

General Capabilities

2023



Improved Pharma

We are a research, consulting, and information company aimed at helping our clients bring drugs to market

Experts in pharmaceutical development

■ Industry leaders for decades

- Focus on R&D to bring cutting-edge technologies and applications to our clients
- Formulation development: synchrotron, levitated drop, amorphous dispersions, reformulations, reverse-engineering
- Polymorph, salt, cocrystal, crystallization, amorphous and microgravity screens
- Analytical characterization: diffraction, spectroscopy, microscopy, thermal analysis, water determination, HPLC, dissolution, viscosity, micromeritics, particle size
- Abuse deterrent testing: pseudoephedrine and opioid formulations
- Quality, regulatory, lean six sigma, operations, and intellectual property expertise

■ Metrics and accomplishments

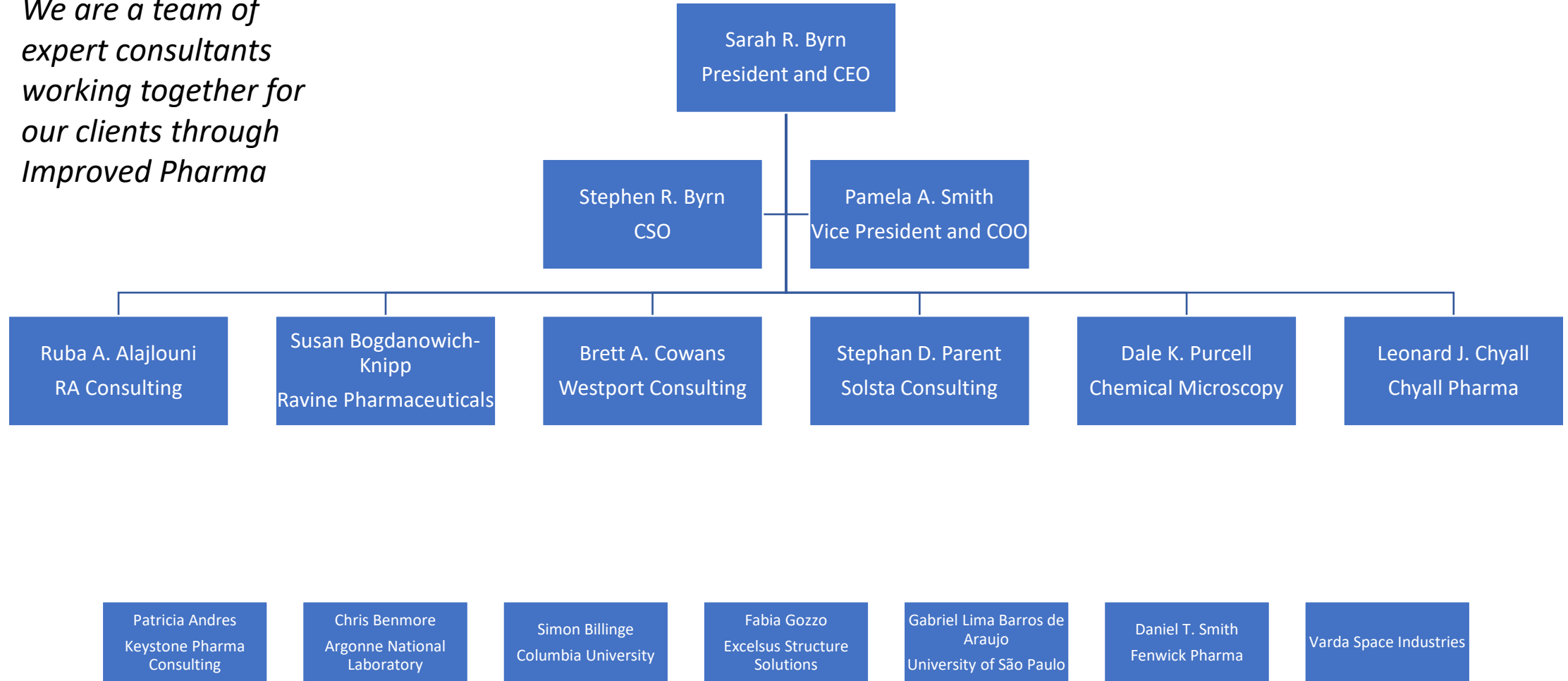
- Decades of experience working together as a team through Purdue, SSCI, and Improved Pharma
- Hundreds of presentations, peer-reviewed publications, and books
- IP development for over 100 patents/applications in the US
- Technical and legal support for hundreds of companies
- Able to handle schedules I – V controlled substances

Company history

- Late 60's:
 - Prof. Byrn's research in polymorphism begins and has continued through today
- 1991:
 - The Byrns found SSCI, the first solid-state service provider and the gold standard in the industry for decades
- 2006
 - SSCI grows to 100 employees and \$20M revenue; sold to Aptuit
 - The Byrns found Improved Pharma as a research and information company
- 2018
 - COO added
 - Collaborations established
- 2020
 - Laboratory space acquired
 - First consultants join
- 2021
 - Laboratory space doubles
 - Additional consultants join
- 2022
 - Additional consultants join
 - Additional collaborations established

The Improved Pharma Team and Collaborators

*We are a team of
expert consultants
working together for
our clients through
Improved Pharma*

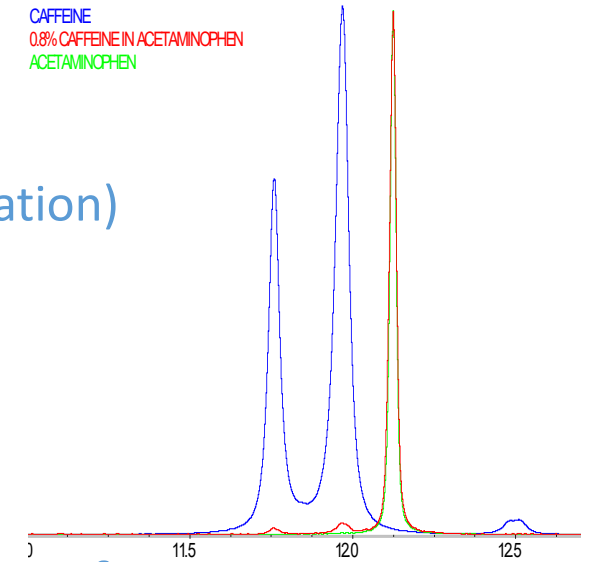


Capabilities outline

- Cutting-edge synchrotron capabilities with global capacity
- Formulation capabilities
- Solid-state form studies
- Microscopy-based screens
- Microgravity studies
- Analytical capabilities
- Consulting services

