

Counterfeit Drugs – An FDA Perspective



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Forensic Chemistry Center

- Forensic casework serving FDA's Office of Criminal Investigations (OCI)
- Laboratory support in traditional FDA investigations as needed
- Research and method development related to product tampering, counterterrorism, counterfeiting, and fraud
- National and international public health emergencies
- Provide assistance to other regulatory and law enforcement agencies as needed



FCC Casework

Chemical Contamination/Product Tampering/Terrorism

Unintentional vs. Intentional (includes economic adulteration)

Develop supporting evidence

Method development and research

Counterfeit Foods and Pharmaceuticals

Finished dosage and API

Establish physical and chemical profiles

Differentiate by lot, manufacturer, etc.

Unapproved Drugs

Dietary supplements

Identification and quantitation

Our Customers

FDA District Offices and Field Laboratories

FDA Office of Criminal Investigations (OCI)

FDA Centers (CFSAN, CDER, CBER, CVM, CDRH, CTP)

Federal Bureau of Investigation

Customs and Border Patrol

Drug Enforcement Agency

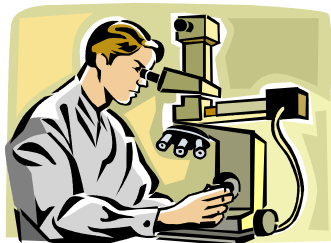
Other federal government agencies

Numerous state and local law enforcement officials



FCC – What We Do

Microscopy



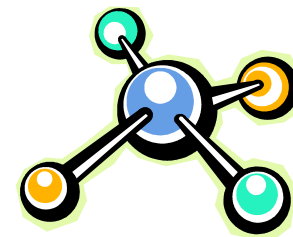
Chromatography



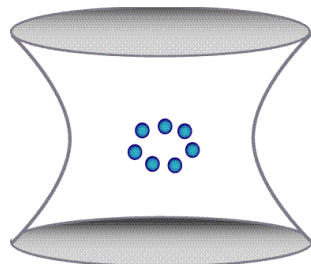
Elemental
Analysis



Molecular
Spectroscopy



Mass
Spectrometry



Microbiology and
Molecular Biology





Counterfeit Pharmaceuticals



Sample Sources

- Websites
- Undercover purchases
- Intercepted packages
- Consumer complaints
- Pharmacies

Imported teddy bear...



...stuffed with counterfeit Viagra



What are we requested to do?

- Determine the presence of active ingredient(s)
- Determine whether the product is consistent with authentic
- Determine whether the product is similar to other submissions

Requests to Manufacturers

- Drug substance
- Finished Product
- Methodology
- Formulation
- Packaging

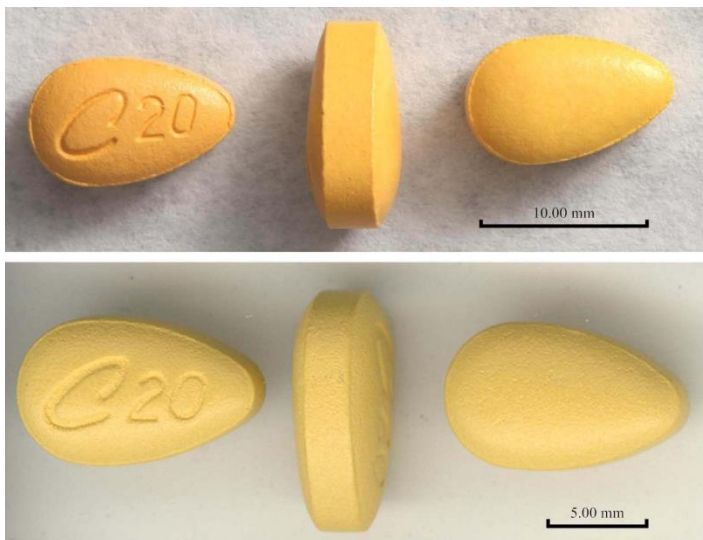
Counterfeit Analysis

- Typical Analyses
 - Physical measurements (dosage unit weights, dimensions)
 - Image/imprint analysis
 - Determination of print processes
 - FT-IR of tablet coating/core, capsule shell/contents
 - ID of active using GC-MS, LC-MS, etc.
 - Determination of residual solvents using headspace GC-MS
 - Quantitation of API using HPLC-UV
 - Formulation (injectables) – GC-MS, ion chromatography, ICP-MS

Counterfeit Analysis

Preliminary Analysis

- Finished dosage and API
- Compare to authentic product and packaging



Counterfeit Detection Device Version 3 (CD3)

Description:

A handheld portable device used in the detection of counterfeit or adulterated products and packaging. The light source of the device emits different wavelengths of light onto a sample.

