Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeial Convention

The USP Excipients Stakeholder Forum
June 7, 2013

USP Spectral Library Updates

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Manager, International Business Development
U.S. Pharmacopeial Convention

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USP Mission

To improve the health of people around the world through **Public Standards** and related programs that help ensure the **Quality**, **Safety**, and **Benefit** of **Medicines** and **Foods**

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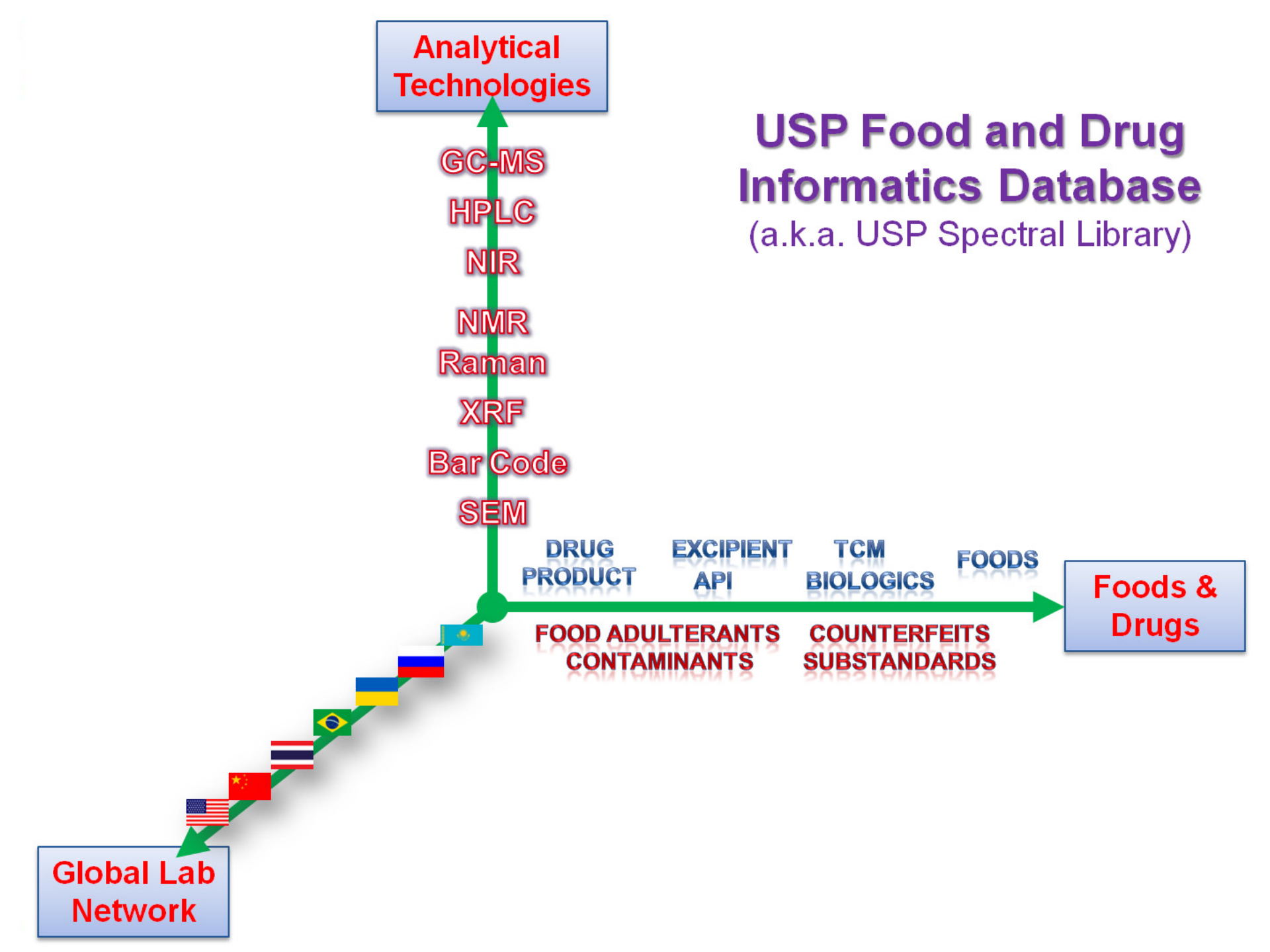
Analytical Technologies
GC-MS
HPLC
NIR
NMR
Raman
XRF
Bar Code
SEM
USP Food and Drug Informatics Database
(a.k.a. USP Spectral Library)
DRUG PRODUCT
EXCIPIENT API
TCM BIOLOGICS
FOODS
Foods & Drugs
FOOD ADULTERANTS CONTAMINANTS
COUNTERFEITS SUBSTANDARDS
Global Lab Network

USP SPECTRAL LIBRARY

USP DRUG PRODUCT SPECTRAL LIBRARY

- RAMAN SPECTRA
  - Handheld
  - Benchtop
- NIR SPECTRA
  - Handheld
  - Benchtop
- Other Analytical Technologies
  - Various Brands
- PIC, GPS, Text … Other Information

USP EXCIPIENT SPECTRAL LIBRARY

- RAMAN SPECTRA
  - Handheld
  - Benchtop
- NIR SPECTRA
  - Handheld
  - Benchtop
- Other Analytical Technologies
  - Various Brands
- PIC, GPS, Text … Other Information

USP API SPECTRAL LIBRARY

- RAMAN SPECTRA
  - Handheld
  - Benchtop
- NIR SPECTRA
  - Handheld
  - Benchtop
- Other Analytical Technologies
  - Various Brands
- PIC, GPS, Text … Other Information

UPLOAD

DOWNLOAD

Rapid Screening ~ Orthogonal Methodology ~ Instrument Dependent

Other Information to be Collected … …

- Compound Name
- CAS No.
- Molecular Formula
- Molecular Weight
- High Resolution Image
- Geographic Location
- Packaging Information
- Storage Conditions
- Bar Code / Serialization
- Manufacturer
- Lot No. / Batch No.
- FDA USP UNII Number (if applicable)
- FDA Unique Facility Identifier (if applicable)
- … …

