Webinar Series

Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 1 – Discovery

1. **The Power of Knowing the Crystal Structure of Your Compound,** presented by Pierre Le Magueres, PhD
2. **Streamlining the Wet Lab: Best Practices for Managing Stock Solutions**, presented by Amy Syverson

Starting at 1 pm CST

- *You will be muted during the workshop*
- *You can ask questions using the Q&A tool.*
- *You should hear music if your sound is working*

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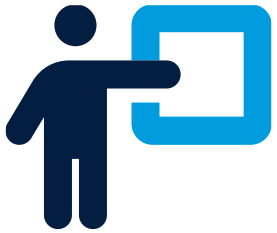
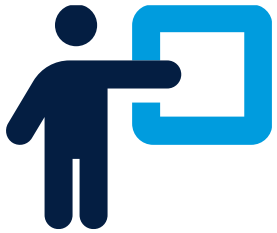
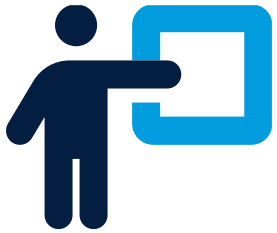
We are starting now



Presenter:
Pierre Le Magueres
Single Crystal Lab Manager, Life Sciences



Presenter:
Amy Syverson
General Manager



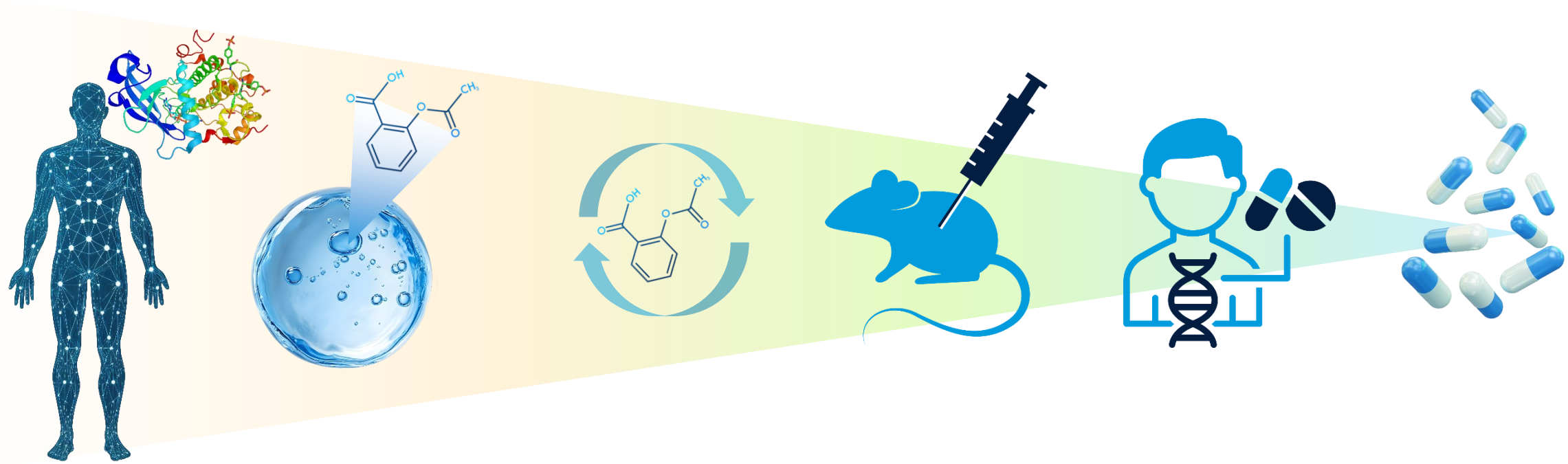
Co-Presenter:
Simon Bates, PhD
VP of Science and Technology

Host:
Aya Takase
Head of Global Marketing

You can ask questions during the presentation. Please use the Q&A to ask questions.

Recording will be available tomorrow.

Target Identification ▶ Lead Generation ▶ Lead Optimization ▶ Preclinical ▶ Clinical ▶ Approved Drug



Discovery ▶ Development Pre-formulation ▶ Formulation ▶ Manufacturing

1

The Power of Knowing the Crystal Structure of Your Compound

presented by Pierre Le Magueres, PhD

Agenda

1. Crystal structures and the information they provide
2. Some fundamentals about single crystal X-ray crystallography
3. One step further with electron crystallography, or MicroED

