PharmaTech
HYDERABAD 2008

USER EXPERIENCE IN DEPLOYING AUTOMATION FOR IMPLEMENTING PAT

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7th March 2008, Hyderabad

Agenda

1. What is PAT?
2. Process Analytical Technology tools
3. A desired goal of the PAT framework
4. Application of PAT in pharma industry
5. NIR,
   a. Introduction
   b. Principle NIR
   c. Hardware & Software
   d. Project & Validation Plan
6. Benefits of PAT

What is PAT?

PAT stands for Process Analytical Technology

FDA perspective.

FDA issued a guidance for industry in Sep' 2004.

The CDER, CVM, ORA worked closely with industry and held workshops and seminars to give a way forward on following:

- **Challenges for PAT system implementation,**
- **Computer compliance/ Electronic records,**
- **PAT for drug substance PSD monitoring,**
- **Validation perception that may slow down development and implementation,**
- **Validation of Rapid microbial testing systems.**

Contact FDA,
pat@cder.fda.gov

What is PAT?

Other References,

- **ASTM standards,**
- **GAMP guideline, issued in Dec' 2003,**
- **PDA, issued TR-33 in May/ June 2000; "Evaluation, Validation and Implementation of new rapid microbial testing methods.**
- **PDA journal of pharmaceutical sciences and Technology 54(3), supplement TR-33.**

What is PAT?

Definition-

Process Analytical Technology

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

PAT application v/s process validation

Process Analytical Technology tools

There are many current and new tools available that enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance.

In the PAT framework, these tools can be categorized as:

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools

Process Analytical Technology tools

- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance.

A desired goal of the PAT framework

Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:

- **Non-intrusive and non-destructive sampling of RM.**
- **Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.**
- **Preventing rejects, scrap, and re-processing.**
- **Considering the possibility of real time release.**
- **Increasing automation to improve operator safety and reduce human error.**

Process Understanding

A process is generally considered well understood when :

1. **All critical sources of variability are identified and explained.**

2. **Variability is managed by the process**

3. **Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.**

A desired goal of the PAT framework

- **Facilitating continuous processing to improve efficiency and manage variability**
  - **Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities.**
  - **Improving energy and material use and increasing capacity.**

Application of PAT in pharma industry

- Granulation, by image processing
- FBD granulation, by NIR
- Determination of tablet hardness, by NIR
- Determination of formaldehyde induced cross-linking in hard gelatin caps, by NIR
- Determination of cumulative PSD of MCC, by NIR
- Determination of CU, Assay, ID by NIR
- Rapid Microbiological Testing by NIR

Application of PAT in pharma industry

- In line moisture measurement, by NIR
- Determination of Indomethacin crystallanity, by NIR
- Determination of residual moisture in lyophilized protein pharmaceuticals, by NIR
- Determination of of polymorph composition in physical mixtures, by NIR

Introduction - NIR

- Near-Infrared Spectroscopy (NIR) is a valuable tool in the analysis of Raw materials, intermediates, fresh and Recovered solvents.
- The NIR spectroscopy extends from 780 to 2500 nm (~12800 - 4000cm-1).
- NIR is used for both qualitative and quantitative assessment of the chemical composition of samples. It may also sensitive to physical properties of the sample.

Principle - NIR

- **NIR measurement are based on passing light radiation through or into a sample and measuring attenuation of emerging (Transmitted, Scattered, or reflected) beam.**

NIR- Light Source/ Detector

- **NIR spectrometers consist of a suitable light source such as quartz or tungsten lamps**

- **Silicon, Lead sulphate, Indium gallium arsenide and deuterated triglycine sulphate are commonly used detector materials.**

Sampling Device-NIR

- Conventional cuvette sample holders, Fiber optics probes, Transmission dip cells, and spinning or Transversing sample holders are some common sampling arrangements.

- Fiber-optic technology is readily implemented in the NIR range, which allow monitoring of processes in inaccessible, remote, and challenging environments.

  Limitation is the cable length.

About NIR system

FOSS

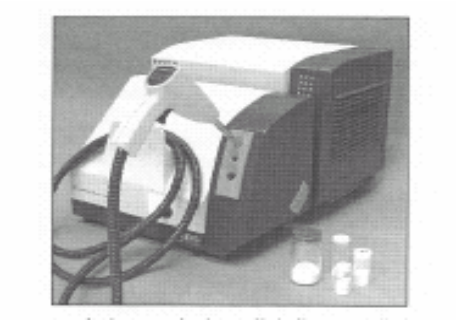
Version No.: 3.10

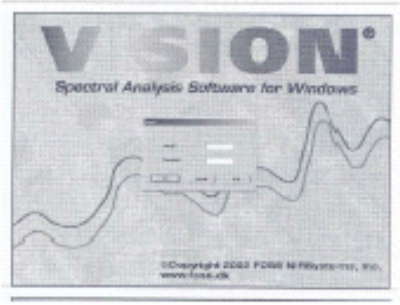
Model : XDS Smart Probe Analyzer (Shown in fig.1.0)

Software : VISION (Shown in fig.2.0)

Probe : The probe is attached with Optical fiber bundle length 3-meter (Shown in Fig. 3.0)

About NIR system





About NIR system

The instrument uses near-infrared (NIR) spectral energy to illuminate the sample.

By measuring the energy refelected off (or passing through) the sample, chemical information and composition may be determined.

This information may be used for Quantification of constituents, or for comparison to a library of known materials, providing identification and Qualification of materials

About NIR system

About Software

Software used in FOSS-NIR is 'VISION' version 3.1; it is fully validated and suitable for use on computers system in a validated environment.

The 'VISION' software is complying 21 CFR part 11.

Identification of Raw Material

Sample selection :

For identification of raw material, select minimum 10 previously approved batches

Previously analyzed and released by conventional technique.