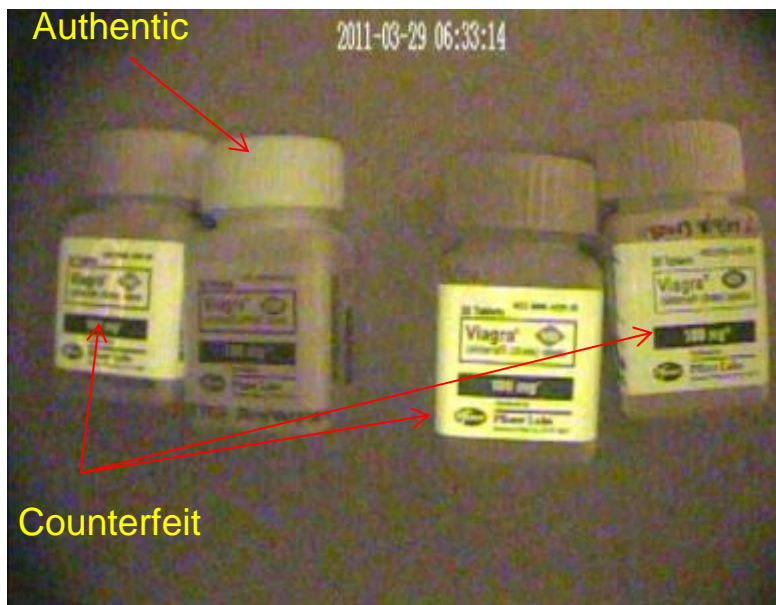


Features:

- Excellent inks/dyes/pigments discriminator
- Non-destructive imaging technique
- Sample is preserved for subsequent physical or chemical analysis

UV-Vis Imaging of Packaging

(Use of visible range imaging)



Infrared Imaging

(Use of visible and infrared range imaging)

Label Revealing



Note: top label and bottom label are different

CD3 Real Time Scan

(captured images of counterfeit versus authentic finished dosages)



**Zyprexa
10 mg**

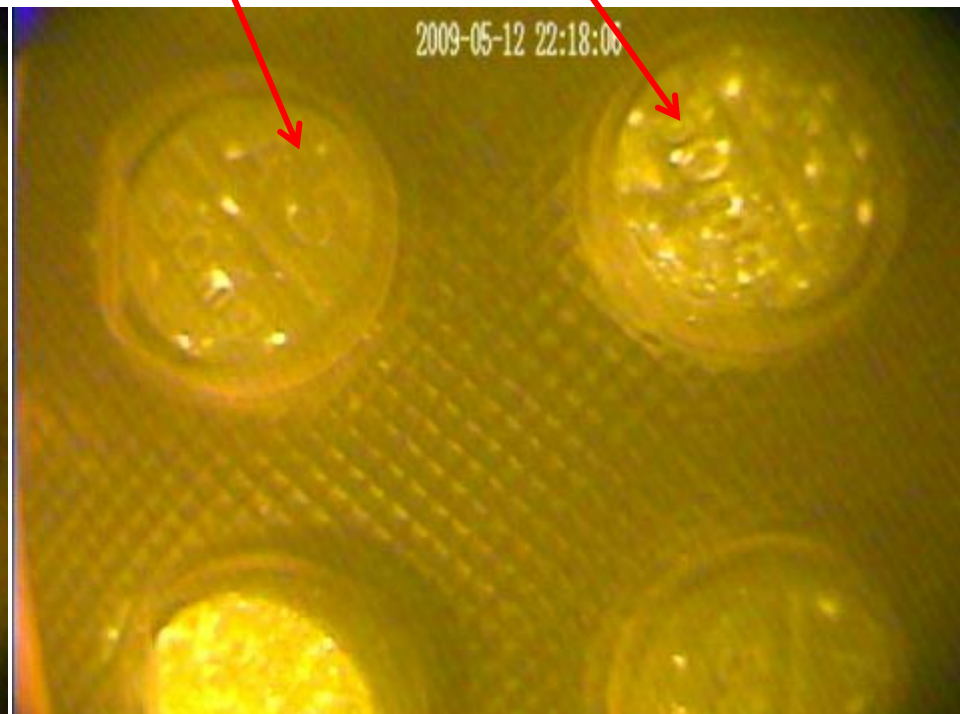
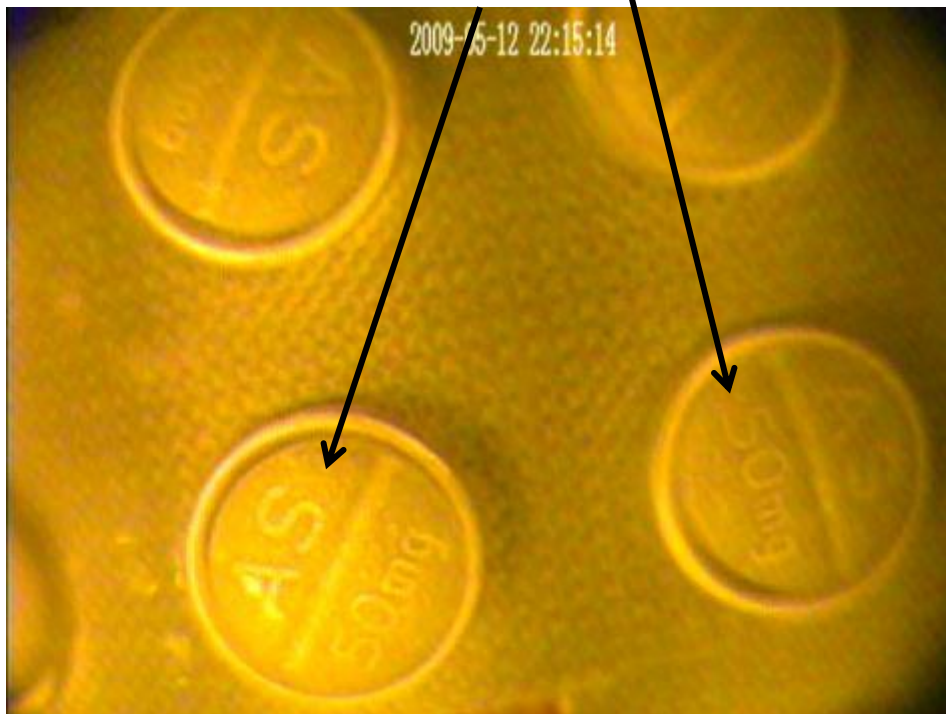