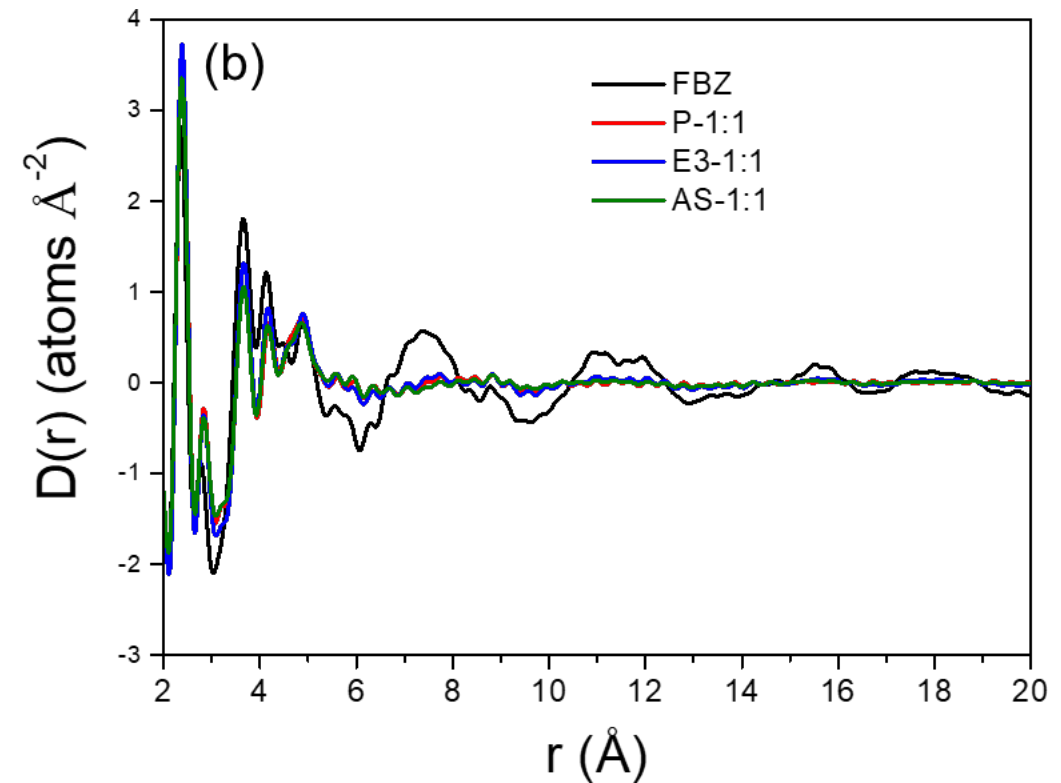
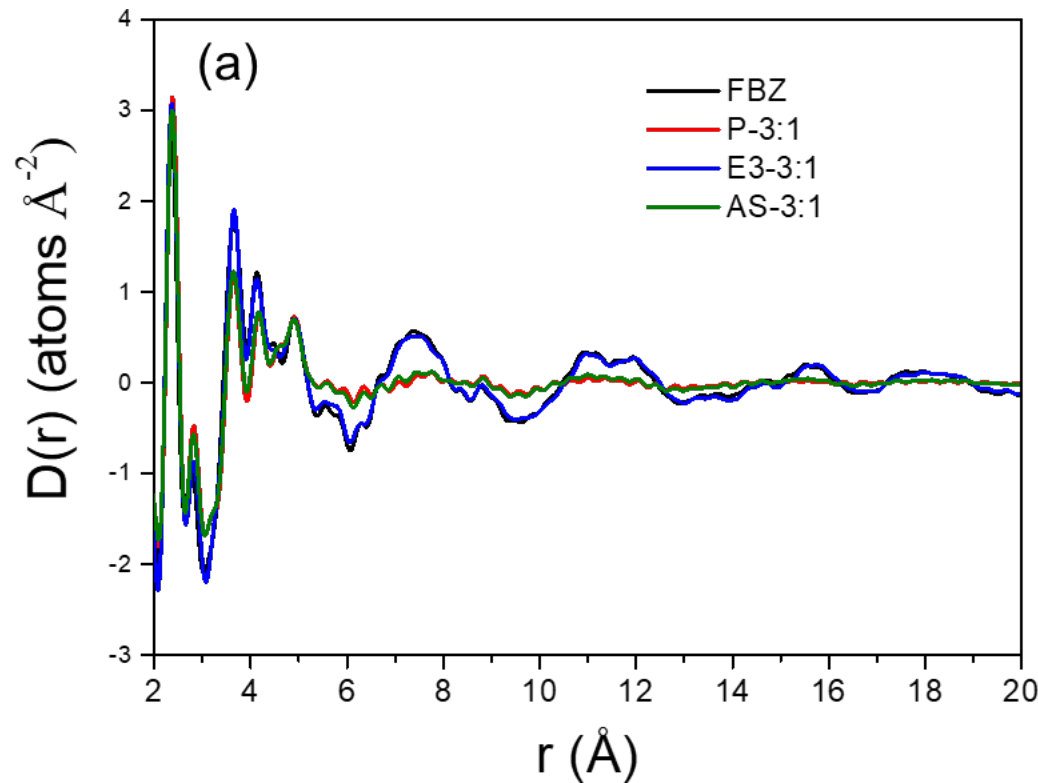
Cutting-edge synchrotron capabilities with global capacity

- Trained users at the Advanced Photon Source (Argonne)
 - Beamline 6-ID-D for high-energy x-ray PDF work
 - Characterization of amorphous materials (e.g. sameness)
 - Variable RH and temperature (detection of hydration prior to crystallization)
 - Beamline 11-BM-B for high-resolution powder diffraction
 - High-resolution (better specificity for resolving complex mixtures)
 - High-sensitivity (easily detect tenths of a percent of an impurity)
- National Synchrotron Light Source
 - Collaboration with Dr. Simon Billinge, an expert in the structure of nanoparticles
- Swiss Light Source (Paul Scherrer Institute)
 - Collaboration with Dr. Fabia Gozzo of Excelsus Structure Solutions
 - Ab-initio structure solution
 - Quantitative phase analysis
 - PDF



