

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

6th & Kipling St. (P.O. Box 25087)  
Denver, CO 80225-0087  
(303) 236-3000 Fax: (303) 236-3100  
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

04/19/2011 - 05/06/2011

FEI NUMBER

1717759

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Gaspar A. Zunga, Vice President of Technical Operations

FIRM NAME

Sandoz Incorporated

STREET ADDRESS

2555 West Midway Boulevard

CITY, STATE, ZIP CODE, COUNTRY

Broomfield, CO 80020-1632

TYPE ESTABLISHMENT INSPECTED

Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

(b) (4) blenders, (b) (4) were used interchangeably for the production of Triamterene and Hydrochlorothiazide (50/25) Capsules between 1998-2007. Blenders (b) (4) are identical in the (b) (4) construction. Blender (b) (4) was used for the process validation of Triamterene and Hydrochlorothiazide (50/25) Capsules. Blender (b) (4) was equipped with a (b) (4) which was removed for the production of Triamterene and Hydrochlorothiazide (50/25) Capsules, leaving (b) (4)

(b) (4) The average finished product dissolution history documented a downward trend for Triamterene and Hydrochlorothiazide (50/25) Capsules per deviation #10-0065, dated 02/11/2010, and was attributed by the firm as being "directly associated with the use of blender (b) (4) based on review of product history." "It is suspected that the blending of in-process material is optimized with the use of blender (b) (4) which does not have the (b) (4) In 2007, blender (b) (4) was removed from service. Blender (b) (4) were used interchangeably between 1998-2007 without any form of process validation for the production of Triamterene and Hydrochlorothiazide (50/25) Capsules with blender (b) (4)

Currently manufactured products blended with blenders that were not validated for the product during process validation include:

Product	Blender # for Validation	Blender # for current Commercial Use

EMPLOYEE(S) SIGNATURE

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OF THIS PAGE

Erika V. Butler, Investigator  
Kimberley A. Hoefen, Investigator  
Zachery L. Miller, Investigator

*Erika V. Butler*  
*Kimberley A. Hoefen*  
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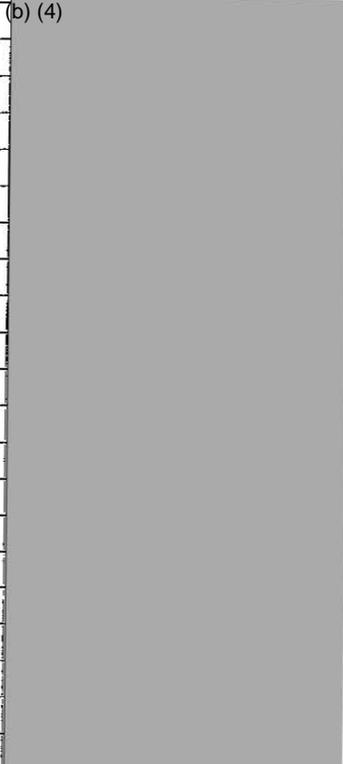
CITY, STATE, ZIP CODE, COUNTRY

Broomfield, CO 80020-1632

TYPE ESTABLISHMENT INSPECTED

Drug Manufacturer

Amitriptyline 10
Amitriptyline 100
Amitriptyline 75
Chlorpromazine 100
Chlorpromazine 25
Chlorpromazine 50
Desipramine 50
Diclofenac 50
Fluoxetine 20 Cap
Fluoxetine 40 Cap
Furosemide 40
Furosemide 80
Glipizide 5
Hydroxychloroquine 200
Meclizine 12.5
Meclizine 12.5
Promethazine 25
Terazosin 5 Cap
Triam/Hctz 50/25
Trifluoperazine 10
Trifluoperazine 5



(b) (4)

This is a repeat observation from the 5/28/2010 FDA inspection.

OBSERVATION 2

Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Specifically,

14 out of 79 (18%) laboratory investigations (LBINV) lacked documentation of an investigation into other batches or products or the establishment of a corrective action:

a) In-process specification for blend uniformity was not met for validated processes, including:

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	Erika V. Butler, Investigator <i>Erika V. Butler</i> Kimberley A. Hoefen, Investigator <i>chBH</i> Zachery L. Miller, Investigator <i>Zachery L. Miller</i>	05/06/2011

