Pharmaceutical Surveillance with Rapid Spectroscopic Screening Technologies

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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.
Rapid Screening: Instruments and Methods

Four types of portable instruments have been evaluated for use at dockside or at manufacturing facilities and are currently being deployed. Materials failing rapid screening would be quarantined and sent to FDA laboratories for further testing:

- X-Ray Fluorescence (XRF) Spectrometer for detection of toxic metals
- Ion Mobility Spectrometer (IMS) for detection of weight loss drugs in dietary supplements
- Raman and Near Infra-Red (NIR) Spectrometers for detection of contaminants in pharmaceutical ingredients

Raman and NIR could also be used to identify or verify material if FDA had a robust/complete library.

Identification and Verification of Pharmaceutical Excipients with Spectral Libraries

- Acquire “certified” reference materials
- Measure the spectra of reference materials and store in a database for future use
- Applications
  - Material identification
  - Material verification
The Hit Quality Index (HQI)

- Term derived from ID and verification applications.
- The most common HQI is the spectral correlation coefficient.
  
  \[HQI = 1.000 \text{ is best match, indicates perfect correlation}\]
  \[HQI = 0 \text{ is worst match, indicates complete lack of correlation}\]

Typical Applications

- **ID**: material’s identity is unknown
  - Compare an unknown’s test spectrum to an entire library of known spectra to determine its most likely identity.
    - Library spectrum with highest HQI
- **Verification**: identity known but unconfirmed
  - Compare a test spectrum to its library spectrum to verify its identity
    - Require the HQI to exceed a predetermined threshold
Recent Work at the DPA

- Characterize the capabilities of spectral library-based correlation methods to identify and verify materials
- Evaluate procedures to transfer Raman and NIR libraries from one instrument to another
- Develop advanced procedures for transferring Raman and NIR libraries.

Examples of Spectra and their HQIs:
Master Instrument Spectra against Castor Oil
Derivative Spectra and their HQIs:
Master Instrument Spectra against Castor Oil

[Graph showing derivative spectra and their HQIs for Na_CMC (HQI = 0.00002), Cocoa Butter (HQI = 0.229), Sesame Oil (HQI = 0.955), and Castor Oil (Target, HQI = 1.000).]

Evaluation of HQI after Library Transfer

Master library measured on benchtop instrument.
Test samples measured on library instrument.
Test samples measured on four “field” instruments.
**Benchmark: Test spectra measured on Master instrument without library transfer**

Average HQI = 0.98 ± 0.03

<table>
<thead>
<tr>
<th>Sample</th>
<th>Hit #</th>
<th>HQI</th>
<th>Verification</th>
<th>Sample</th>
<th>Hit #</th>
<th>HQI</th>
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</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>1</td>
<td>0.989</td>
<td>10 ibuprofen</td>
<td>1 ibuprofen</td>
<td>1</td>
<td>0.979</td>
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<td>acetylsalicylic acid</td>
<td>1</td>
<td>0.975</td>
<td>20 ketoprofen</td>
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<td>1</td>
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<td>alphalactose</td>
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<td>0.994</td>
<td>21 magnesiumstearate</td>
<td>1 magnesiumstearate</td>
<td>1</td>
<td>0.996</td>
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<tr>
<td>benzoic acid</td>
<td>1</td>
<td>0.985</td>
<td>22 melemine</td>
<td>1 melamine</td>
<td>1</td>
<td>0.987</td>
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<tr>
<td>benzylic alcohol</td>
<td>1</td>
<td>0.997</td>
<td>23 metformin</td>
<td>1 metformin</td>
<td>1</td>
<td>0.993</td>
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<tr>
<td>caffeine</td>
<td>1</td>
<td>0.984</td>
<td>24 microcrystalline cellulose</td>
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<td>1</td>
<td>0.970</td>
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<tr>
<td>calcium phosphate d.</td>
<td>1</td>
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<td>25 naproxen sodium</td>
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<td>carbamazepine</td>
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<td>0.981</td>
<td>27 pgstarch</td>
<td>1 pgstarch</td>
<td>1</td>
<td>0.998</td>
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<td>crospovidone</td>
<td>3</td>
<td>0.980</td>
<td>28 propylene glycol</td>
<td>1 propylene glycol</td>
<td>1</td>
<td>0.998</td>
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<tr>
<td>diclofenac</td>
<td>1</td>
<td>0.989</td>
<td>29 pseudoephedrine</td>
<td>1 pseudoephedrine</td>
<td>1</td>
<td>0.973</td>
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<tr>
<td>diethylene glycol</td>
<td>1</td>
<td>0.999</td>
<td>30 sodium starch</td>
<td>1 sodium starch</td>
<td>1</td>
<td>0.924</td>
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<tr>
<td>estradiol</td>
<td>1</td>
<td>0.995</td>
<td>31 sorbitol</td>
<td>1 sorbitol</td>
<td>1</td>
<td>0.998</td>
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<tr>
<td>ethyleneglycol</td>
<td>1</td>
<td>1.000</td>
<td>32 sulfanilamide</td>
<td>1 sulfanilamide</td>
<td>1</td>
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<tr>
<td>gelatin</td>
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<td>0.851</td>
<td>33 tinidazole</td>
<td>1 tinidazole</td>
<td>1</td>
<td>0.993</td>
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<tr>
<td>glycine</td>
<td>1</td>
<td>0.999</td>
<td>34 triclosan</td>
<td>1 triclosan</td>
<td>1</td>
<td>0.975</td>
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<tr>
<td>HPMC</td>
<td>1</td>
<td>0.964</td>
<td>35 xylometazoline</td>
<td>1 xylometazoline</td>
<td>1</td>
<td>0.993</td>
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<tr>
<td>hydrocortisone</td>
<td>1</td>
<td>0.978</td>
<td></td>
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</tr>
</tbody>
</table>