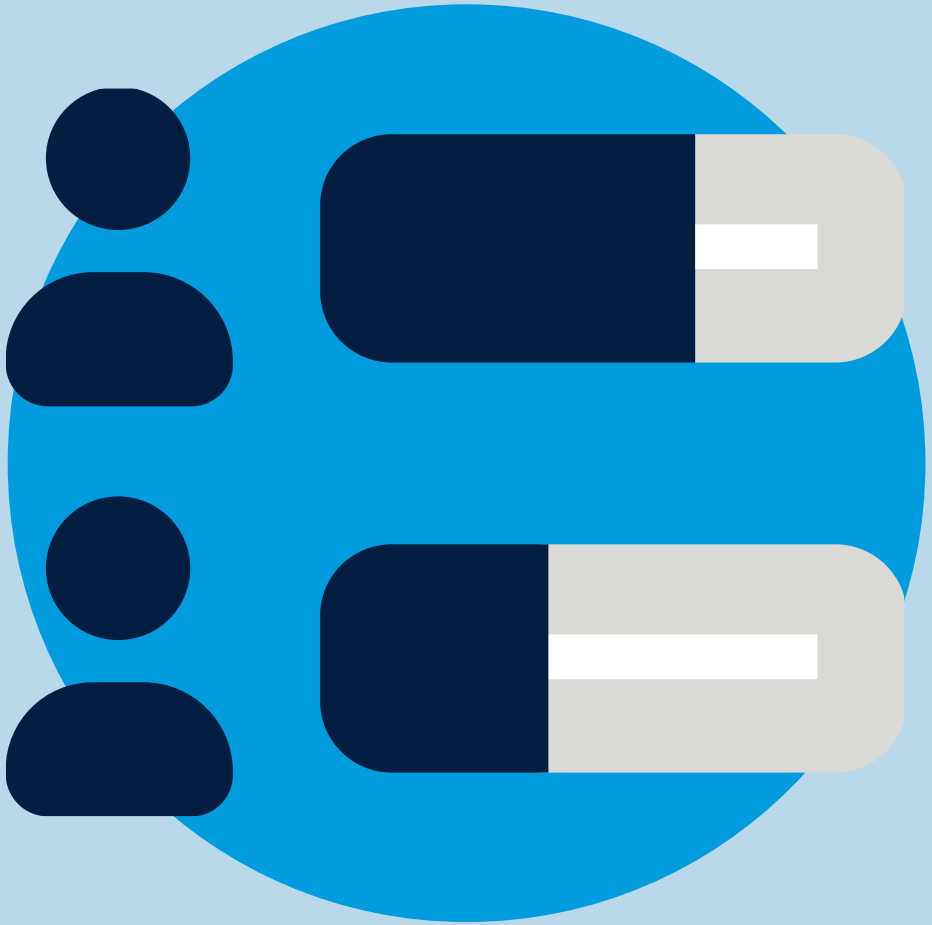
1. Introduction to crystal structures

How much time do you lose:

1. Unambiguously characterizing new compounds?
2. Trying to scale-up, purify and crystallize new compounds?
3. Looking for polymorphs and characterizing each of them?

Polling Question

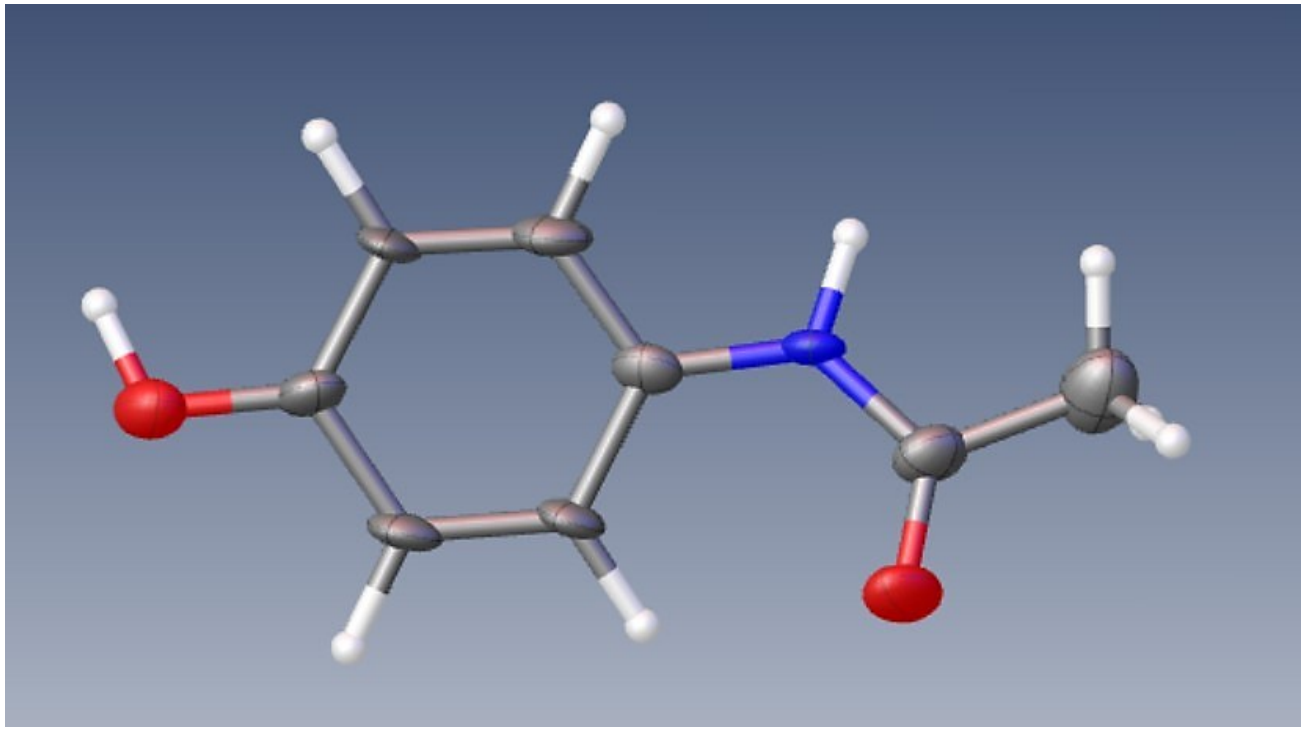
#1



The best way to mitigate time loss is to determine crystal structures:

