General Capabilities

2024

Improved Pharma

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

Experts in pharmaceutical development

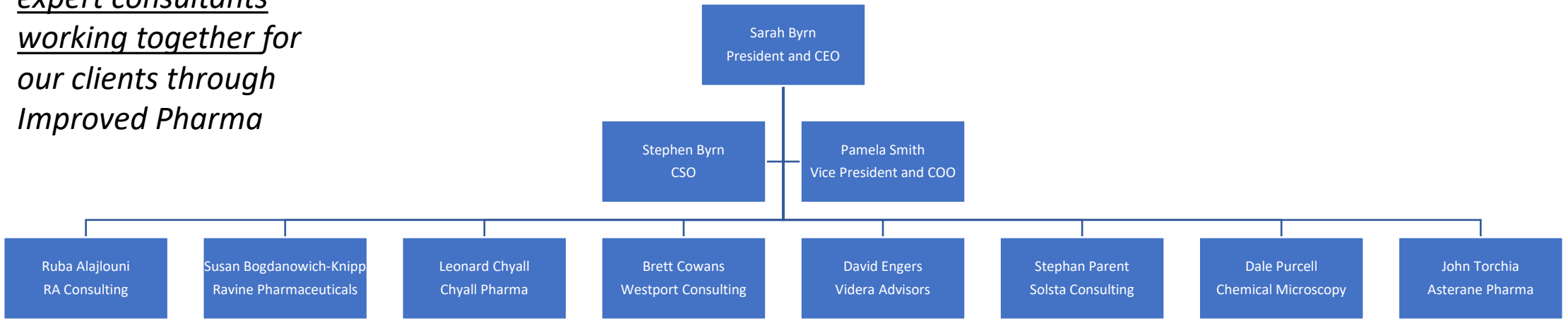
- Industry leaders for decades
  - Focus on R&D to bring cutting-edge technologies and applications to our clients
  - Formulation development: synchrotron, levitated drop, amorphous dispersions, reformulations, reverse-engineering, solid lipid nanoparticles
  - Polymorph, salt, cocrystal, crystallization, amorphous and microgravity screens
  - Analytical characterization: diffraction, spectroscopy, microscopy, thermal analysis, water determination, HPLC, LC-MS, dissolution, viscosity, osmometry, micromeritics, particle size
  - 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
  - Non-GMP laboratory
  - All work is US-based

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
- 2023
  - Laboratory space grows another 50%
  - Panalytical XRPD acquired
  - First polymorph screening experiments launched into space
- 2024
  - Laboratory space grows another 50%
  - UPLC and LC-MS acquired
  - Additional consultants join

The Improved Pharma Team and Collaborators

We are a team of <u>expert consultants working together</u> for our clients through Improved Pharma



Patricia Andres
Keystone Pharma Consulting

Chris Benmore
Argonne National Laboratory

Simon Billinge
Columbia University

Fabia Gozzo
Excelsus Structure Solutions

Gabriel Lima Barros de Araujo
University of São Paulo

Daniel Smith
Fenwick Pharma

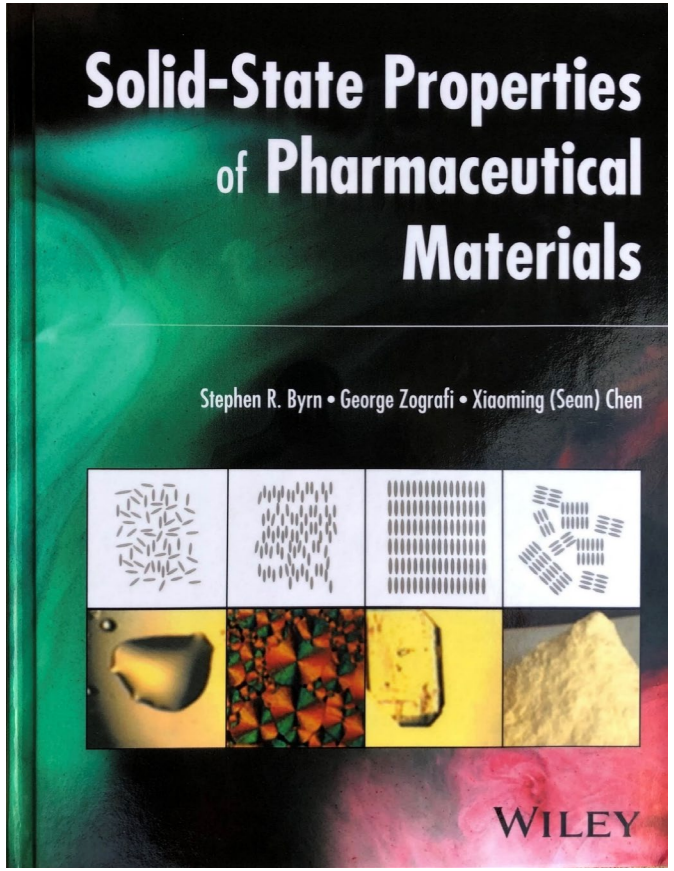
Varda Space Industries

Capabilities outline

- Solid-state form studies
- Microscopy-based screens
- Microgravity and hypergravity studies
- Analytical capabilities
- Cutting-edge synchrotron capabilities
- Formulation capabilities
- Consulting services