CD3 on Anti-malarial Drug Products

(UV-Vis-IR Modes on white tablets through blister-packs)

Authentic tablets show distinct debossing patterns and homogeneous quality of excipient

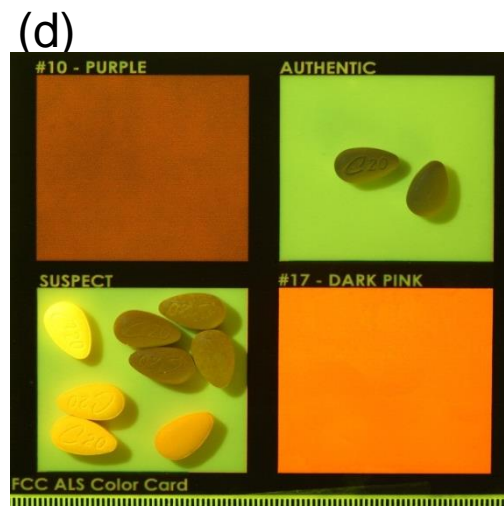
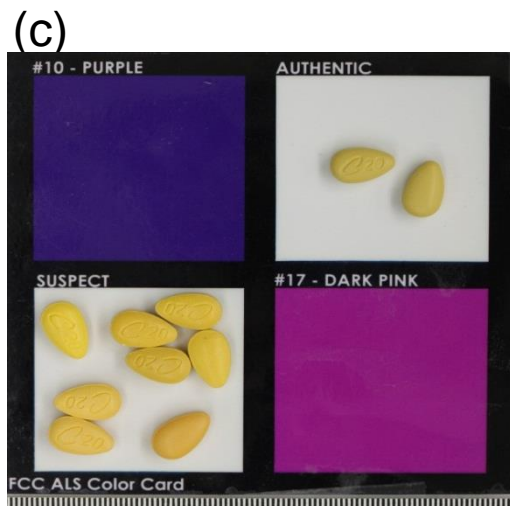
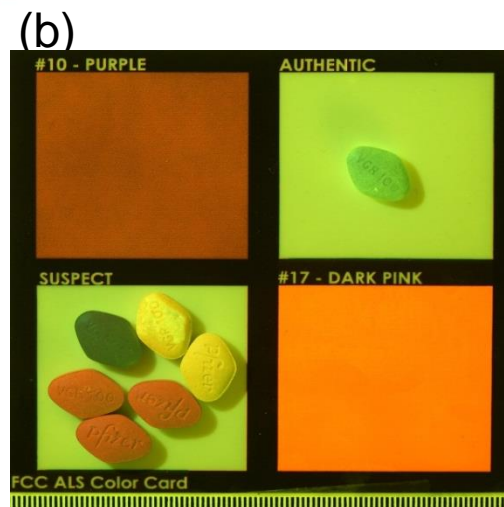
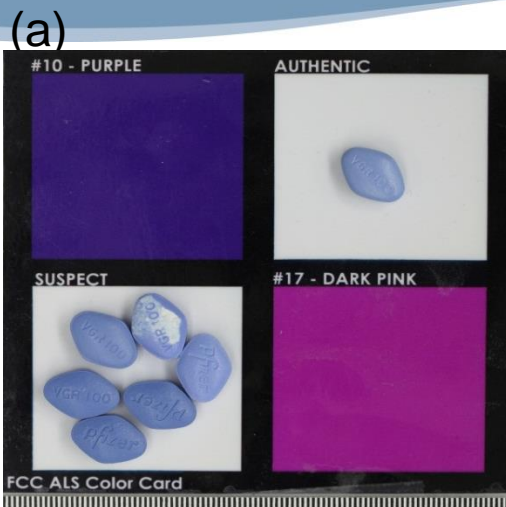
Counterfeit tablets show poor debossing patterns and heterogeneous quality of excipient



Suspect

Authentic





Normal/white light (a, c) and 455 nm visible light with a yellow filter (b, d) images of suspect Viagra 100 mg tablets (a, b) and suspect Cialis 20 mg tablets (c, d).