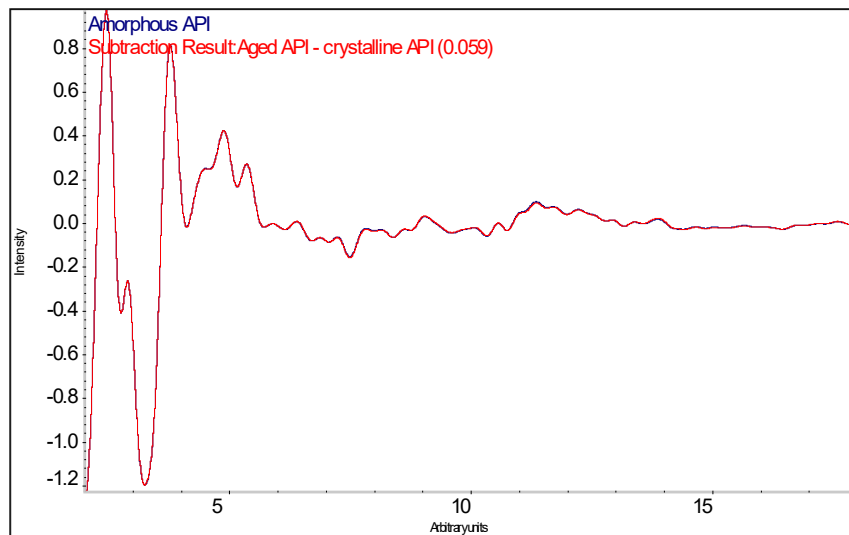
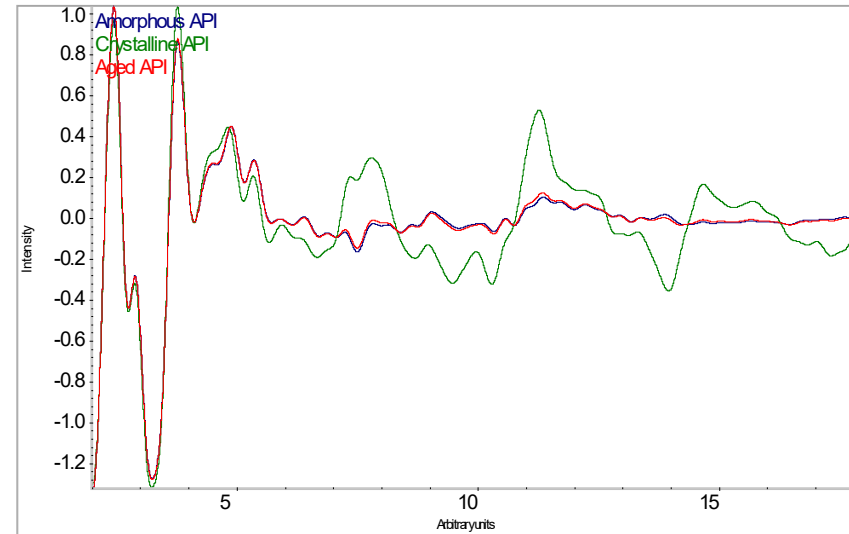
Cutting-edge synchrotron capabilities, example 1

- PDF analysis of amorphous formulations to predict stability of different dispersions
 - The 3:1 flubendazole:HPMC-E3 dispersion PDF shows domains (ordered three-dimensional intermolecular arrangements) and eventually crystallized



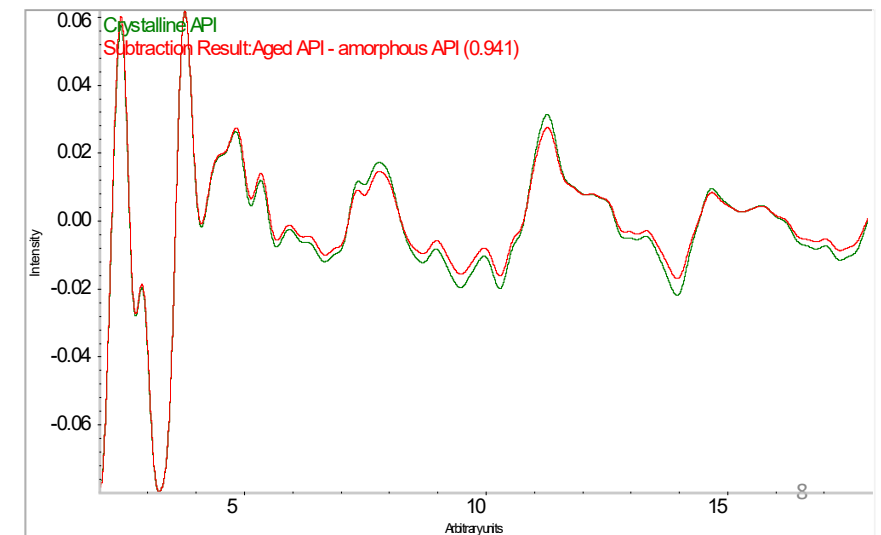
Cutting-edge synchrotron capabilities, example 2

- Quantifying crystalline content in an aged amorphous sample



5.9%
crystalline

94.1%
amorphous



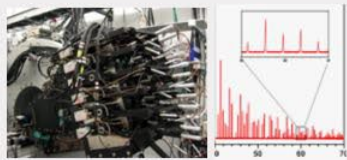
Formulation capabilities

- Improve formulations of existing products
 - Example 1: more than doubled the solubility of the API and improved the pH of an injectable product
- Reverse engineering
 - Example 2: reverse-engineered an existing suspension-based formulation and developed a new formulation using alternative materials
- Synchrotron-based formulation design
 - Especially helpful for spray dry formulations, as multiple parameters such as solvent, polymer, polymer to drug ratio, salt formation, surfactants, and drying rate can be optimized via DOE, PDF, stability tests, and dissolution performance
- Synchrotron-based fast to IND (s-fIND)
 - Accelerated development
- Lab on a Drop
 - Amorphous screens

