Bench Scale and Beyond

FT- NIR Spectrophotometry

Validation Hurdles
Chemical Issues
and Benefits

PDA – August 2011
Chromatography - vs - Spectrophotometry

**Chromatography** is the collective term for a set of laboratory techniques for the separation of mixtures. It involves passing a mixture (a mixture dissolved in a mobile phase) through a stationary phase, which separates the analyte to be measured from the other molecules in the mixture based on differential partitioning between the mobile and stationary phases. Subtle differences in a compound’s partition coefficient result in differential retention on the stationary phase (SEC or IE) and thus separating molecular configurations.
Chromatography - vs - Spectrophotometry

- **Spectrophotometry** is the quantitative measurement of the reflection or transmission properties of a molecule or material as a function of wavelength. It is more specific than the general term electromagnetic spectroscopy in that spectrophotometry deals with visible light, near-ultraviolet, and near-infrared, but does not cover time-resolved spectroscopic techniques. Spectrophotometry involves the use of a spectrophotometer. A spectrophotometer is a photometer (device for measure light intensity) that can measure intensity as a function of the light source wavelength. Important features of spectrophotometers are spectral bandwidth and linear range of absorption or reflectance measurement.

- So once we have separated the molecules we can now either identify the molecule or measure the quantity.
When measuring, we utilize the fact that individual components of mixtures based on the molecular bond absorb light at different wavelengths. Therefore in order to identify or quantitate a component, it is only necessary to precisely know the degree of absorption of the individual substances within the mixture in order to determine appropriate measuring and reference wavelengths from four possible spectral ranges:

- Ultraviolet (UV) – 200-400 nm
- Visible (VIS) – 400-700 nm
- Near Infrared – 700-2500 nm
- Infrared – 2500-4700 nm

This where the hurdles starts - precise separation between compounds, instrument calibration and routine application
FT – Fourier Transform

• FT is a mathematical operation that decomposes a signal into its constituent frequencies. Thus the FT of a musical chord is a mathematical representation of the amplitudes of the individual notes that make it up.

• Welcome to the world of trigonometry
FT – Fourier Transformation
FT – Fourier Transformation

FTIR can trace its roots back to the early 1900s. After Michaelson invented the interferometer, it was used by the astronomical community to measure the spectra of stars. Back then, they had to do the FT without computers, which weren't invented for quite a while. The Fast Fourier Transform didn't exist yet then, either. So it was used, because it was the only thing available that would work, but it wasn't a very popular technique!

Chemists didn't latch on to the term "FTIR" until Block Engineering, and then Digilab, developed an instrument specifically for use in chemical analysis, in the 1960's. Those instruments were specifically for the mid-IR region.
Dispersive instruments were the first technology in IR, NIR, visible, and UV spectroscopy. FT instruments are easier to operate at longer wavelengths - the Infrared, and the first commercial lab FT machines were IR. Around the early 1990s some labs decided to try FT in the NIR, for reasons initially relating to calibration transfer. These machines were called FT-NIR machines, they worked, and the name has stuck. One feature which is different, the natural X scale of an FT machine is cm⁻¹ (wave numbers). You measure signal as a function of distance, when you do an FT you get the inverse of distance, cm⁻¹.
FT – Fourier Transformation

When modern NIR analysis became commercially available in the late 1970's, roughly 20 years later, all those initial instruments were based on either interference filters or diffraction gratings for wavelength selection.