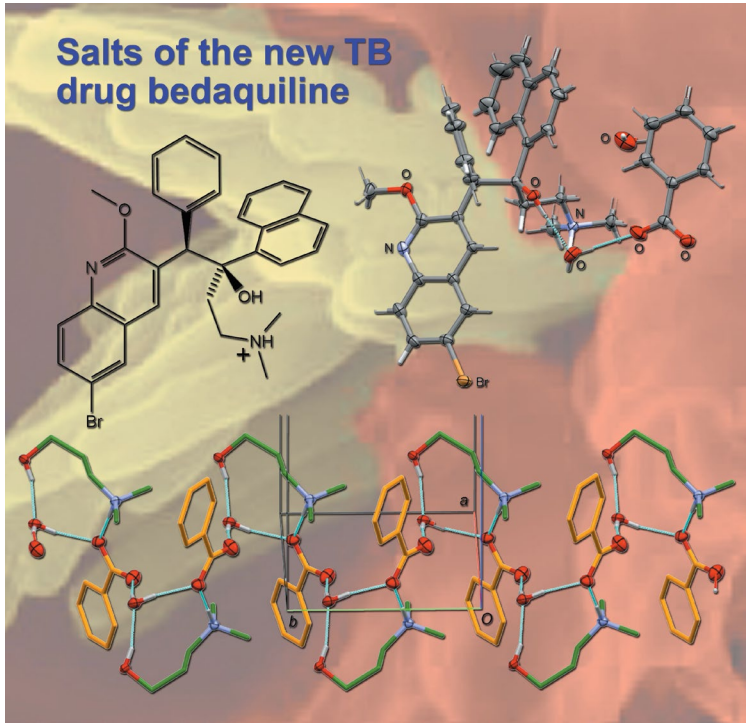
Solid-state form studies

- 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



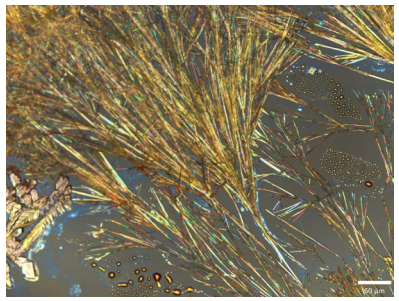
Example: Bedaquiline

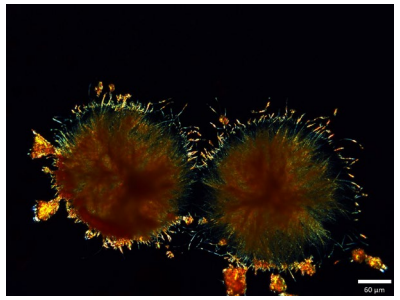
- The Bill and Melinda Gates Foundation was interested in developing a new form of bedaquiline that could be manufactured and developed for third-world countries
- Marketed in the US as a fumarate salt; several other inventors patented about a dozen new salts
- Salt screening experiments were conducted 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