**Library Transfer Across Instruments:**

Uncorrected First Derivative Spectra

<table>
<thead>
<tr>
<th>Verification</th>
<th>ID</th>
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</thead>
<tbody>
<tr>
<td>LSI</td>
<td>100</td>
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<tr>
<td>Enwave</td>
<td>94.5</td>
</tr>
<tr>
<td>Ahura</td>
<td>100</td>
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<tr>
<td>BWTek</td>
<td>100</td>
</tr>
<tr>
<td>Delnu</td>
<td>100</td>
</tr>
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</table>
Library Transfer Across Instruments: Corrected First Derivative Spectra

Verification

ID

Shift correction
Intensity correction
Resolution correction

Recent Work at DPA

• Determine the sensitivity of Raman library-based spectral correlation methods to the presence of contaminants in excipients
  – Economically motivated adulterants (EMAs)

• Develop advanced procedures to improve the sensitivity to contaminants in excipients
  – Chemometrics
Raman Spectra

Contaminants
- Ethylene Glycol
- Diethylene Glycol
- Propylene Glycol
- Glycerin

Excipients

Raman Shift (cm⁻¹)

Glycerin DEG ~ 18%

Sensitivity to Contaminants: One Instrument

HQI Threshold 0.950

~ 18%

Hit Quality Index (HQI)

% Glycerin

% DEG
Determination of DEG in glycerin by partial least squares regression is very sensitive.

\[ y = 0.99x + 0.1 \]

\[ R^2 = 0.9999 \]

Conclusions

- Baseline removal is essential for HQI sensitivity.
- Corrections have a significant impact on HQI values, and are thus essential for verification.
  - Shift correction—most sensitive
  - Intensity correction
  - Resolution correction—when bandwidth differs from library
- ID analysis of the major component is not sensitive to spectral corrections.
  - ID is observed to be highly accurate for major component, but not for low concentration components/impurities.
- Detection of low levels of contaminants/impurities may require chemometric model development, but is still possible by spectroscopic methods.
Metal/Element work at DPA

- Developed X-ray fluorescence (XRF) to measure metal impurities in drug substances and products
  - Simple, fast, no sample prep, inexpensive
- Determine if XRF is capable of quantifying residual catalysts at the levels specified by the EMA Guideline (expected ICH guideline)
  - Spiked excipients
  - Measure against ICP-MS reference method
- Determine if metal/element profiling in excipients can predict the source
  - Ca, Mg, S, Cl, Br, Fe, Cu, Ti, Si, etc.
  - Verify XRF with ICP-MS

X-ray Fluorescence

- Elemental impurities in pharmaceutical materials
- Toxics
  - As, Pb, Hg, Cr
  - LoDs 8, 14, 20 and 150 ppm
- Catalysts
  - LoDs in the 50-75 ppm range
Example: 25 ppm Arsenic in solution (green), powder (red) and tablet (black)

Role of IPEC

- Provide materials to create library and study metals/elements in excipients
  - We would like to have qualified excipients from several vendors
  - Preferably several lots from each vendor in order to establish normal variability in spectral properties
- Expertise on which excipients to target
How

- Material Transfer Agreement with Division of Pharmaceutical Analysis
  - To allow for DPA to accept material
  - To allow for DPA to share results with IPEC members (if desired)

Most wanted excipients

<table>
<thead>
<tr>
<th>BUTYLATED HYDROXYANISOLE</th>
<th>GELATIN</th>
<th>Povidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUTYLATED HYDROXYTOLUENE</td>
<td>Glycerin</td>
<td>PREGELATINIZED STARCH</td>
</tr>
<tr>
<td>CALCIUM PHOSPHATE (DIBASIC)</td>
<td>HYDROXY PROPYL CELLULOSE</td>
<td>Propylene Glycol (liquid and solid)</td>
</tr>
<tr>
<td>CALCIUM STEARATE</td>
<td>HYDROXY PROPYL METHYLCELLULOSE</td>
<td>SHELLAC</td>
</tr>
<tr>
<td>CARBOXYMETHYL CELLULOSE</td>
<td>LACTOSE</td>
<td>SILICON DIOXIDE</td>
</tr>
<tr>
<td>CASTOR OIL</td>
<td>MAGNESIUM STEARATE</td>
<td>SODIUM STARCH GLYCOLATE</td>
</tr>
<tr>
<td>CRESOL</td>
<td>MALTODEXTRIN</td>
<td>Sorbitol</td>
</tr>
<tr>
<td>CROSCARMELLOSE</td>
<td>MICROCRYSTALLINE CELLULOSE</td>
<td>STARCH (CORN)</td>
</tr>
<tr>
<td>CROSPOVIDONE</td>
<td>Polyethylene Glycol, liquid and solid</td>
<td>STEARIC ACID</td>
</tr>
<tr>
<td>ETHYLCELLULOSE</td>
<td>POLYSORBATE 80</td>
<td>Talc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Titanium Dioxide</td>
</tr>
</tbody>
</table>
Questions?

References:

- **Pharmaceutical Surveillance with Rapid Spectroscopic Screening Technologies**: JF Kauffman et al, American Pharmaceutical Review, 2010
- **Using Portable Ion Mobility Spectrometer to Screen Dietary Supplements for Sibutramine**: JD Dunn et al, Journal of Pharmaceutical and Biomedical Analysis, 2011