S-fIND

■ Synchrotron-based fast-to-IND

SYNCHROTRON X-RAYS

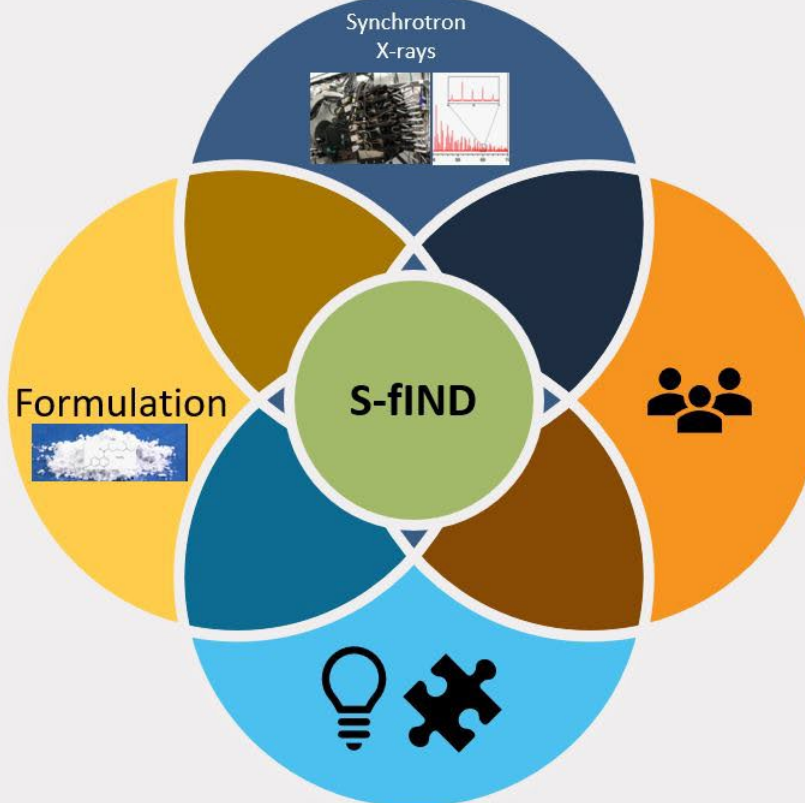


Synchrotron X-ray, because of its sensitivity and capabilities, speeds development and avoids delays. S-X-ray methods allow for the detection of new polymorphs and analysis of formulations with greatly enhanced sensitivity.

FORMULATION DESIGN



Robust formulation design based on strong solid-state chemistry is a key step in drug development. Furthermore, unique solutions often create intellectual property and Improved Pharma transfers all intellectual property to the contractor.



OUR PEOPLE

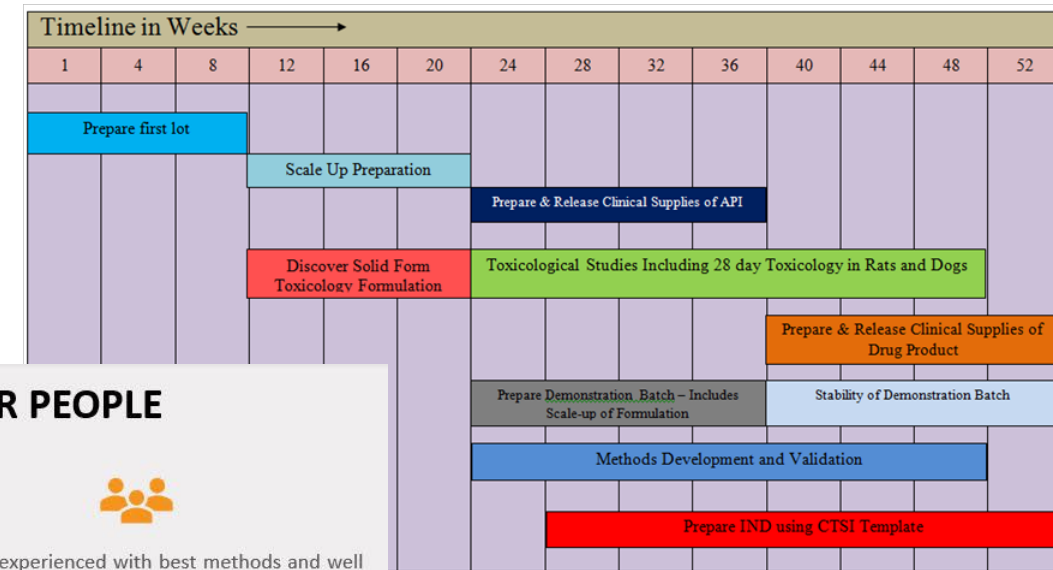


Highly experienced with best methods and well connected with best contractors. Improved Pharma Integrates your development plan to reduce time and avoid waste. Extensive experience allows derisking of project flow and accelerates your project to IND.

PROBLEM SOLVING

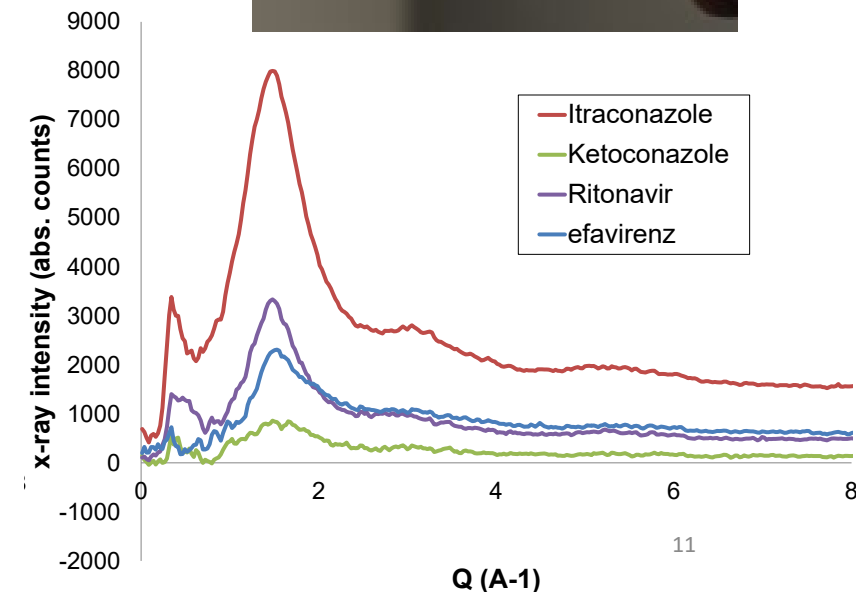
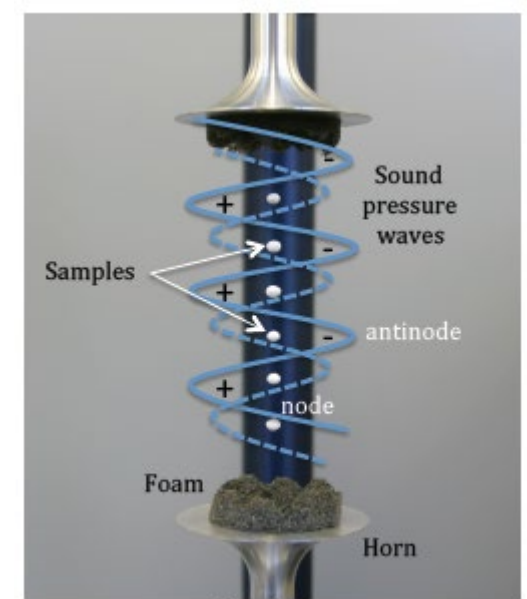


Customized solutions using the best minds in the business. Quickly able to solve problems as they arise giving Improved Pharma the fastest timeline. Improved Pharma has in-house capabilities plus the full complement of Purdue University analytical instrumentation available to solve your problems and get your development back on track.