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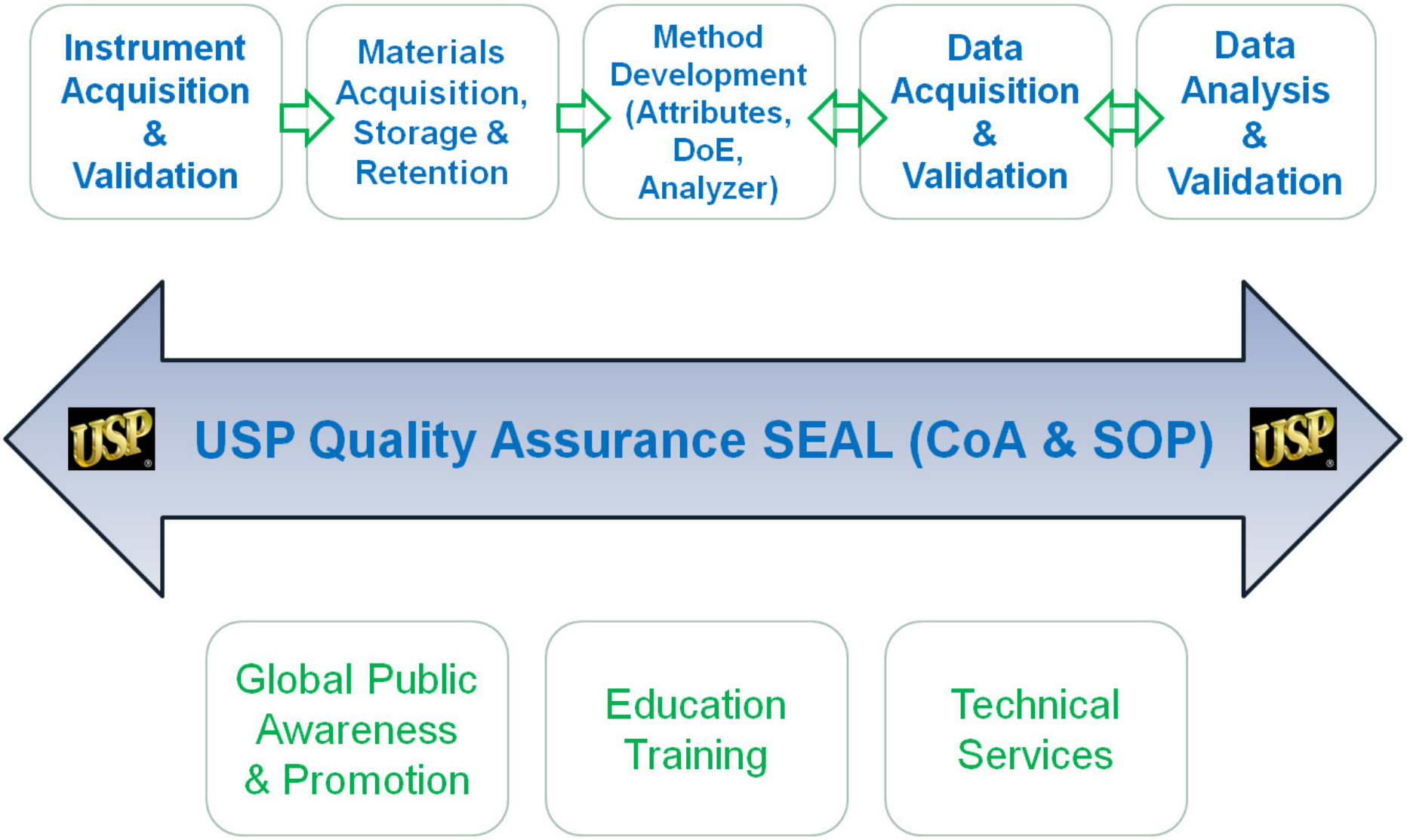
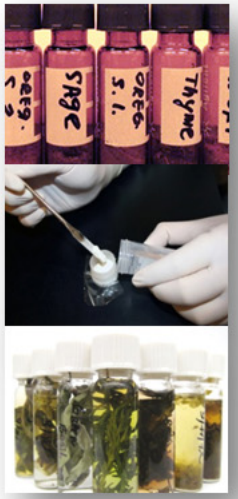
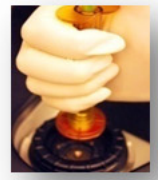
USP Spectral Library: Development Process



USP Spectral Library: Workflow Example

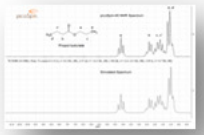


USP SOPs

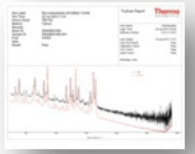



GCMS Data


NMR Data



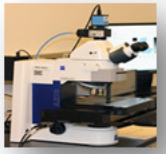

Raman Data



USP SOPs


XRF Data

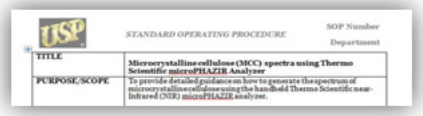
Sample Preparation
Material SOPs

MSP Data

Method Development & Validation
Instrument & Data SOPs

Data Analysis & Validation
Data SOPs



Why USP Spectral Library?