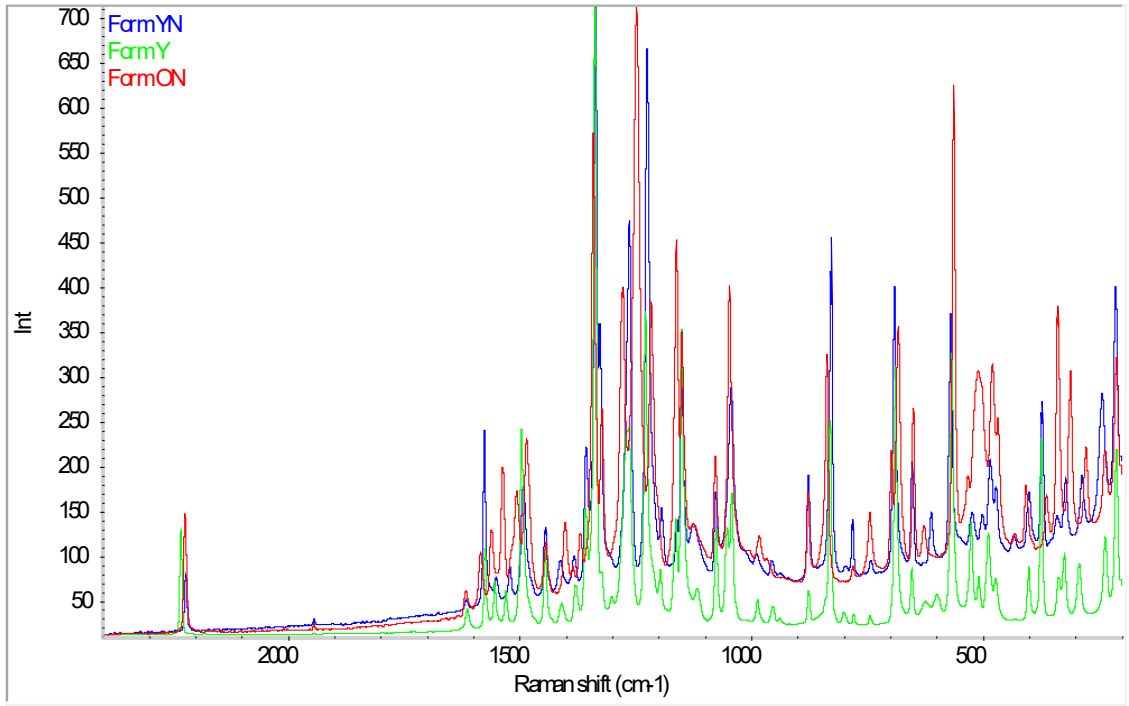


Microscopy-based screens

- 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





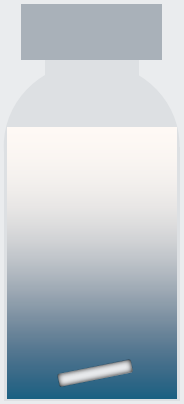


Benefits of processing in microgravity

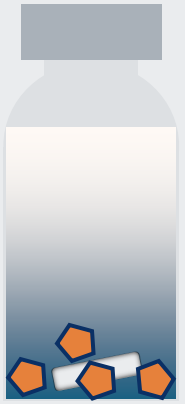
How can microgravity be applied to reduce inhomogeneity to drive improved process results?

What would change if you could turn gravity off?

Concentration Gradients



Sedimentation



Convection

Enable processes and materials that are impossible to replicate on Earth

Poodt, et. al. (2008). Crystal Growth and Design, 8(7), 2194-2199.

How it works

VARDA

Varda's end-to-end platform for materials processing and development

VARDA pipeline

VARDA partners

Improved Pharma involvement

1 Partner sends APIs to Varda

2 Varda conducts hypergravity screening and a feasibility assessment

3 Gravity-validated molecules undergo process development

4 The molecules are loaded into the W-series capsule

5 The capsule and its satellite launch on a SpaceX rideshare

6 Autonomous microgravity processing of space crystals in Varda hardware

7 The capsule re-enters and lands safely

8 Seed crystals with effects "locked" in are grown into larger batches of crystals

9 Terrestrial drug production at scale

10 Medicine is delivered to patients

Analytical capabilities in-house

- X-ray diffraction
  - Panalytical reflection/transmission
  - Synchrotron (at Argonne, Brookhaven, Swiss Light Source)
- Thermal analysis
  - Differential scanning calorimetry
  - Thermogravimetric analysis
  - Kofler hot bench
  - DSC hot stage microscopy
- Spectroscopy
  - FT-IR
  - Raman
  - NMR (at Purdue)
  - UV-Vis
- HPLC/UPLC
- LC-MS
- Dissolution
- Water measurements
  - Dynamic vapor sorption
  - Loss on drying
  - Karl Fischer titration, Coulometric technique
- Viscosity determination
- Osmometry
- Freeze-drying
- Microscopy and microspectroscopy
  - Particle characterization and image processing
  - Unknown foreign particulate analysis
  - Counterfeit analysis
  - Chemical mapping and imaging

Microscopy capabilities (1 of 2)

Chemical Microscopy
CURIOSITY. INNOVATION. ADVANCEMENT

Analytical Characterization

Light Microscopy

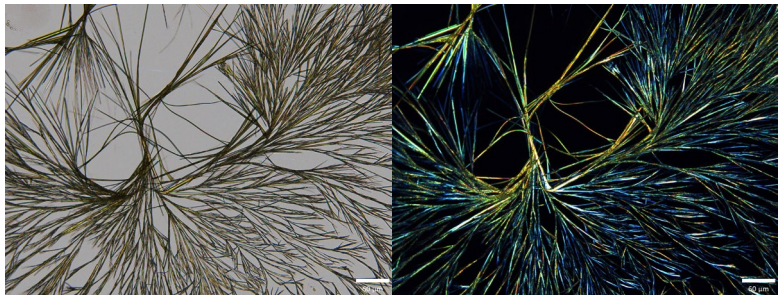
- Stereomicroscope
- Polarized light
- Fluorescence
- Bright field / Dark field
- Differential interference contrast
- Dispersion staining
- Phase contrast

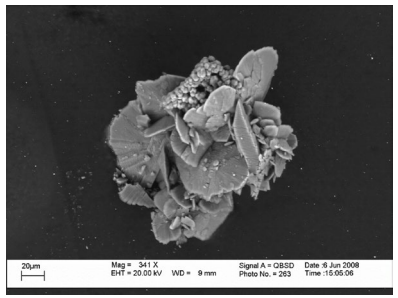
Electron Microscopy

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

Elemental Analysis

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





Improved Pharma

Microscopy capabilities (2 of 2)

