director collected rogue tablets from the manufacturing areas and packaging lines, kept them in a gowning hat in her office, and failed to alert site and above-site quality personnel.

75. On or about November 20, 2004, the FDA informed **SB PHARMCO** in Form 483 observations that:

> Procedures for the cleaning and maintenance of equipment are deficient regarding inspection of the equipment for cleanliness immediately before use. Specifically, line clearance's procedures and controls are not appropriate to prevent mix-ups during the manufacturing/packaging processes. The following line clearance's related incidents occurred at the firm during the period of January-August 2004 in products that were released . . . [listing eight separate instances].
>
> About three (3) complaints related to product packaging/mix-ups have been received since 12/2003 that could be related to batches manufactured/packaged within the same period of time and/or the same area of the complaint's lots.

> However, your firm relied on the adequacy of cleaning and line clearance's controls to conclude that it was unlikely that the situation was originated within the packaging area at GSK-Cidra. There is no assurance that adequate controls are in place as to prevent mix-ups during your manufacturing operations . . . .
>
> The responsibilities and procedures applicable to the quality control unit are not fully followed. Specifically, your Quality Unit failed to conduct a thorough investigation of all the events associated with line clearance to prevent mix-ups during the manufacturing/packaging process according to your written procedures. . . . [citing two examples in 10/2004].

76. In or about August 2003, **SB PHARMCO** released Lot 161-3P07 of Paxil CR which contained commingled dosages of Paxil CR for distribution in interstate commerce, including in the District of Massachusetts, which was adulterated because the manufacturing and packing processes were insufficient to assure that the Paxil CR was of the strength, identity, quality and purity that it was represented to possess.

COUNT 1

(21 U.S.C. §§ 331(a), 333(a)(2), 351(a)(2)(B) - Interstate Shipment of Adulterated Drugs)

77. The allegations of paragraphs 1 through 76 are realleged and incorporated herein by reference.

78. Between in or about March 2003 and in or about October 2004, in the District of Massachusetts and elsewhere,

SB PHARMCO PUERTO RICO, INC.

defendant herein, did, with intent to defraud and mislead, cause to be introduced and delivered for introduction into interstate commerce quantities of drugs – to wit Kytril, Bactroban, Paxil CR and Avandamet – that were adulterated in that the methods used in, and the controls used for, drug manufacturing, processing, packing and holding did not conform to and were not operated and administered in conformity with current good manufacturing practices.

All in violation of Title 21, United States Code, Sections 331(a), 333(a)(2) and 351(a)(2)(B).

FORFEITURE ALLEGATIONS

1. Upon conviction of a violation of Title 21, United States Code, Section 331(a),

SB PHARMCO PUERTO RICO, INC.

shall forfeit to the United States pursuant to Title 21, United States Code, Section 334 and Title 28, United States Code, Section 2461(c) any quantities of Paxil CR, Avandamet, Kytril and Bactroban which were introduced into interstate commerce in violation of Title 21, United States Code, Section 331 and/or 351(a)(2)(b);

2. If any of the property subject to forfeiture, as a result of any act or omission of the defendant:

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the Court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 21, United States Code, Section 853(p), incorporated by reference in Title 28, United States Code, Section 2461(c), to seek forfeiture of any other property of the defendant up to the value of the property subject to forfeiture.

All pursuant to Title 21, United States Code, Sections 334 and 853 and Title 28, United States Code, Section 2461(c), and Rule 32.2 of the Federal Rules of Criminal Procedure.

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