1. Picture of the **molecules**

    a) Molecular connectivity

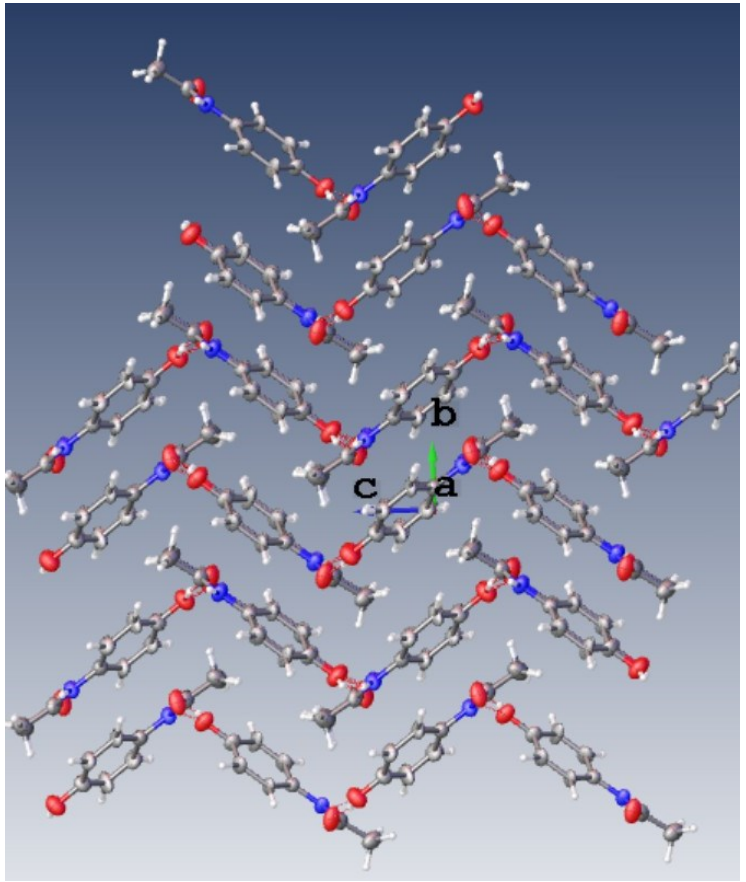


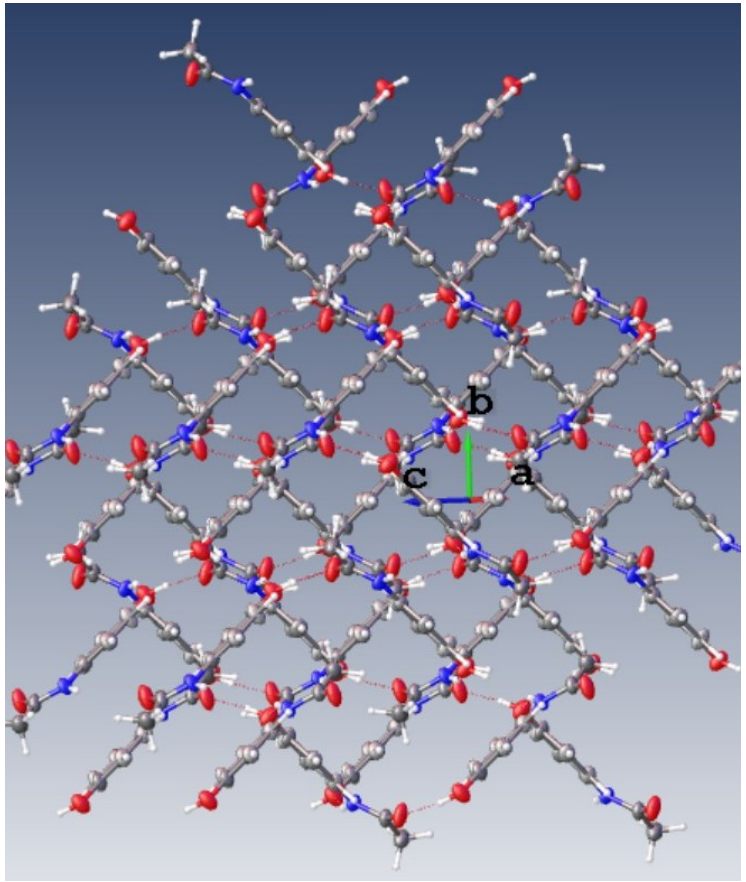
Acetaminophen

The ultimate answer is the crystal structure:

1. Picture of the molecules … in a pure crystal form

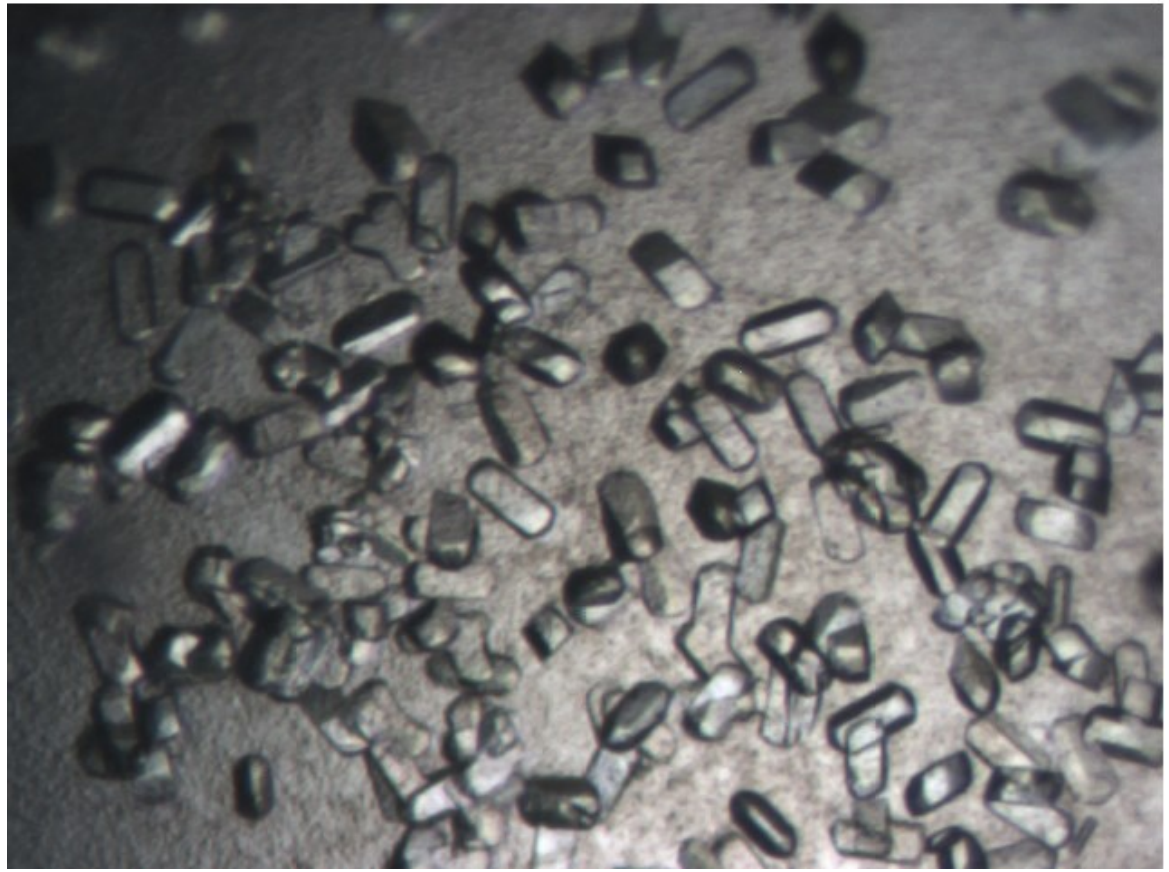
b) Crystal packing





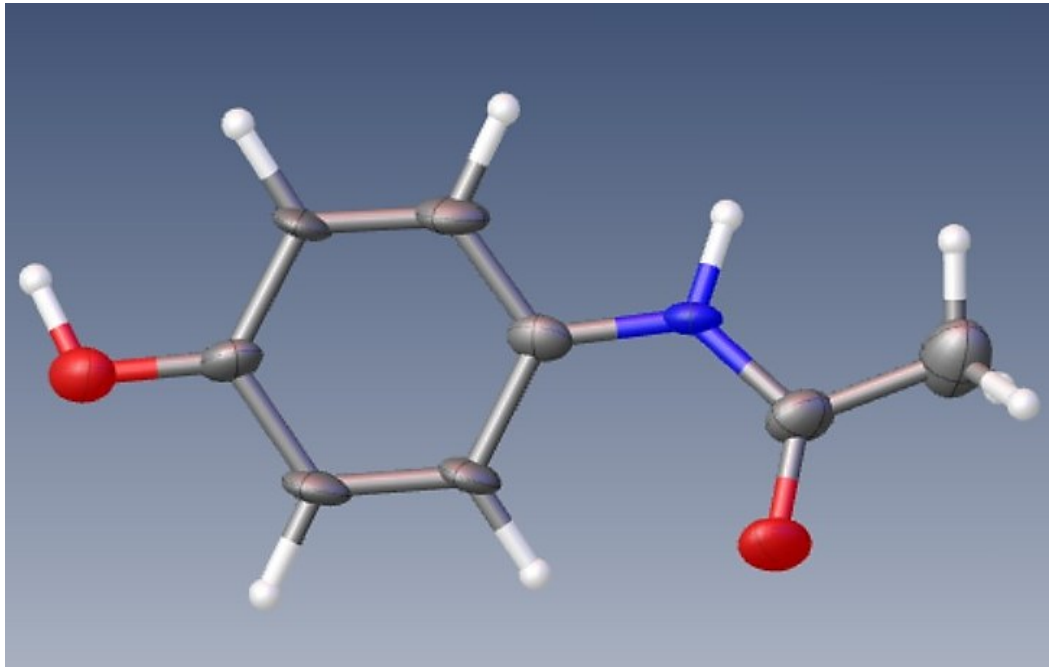
The answer to all questions comes from the crystal structure:

1. Picture of the molecules … in a pure crystal form



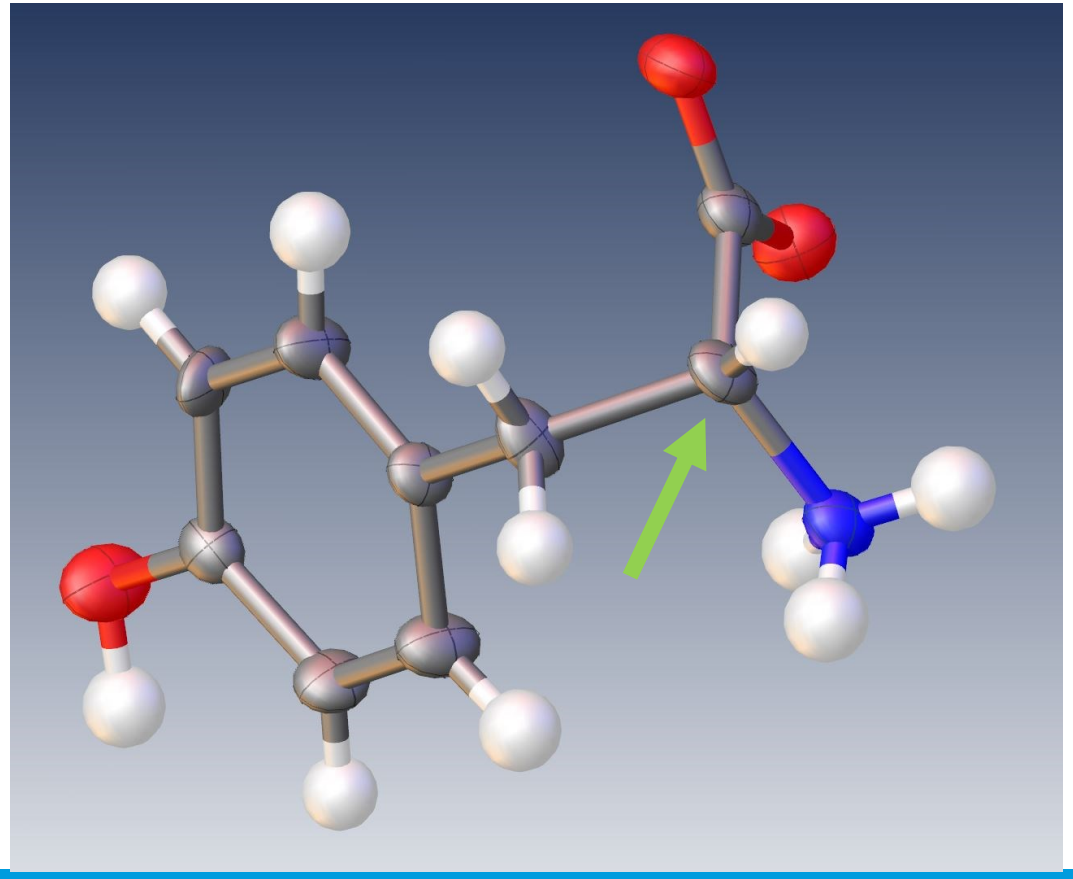
Direct applications in drug research:

1. Molecular connectivity
    a) Unambiguous compound identification



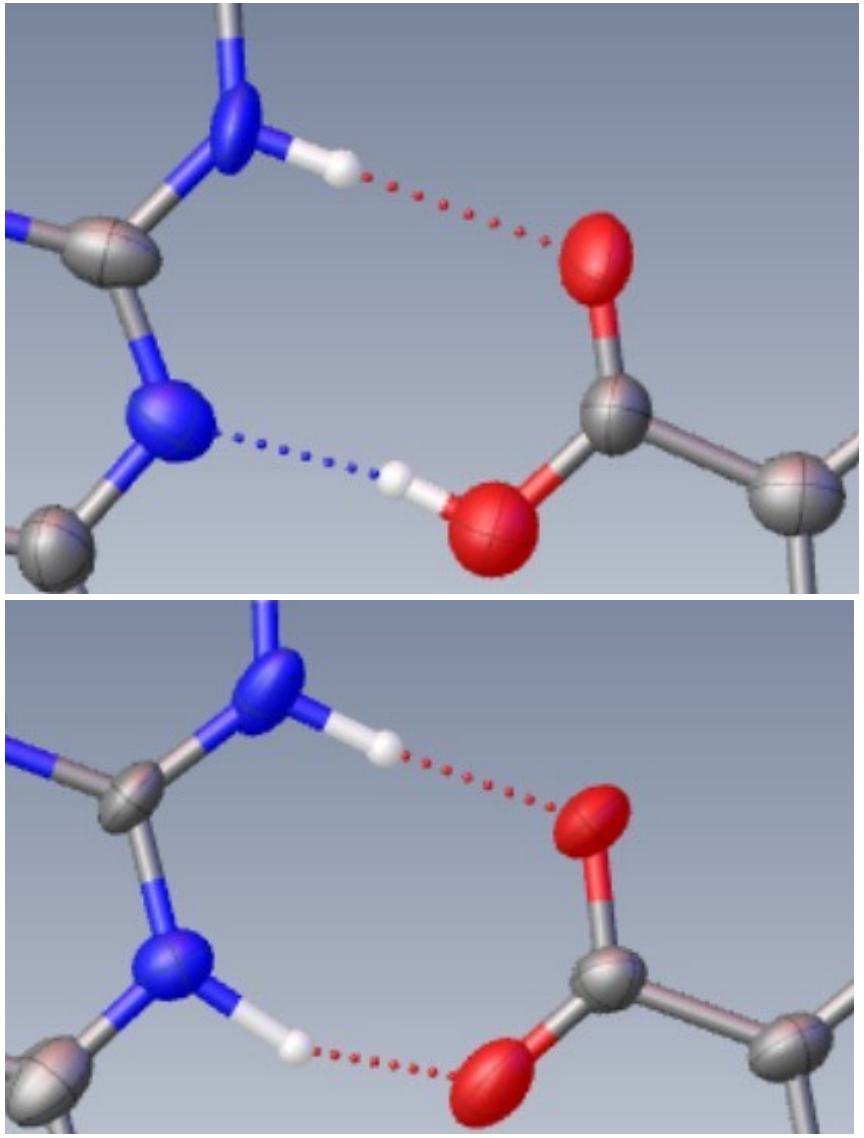
Direct applications to drug research:

1. Molecular connectivity
    a) Unambiguous compound identification
    b) Absolute configuration



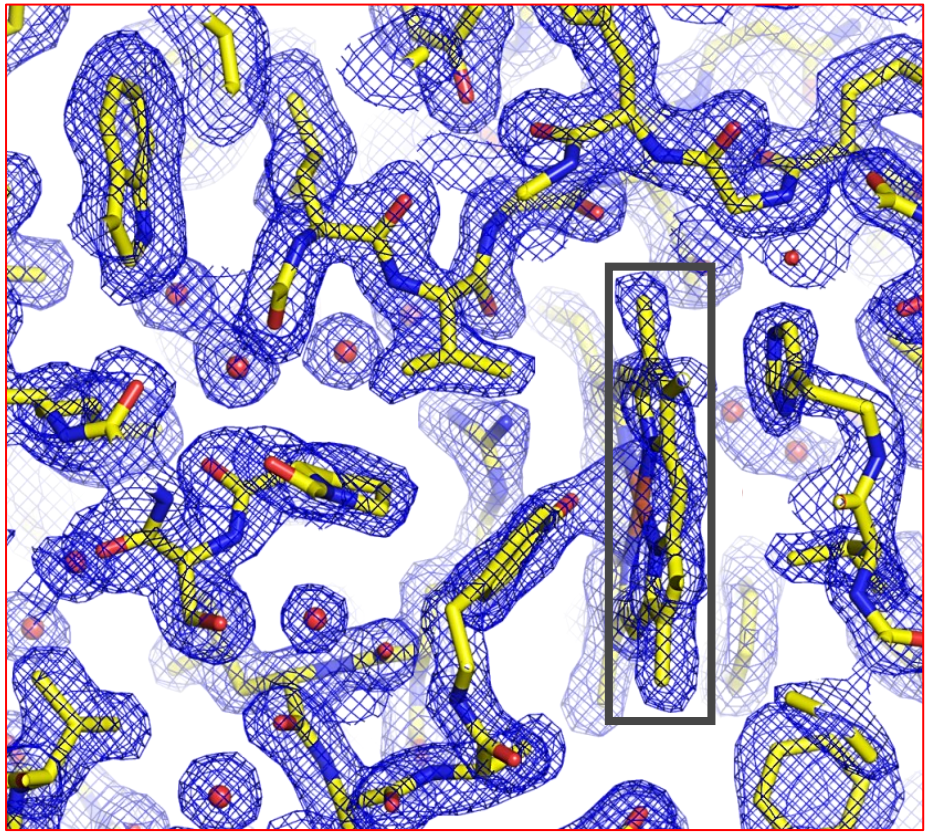
Direct applications to drug research:

1. Molecular connectivity
    a) Unambiguous compound identification
    b) Absolute configuration
    c) Salt or a co-crystal



Direct applications to drug research:

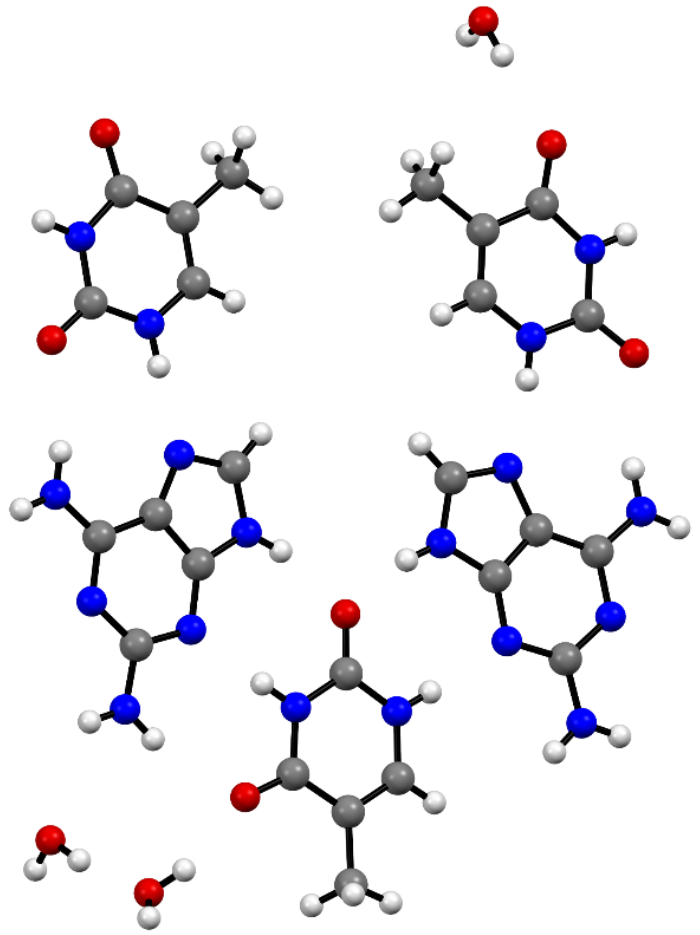
1. Molecular connectivity
   a) Unambiguous compound identification
   b) Absolute configuration
   c) Salt or a co-crystal
   d) Drug candidate in protein target's active site?