Image Analysis





Authentic



Suspect w/ poor debossing & thicker bevel

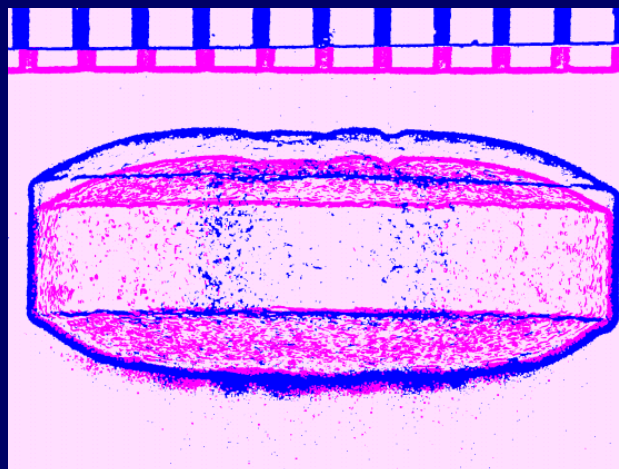
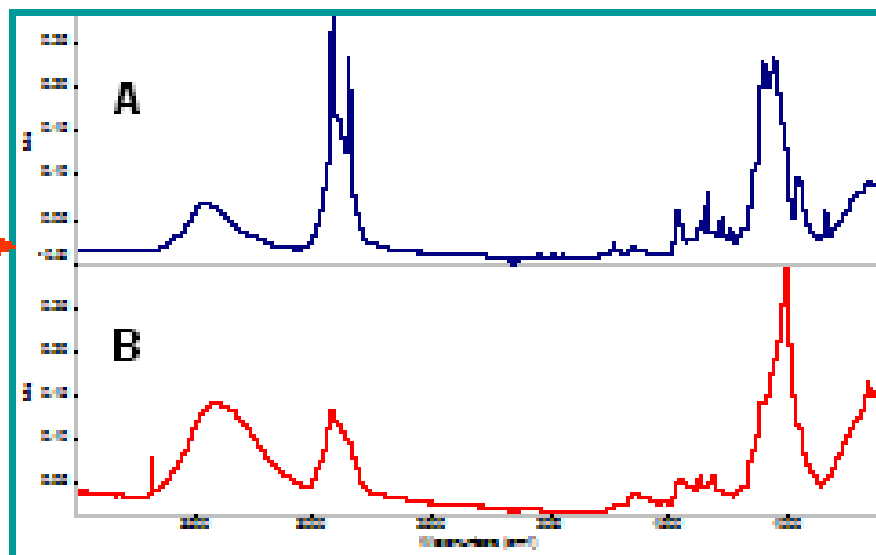
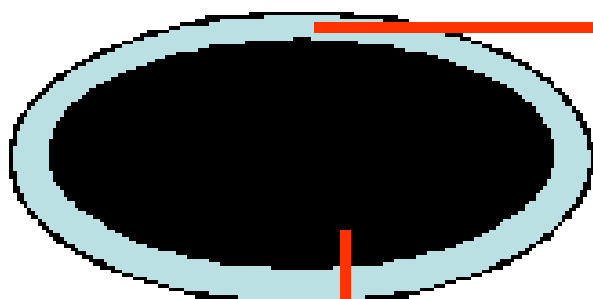


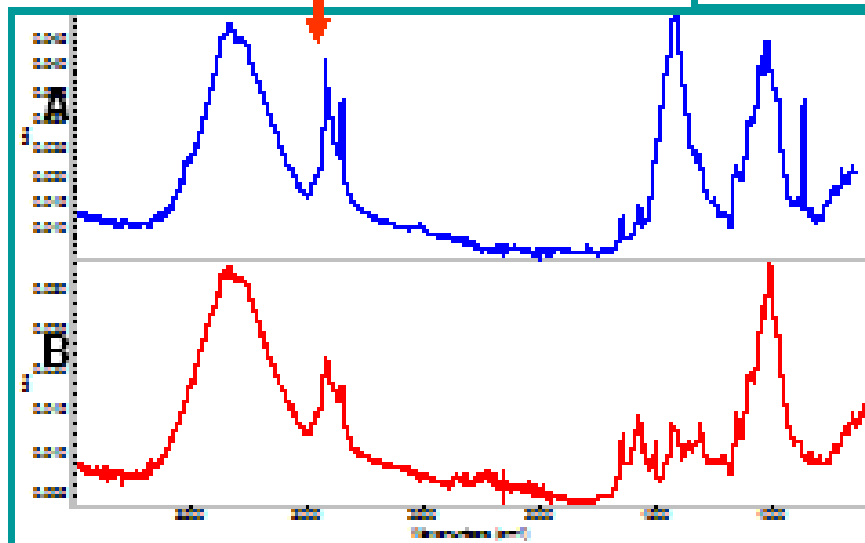
Image overlay of lateral view of both tablets - Suspect vs Authentic

FT-IR Analysis

Advantage: Complete "snapshot" of product can be obtained



(A) Authentic tablet coating
(B) Suspect counterfeit coating



(A) Authentic tablet core
(B) Suspect counterfeit tablet core.