Chemical Microscopy
CURIOSITY. INNOVATION. ADVANCEMENT

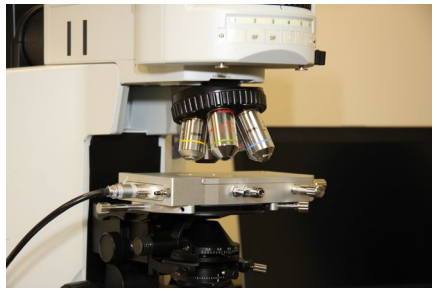
Analytical Characterization

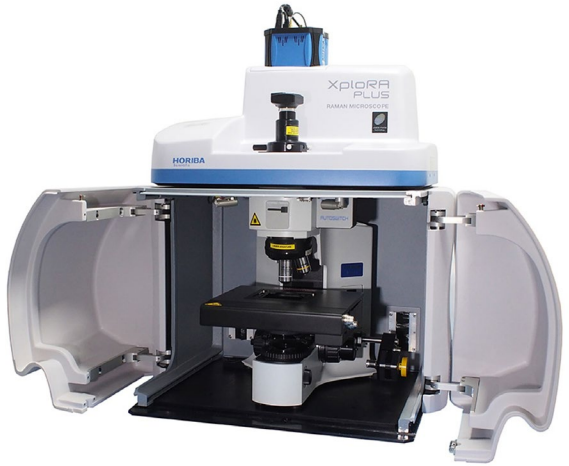
Thermal Analyses

- 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

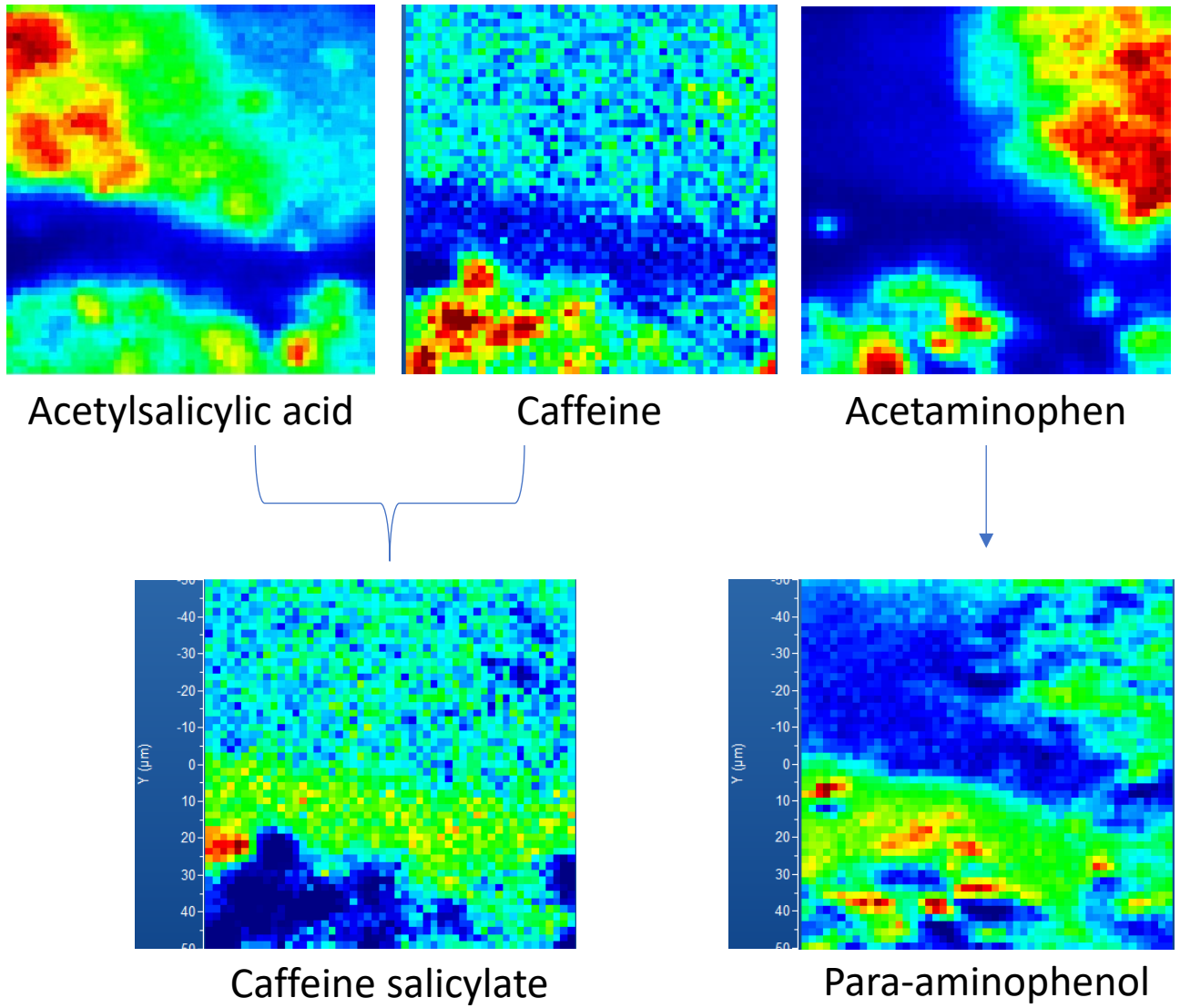




Improved Pharma

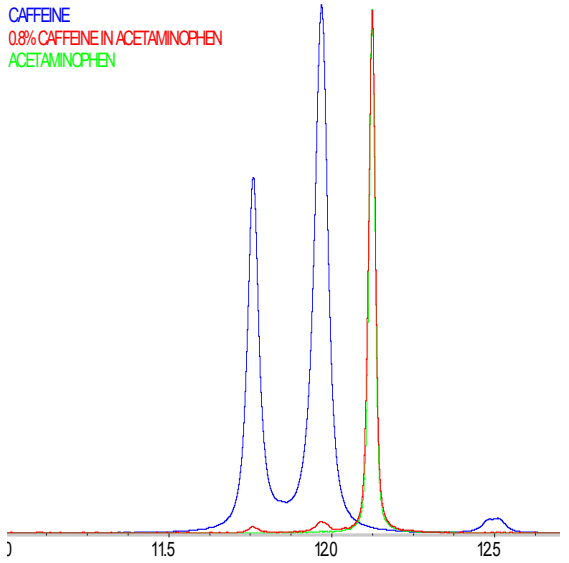
Example: Identifying degradation products in a tablet

- 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



Cutting-edge synchrotron capabilities with global capacity

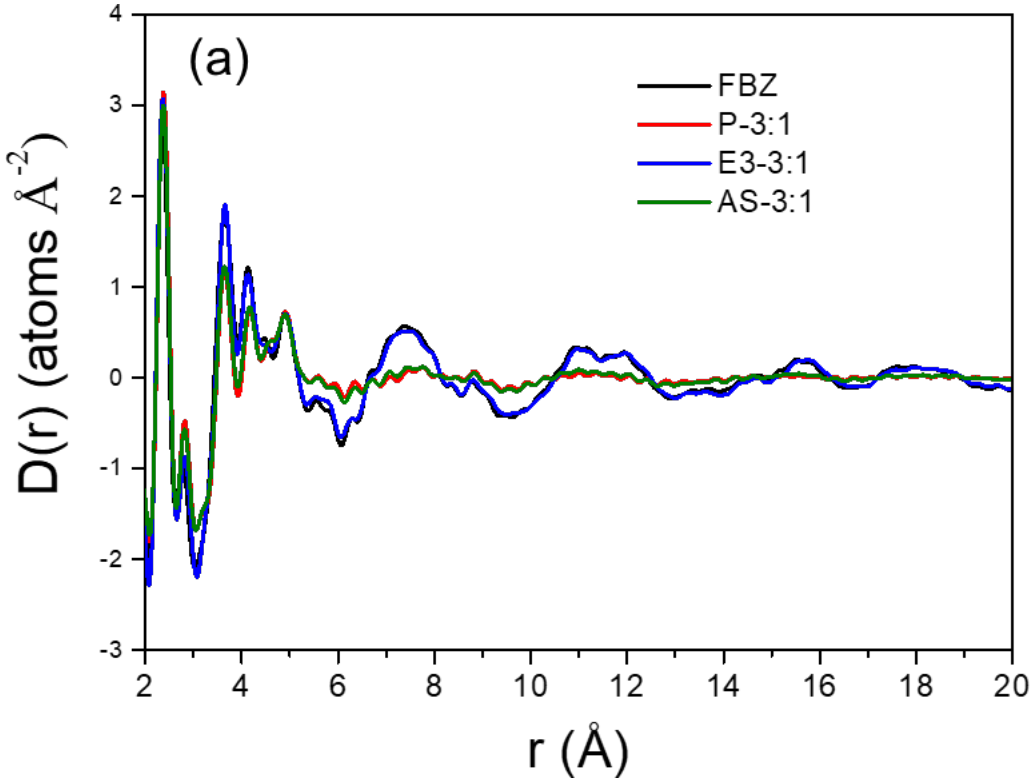
- Trained users at the Advanced Photon Source (Argonne)
  - Beamline 6-ID-D for high-energy x-ray PDF work
    - Characterization of amorphous materials (e.g. sameness)
    - Variable RH and temperature (detection of hydration prior to crystallization)
  - Beamline 11-BM-B for high-resolution powder diffraction
    - High-resolution (better specificity for resolving complex mixtures)
    - High-sensitivity (easily detect tenths of a percent of an impurity)
- National Synchrotron Light Source (Brookhaven)
  - Trained users at NSLS-II for high energy x-ray PDF work and XRPD
  - 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 for work needing to be conducted in Europe
    - Ab-initio structure solution
    - Quantitative phase analysis
    - PDF