Catalase

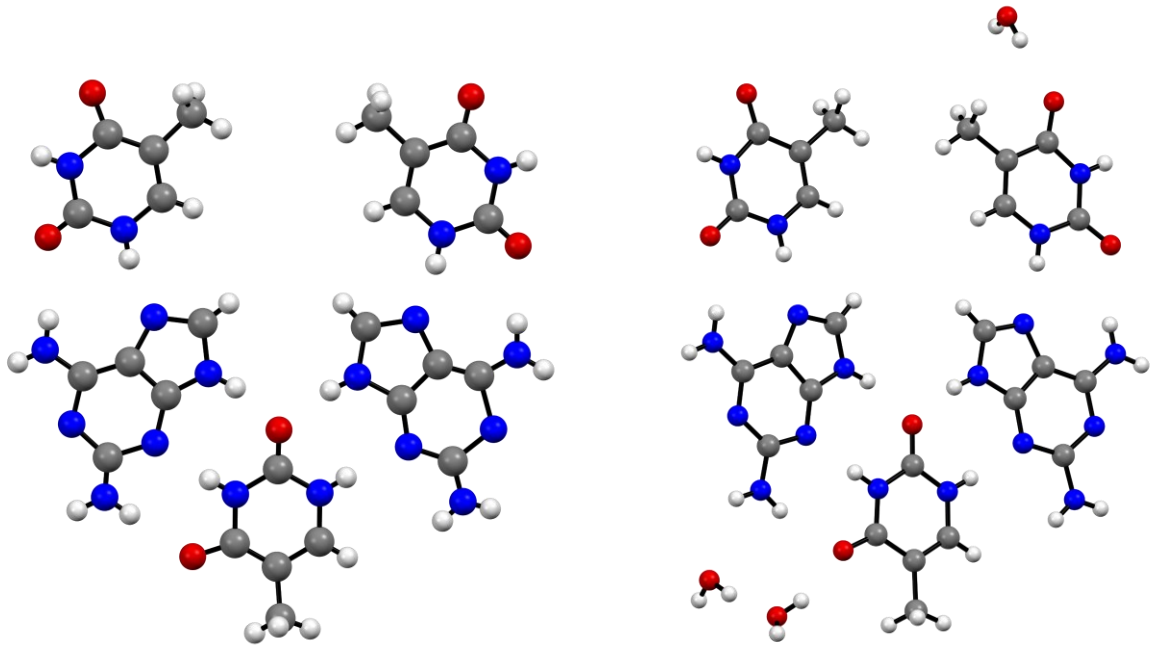
Direct applications to drug research:

1. Molecular connectivity
   a) Unambiguous compound identification
   b) Absolute configuration?
   c) Salt or a co-crystal?
   d) Drug candidate within active site?
2. Crystal packing
   a) Hydrate or solvate?



Direct applications to drug research:

1. Molecular connectivity
   a) Unambiguous compound identification
   b) Absolute configuration
   c) Salt or a co-crystal?
   d) Drug candidate within active site?
2. Crystal packing
   a) Hydrate or solvate?
   b) Polymorphs?



No water in the crystal Co-crystallizes with water

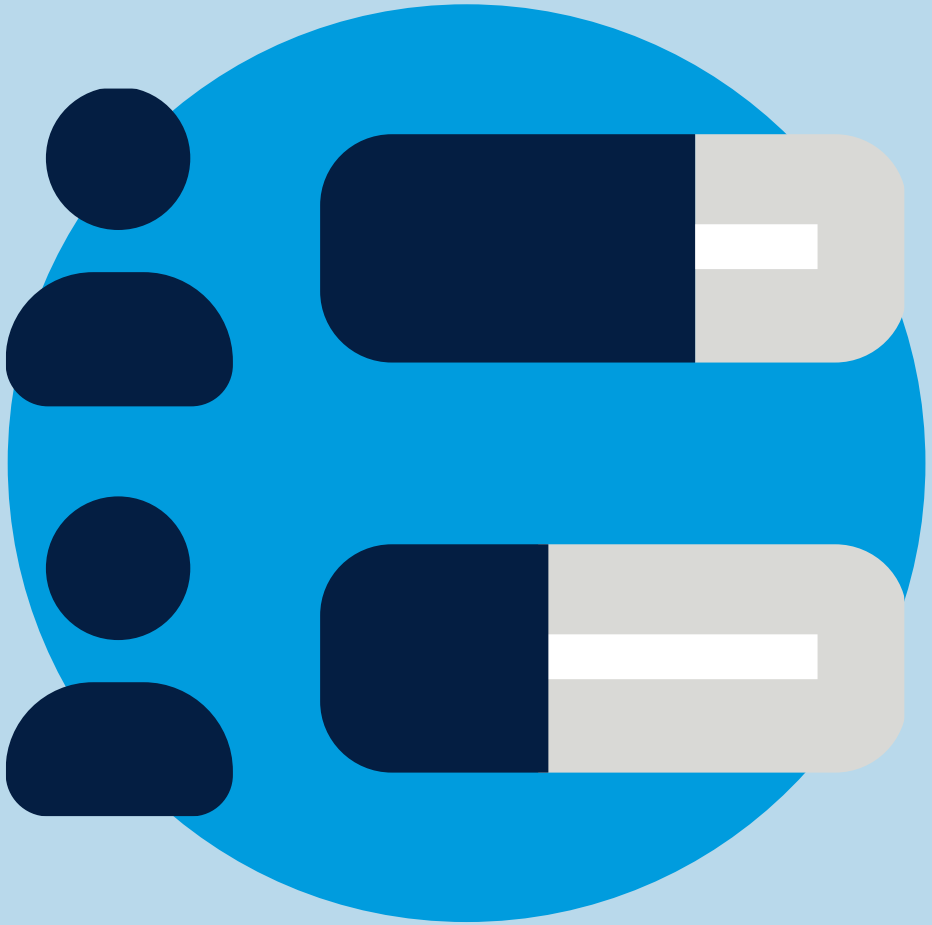
iScience, 2024, 27, 109894

Questions?