When FT instrumentation started to be applied to NIR analysis, the term "FT-NIR" came along with it, both to distinguish the application of the interferometric measurement to the NIR region from its historical application to mid-IR, and also to distinguish it from the generations of grating-based instruments that were previously exclusively used for NIR analysis.
Our industry has been moving analytical techniques on to or in to the production areas now for decades. One of the first which I was the installer was measuring the ETO concentration within the sterilization chamber. Fortunately, the application of spectroscopic and electronic analytical equipment during process development, validation, and operation continues to allow EtO users to increase the efficiency and efficacy of the process while reducing turnaround times, labor requirements, raw material use and patient safety. To gain these improvements, EtO users are focusing on:

1. temperature, pressure, and humidity as each affects ETO effectively during sterilization (penetration of the spore coat – or cell wall)
2. Releasing product parametrically.
3. Managing product load configuration within validated parameters.
4. Adopting new products into already-validated product families.
Analytical Lab - vs – In-process

PCR was one of my next major industry advances. Even though its not yet an in-process monitoring device (time dependent), it has basically put the artificial blood industry out of business because donated blood and the resultant products are so safe. The test lab in Raleigh was one of the very first to have PCR validated for donor plasma.
Analytical Lab - vs – In-process

Lab testing is typically “after the fact”. Actually all testing is the status right now. In-process though allows us to have a better prediction of the final product quality (CPPs). In our world of the pharmaceutical industry, we can’t wait until the product is final to determine if it is going to be acceptable or not, so we have to have in-process monitoring to provide a high level of confidence that the final testing is going to be really boring because its ALWAYS acceptable!

More and more analytical tests that could only be done in the laboratory are now being used in production (test samples or in-line)
Implementing New Technology
Implementing New Technology

- Confidence
- Robustness
- Repeatability
- Accuracy

Known variables that can cause false positives or false negatives, or other elements that can cause data variation that might not be easily simulated or detected (electronic noise).
Regulatory Issues

- Data Transfer
- Data Storage
- Selection of data to be archived
- Part 11 impact
- Analytical Methods for Data Assessment
- Validation Capabilities
Regulatory Issues

• NIR has become an essential method of PAT in our industry. While the technology is rich in chemical and physical information, using the data effectively for PV applications is sometimes difficult to know what or how to extract essential process knowledge from spectral data. Its not just computer validation or LIMS and does not need to be more difficult or falsely expanded into non-applicable activities such as Part 11 if Part 11 criteria are not being applied (quality release or an electronic batch record).

• Multivariate data analysis techniques, such as principal component analysis (PCA) and partial-least squares regression (PLS), are typical techniques for the analysis of NIR spectral data.

• The objective of this work is to apply PCA and NIR spectroscopy to gain critical knowledge of a pharmaceutical manufacturing process – PV Understanding
Key to Innovative Integration of New Technology

The intuitive mind is a SACRED GIFT, and the rational mind is a faithful servant. We have created a society which honors the servant, and forgets about the gift.

*Albert Einstein*

Narrow minded thinking / behavior has a strong tendency to resist change even for the sake of an improved, higher quality and cheaper alternative.
Key to Innovative Integration of New Technology

Gaining internal approval to change requires significant comprehension by all parties involved. Unfortunately, SMEs and authority all too often become driven by ego. As Lincoln said, “If you want to test a man’s integrity [and self confidence] give him authority”.

Main Idea

Main Idea
Key to Innovative Integration of New Technology

The new PV Guideline issued in January provides a challenge, but a very substantial means of making change easy. PV is defined as the collection and evaluation of data from design through production which establishes scientific evidence of quality (SSR - sound scientific rationale).
Examples of Spectroscopy Implementation

Two independent data sets for theophylline (T) and furosemide (F) tablets were generated according to predefined experimental design (DOE) protocols. Both were manufactured by direct compression and wet granulation. Coating was slightly different. Samples were collected from each batch, scanned using NIR reflectance spectroscopy and subjected to hardness and dissolution testing. A PCA model was created and used to analyze the effect of processing changes on tablet spectra.
Examples of Spectroscopy Implementation

The PCA model identified a minor link between coating level and drug dissolution confirming NIR as a PAT tool. A similar application has been applied to determine the end-point for lyophilization – temperature is not the right yard-stick to determine when the cake has reached the level of dryness needed to preserve product stability. It works but is not efficient and has cost the industry lots of lost time (over dry).
VALIDATION CHALLENGES

VENDOR VALIDATION

GOLD STANDARD CALIBRATION

CHEMOMETRICS
Antaris Qualification Report

Type of qualification: Software and Algorithm Verification
Date of report: 2010-06-04 062726 GMT+00:00
Operator name: OMNICAL
ValPro version: ValPro 3 SP3

Beers Law 1 Test

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Value</th>
<th>Acceptance limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene - large peak</td>
<td>2.9267</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the thickness of a polystyrene sample by Beer's Law using a large peak in the spectrum. The expected result is 2.9267.

