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

White Light

IR Imaging

UV-Vis Imaging

Note: top label and bottom label are different
CD3 Real Time Scan
(captured images of counterfeit versus authentic finished dosages)

Counterfeit  Authentic

Counterfeit  Authentic

Zypraxa 10 mg

Counterfeit  Authentic
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
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

SUSPECT

AUTHENTIC

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

Authentic

Suspect w/ poor debossing & thicker bevel
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

First submission:
Contained 3 mg diazepam, not 10 mg
Diazepam

Suspect 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-acetylcodene
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
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**
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
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  - Adam Lanzarotta
  - Frank Platek
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