- **USP: Independent Standard-Setting Organization**
  - Provide Confidentiality Internationally
- **USP: Globally Recognized Organization**
  - Globally Recognized in over **140** Countries
  - Globally Focused with Facilities in Brazil, China, India, Switzerland and Ethiopia
- **USP: Internationally Recognized Standards**
  - Total **3000 +** Reference Standards
  - Drug Substances, Drug Products, Excipients, Food Ingredients, Dietary Supplements, Biologics ……

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Uniqueness & Key Features

- **USP Quality Assurance SEAL**
  - Fully implemented through the entire process
- **USP SOPs and CoAs**
  - Each data (e.g. spectrum has associated USP CoA and SOP)
  - Fully traceable
- **Orthogonal Methodology**
  - Multiple analytical technologies implemented
  - Instrument platform dependent
- **Key Attributes**
  - Maintain full history and information of materials
- **Alternatives to Traditional ID Testing**
- **Wizard Approach**

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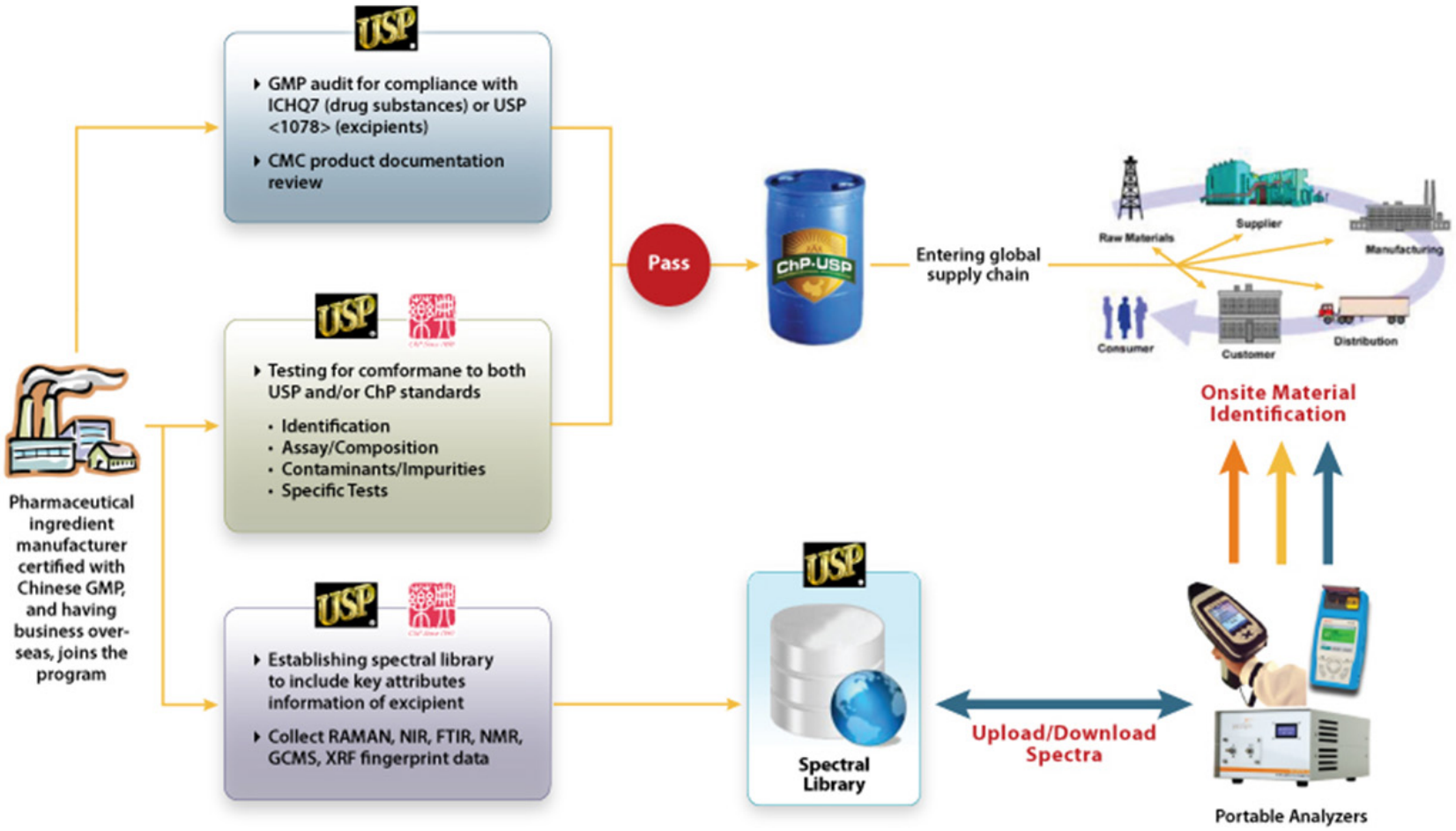
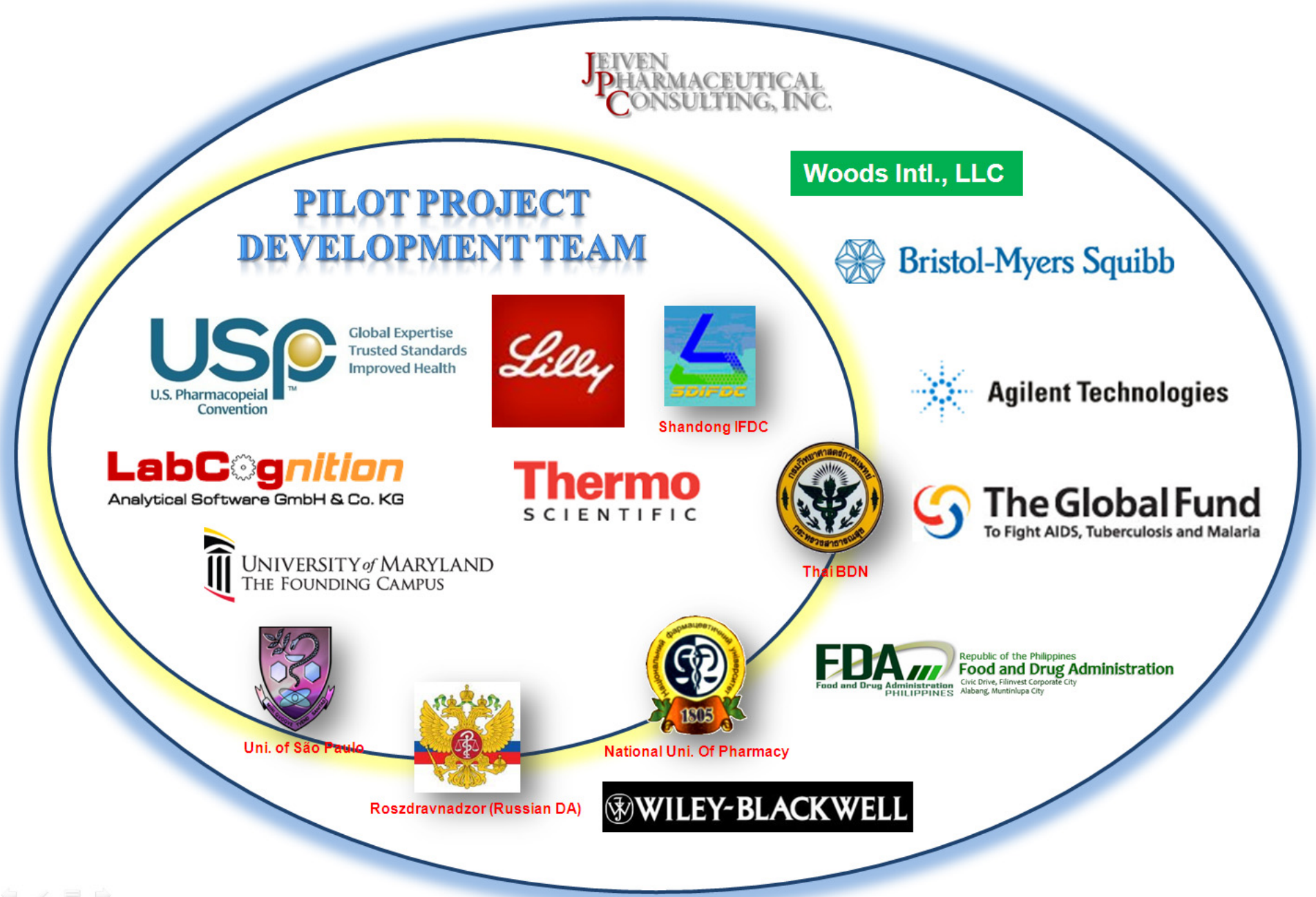
Conformity Assessment - Global Supply Chain - Risk Management