Identification of Raw Material

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products

amples

ACICLOVIR

- B.No. # 1433605
- B.No. # 1373516
- B.No. # 1436878
- B.No. # 1430034
- B.No. # 1385638
- B.No. # 1370035
- B.No. # 1378840
- B.No. # 1436879
- B.No. # 1433602
- B.No. # 1426029

de Sample

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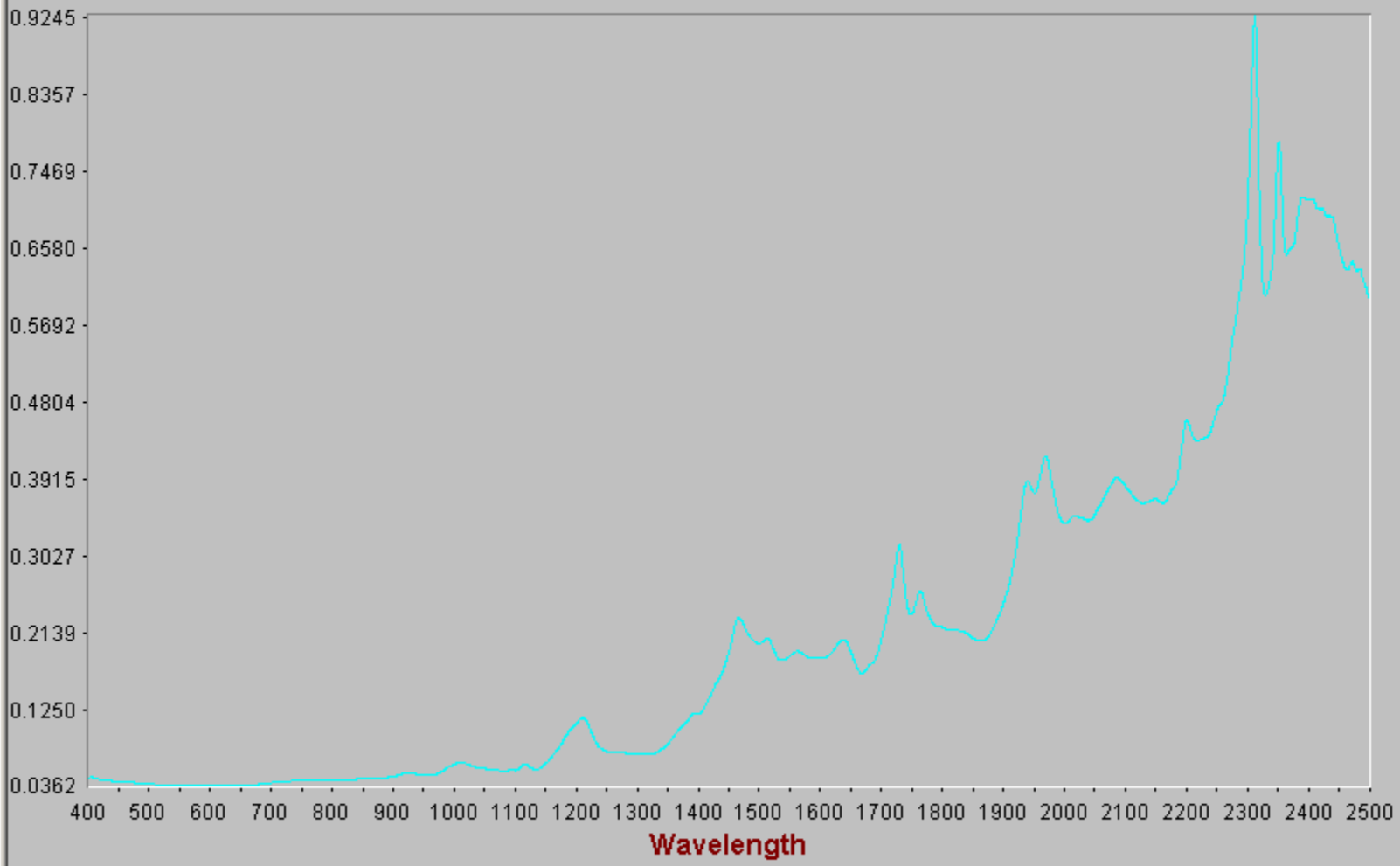

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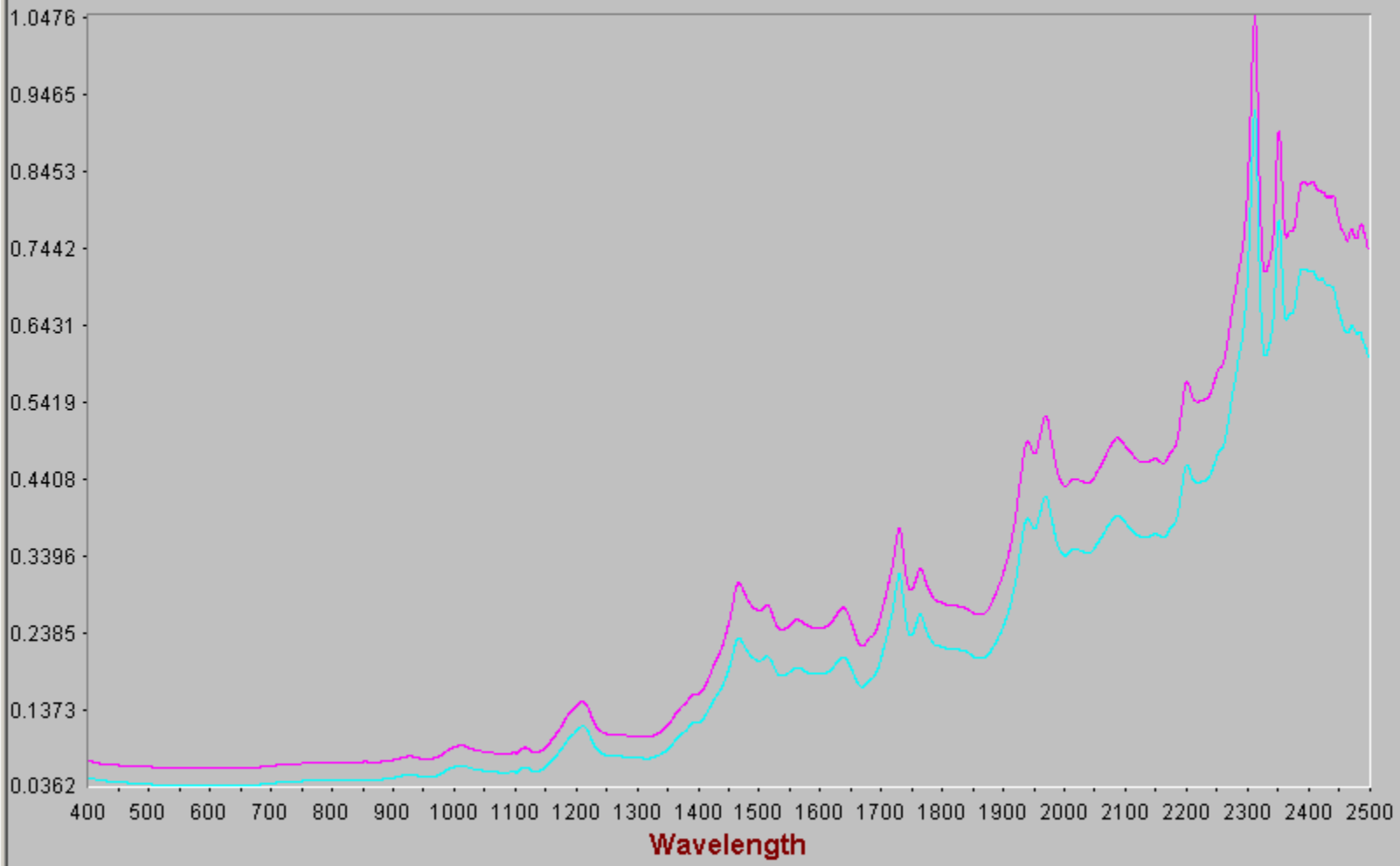