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Drug Manufacturer

Product	Lot #	OOS #	Distributed
Fluoxetine 10 mg Capsules	182763	LBINV#09-0046 Blend Uniformity on 01/28/2009	Yes
Fluoxetine 10 mg Capsules	184007	LBINV#09-0224 Blend Uniformity on 04/30/2009	Yes
Fluoxetine 10 mg Capsules	196304 196842	LBINV#10-0268 Blend Uniformity on 06/09/2010	Yes
Fluoxetine 10 mg Capsules	085551	LBINV#09-0282 Blend Uniformity On 06/15/2009	Yes
Fluoxetine 10 mg Capsules	178361	LBINV#08-0430 Blend Uniformity on 09/22/2008	Yes
Fluoxetine 10 mg Capsules	189623	LBINV#09-0568 Blend Uniformity on 10/09/2009	Yes
Cetirizine 5 mg/Pseudoephedrine Hydrochloride 120 mg extended release Tablets	195904	LBINV#10-0417 Blend Uniformity On 09/13/2010	Yes
Nadolol 20 mg Tablets	203298 203299	LBINV-10-0477 Blend Uniformity on 10/19/2010	Yes

EMPLOYEE(S) SIGNATURE

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Kimberley A. Hoefen, Investigator  
Zachery L. Miller, Investigator

*Erika V. Butler*

*K.A.H.*

*Zachery L. Miller*

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b) API identity (b) (4) out of specifications for (b) (4) (b) (4) on 03/15/2011 and finished product related compound (b) (4) (b) (4) on 12/07/2011 were rerun without the establishment of root cause or corrective actions.

c) The purified water in the laboratory failed specification for microbiology testing on 02/07/2011 for water sampling point (b) (4) on 02/14/2011 for water sampling point (b) (4) on 02/22/2011 for water sampling point (b) (4) and on 03/07/2011 for water sampling point (b) (4). The laboratory investigation stated that "the assignable cause is biological contamination due to stagnation of water in a non-circulating branch of the water system." "Laboratory water is not a product ingredient and does not affect product quality." Each time the problem was fixed with flushing of the system and retesting. Investigations were not performed on any impact the purified water might have had on the laboratory tests performed between the previous check and the one that was out of specification.

This is a repeat observation from the 5/28/2010 FDA inspection.

**OBSERVATION 3**

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically,

- a) On 6/30/2010, a report was received from your contract packager that black specks were observed on tablets while blister packaging Loratadine 10 mg batches 195524, 195525 and 195529. Your investigation found an "excess amount of the active" present in the extracted dark particles. The Quality Assurance evaluation concluded the dark spots are characteristic of the material and closed the investigation on 7/9/2010. There was no investigation as to the potency or purity of the speckled tablets or if they would pose harm to the consumer. The finished product lots were released and distributed.
- b) On 04/19/2011, the (b) (4) located in suite (b) (4) was "On Hold" as noted in the Equipment/Room Use and Cleaning Log for "On hold for rust and paint bubble. Previously (b) (4) An investigation was not performed to evaluate any impact on previously run drug products.

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**OBSERVATION 4**

Equipment and utensils are not cleaned and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

Equipment was observed not clean and in sanitary condition. Below is a list of the unclean equipment observed:

Room #/ Location	Observed	Status
b) (4)	Observed a thick build-up of white and yellow residue adhering to an Axial Fan located inside the tablet press. The fan blows air into the tableting chamber and is located directly above tablet tooling, where powder is pressed into tablets.	Complete Clean accomplished and verified, equipment is on hold status.
	Observed a thick build-up of pink coating material adhered to a light frame. The light frame is located directly above the porous coating pan in the product pathway.	Complete Clean accomplished and verified, ready to use. Diclofenac 75 mg Tablets, Batch (b) (4) was coated prior to the complete clean.
	Observed a thick (approximate 1 inch) build-up of pink coating material adhering to the exhaust bypass valves. Exhaust valve is located within the confines of the porous coating pan.	Complete Clean accomplished and verified, ready to use. Diclofenac 75 mg Tablets, Batch (b) (4) was coated prior to the complete clean.
	Observed Kettle (b) (4) and a parts cart had incorrect status labeling, indicating "in-process" instead of the "complete clean" performed status.	Room labeled "Complete Clean," on 4/25/11.
	Observed a cleaned processing hose return line stored on the floor after "complete clean" had been performed. Hose transfers coating material from mixer into the tablet coater	
	Observed a dirty cloth wipe underneath the tablet coater after the room had been labeled, "complete clean."	

