Division of Pharmaceutical Analysis
Center for Drug Evaluation and Research
US FDA

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Office of the Commissioner

Office of Regulatory Affairs (ORA, field & counterfeit anal.)

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Center for Veterinary Medicine (CVM)

Center for Tobacco Products (CTP)

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

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Office of New Drugs (OND)

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Division of Pharmaceutical Analysis (DPA)
Division of Pharmaceutical Analysis

• Evaluation of analytical methods submitted by pharmaceutical companies
• Rapid response projects (adverse events, counterfeits)
• Research
  – Emerging technologies
    • Evaluation and new applications
    • Standards for emerging technologies
  – Methods development
    • Special dosage forms
• Surveillance samples (post marketing safety)
  – Identity, purity, potency, uniformity, stability, rate of delivery
Gas Chromatography

Liquid Chromatography/Mass Spec

500 MHz NMR

Dissolution

Spectroscopy
Rapid Response: Heparin

• Indications: Kidney Dialysis, Surgery, especially Cardiac-Invasive, Heart Attack, Cardiac Arrhythmia, Acute Coronary Syndrome, Pulmonary Embolism, or Stroke, Deep-vein Thrombosis, Blood Clot Prevention

• Adverse Events:
  – In early January 2008, small clusters of adverse events in dialysis centers.
  – Many lots of heparin sodium were recalled by the manufacturers due to an increase in the rate of adverse events with these lots.
  – Serious reactions included difficulty breathing, nausea, vomiting, excessive sweating, and rapidly falling blood pressure that can lead to life-threatening shock.
Heparin Regulatory History

• Heparin sodium is an old drug which has been in use since early 1930s.
• First new drug application (NDA) for Heparin Sodium was approved in 1939.
• Since then, many applications for heparin sodium have been approved.
• All current active applications use heparin sodium isolated from porcine intestinal mucosa.
Glycosaminoglycans structures and main disaccharide units

- **Iduronic acid and Glucosamine**
  - Heparin
  - Keratan Sulfate

- **Glucuronic and Glucosamine**
  - Heparan Sulfate
  - Dermatan Sulfate

- **Glucuronic Acid and Galactosamine**
  - Chondroitin Sulfate A
  - Chondroitin Sulfate C

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Trisulfated disaccharide  Disulfated disaccharide  Antithrombin Pentasaccharide Binding Site  Trisulfated disaccharide
Testing of contaminated batches by HHS/FDA labs

- Centers for Disease and Prevention Control in Atlanta, GA
- FDA’s Forensic Science Chemistry Center in Cincinnati, OH
- FDA DPA in St. Louis, MO.

- The contaminated/recalled batches (API and finished products) were tested for the presence of porcine viruses, bovine tissues, toxins, peptides and proteins, nucleic acids, histamine, small molecules, solvents, heavy metals, etc,

- Techniques included GC, HPLC, ELISA, PCR, CE, 1D $^1$H-NMR, 1D $^{13}$C-NMR and 2-D NMR, UV, IR, PAGE, nitrous acid degradation, enzymatic and monosaccharide analysis, precipitation, chromatography, etc.
Proton NMR

Contaminated Heparin

Heparin containing natural DeS

Standard Heparin

2.18 ppm
Suspect Material

2.04 ppm
Heparin

2.08 ppm
Dermatan Sulfate

Acetyl Region

ppm
Heparin/contaminated Heparin overlay

Control (red)
Contaminated (black)

C1 GlcA$_{2,3}S$
C3 GlcA$_{2,3}S$
C4 GalNAc$_{4,6}S$
C5 GalNAc$_{4,6}S$
C4 GlcA$_{2,3}S$
C2 GlcA$_{2,3}S$
C3 GalNAc$_{4,6}S$
C2 GalNAc$_{4,6}S$
C5 GlcA$_{2,3}S$
C3 GalNAc$_{4,6}S$
C1 GlcA$_{2,3}S$
C1 GalNAc$_{4,6}S$
Heparin Disaccharide I2S-ANS (~80%)

Iduronic Acid (I) Ring  Amine containing (A) Ring
Chondroitin Sulfate A (CSA)

G
Glucuronic Acid

A
Galactosamine
Oversulfated Chondroitin Sulfate (OSCS)
Heparin Conclusions

• The molecule OSCS is not a natural product and was determined to have been synthesized and introduced into the heparin supply chain.

• Heparin also contains the natural impurity dermatan sulfate.