Diazepam

Suspect Valium



U.S. market Valium



Foreign market Valium



First submission:

Contained 3 mg diazepam, not 10 mg

Diazepam

Suspect Valium



U.S. market Valium



Foreign market Valium



Second submission:

Contained acetaminophen and melatonin

Suspect alprazolam



- Imprints indicate it should contain 2 mg alprazolam
- Analyzed using GC-MS

Suspect alprazolam



- First submission: diazepam

Suspect alprazolam



- First submission: diazepam
- Second submission: chlorpheniramine and dextromethorphan

Suspect alprazolam



- First submission: diazepam
- Second submission: chlorpheniramine and dextromethorphan
- Third submission: diazepam, acetaminophen and chloramphenicol

Schedule II controlled substances



Declared: Acetaminophen,
hydrocodone

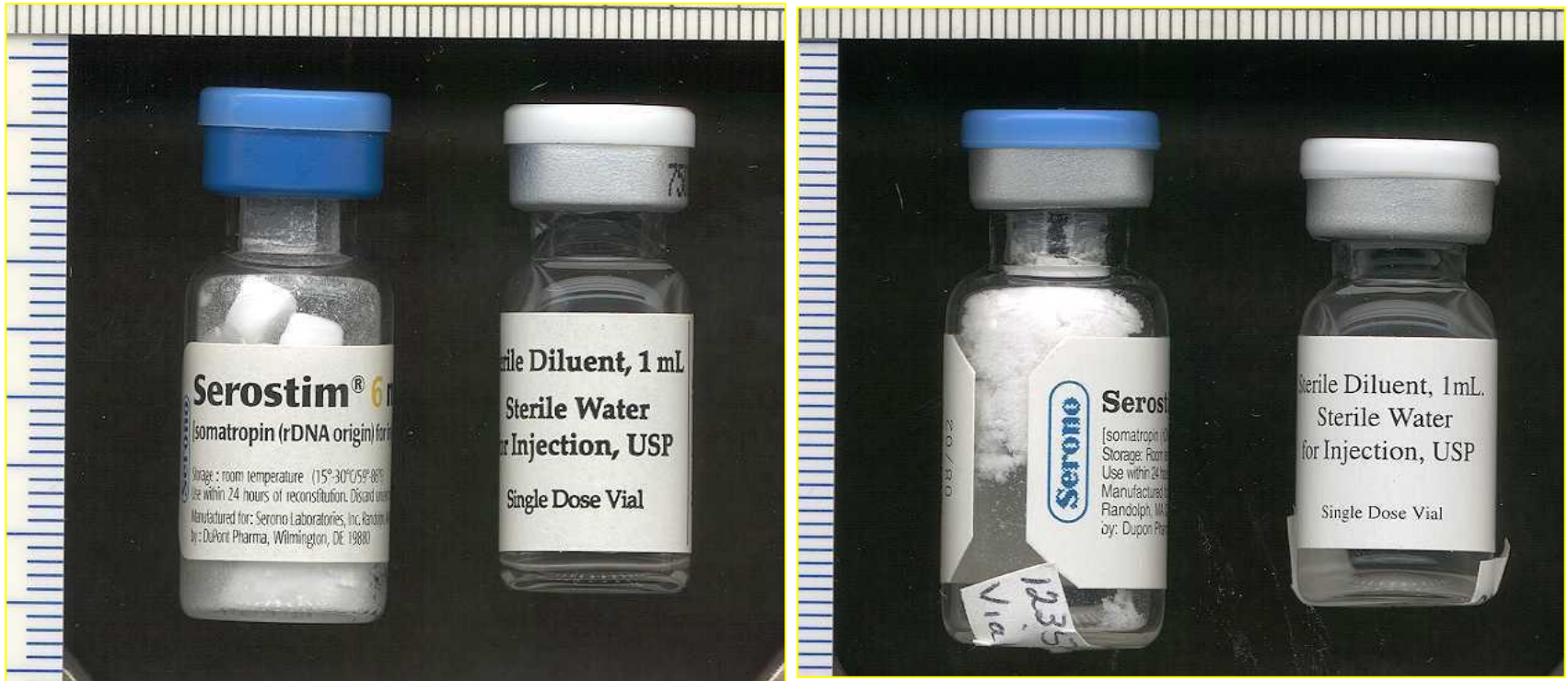
Found: Heroin, morphine,
ibuprofen, chlorpheniramine,
diphenhydramine, caffeine