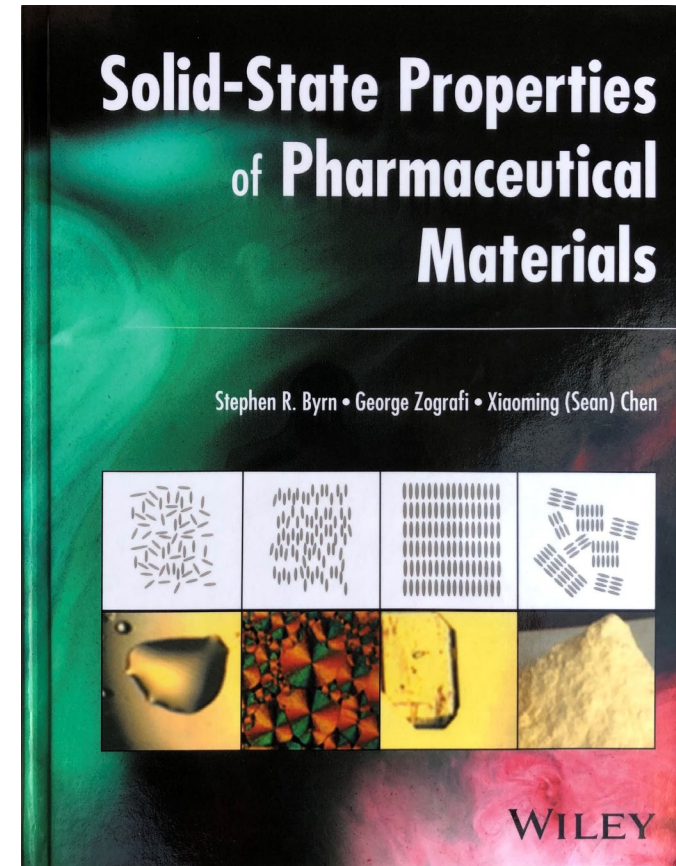
Lab on a drop

- Study samples in microgravity with acoustic levitation
 - <http://www.youtube.com/watch?v=669AcEBpdsY>
- Lab model for spray drying
 - Suspend a droplet of API dissolved in a solvent in the sample beam and obtain patterns as the drop evaporates, leaving amorphous material behind
 - Each drop contains ~0.1mg of API
- Vitrification by containerless melting
 - Obtain hard-to-get amorphous materials
- Amorphous screen
 - Up to 16 amorphous screens in about 8 hours of synchrotron time
- Drug/polymer dispersion screen
 - Quickly screen several different formulations on an extremely small scale



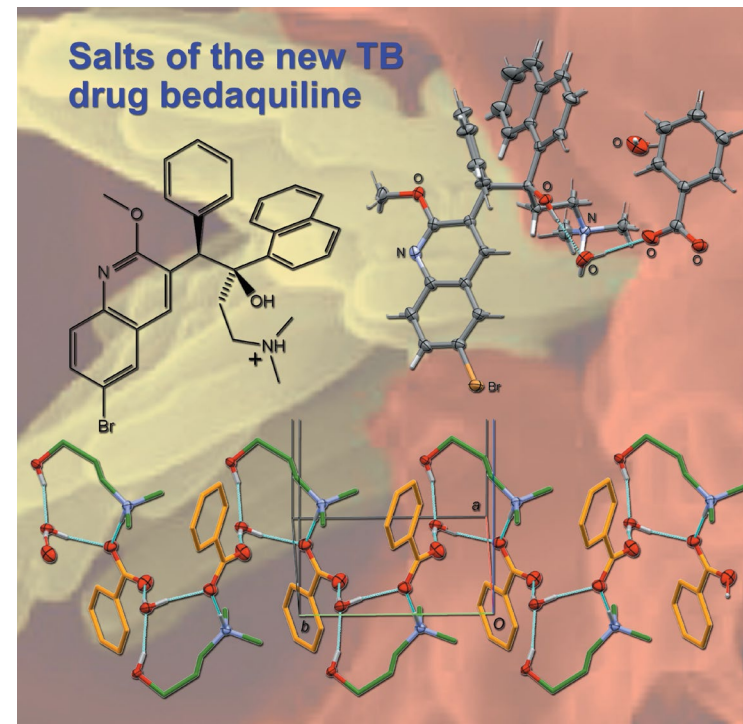
Solid-state form studies

- Fit for purpose approach, tailored to the properties of the drug and the client's goals and conducted by hand by experienced solid-state chemists
 - Polymorph screens
 - Salt and cocrystal screens
 - Crystallization screens
 - Amorphous screens
 - Structural studies
 - Liquid crystals and cocrystals
 - Phase diagram construction of complex systems
 - Microscopy-based screens