• The USP monographs have been updated to assure the absence of oversulfated GAGs and minimize the presence of the impurities.
Heparin in the Marketplace

Heparin Crisis: Feb-April 2008

- 38% of heparin API samples tested were contaminated with OSCS
- Uncontaminated heparin had average DS levels of 1.9% with a range of 0.1 to 9.7%

Marketplace survey (sampled September 2009)

- No contamination
- DS levels below 1% USP Specification
Research: Pharmaceutical Surveillance with Rapid Spectroscopic Screening Technologies

![Graph showing absorbance over wavelength and OSCS concentration.](Image)

- **Absorbance (a.u.)**
- **Wavelength (nm)**
- **% OSCS**: 10, 1, 0.1, 0.01, 0.001, 0% + heparin

- **Lines and Colours**:
  - Red: No OSCS
  - Blue: 10% OSCS
  - Brown: 1% OSCS
  - Cyan: 0.1% OSCS
  - Green: 0.01% OSCS
  - Maroon: 0.001% OSCS
Why Rapid Screening?

• Rapid screening will dramatically increase the number of containers of material that can be examined without a dramatic increase in personnel.
  – Materials failing rapid screening will be sent to FDA laboratories for further testing.

• Rapid screening can support rapid response.
Instruments and Methods

- X-ray Fluorescence (XRF)
- Ion Mobility Spectrometry (IMS)
- Raman Spectroscopy
- Near Infrared Absorbance (NIR)

- Goal: robust, rapid, sensitive methods with:
  - Good calibration transfer
  - Simplified user interfaces
  - Pass/fail decision metrics

- Collaborative studies with FDA field labs were used to set detection limits and finalize procedures
Ion Mobility Spectroscopy (IMS)

- Weight loss drugs in herbal supplements
  - Sibutramine LoD = 2 ng, 0.4 mg in tablet
  - Fluoxetine LoD = 2 ng, 0.4 mg in tablet
- Good for molecules that volatilize @ <190 °C
- Methods require an extraction
- <1 minute per sample
- Currently deployed at mail facilities where dietary supplements enter the country
Raman and NIR Spectroscopy

• Libraries
  – Characterize the capabilities of spectral library-based correlation methods to identify and verify materials
  – Evaluate and develop procedures to transfer Raman and NIR libraries from one instrument to another

• More sensitive models to detect adulterants/contaminants
  – Diethylene glycol (DEG) in propylene glycol or glycerin
  – Melamine
  – Custom made user interface
    • Performs transfer of calibration
    • Predicts adulterant concentration
    • Makes a Pass/Fail decision

B&W Tek MiniRam II

Delta Nu Reporter ID
Special Dosage Forms

Research and Surveillance

Examples:

• Inhalation Products

• Transdermal Products
Particle Size of Inhalation Products

• Particle size and particle size distribution are key product quality parameters:
  – Important in vitro indicators of the bioavailability of a given formulation
  – Can predict the dynamics of drug release

• Prior to formulation into a finished product, drug particles can be sized using sieving techniques, Optical microscopy, Laser diffraction, etc.

• How to determine the particle size and size distribution in the finished products in the presence of other un-dissolved components?
Nasal Spray Suspension Formulation

Beclomethasone Dipropionate (BDP)
an anti-inflammatory corticosteroid

- **Drug** --- Beclomethasone Dipropionate
  - Median particle size 2 – 5 µm
- **Inactive suspended Ingredient** --- microcrystalline cellulose (MCC)
  - larger particle size, but some in the same size range as the drug
  - broader PSD
- **Many Dissolved Additional Inactive Ingredients**
Raman Spectroscopy: shifts are intrinsic to molecular structure

The drug BDP is a relatively strong Raman scatterer
Raman Chemical Imaging of Nasal Spray

A. Brightfield reflectance image
B. Polarized light image
C. Brightfield/Raman overlay image

D. Raman emission at 1664 nm
Evaluation of the effect of spacers on the *in vitro* performance of orally inhaled drug products

- **Spacer devices**
  - serve as holding chambers for the aerosol plume of metered dose inhaler (MDI) drug products.
  - are used for young children who cannot coordinate inhalation with inhaler actuation.

- How is drug delivery affected by use of a spacer?
Research Plan

• Methodology assessment
  – aerodynamic particle sizer (APS)
  – laser light scattering (LLS)
  – cascade impaction (CI)

• Compare product performance and vary parameters:
  – Hold time to simulate actuation patient use
  – Flow rate within the spacer to simulate actuation by various age groups
  – Spacer cleaning intervals
  – Static charge
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Thank You

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