Declared: Oxycodone HCl

Found: Heroin, ketamine,
caffeine, 6-acetylcodeine

Counterfeit Serostim

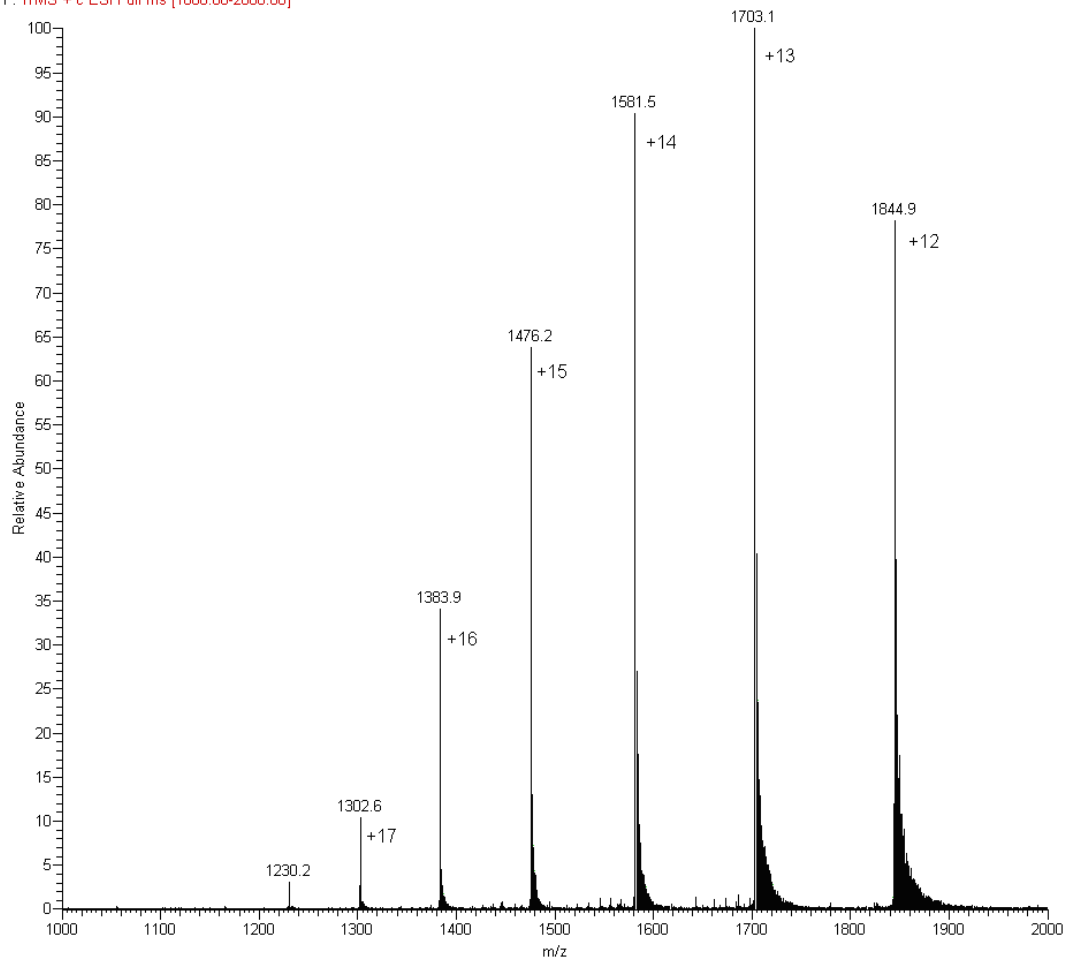


Boston Globe, 1/31/2001:

“Serostim, a human growth hormone used by about 6,000 AIDS patients a year to fight the dangerous loss of weight the disease can cause, costs about \$21,000 for the recommended 12-week dose.”

Full scan mass spectral data with charge state distribution for hGH using an ion trap LC-MS

10150905 #4100-4185 RT: 17.87-18.09 AV: 86 NL: 1.40E5
F: ITMS + c ESI Full ms [1000.00-2000.00]



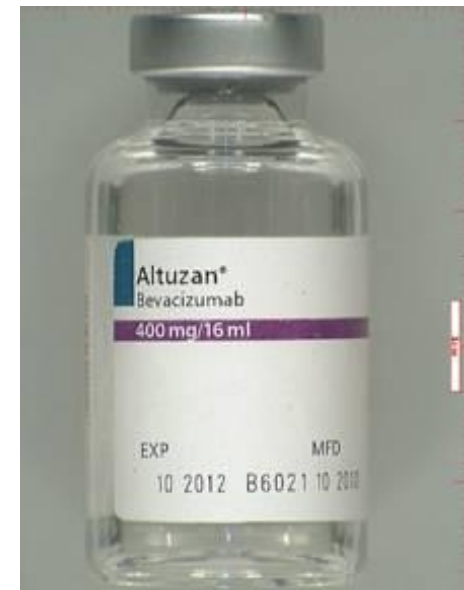
hGH Formulations

- Right active, wrong amount, wrong excipients
- Right active, right amount, wrong excipients
- Wrong active
 - Variant of native protein
 - Chorionic gonadotropin
 - Omeprazole
- No active

Counterfeit Altuzan/Avastin

Subject of FDA press releases in February and April 2012

- Avastin purchased from “Quality Specialty Products, a foreign supplier...that may also be known as Montana Health Care Solutions.”
- Altuzan purchased from “Richards Pharma, also known as Richards Services, Warwick Healthcare Solutions, or Ban Dune Marketing Inc.”