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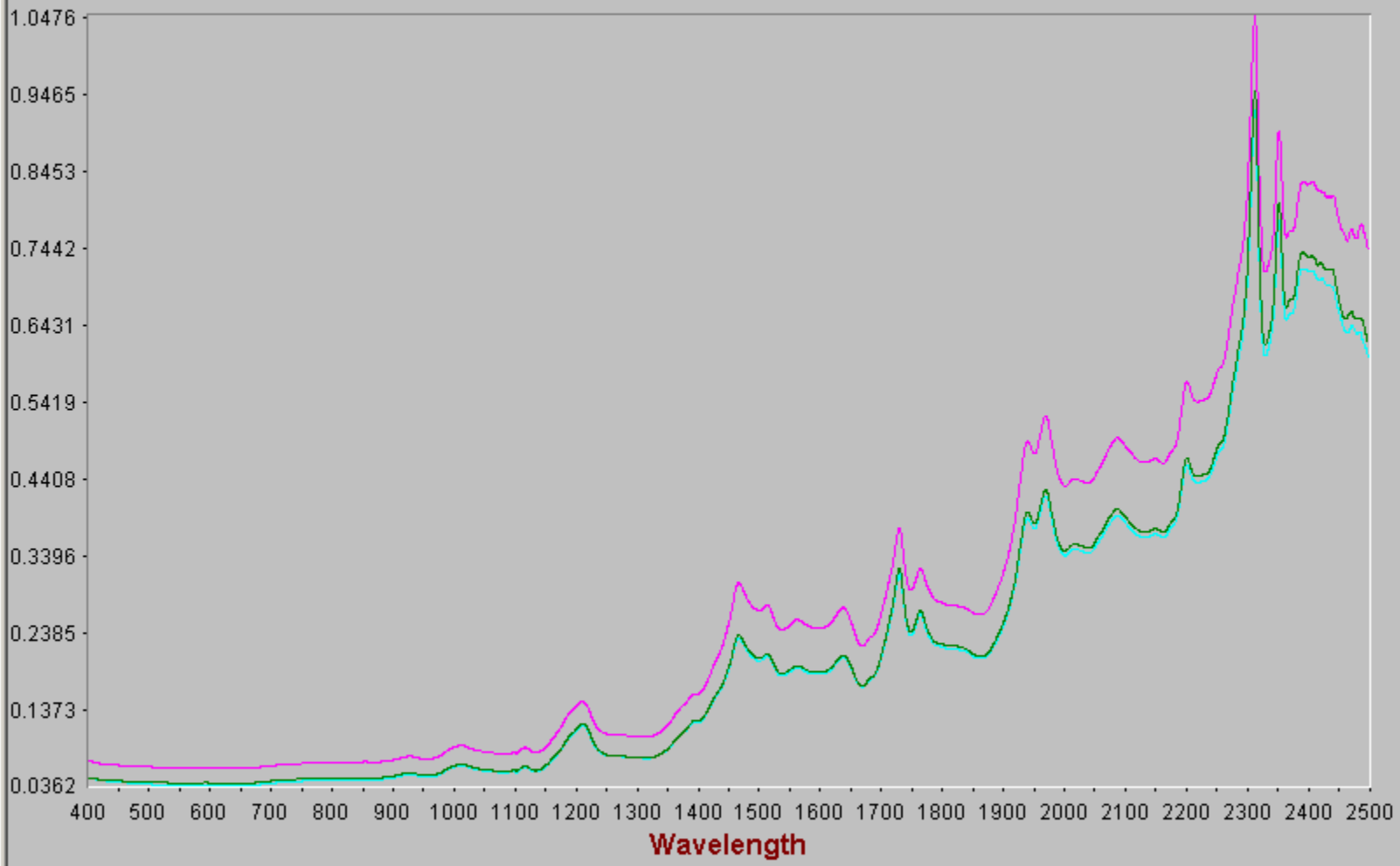