Joint Certification Program – Pharmaceutical Ingredient Pilot



To Ensure Global Supply Chain Integrity

Strategic Alliances: USP Spectral Library Consortium



Partnerships: Global Spectral Library Lab Network

Shandong Institute for Food and Drug Control

USP Spectral Library Development Laboratory

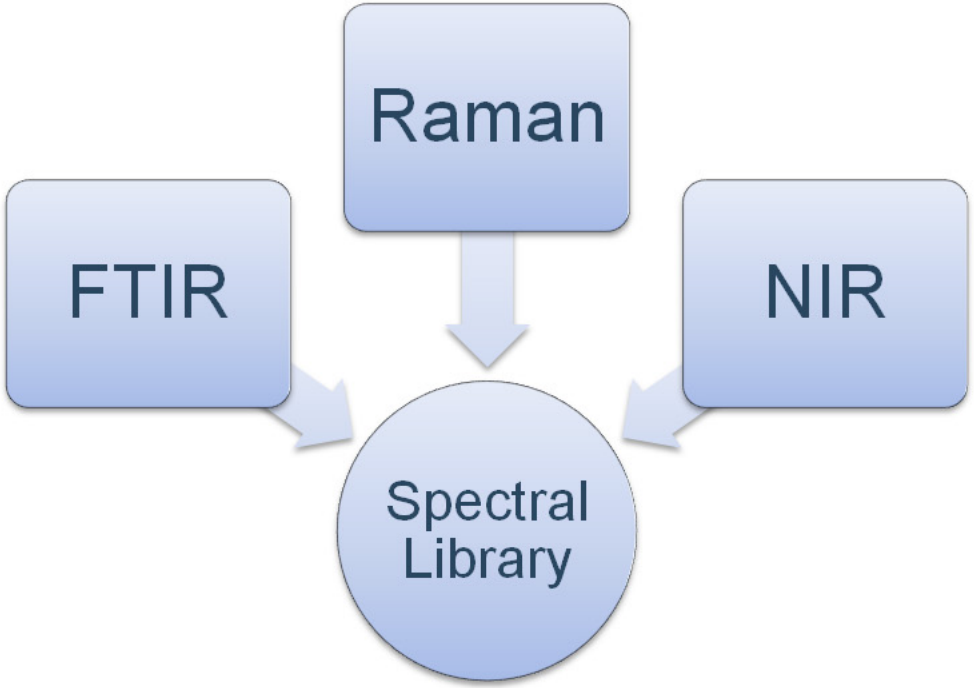
Inauguration: March 21, 2013

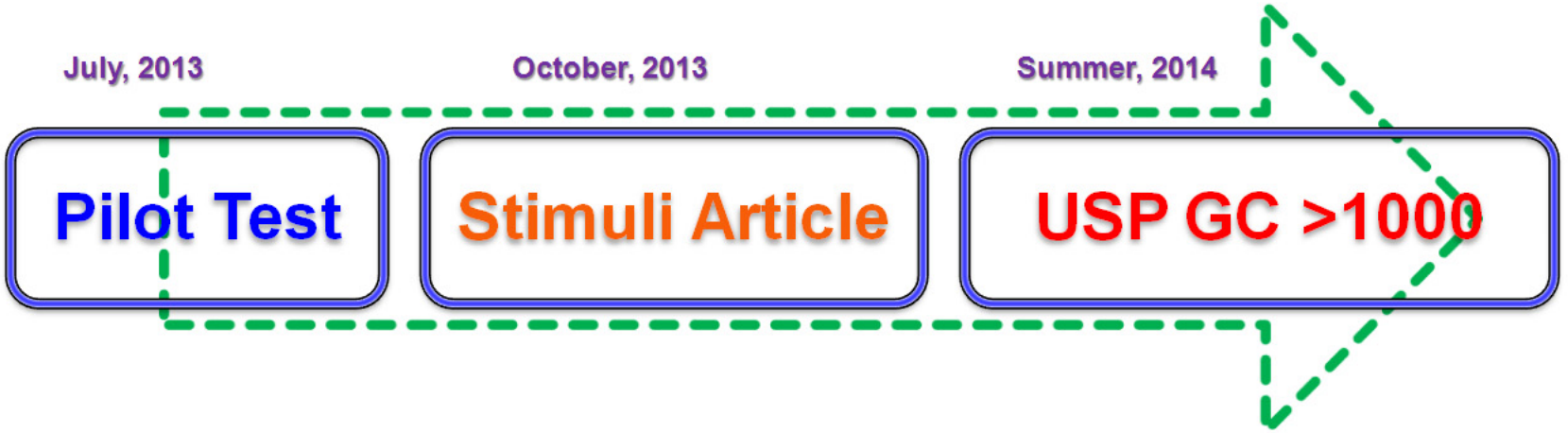
Partnerships: Eli Lilly – USP

USP U.S. Pharmacopeial Convention
Global Expertise
Trusted Standards
Improved Health
Lilly

Thermo SCIENTIFIC

Agilent Technologies





Answers That Matter.

USP Spectral Library Pilot

Michael Dotlich - Product R&D
Jeff Denault - Global Quality Labs
Eli Lilly and Company

Bei Ma
U.S. Pharmacopeial Convention

Answers That Matter.

Collaboration

Eli Lilly and Company is interested in partnering with the USP in establishing a global spectral library as an alternate means to test pharmaceutical raw materials such as excipients and finished drug products. The collaboration will provide an alternate industry standard for sample identity testing that will reduce the potential for introducing counterfeit or adulterated material into the consumer drug system. Lilly continues to develop, evaluate, and implement standard libraries across its drug network and appreciates the opportunity to participate in the shared learning of both generating and evaluating the spectral library data.

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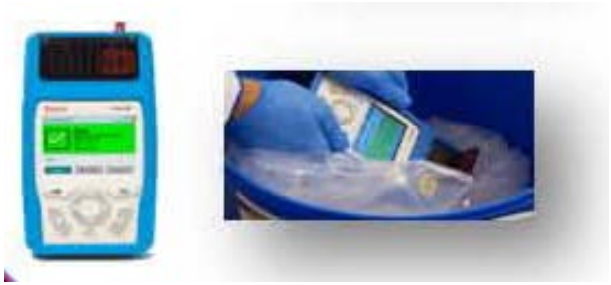
Instrumentation

Raman
Truscan RM



FTIR
Agilent Cary 630

NIR

NIR was considered: Experimental design requirements limited its evaluation within the pilot time window.

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Instrumentation Pros and Cons

Raman

- ✓ Portable / Handheld
- ✓ Chemical specificity (characteristic chemical bonds)
- ✓ "Wet" samples may be analyzed directly
- ✓ Limited number of samples required to begin analysis
- ✓ Direct comparison of reference to sample
- ✓ Electronic Records
- ✓ Rapid analysis
- ✓ **No sample preparation**
- ✓ **Limited sampling - Analysis through most packaging materials**
- ✗ Not a typical Quality Control technology

FT-IR

- ✓ Portable / Handheld
- ✓ Chemical Specificity (characteristic chemical bonds)
- ✓ Limited number of samples required to begin analysis
- ✓ Electronic Records
- ✓ Direct comparison of reference and sample
- ✗ Sample preparation can be tedious
- ✗ Sampling for "off-line" analysis
- ✗ Packaging

NIR

- ✓ Portable / Handheld
- ✓ Non-specific chemical response – strong hydrogen bonding influence
- ✓ No sample preparation
- ✓ Electronic Records
- ✓ Limited sampling
- ✓ Rapid analysis
- ? Packaging
- ✗ **Requires chemometric modeling and expertise to manage**
- ✗ **Many samples needed to build model to account for material variability,**
- ✗ Requires model maintenance to ensure appropriateness for intended use
- ✗ Not a typical Quality Control technology

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Reference Material

1. Raman – Include single reference scans in library. Reference material is to be representative of tested material and in most cases highly pure (99%+) raw materials. Materials with low level contaminants can be included; however, important that the testing capability is not diluted (e.g. lactose anhydrous with 5% lactose monohydrate).
2. FTIR – Include multiple standard scans, but must exercise caution to make sure items that require failure, will fail..
3. NIR – Model the options, however, the model must be challenged to show specificity to the material and not of a secondary component such as water in the material. Building models can be time consuming.
4. Materials of lower purity are acceptable provided the standard is consistent with all future samples.
5. Most ID methods will not be designed to capture low level impurities, unless, of course the technology is capable (mass spec, GC, NMR).

