Analyses for the Future

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We want to prove:

• The proprietary product was manufactured by the license holder, eg Viagra tablets were made by Pfizer.
• The product was manufactured by the license holder and it contained the right active at the right potency, eg Cox made the diazepam 5mg tablets and they contained 5 mg of diazepam.
• The generic product contained the right active at the right potency, eg erythromycin tablets 250 mg contained 250 mg of erythromycin.
WHY NIRS

• No sample preparation
• Quick and easy
• Non-destructive
• Analyses both active and excipients
• Qualitative and quantitative
• Fingerprints whole matrix
• Huge amount of information
NIR Absorbance Spectra of Lipitor Tablets

Absorbance (Log10(1/R))

Wavelength/nm

10 mg
20 mg
40 mg
NIR SNV of Absorbance Spectra of Lipitor Tablets

-2  -1.5  -1  -0.5  0  0.5  1  1.5  2  2.5  3
1100 1300 1500 1700 1900 2100 2300 2500
Wavelength/nm
SNV of Absorbance (Log10(1/R))
10 mg
20 mg
40 mg

BESITRAN 50mg Tablets, Pfizer, Spain

Sertraline hydrochloride
Calcium hydrogen phosphate
Hydroxypropylmethyl cellulose
Magnesium stearate
Microcrystalline cellulose
Polyethylene glycol
Polysorbate-80
Sodium starch gycollate
Titanium dioxide
Iron Oxide
BESITRAN 50mg Tablets, Pfizer, Spain

C of G Plots of four different manufacturers of 100mg allopurinol tablets (1750-1850nm)
Cialis

4 batches A – 1 batch C – 8 batches C

Cialis List of Excipients

<table>
<thead>
<tr>
<th>Tablet core:</th>
<th>Lactose monohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Croscarmellose sodium</td>
</tr>
<tr>
<td></td>
<td>Hydroxypropylcellulose</td>
</tr>
<tr>
<td></td>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td></td>
<td>Sodium laurilsulfate</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Film coat:</th>
<th>Lactose monohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypromellose</td>
</tr>
<tr>
<td></td>
<td>Triacetin</td>
</tr>
<tr>
<td></td>
<td>Titanium dioxide (E171)</td>
</tr>
<tr>
<td></td>
<td>Iron oxide yellow (E172)</td>
</tr>
<tr>
<td></td>
<td>Talc</td>
</tr>
</tbody>
</table>
Cialis Tablets by NIRS
Blue: mean of 4 batches authentic tablets
Brown: 1 batch counterfeit tablets

Cialis by HPLC

Standards

Counterfeit Cialis
Viagra
7 batches A – 1 batch C – 14 batches C

Viagra Tablets by NIRS
Blue: mean 7 batches authentic tablets
Brown: 1 batch counterfeit tablets
Levitra Tablets by NIRS
Blue: mean of 3 batches authentic tablets
Brown: 1 batch counterfeit tablets

Correlation in Wavelength Space

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Authentic</th>
<th>Counterfeit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cialis</td>
<td>0.999</td>
<td>0.796</td>
</tr>
<tr>
<td>Levitra</td>
<td>0.999</td>
<td>0.898</td>
</tr>
<tr>
<td>Viagra</td>
<td>0.998</td>
<td>0.947</td>
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</tbody>
</table>
Four component mix
Viagra Tablets
Spectra correlated with Sildenafil

Stylised particle size differences of an active in two different manufacturer’s tablets
## Excipients

<table>
<thead>
<tr>
<th>EXCIPIENT</th>
<th>A</th>
<th>B</th>
<th>Br</th>
<th>G</th>
<th>S</th>
<th>St</th>
<th>T</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium stearate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Maize starch</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Methyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Povidone</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Propyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Silicone dioxide</td>
<td>X</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Stearic acid</td>
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<td></td>
<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calibration and Validation Graphs (% m/m)

Calibration Plot  Validation Plot

Results of Powders and Single Tablet Analyses (NIR Predicted % Paracetamol Label Claim)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powders, RCA</td>
<td>99.9</td>
<td>98.0 - 102.4</td>
</tr>
<tr>
<td>Intact Tablets, RCA</td>
<td>96.3</td>
<td>93.2 - 102.5</td>
</tr>
<tr>
<td>Intact Tablets, Probe</td>
<td>101.3</td>
<td>97.3 - 104.1</td>
</tr>
</tbody>
</table>
The School of Pharmacy

Analytical Spectral Devices
FieldSpec 3 (wireless)

Laser 2000 – EPP2000 NIR InGaAs Spectrometer

The School of Pharmacy
Acknowledgements

Dr Roger Jee
Dr Andrew O’Neil
Mr Yat Hang Mark Shek
Dr Myoung-Hee Shin
Dr Nicola Wilson
Half of Lipitor recalled in counterfeit scare was fake

Over 50 per cent of Lipitor (atorvastatin) packs recalled from pharmacies by Pfizer in a counterfeit scam last year were fake [J9, 6 August 2005, p30].

This was revealed during a House of Commons debate on counterfeit medicines last week by Charles Walker (Con., Broxbourne).

Mr Walker said that a “Bermuda triangle” of medicine supply had been formed by parallel trade, counterfeiters and online pharmacies. There were now 2,500 websites selling drugs directly to the consumer and the four most advertised drugs were Viagra (sildenafil), Adipex (phentermine), Xenical (orlistat) and Propecia (finasteride), he said.

“In the UK, internet pharmacies pose a growing threat to public health,” he said. “They are largely unregulated. In the best case, these illegal pharmacies are dispensing sugar and, in the worst case, poison.”

Responding, health minister Jane Kennedy said that 103 cases involving internet sales of counterfeit medicines were currently being investigated by the Medicines and Healthcare products Regulatory Agency. She said that the agency would “not hesitate to taking appropriate enforcement action” for illegal supply and pointed to 12 prosecutions since 2006.

Mrs Kennedy agreed that the counterfeit trade was increasingly being taken over by organised criminals who were “growing in enterprise and sophistication.”

She said: “It is certainly true that some websites offering medicines belong to unscrupulous vendors . . . who sell unlicensed and prescription-only medicines and counterfeit drugs that are potentially harmful.

“That is particularly true of so-called lifestyle drugs — medicines aimed at male impotence, slimming products or hair loss products. We are here to ensure that the public make informed choices about their health, and they need to be aware that products purchased in that way cannot be guaranteed for safety, quality or efficacy.

“Given the uncontrolled nature of the internet, and the fact that many sites will be based abroad, a key aim is to ensure that the public understand the risks of buying medicines from such sites and are warned against them.”

She said that the MHRA was targeting information and advice with respect to specific products, and liaison with other regulatory and enforcement agencies at home and abroad. It was heading a Europe-wide counterfeit Tamiflu surveillance project and recently saved 6,800 packets of the medicine in London with a retail value of over £1m.

Mrs Kennedy added that the legitimate supply chain in the UK was tightly controlled and internationally recognised as difficult to penetrate. She said that there was little evidence that parallel traders had been used to get counterfeit products into the UK.
Lustral 50 mg – Madrid & Barcelona

BESITRAN - 2nd PCA LOADING

2nd component loadings

Hydroxypropylmethylcellulose
Authentic Cialis (blue), Levitra (brown) and Viagra (green) Tablets and Pure Drugs

Cialis PCA
Levitra

Overlaid Chromatogram

Standards

Overlaid Chromatogram

Counterfeit Levitra

Centre of Gravity Plot
(95% equal frequency ellipses)

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Comparison between Samples

Good sample  Sticking sample