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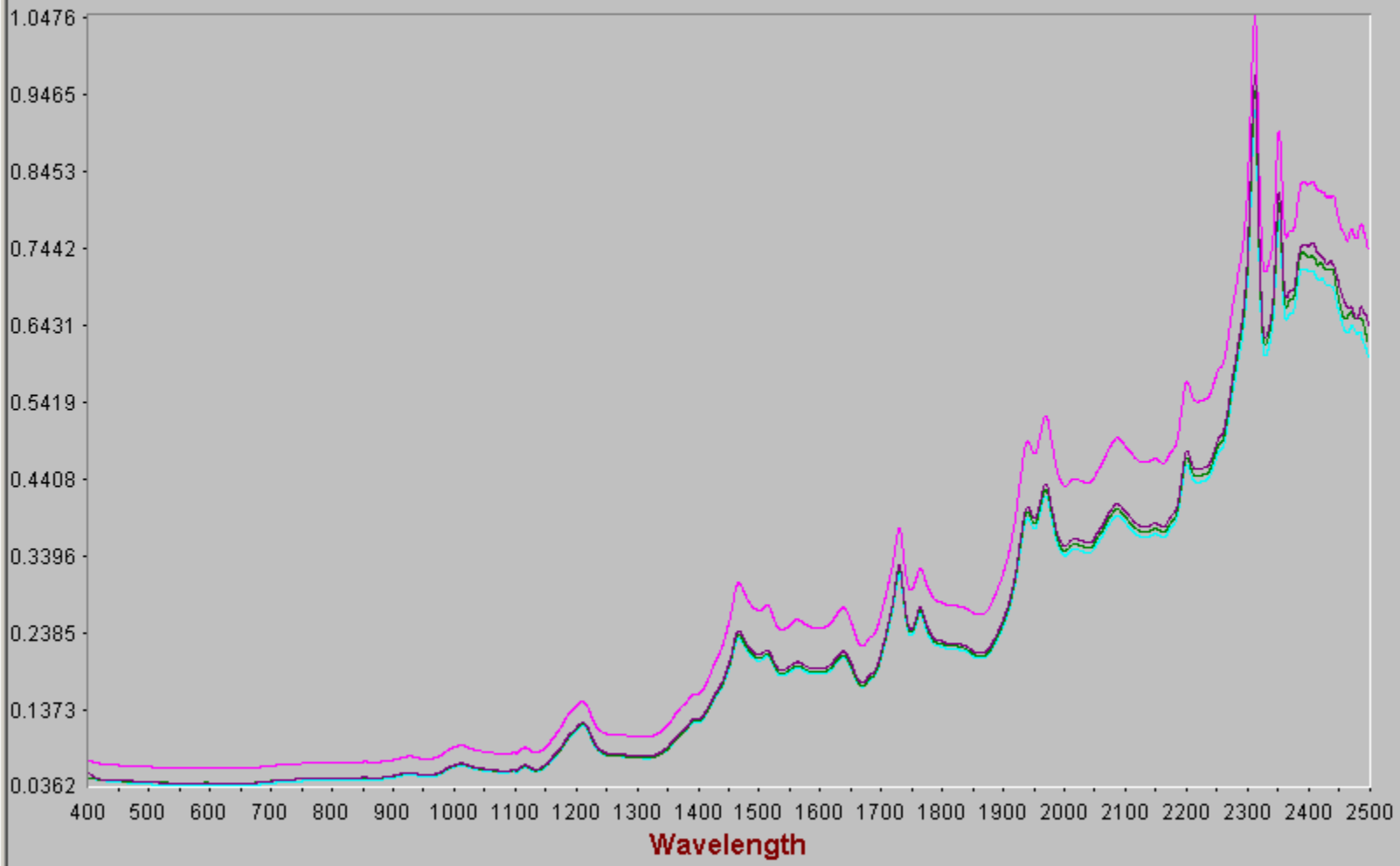

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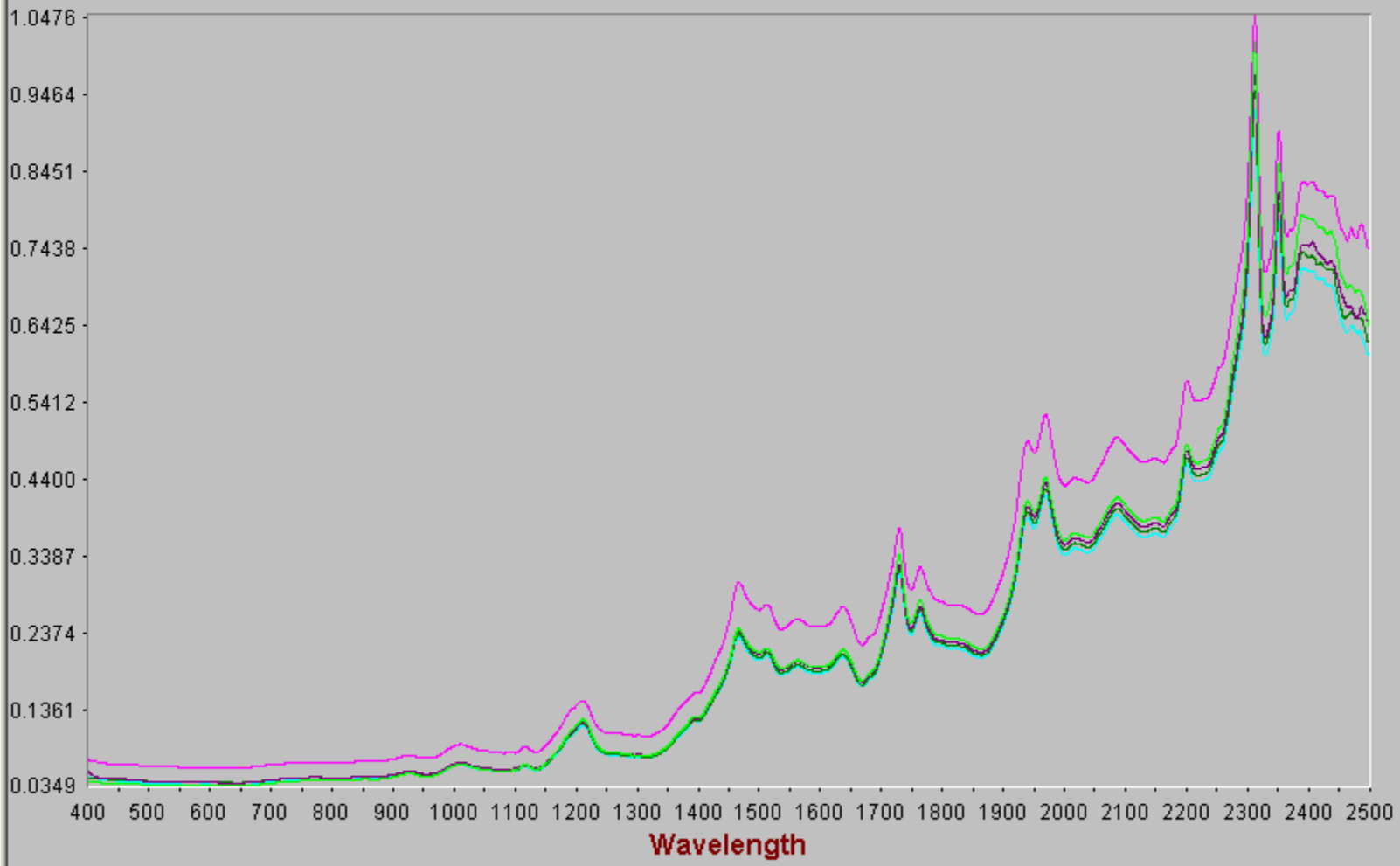