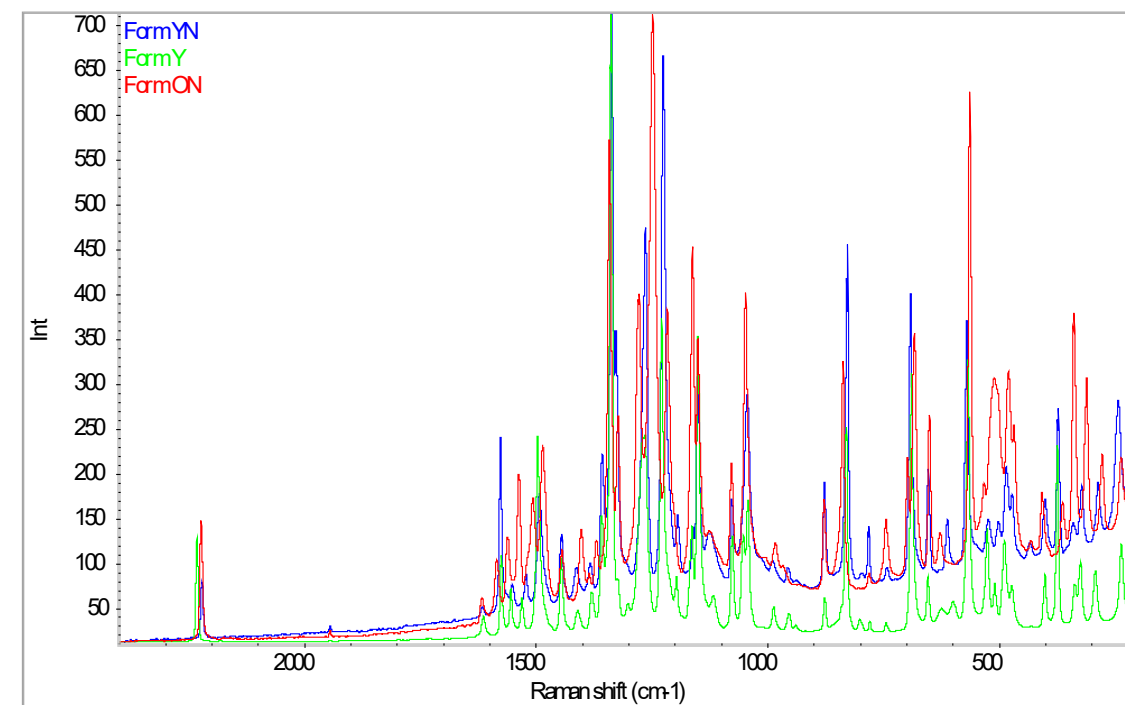
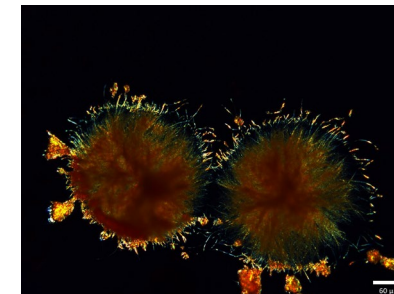
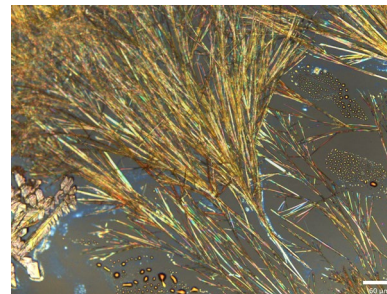
Example: Bedaquiline

- The Bill and Melinda Gates Foundation was interested in developing a new form of bedaquiline that could be manufactured and developed for third-world countries
- Marketed in the US as a fumarate salt; several other inventors patented about a dozen new salts
- Salt screening experiments were conducted in two labs (Purdue and Improved Pharma) and many new salt forms were discovered
 - Crystal structures were obtained and published for all the new salts
 - Research selected for the cover of Acta Crystallographic in Nov, 2020
 - Article remains in the top 10 list of most read articles
- One of the benzoate salt forms is currently undergoing scale-up and manufacturing



Microscopy-based screens

- Requires only nanogram to microgram amounts of material
- Uses microscopic techniques to mimic traditional larger scale screening studies
 - Vapor crystallization within a small, closed glass chamber
 - Microscope well-plate
 - Thin films
- Crystals obtained can be analyzed by FTIR and Raman microscopy, as well as melting point determination
- Crystals can be used as seeds to scale-up for further characterization



Microgravity and polymorph screening

- Microgravity (0g) effects on crystallization
 - Microgravity dramatically alters buoyancy, natural convection, sedimentation, and alters phase separation
 - Can improve particle size distributions, increase ordering within crystals, reduce defect concentration, and enable control over polymorphism
 - Containerless processing prevents heterogenous nucleation and creates ultra-high purity materials
 - Expands the parameter space available to discover new forms
 - Opportunity to find a stable form when only metastable forms exist in 1g (e.g. L-histidine)

“The stable polymorph was obtained in both continuous and batch modes of crystallization in the microgravity experiments while only metastable polymorph can be produced in the ground experiments.”

“The difference in the polymorphs is also attributed to the extremely ordered flow field of the system under microgravity.”

Zhang, Y., Cheng, J., Glick, Y. *et al.* Antisolvent Crystallization of L-histidine in Micro-Channel Reactor under Microgravity. *Microgravity Sci. Technol.* **32**, 27–33 (2020). <https://doi.org/10.1007/s12217-019-09728-4>



How it works

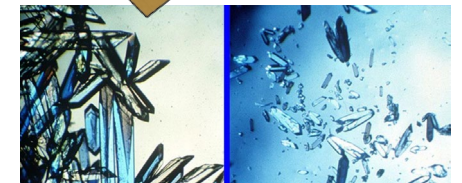
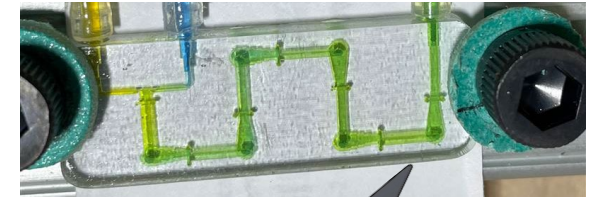
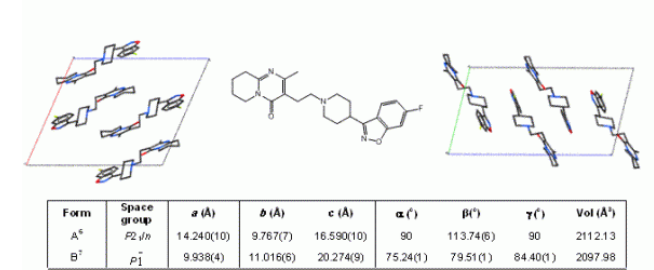
Partner provides polymorph problem statement

Improved Pharma runs ground studies and select conditions for microgravity

Varda modulates screening hardware to fit process window

Varda integrates, launches and operates mission

Finished material sent to Improved Pharma for analysis



Analytical capabilities

- X-ray diffraction
 - Standard (Purdue)
 - Synchrotron (Argonne)
- Thermal analysis
 - Differential scanning calorimetry
 - Thermogravimetric analysis
 - Kofler hot bench
- Spectroscopy
 - FT-IR
 - Raman
 - NMR (Purdue)
 - UV-Vis
- HPLC
- Dissolution
- Water measurements
 - Dynamic vapor sorption
 - Loss on drying
 - Karl Fischer titration, Coulometric technique
- Viscosity determination
- Microscopy and microspectroscopy
 - Particle characterization and image processing
 - Unknown foreign particulate analysis
 - Counterfeit analysis
 - Chemical mapping and imaging