Beers Law 2 Test

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Value</th>
<th>Acceptance limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene - small peak</td>
<td>2.9736</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the thickness of a polystyrene sample by Beer's Law using a small peak in the spectrum. The expected result is 2.9736.

CLS Test

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Value</th>
<th>Acceptance limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene - range</td>
<td>0.9640</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the thickness of a polystyrene sample using the Classical Least Squares (CLS) algorithm using a spectrum region. The expected result is 0.9640.

CLS-C Test

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene - range</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

file://C:\RESULT Data\Archive\Algorithm\Antaris Qualification Report 7D7AA29D-78A0-...  7/8/2011
<table>
<thead>
<tr>
<th>Attribute</th>
<th>Value</th>
<th>Acceptance limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>0.8284</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the area of a peak in a polystyrene spectrum after a reference spectrum has been subtracted. The expected result is 0.8284.

**Peak Width at Percent of Maximum Test**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Width at 40%</th>
<th>FWHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>132.449</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the peak width at 40 percent of the peak maximum for a peak in a polystyrene spectrum. The expected result is 132.449.

**Peak Area Within Percent of Maximum Test**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>40% measurement</th>
<th>FWHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>43.368</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the peak area within 40 % of the peak maximum for a peak in a polystyrene spectrum. The expected result is 43.368.

**Peak Width Low Location Referenced Test**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Width low freq, ref.</th>
<th>FWHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>95.893</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the peak width at the "Low Location Referenced" for a peak in a polystyrene spectrum. The expected result is 95.893.

**Peak Width High Location Referenced Test**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Width high freq, ref.</th>
<th>FWHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>105.133</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Measures the peak width at the "High Location Referenced" for a peak in a polystyrene spectrum. The expected result is 105.133.

**Location Low Location Referenced Test**
Quantitative standards are a major challenge in most every aspect of our science based business. Particularly difficult in the spectrophotometric arena, developing a range of standards and associated variables to be used for the next phase is a significant challenge. A single chemical or separated (chromatography) makes this process easy. Final products are rarely a single chemical.
CHEMOMETRICS

Chemometrics is the science of extracting information from chemical systems by data-driven means. It is a highly interfacial discipline, using methods frequently employed in core data-analytic disciplines such as multivariate statistics, applied mathematics and computer science in order to address problems in chemistry, biochemistry, medicine, biology and chemical engineering.
CHEMOMETRICS

• Chemometrics is applied to solve both descriptive and predictive problems in experimental life sciences, especially in chemistry. In descriptive applications, properties of chemical systems are modeled with the intent of learning the underlying relationships and structure of the system (i.e., model understanding and identification).

• In predictive applications, properties of chemical systems are modeled with the intent of predicting new properties or behavior of interest. In both cases, the datasets can be small but are often very large and highly complex, involving hundreds to thousands of variables, and hundreds to thousands of cases or observations.
CHEMOMETRICS

• Chemometric techniques are particularly heavily used in **analytical chemistry** and the development of improved chemometric methods of analysis also continues to advance the state of the art in analytical instrumentation and methodology.

• It is an application driven discipline, and thus while the standard chemometric methodologies are very widely used industrially, academic and method development groups are dedicated to the continued enhancement of chemometric techniques for process monitoring and analysis.
The Last Thing We WANT
Bench Scale and Beyond

Thank You!!!

These are discussions that could go on for days, so if you have comments or questions, I look forward to the hallway discussions that are typically more fun and rewarding than these “official” presentations, but shout out a quick one NOW!!

JERRY DALFORS
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