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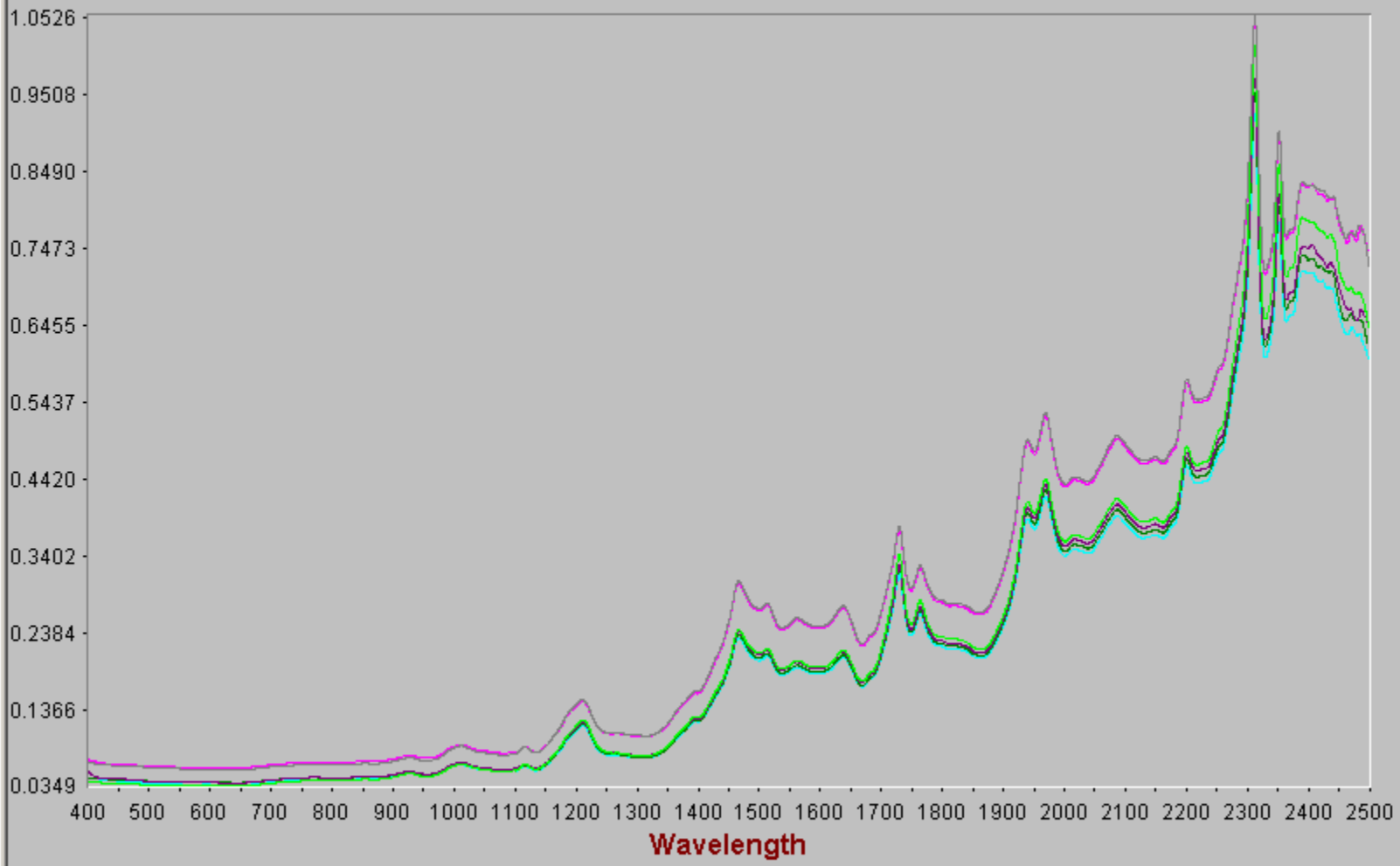

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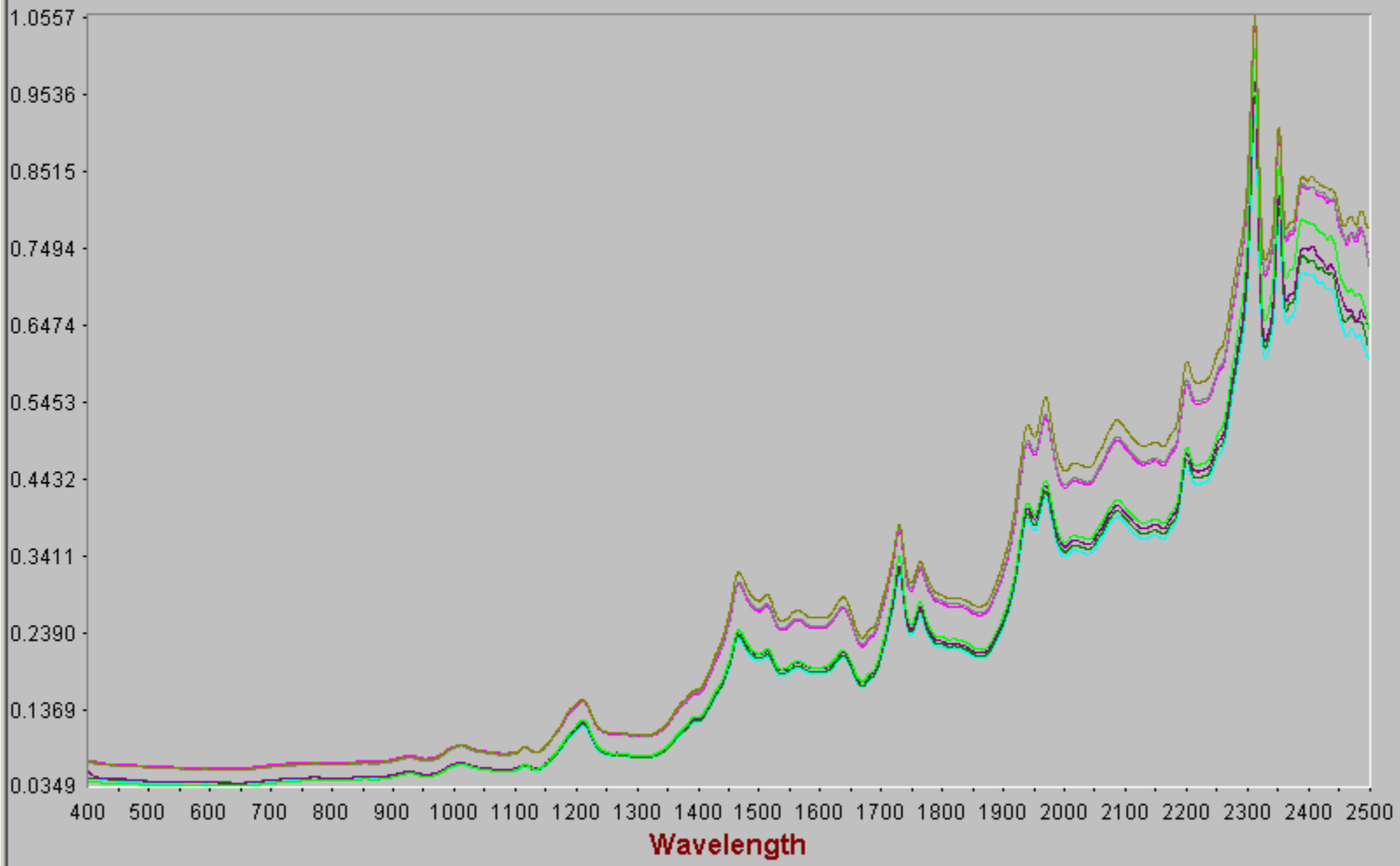