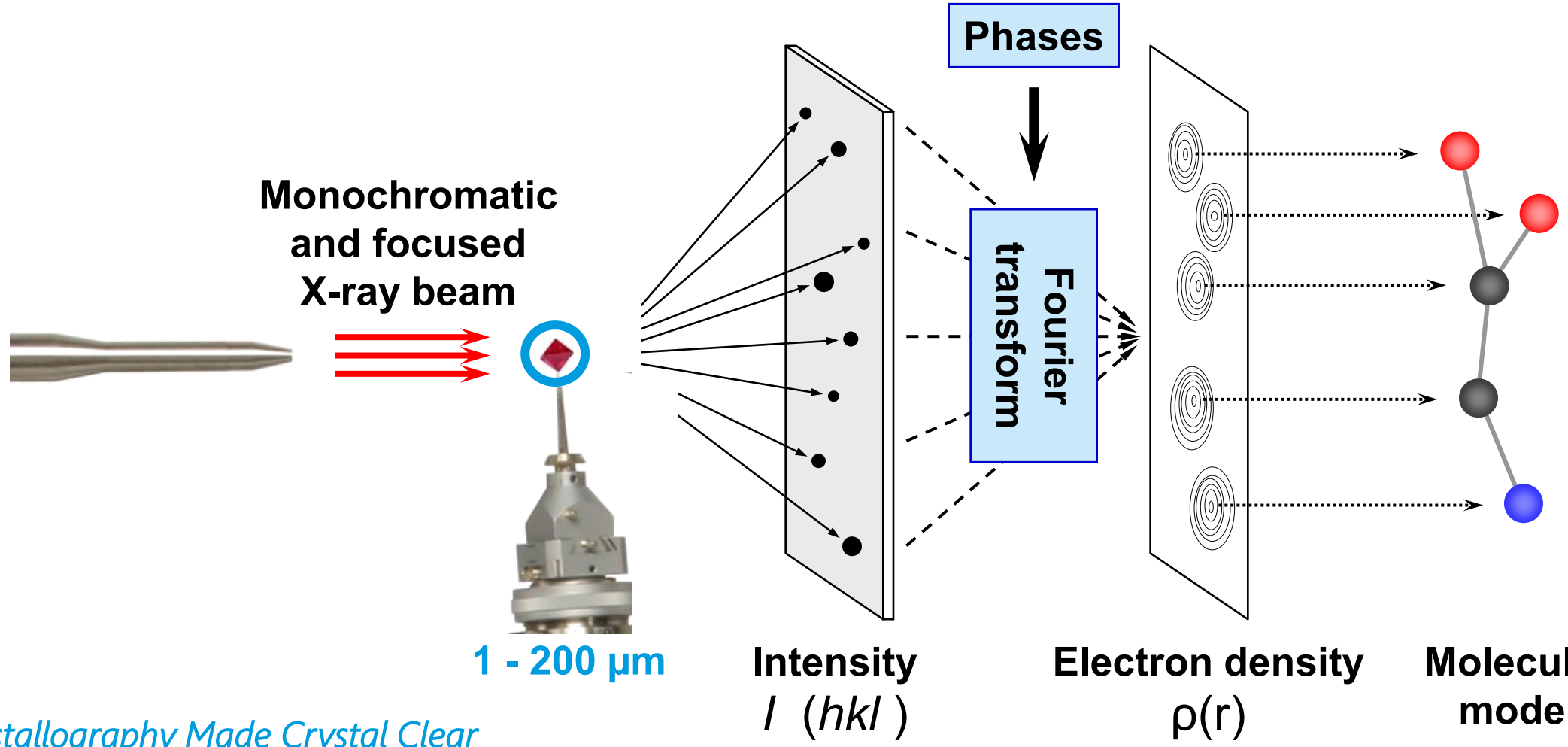
2. Basics of X-ray single-crystal crystallography