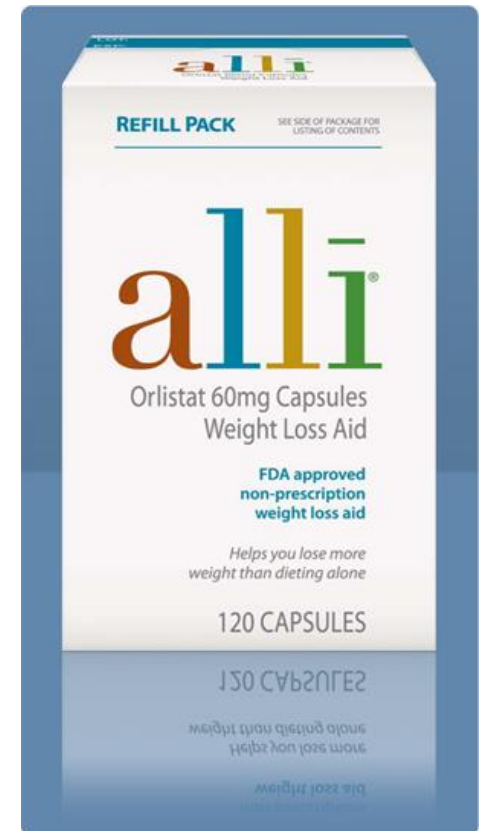
Counterfeit Altuzan/Avastin

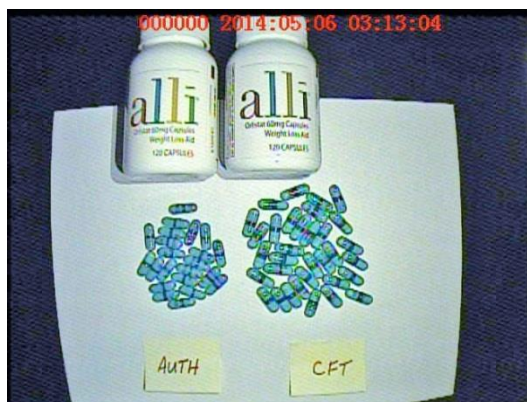
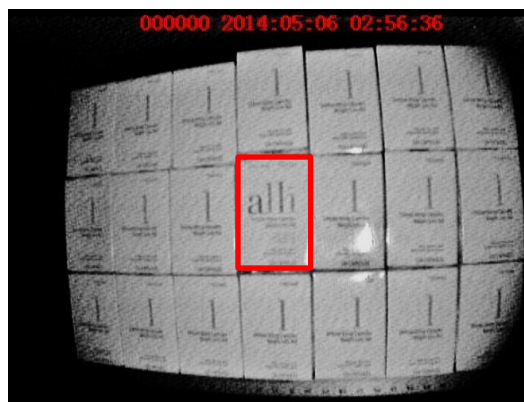
Results of Analyses:

- Packaging and printing were not consistent with authentic
- Printing defects and perforation marks on the carton were consistent with known counterfeit cartons provided by the manufacturer
- SDS-PAGE – no API (bevacizumab) detected
- LC-MS – found albuterol
- GC-MS – found benzoic acid
- Microbiology – found *Penicillium* sp.

Suspect alli

- Began as an investigation into dietary supplements imported and marketed for weight loss
- Customs seized packages in San Francisco
- Products were found to contain sibutramine, a DEA Schedule IV substance
- Sibutramine was withdrawn from the US market in October 2010
- During the investigation, it was discovered that the company was also importing alli, a GSK product





Normal/white light (a, d), monochromatic infrared light with IR cutoff filter (b, e), and monochromatic visible light with visible color filter (c, f) images of authentic and counterfeit product.

Authentic

Suspect

Use

- for weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet

Warnings

Organ transplant alert:

- do not use if you have had an organ transplant. Orlistat interferes with the medicines used to prevent transplant rejection.

Allergy alert:

- do not use if you are allergic to any of the ingredients in orlistat capsules

Do not use

- if you are taking cyclosporine
- if you have been diagnosed with problems absorbing food
- if you are not overweight

Ask a doctor before use if you have ever had

- gallbladder problems • kidney stones • pancreatitis

Ask a doctor or pharmacist before use if you are

- taking warfarin (blood thinning medicine), or taking medicine for diabetes or thyroid disease. Your medication dose may need to be adjusted.
- taking other weight loss products

When using this product

- take a multivitamin once a day, at bedtime. Orlistat can reduce the absorption of some vitamins.
- follow a well-balanced, reduced-calorie, low-fat diet. Try starting this diet before taking orlistat.
- orlistat works by preventing the absorption of some of the fat you eat. The fat passes out of your body, so you may have bowel changes. You may get:
 - gas with oily spotting
 - loose stools
 - more frequent stools that may be hard to control
- eating a low-fat diet lowers the chance of having these bowel changes
- for every 5 pounds you lose from diet alone, orlistat can help you lose 2-3 pounds more. In studies, most people lost 5-10 pounds over 6 months.

Stop use and ask a doctor if

- severe or continuous abdominal pain occurs. This may be a sign of a serious medical condition.

If pregnant or breast-feeding, do not use.

- Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Drug facts (continued)

Directions

- read the enclosed brochure for other important information
- diet and exercise are the starting points for any weight loss program. Try these first before

Ht. / Wt.
4' 10" 129 lbs.
4' 11" 133 lbs.
5' 0" 138 lbs.