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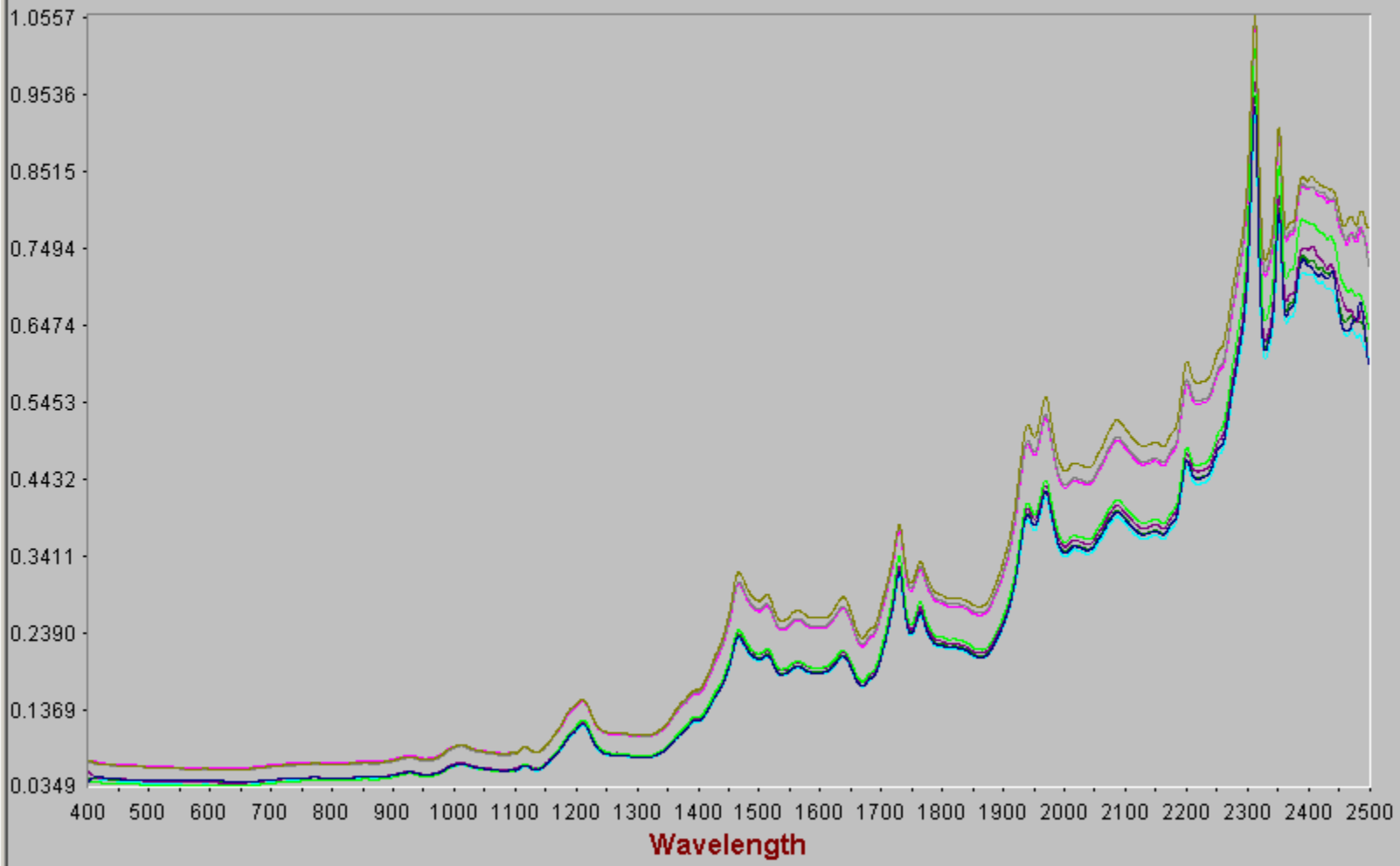