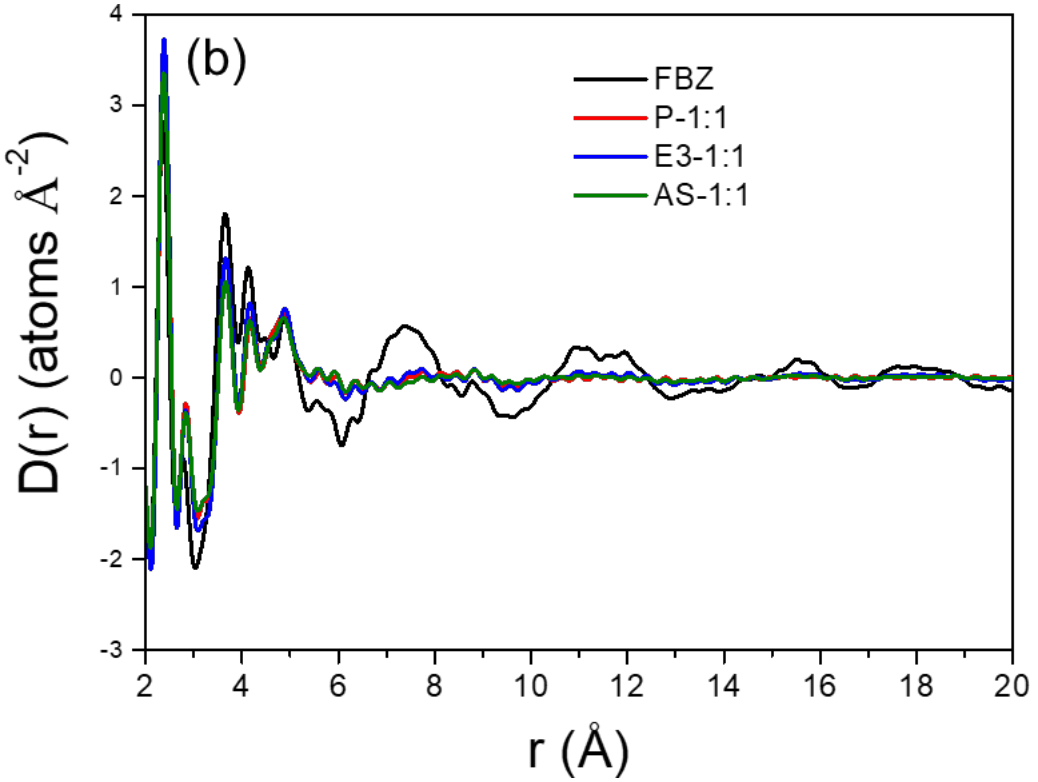


Improved Pharma

Cutting-edge synchrotron capabilities, example 1

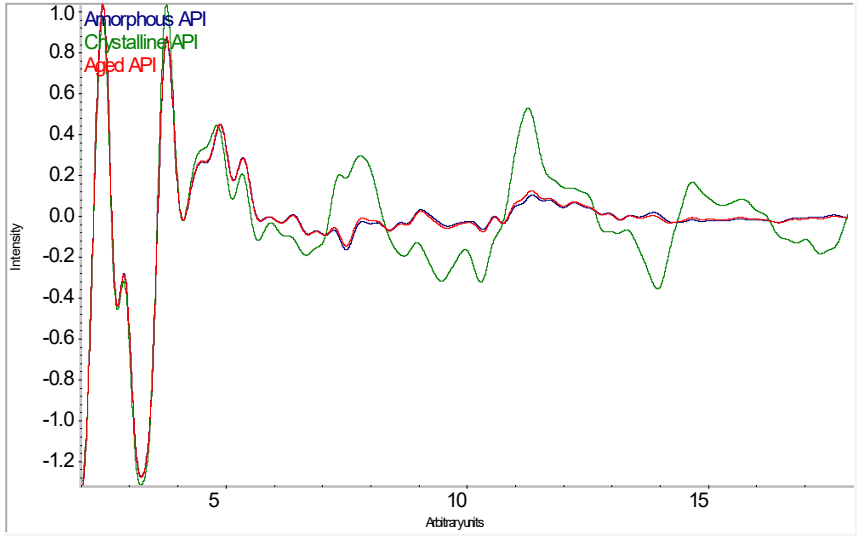
- PDF analysis of amorphous formulations to predict stability of different dispersions
  - The 3:1 flubendazole:HPMC-E3 dispersion PDF shows domains (ordered three-dimensional intermolecular arrangements) and eventually crystallized