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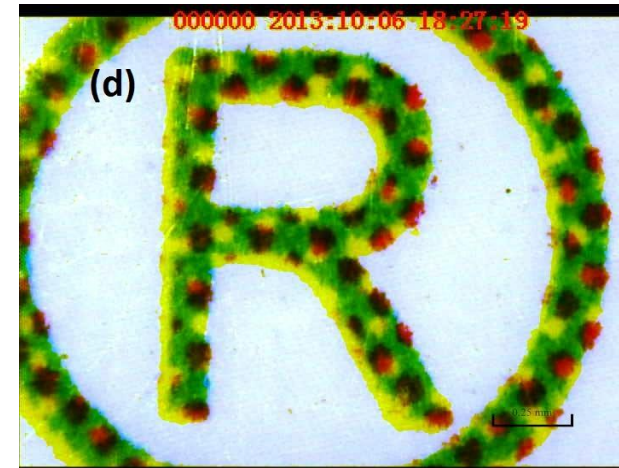
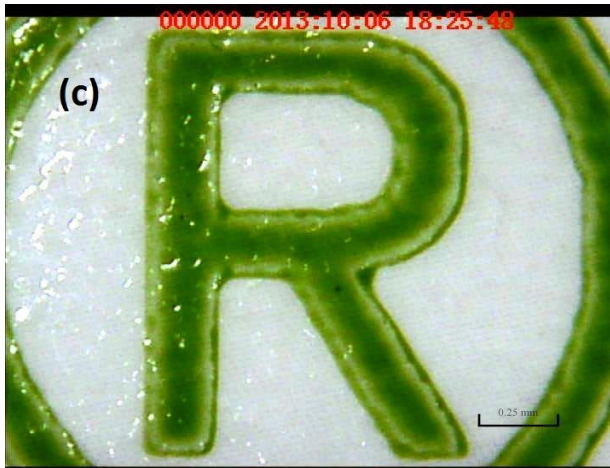
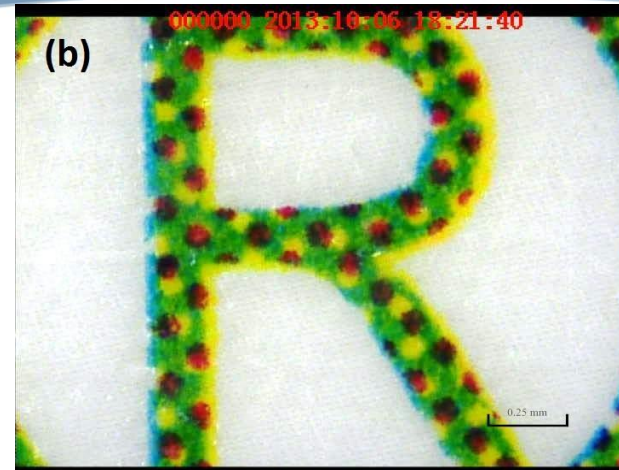
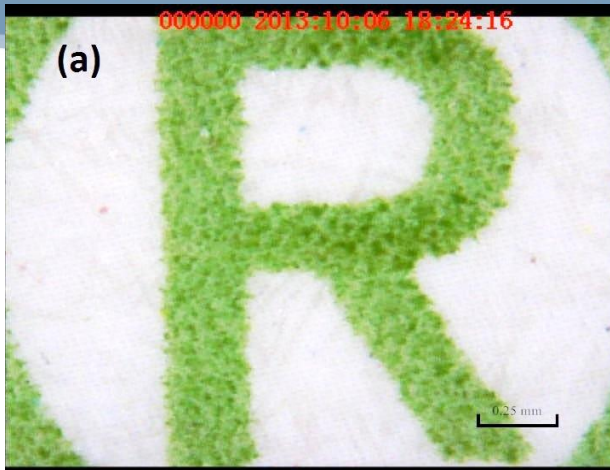
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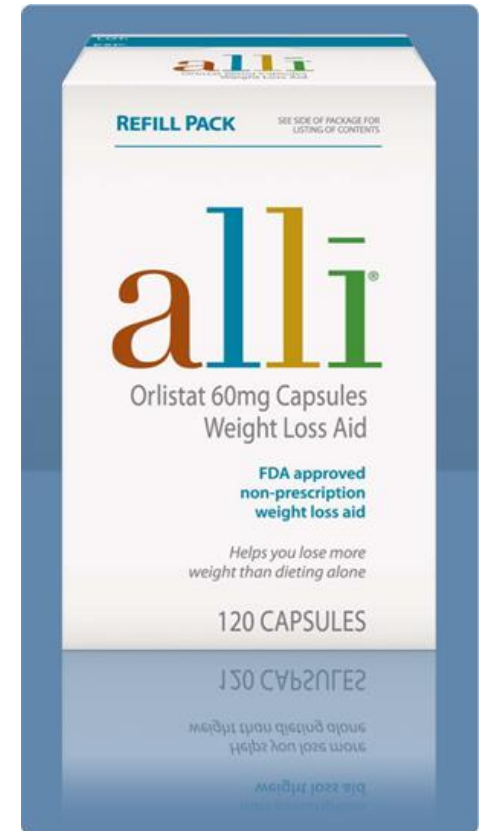
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Images highlighting the offset printing on the authentic carton graphics (a), four color halftone offset printing on the suspect carton graphics (b), flexographic printing on the authentic bottle label graphics (c), and four color halftone offset printing on the suspect bottle label graphics (d).

Counterfeit case outcome - alli

- Products were found to contain sibutramine, not orlistat as declared
- Shengyang Zhou, aka “Tom”, of Kunming, Yunnan, China, was sentenced to serve 87 months in federal prison
- Zhou was ordered to pay restitution totaling \$504,815.39
- Following his prison sentence Zhou will be deported
- Collaboration among OCI, ICE and US Postal Service



CD3 On-site Analysis by LOS-DO Imports at an International Mail Facility



Note: large sample being analyzed quickly

Manufacturing the CD3

- CD3 designed / built at FCC

- Doug Albright
- Sara Andria
- JaCinta Batson
- John Crowe
- Moseley Fulcher
- Adam Lanzarotta
- Frank Platek
- Nicola Ranieri
- Mark Witkowski



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Nico Ranieri

Jill Robinson

Valerie Toomey

Dr. Mark Witkowski