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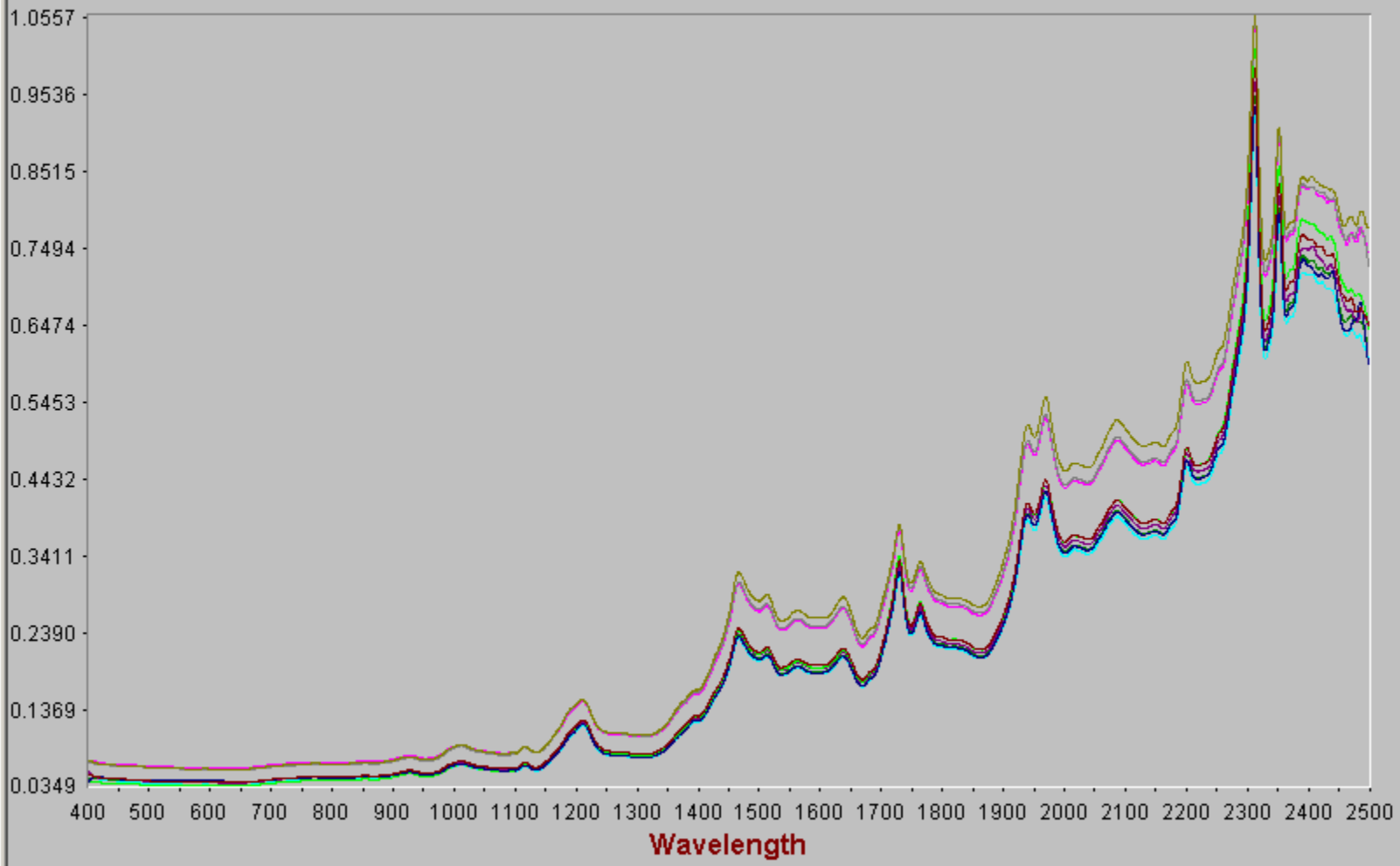

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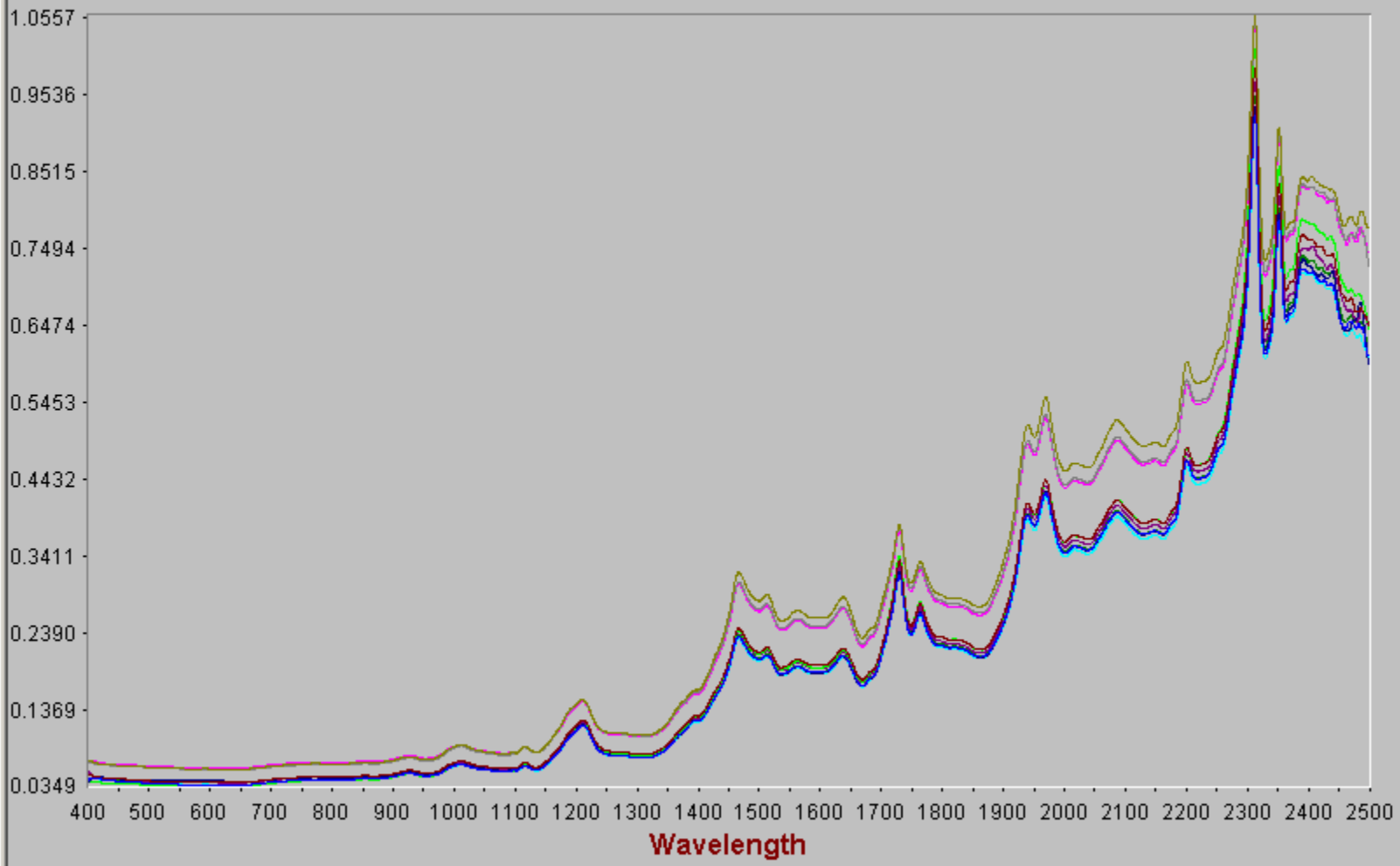