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Chemical Selectivity

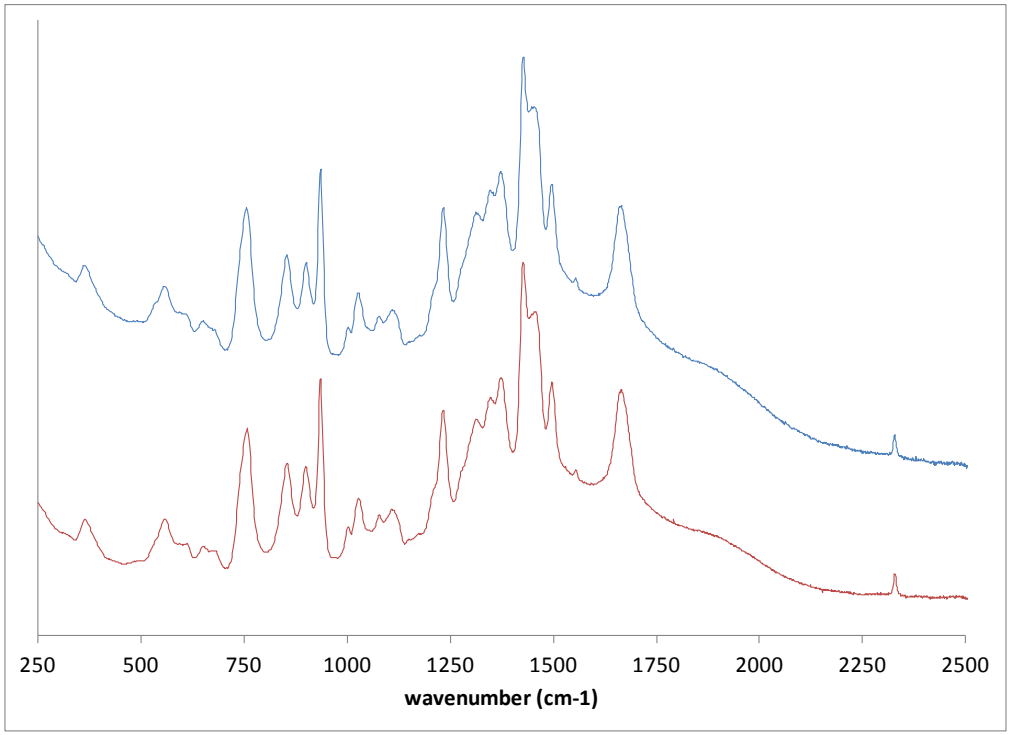
Selectivity Challenges

Some materials are too similar to be analyzed by Raman alone.

For povidone and crospovidone, two commonly used pharmaceutical excipients, the Raman spectra are not distinguishable.

This lack of selectivity may be addressed through supplemental testing, e.g., Raman plus solubility test or NIR.

Crospovidone and Povidone Reference Scans



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Pilot Materials

Material Name	Compendial Class	CAS No.	Supplier 1	Supplier 2	USP RS	Rationale
Fluoxetine HCl	API	59333-67-4	Eli Lilly	Eli Lilly	Yes	Small molecule API with strong raman scattering
Anhydrous Lactose	Excipient	63-42-3	Kerry Bio-Science	Sigma-Aldrich	Yes	Similar materials
Lactose Monohydrate	Excipient	5989-81-1	Sigma-Aldrich	Fisher Scientific	Yes	
Lactose Monohydrate	Excipient	64044-51-5	Foremost Farms USA	Sigma-Aldrich	No	
Sodium Bicarbonate	Excipient	144-55-8	Avantor	Sigma-Aldrich	Yes	Similar materials
Sodium Carbonate	Excipient	497-19-8	Strem Chemicals	Fisher Scientific	Yes	
Microcrystalline Cellulose	Excipient	7558-79-4	JRS Pharma	Sigma-Aldrich	Yes	Medium Raman Scatterer
Titanium Dioxide	Excipient	1317-70-0 (Anatase)	Sigma-Aldrich	Alfa Aesar	No	Similar materials of different crystal forms.
Titanium Dioxide	Excipient	13463-67-7 (Rutile)	Acros Organics	Strem Chemicals	Yes	
Talc	Excipient	14807-96-6	IMI FABI LLC	Sigma-Aldrich	No	Poor raman scatterer – good for FTIR/ NIR

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Sample Presentation

Reference scan robustness was assessed by testing different sample presentations.

1. Polyethylene bags – Ideal for raman and is consistent with testing warehouse stored bulk materials. Will not work with FTIR and possible option for NIR if polyethylene peaks are not included in the model.
2. Glass Vials (1 dram) – Raman and NIR option if sampling is necessary.
3. Neat – A subset of the USP's digital reference spectral library. Sample placed 5 mm from nose cone.

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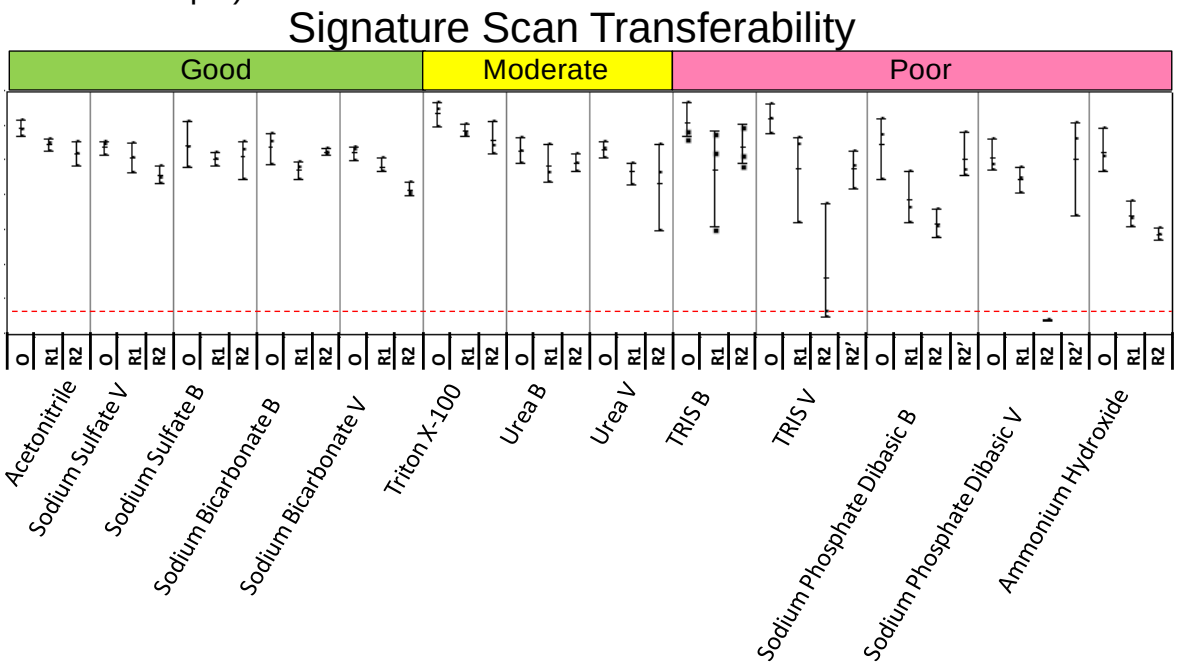
Sources of Variability