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**OBSERVATION 5**

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically,

On 12/29/2010, your firm received a complaint from a pharmacist who reported finding a Methazolamide 50 mg tablet (batch number 191103) that appeared to look "twice as large as the others." Your investigation found the tablet weighed (b) (4) heavier than the targeted tablet weight of (b) (4). This exceeded your upper specification limit of (b) (4) grams. The FDA Denver District was not notified of this out of specification.

**OBSERVATION 6**

Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information.

Specifically,

Since 10/2008 until 04/15/2010, there were 6082 Serious and Unlisted Adverse Drug Experience Alert Reports submitted to FDA by your firm, of which 116 were not submitted in a timely manner. For example the following is a list of ADE reports submitted past the 15 day time frame:

Case Number	Product	Day Submitted to FDA	Manufacture Receipt date of ADE	Number of days Late to FDA
GXKR2009GB12154	Citalopram/Lamotrigine	1/11/2010	11/4/2009	53
CHNY2008GB01114	Ibuprofen	3/19/2010	3/3/2008	731
GXKR2009GB07550	Omeprazole	3/30/2010	7/1/2009	257
GXKR2010US10030	Carisoprodol	10/25/2010	9/3/2010	37

This is a repeat observation from the 10/08/2008 FDA inspection.

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Broomfield, CO 80020-1632	Drug Manufacturer

**OBSERVATION 7**

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its cleaning and maintenance.

Specifically, observed the following equipment not maintained.

Equipment:	Observed:	Status:
(b) (4)	Observed too numerous to count gouges/dents throughout the mixer, impeller blade, and chopper.	Complete Clean accomplished and verified, ready for use.
	Observed metal filters in disrepair, jagged strands protruding from filtering surface.	Complete Clean accomplished and verified. Previously run product was Orphenadrine, lot# (b) (4)

This is a repeat observation from the 5/28/2010 FDA inspection.

**OBSERVATION 8**

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically,  
Multiple production rooms were observed not clean and in sanitary condition after a "Complete Clean" was accomplished and verified, including:

Room #/Location:	Observed:	Status:
(b) (4)	Observed a used pipe seal, and piece a paper approximately 2 X 2 inches located underneath a vertical mixer after complete clean.	Room labeled "Complete Clean," on 4/25/11.
	Observed a pool of standing water on the floor, directly under mixer and below mixer outlet, contained within an approximate 2 X 2 foot floor stain.	
(b) (4)	Observed a nest of plastic and cardboard packaging debris underneath a (b) (4) scale.	Room labeled, "Complete Clean," on

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TYPE ESTABLISHMENT INSPECTED

Drug Manufacturer

components - cleaned weekly.

4/26/11.

(b) (4)

Observed plastic packaging debris throughout.

Room labeled,  
"Complete Clean," on  
4/26/11.

Observed clumped debris (approximate 1/2 inch in size)  
along NE corner of room.

Observed a dirt/rust type substance, covering a 2 inch  
square surface on the floor, in the NE corner of room.

OBSERVATION 9

Deviations from written laboratory mechanisms are not recorded.

Specifically,

Standards requiring storage at (b) (4) temperature were not documented to be returned on the day of analysis between 2010-2010.

Standard	Standard Name	Date Taken	Date Returned
(b) (4)		09/30/2010	Not listed
		10/07/2010	Not listed
		10/22/2010	Not listed
		11/29/2010	Not listed
		11/29/2010	Not listed
		11/29/2010	Not listed
		12/01/2010	Not listed
		12/01/2010	Not listed
		12/16/2010	Not listed
		12/16/2010	Not listed
		01/11/2011	Not listed
		01/20/2011	Not listed
		02/15/2011	Not listed
		02/15/2011	Not listed
		02/24/2011	Not listed
		02/21/2011	04/18/2011

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Erika V. Butler, Investigator  
Kimberley A. Hoefen, Investigator  
Zachery L. Miller, Investigator

*Erika V. Butler*

KLH

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b) (4)	02/24/2011	Not listed
	03/03/2011	Not listed
	03/14/2011	Not listed
	04/07/2011	Not listed
	04/13/2011	04/14/2011

OBSERVATION 10

Established laboratory control mechanisms are not followed.

Specifically,  
SOP MATA008 "Laboratory Reference Standards", revision 09, validity date 08/30/2010, was not followed in that there was no documentation for:

b) (4)

OBSERVATION 11

There is a lack of rotation so that the oldest approved stock of components is used first.

Specifically,  
For at least two productions of metformin tablets (b) (4), multiple older lots of metformin API (b) (4) were available for use and a newer lot of API (b) (4) was selected by warehouse personnel to send to production.

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