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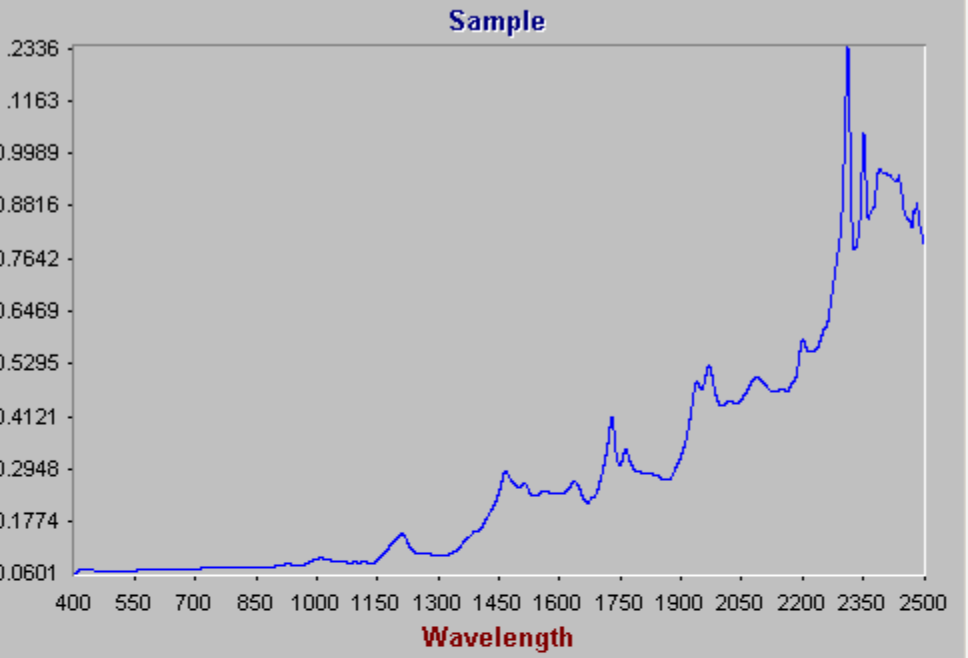

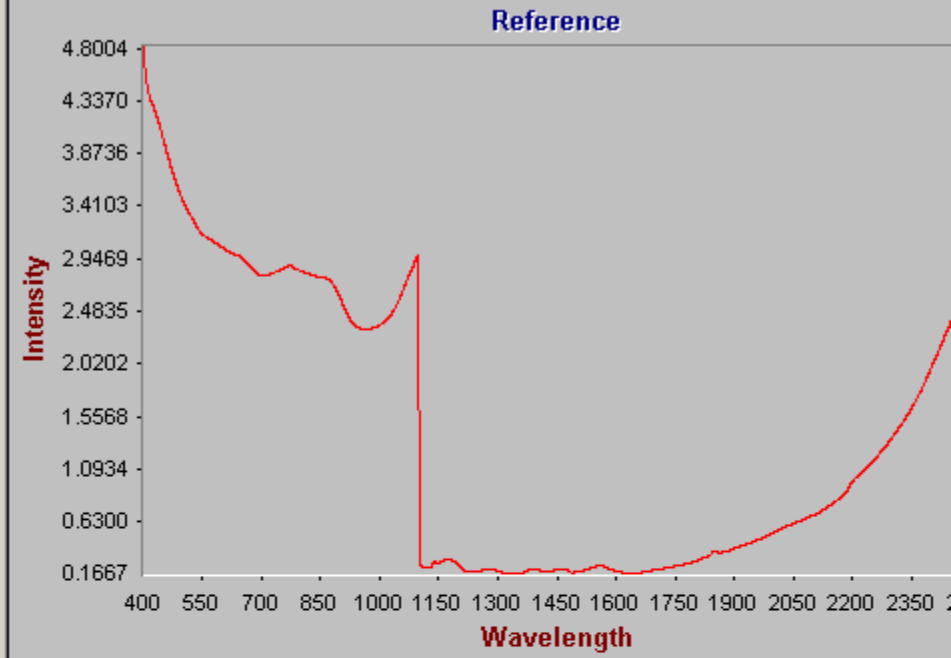

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thor/Operator: ASHISH JOSHI
trument Model: NIRSystems XDS
al number: 3010-0159
Smart probe :3014-055

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2008	15:35:53	B.No. # 1862074 C-1	ACICLOVIR	ACICLOVIR	0.987	Pass

Results

Benefits of PAT – Reducing the Cost of Capital

- Investment projections from industry leaders indicate that CAPEX spending will represent an average 11% of sales
- For the top 10 pharmaceutical companies, this represents an average spend of $3.2 billion
- 2004 average CAPEX spending amounted to 5.3% of sales (or $1.6 billion) among the top 10 pharmaceutical companies
- Looking into the future, PAT technology could become a key enabler to move from batch to continuous manufacturing
- Keeping production volumes same, continuous manufacturing would require significantly smaller space and equipment. It is likely that a several fold reduction factor could be achieved

Drug Quality System & Product Performance

Overall product quality is good, but a gap exists between the level of performance of product quality systems and the level of performance of manufacturing processes.

Drug quality systems currently perform at about a 5.5 sigma level (about 30 defects per one million opportunities), drug production process lag behind at around 2.5 sigma.

A high level of process understanding and PAT implementation are key to pushing the sigma level of the production processess higher. An improvement in overall quality performance and a reduction in quality costs would be possible with a 4.5 sigma production capability, achievable with process understanding.

The Pharmaceutical Industry is Delivering 5.5 Sigma Quality Products to the Market Using Process Generating Less Than 3 Sigma Quality

- The cost of quality includes rejects, rework, investigations and more
- In the pharmaceutical industry, the number of defective products generated during production averages 2.5 sigma or 15.87%
- Through finished product testing and inspection, the number of defects that reach the marketplace is reduced to 5.5 sigma or 0.003%

Sigma Level	Defects per Million Opportunities	Defects %
1	690,000	69
2	308,537	31
3	66,807	6.7
4	6,210	0.6
5	233	0.023
6	3.4	0.00034

Benefits of PAT – Reducing the Cost of Quality

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Each sigma shift Provides a 10% Net income improvement

The Cost of Quality

Sigma Level	Defects per Million Opportunities	Defects %	Cost of Quality
1	690,000	69	N/A
2	308,537	31	30 - 40
3	66,807	6.7	20 - 30
4	6,210	0.6	15 - 20
5	233	0.023	10 - 15
6	3.4	0.00034	10

- **Using the generally accepted figure of 25% of Sales as the current cost of quality, the top 10 pharmaceutical companies spend on average $7.6 billion each year on quality**
- **Assuming that process quality increases to 5.5 sigma level, the cost of quality would be reduced to approximately 10% of sales.**
- **This amounts to average savings of $4.6 billion annually for each of the top 10 pharmaceutical companies across all functions or about $ 1.5 billion for non clinical R&D and manufacturing.**

Thank you