FTIR

- Analyst – Sample preparation/ handling (e.g. ATR)
- Instrument – Four instruments/ analysts to capture instrument variability.
- Material (i.e. source of sample)

Raman

- Analyst – Expect little analyst effect (i.e. fixed nose cone).
- Instrument – Six instruments/analysts to capture instrument variability.
- Material (i.e. source of sample)



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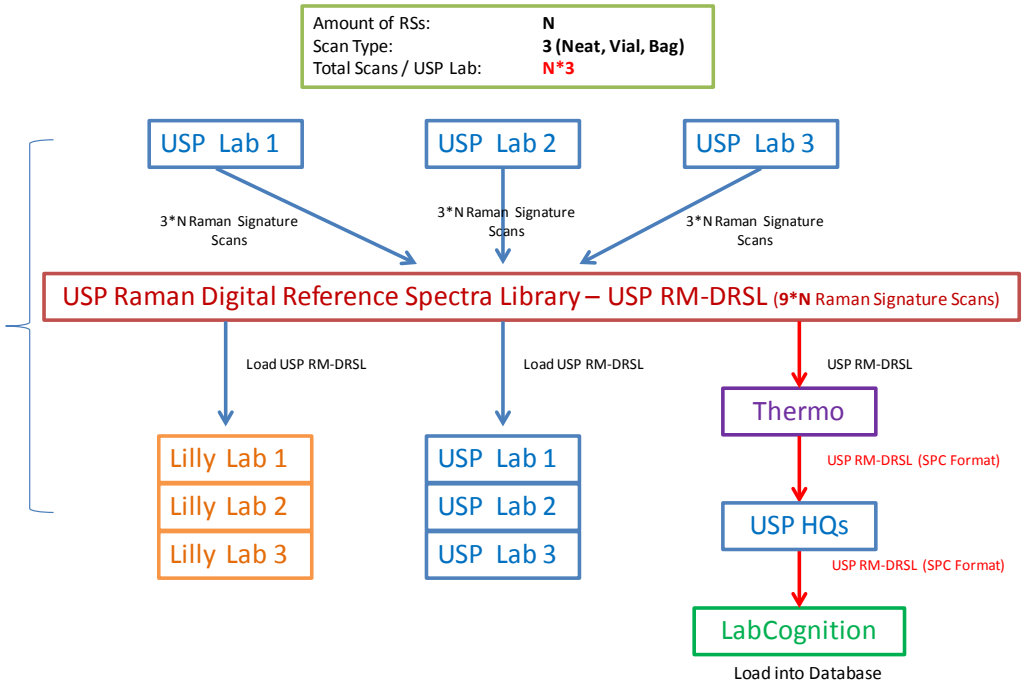
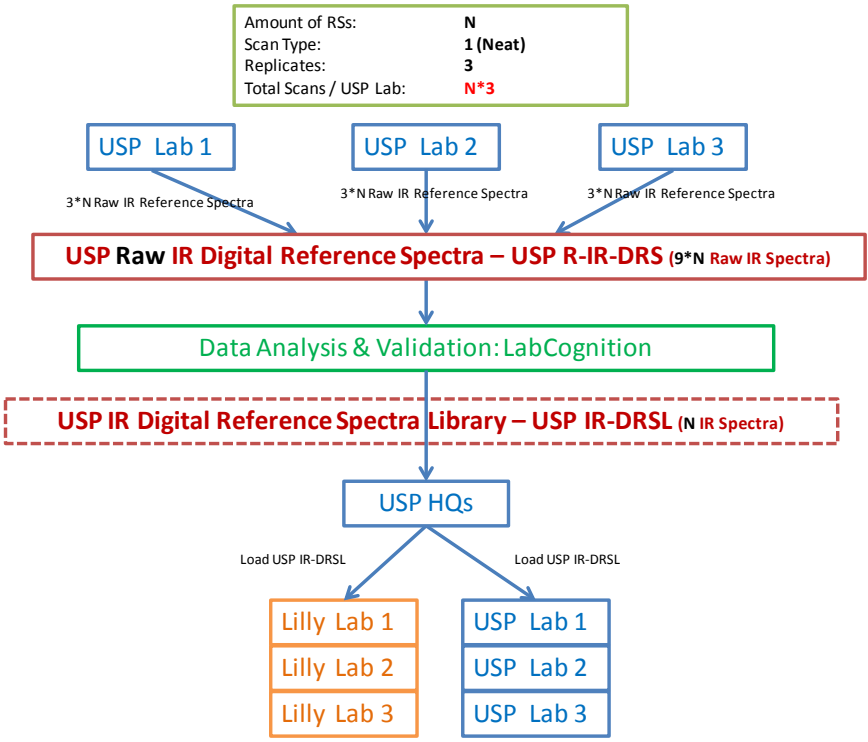
Reference Standard Collection

USP Collaborative Testing Model – Testing and results from multiple labs are averaged for final result to characterize the reference standard.

Raman – Test from three labs will be included in library.



Infrared – Reference standard scans from three labs will be averaged for final reference scan.