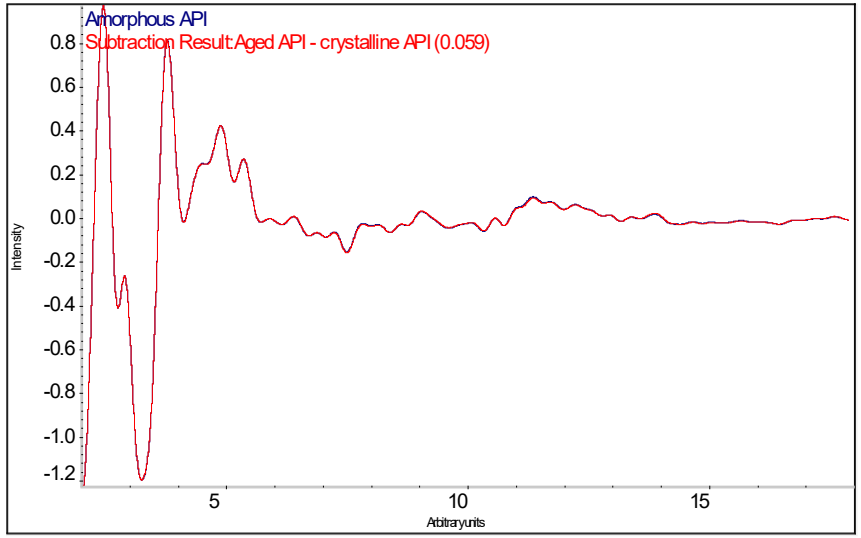




Cutting-edge synchrotron capabilities, example 2

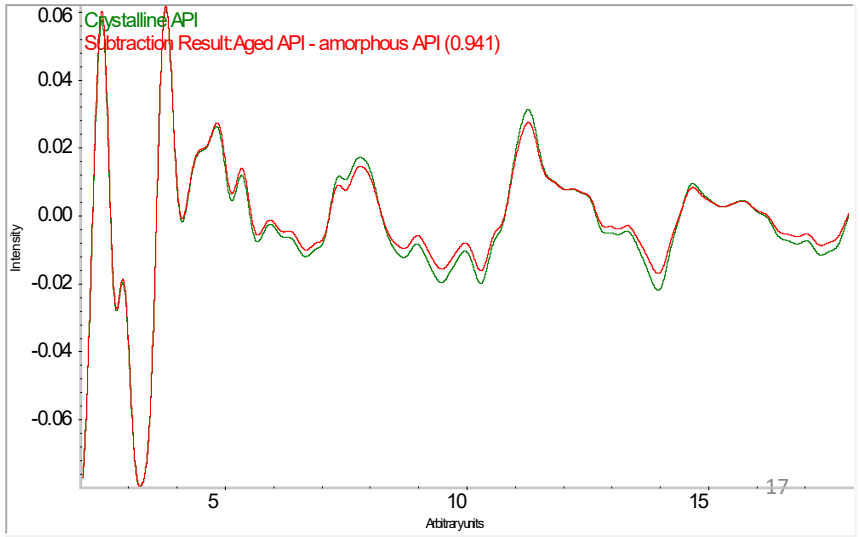
- Quantifying crystalline content in an aged amorphous sample





5.9% crystalline

94.1% amorphous



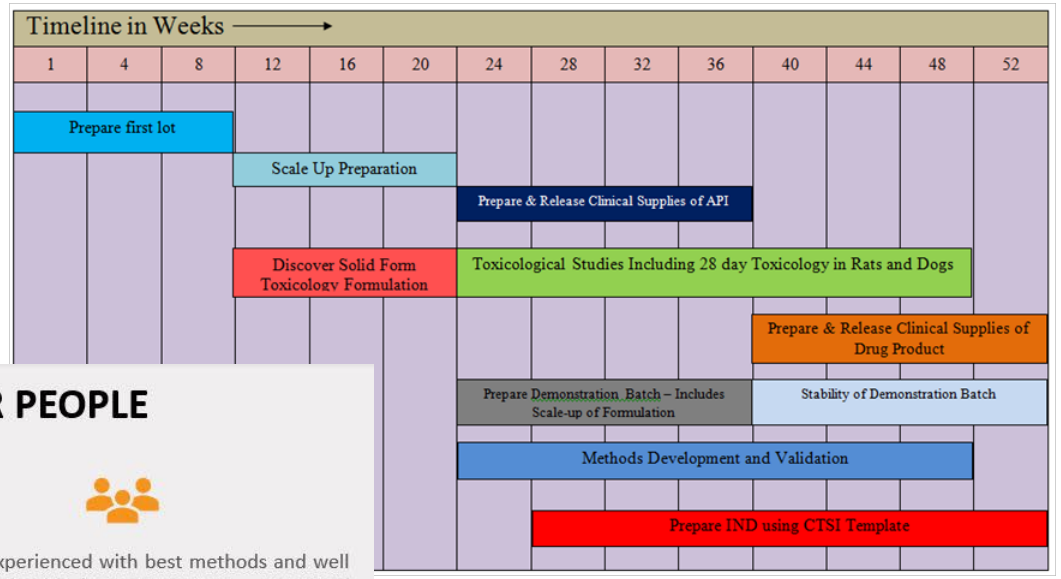
Improved Pharma

Formulation capabilities

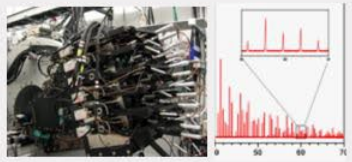
- Improve formulations of existing products
  - More than quadrupled the solubility of the API and improved the pH of an injectable product
- Reverse engineering
  - Reverse-engineered a suspension-based formulation and developed a new formulation using alternative materials
- Synchrotron-based formulation 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