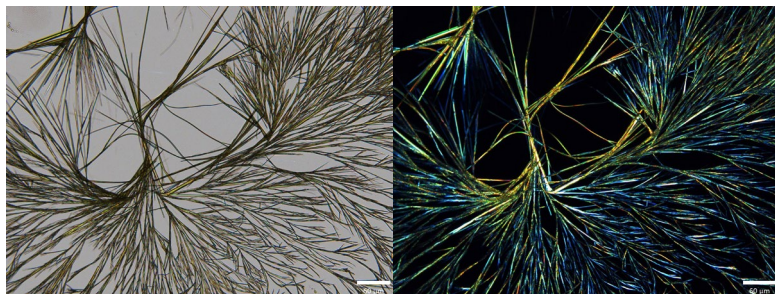
Microscopy capabilities (1 of 2)



Analytical Characterization

Light Microscopy

- ❖ Stereomicroscope
- ❖ Polarized light
- ❖ Fluorescence
- ❖ Bright field / Dark field
- ❖ Differential interference contrast
- ❖ Dispersion staining
- ❖ Phase contrast

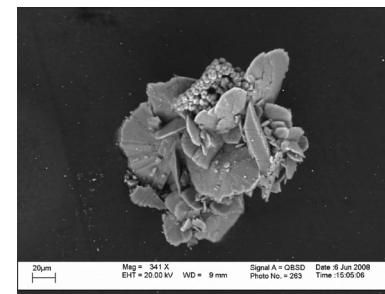


Electron Microscopy

- ❖ SEM: standard and environmental/variable pressure
- ❖ TEM: standard, electron diffraction

Elemental Analysis

- ❖ X-ray fluorescence (EDXRF)
- ❖ Energy Dispersive X-ray Spectrometry (EDS)



Microscopy capabilities (2 of 2)

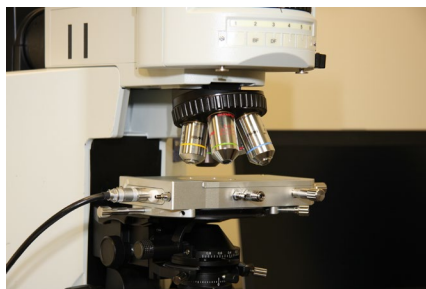


Chemical Microscopy
CURIOSITY. INNOVATION. ADVANCEMENT

Analytical Characterization

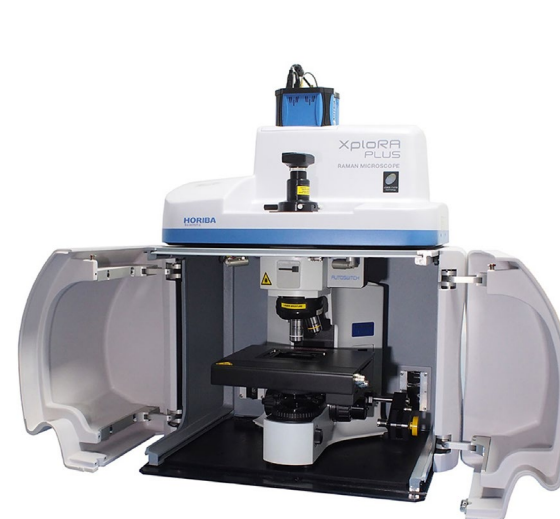
Thermal Analyses

- ❖ Hot stage microscopy: up to 420 °C
- ❖ Cold stage microscopy: down to -196 °C
- ❖ Hot bench
- ❖ Fusion
- ❖ Melting Point
- ❖ Eutectic Melts
- ❖ Dehydration/desolvation



Spectroscopy

- ❖ FT-IR microspectroscopy
- ❖ Raman microspectroscopy
- ❖ UV-Visible microspectroscopy