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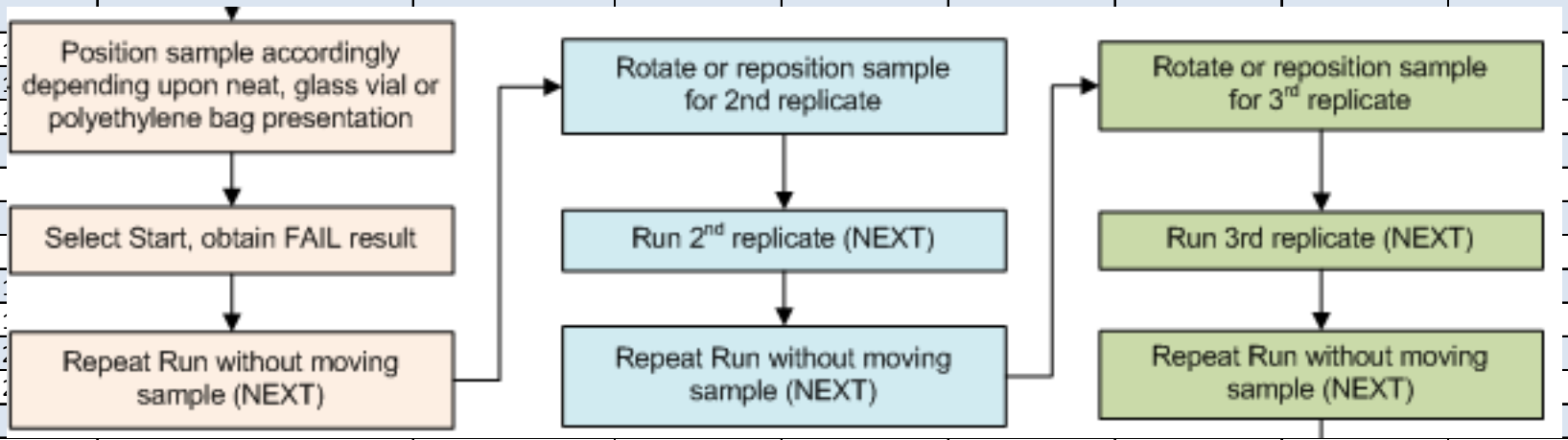
Raman Sample Run (6 Instruments)

RUN ORDER	MATERIAL	PACKAGING	Pos1, Rep1	Pos1, Rep2	Pos2, Rep1	Pos2, Rep2	Pos3, Rep1	Pos3, Rep2
19	Fluoxetine Hydrochloride	neat						
14	Fluoxetine Hydrochloride	vial						
20	Fluoxetine Hydrochloride	bag						
22	Anhydrous Lactose	neat						
17	Anhydrous Lactose	vial						
21	Anhydrous Lactose	bag						
15	Lactose Monohydrate - 1	neat						
24	Lactose Monohydrate - 1	vial						
8	Lactose Monohydrate - 1	bag						
5	Lactose Monohydrate - 5	neat						
27	Lactose Monohydrate - 5	vial						
26	Lactose Monohydrate - 5	bag						
23	Sodium Bicarbonate	neat						
30	Sodium Bicarbonate	vial						
16	Sodium Bicarbonate	bag						
1	Sodium Carbonate	neat						
29	Talc	bag						



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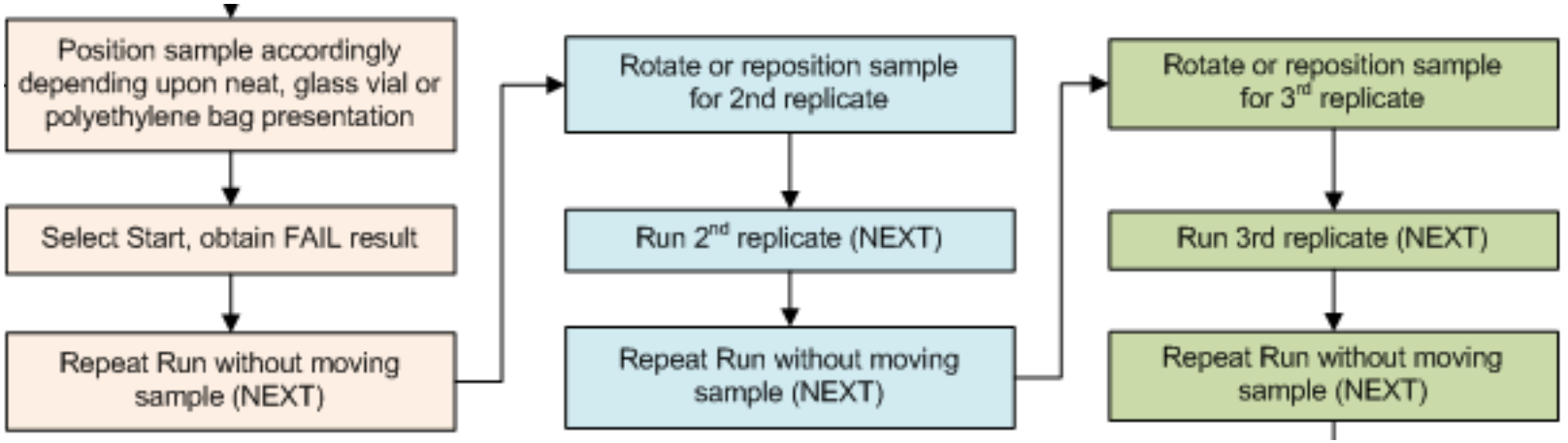
FTIR Sample Run (4 Instruments)

RUN ORDER	MATERIAL	PACKAGING	ATR1, Rep1	ATR1, Rep2	ATR2, Rep1	ATR2, Rep2	ATR3, Rep1	ATR3, Rep2
7	Fluoxetine Hydrochloride	neat						
6	Anhydrous Lactose	neat						
10	Lactose Monohydrate - 1	neat						
5	Lactose Monohydrate - 5	neat						
2	Sodium Bicarbonate	neat						
1	Sodium Carbonate	neat						
8	Microcrystalline Cellulose	neat						
3	Titanium Dioxide - A	neat						
9	Titanium Dioxide - D	neat						
4	Talc	neat						



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Applications of Spectral Library

The USP global spectral library will provide a robust standard library for raw materials that will be tested for variability (e.g. vendor, instrument, container) allowing the user to minimize their time developing their own reference library.

Similar to the USP Reference Standards, digital reference standards will offer a consistent spectroscopic approach to testing materials as an alternate method to traditional wet chemistry identification testing.

A general chapter (>1000) guidance on the application and use of a spectral library will provide a standard approach for spectroscopic identity analysis and help expand the current methods of testing.

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