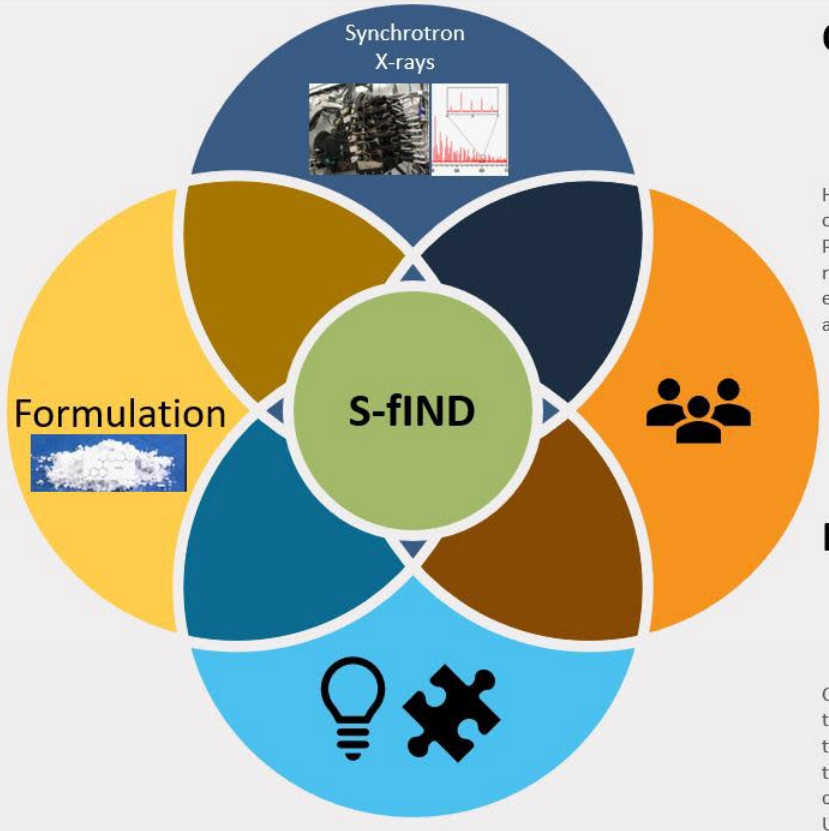
- Synchrotron-based fast-to-IND



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.



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.

FORMULATION DESIGN

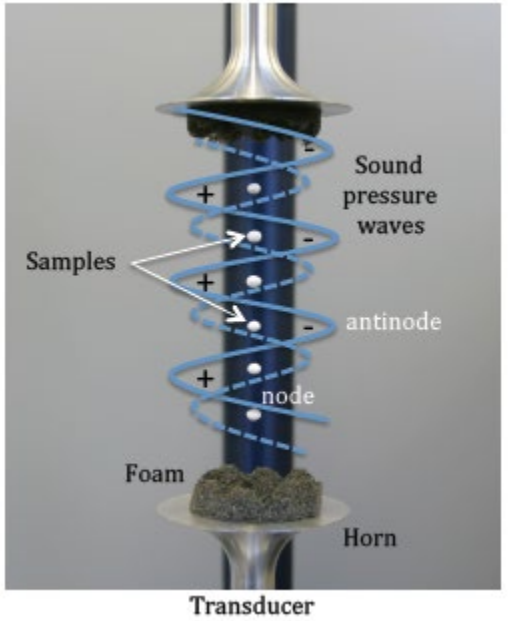
Robust formulation design based on strong solid-state chemistry is a key step in drug development. Furthermore, unique solutions often create intellectual property and Improved Pharma transfers all intellectual property to the contractor.

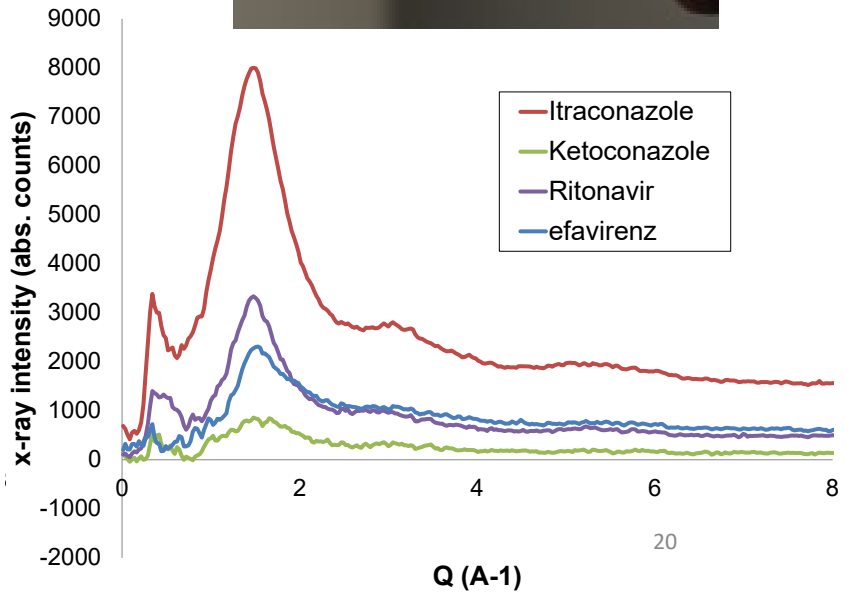
PROBLEM SOLVING

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





Improved Pharma

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
Sarah Byrn
Sally.byrn@improvedpharma.com
(765) 426-2201

CSO
Stephen Byrn, Ph.D.
Steve.byrn@improvedpharma.com
(765) 714-2808

COO
Pamela Smith, Ph.D.
Pam.smith@improvedpharma.com
(765) 412-2677