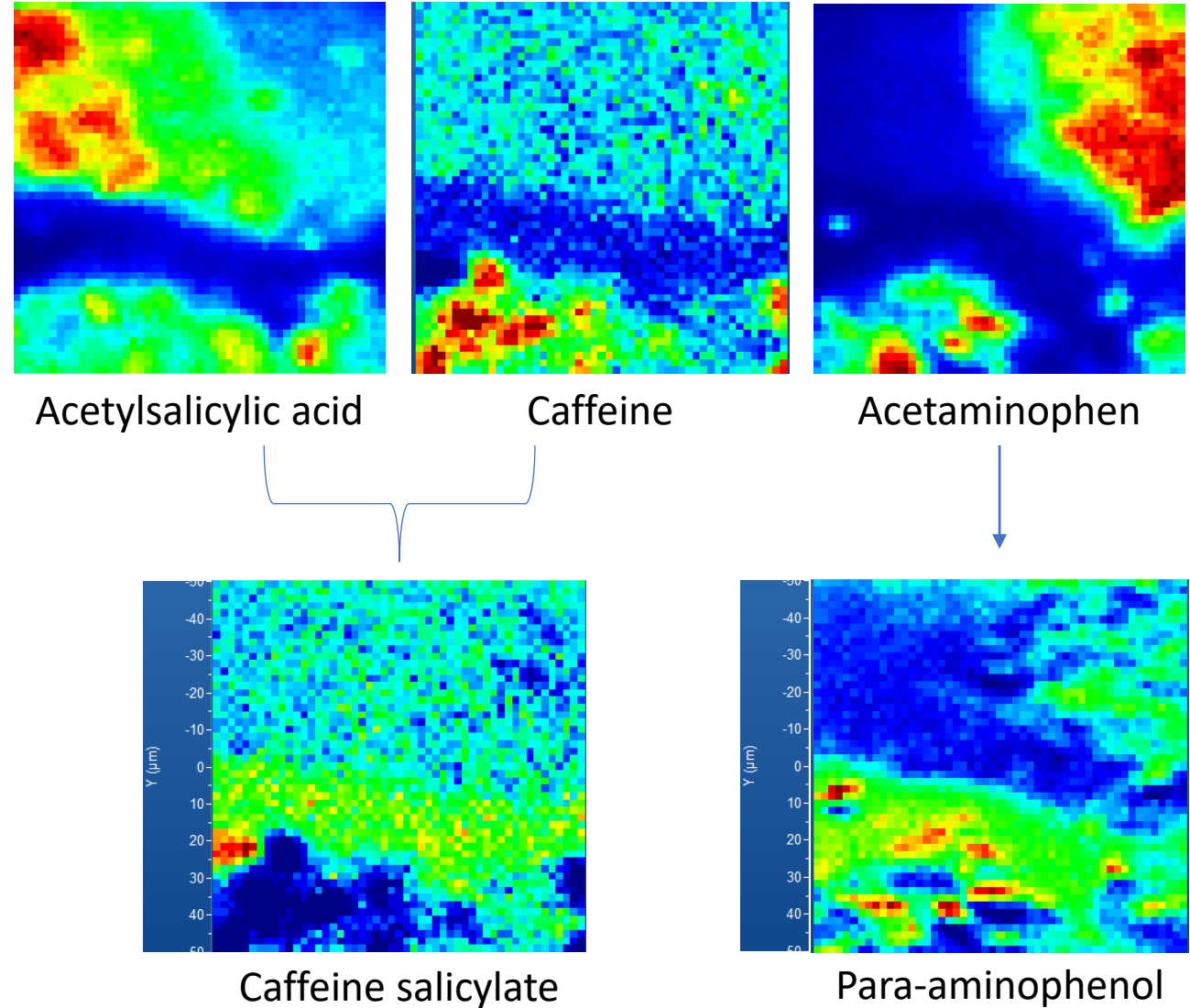


Improved Pharma

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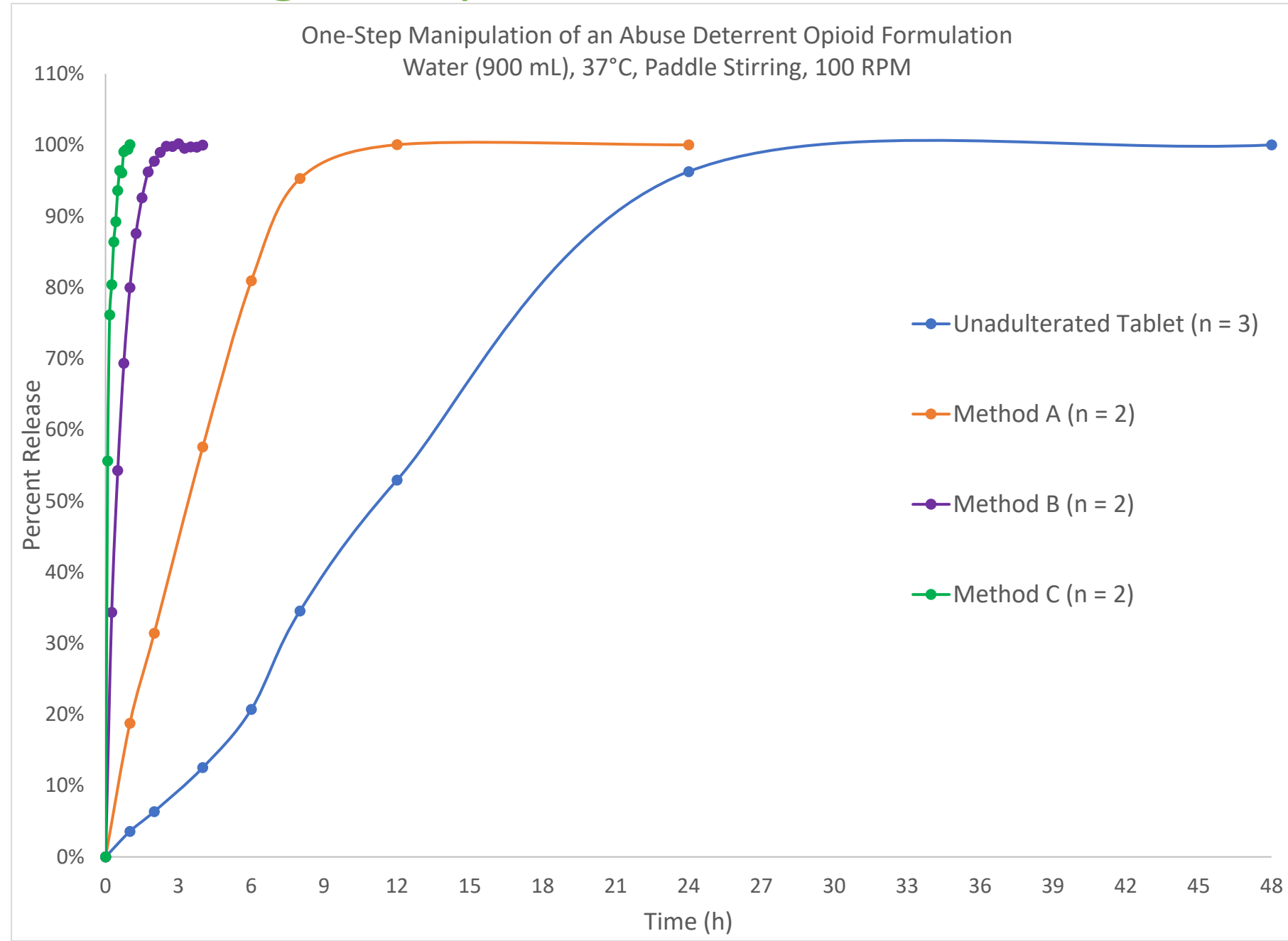
Example: Identifying degradation products in a tablet

- Three active ingredients: acetylsalicylic acid, caffeine, and acetaminophen
- Unknown peaks observed in the Raman map that could not be attributed to the APIs or excipients
- Upon exposure to humidity:
 - Acetylsalicylic acid can decompose to salicylic acid, which can react with caffeine to form caffeine salicylate
 - Acetaminophen can degrade to para-aminophenol
- Profiles and spectral subtractions confirmed the identity and location of the degradation products



Abuse deterrence testing example

- Dissolution results of three different abuse attempts
 - Unadulterated tablet not 100% released until 24 hours
 - Various street-method approaches successfully alter the release rate, with “method C” achieving the fastest release
- We have helped companies test the “breakability” of their formulations and helped them develop better formulations



Consulting services

- Patent litigation
 - Significant experience as fact and expert witnesses
 - Patent reproductions
 - Broad range of analytical capabilities, plus advanced analytical approaches for the most challenging cases
 - Often assists with experimental planning, literature searching, report reviewing, and strategic direction
- Quality and regulatory information
 - Serve on the USP and the FDA Pharmaceutical Sciences Advisory Committee
 - Collaborated with the FDA to teach the first FDA course in Africa
 - Instructors for the Sustainable Medicines in Africa program which includes a master's degree in biotechnology innovation and regulatory science
- Instructional courses and webinars
 - Customized sessions available

A partnership with Improved Pharma

- We are:
 - A service-oriented team of professionals
 - Scientifically curious
 - Cutting-edge researchers
 - Thought leaders
 - Flexible and responsive

CEO

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