Polling Question

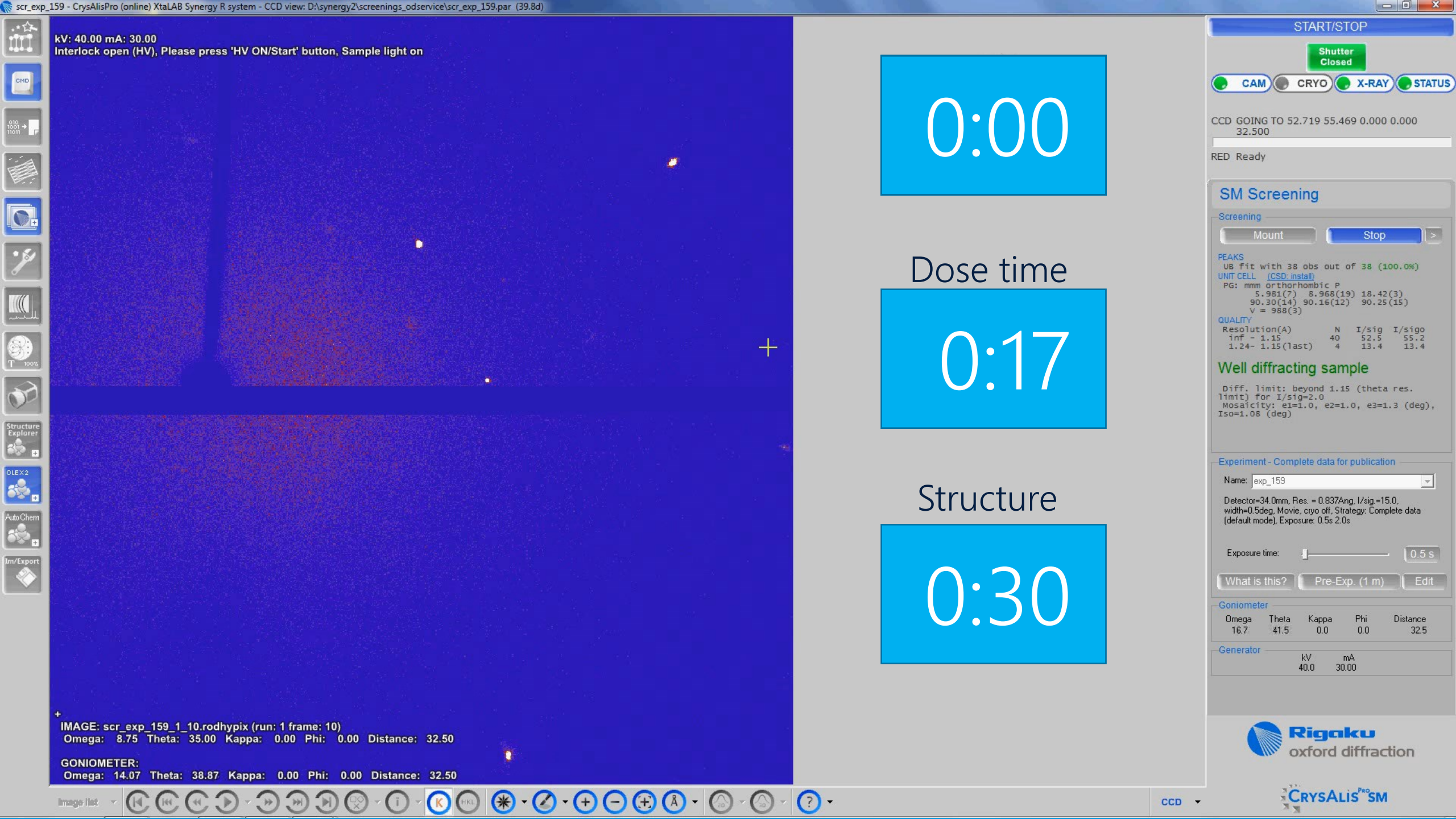
#2



Principle of X-ray crystallography

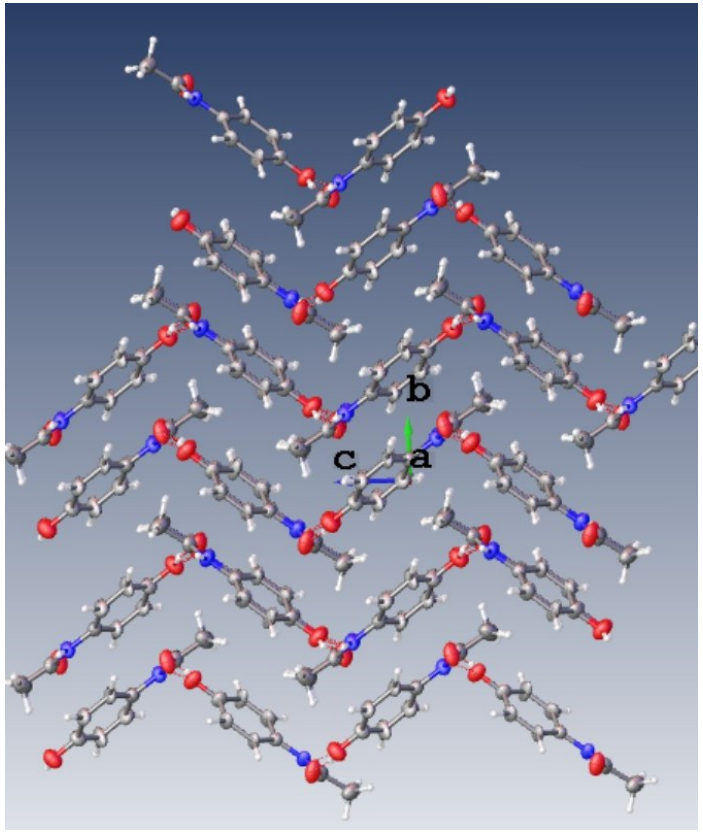


Crystallography Made Crystal Clear

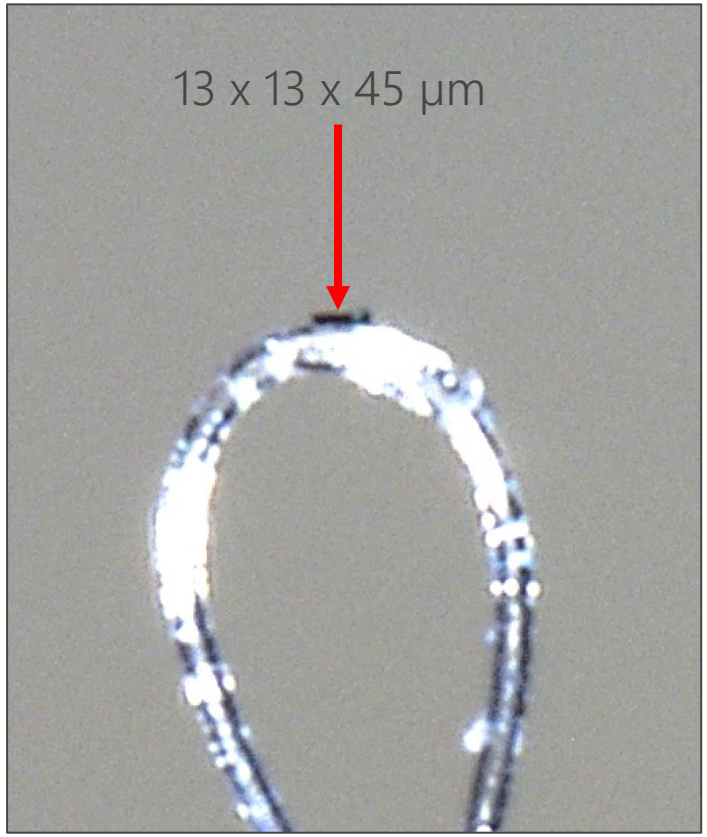

scr_exp_159 - CrysAlisPro (online) XtaLAB Synergy R system - CCD view: D:\synergy2\screenings_odservice\scr_exp_159.par (39.8d)
kV: 40.00 mA: 30.00
Interlock open (HV), Please press 'HV ON/Start' button, Sample light on
IMAGE: scr_exp_159_1_10.rodhypix (run: 1 frame: 10)
Omega: 8.75 Theta: 35.00 Kappa: 0.00 Phi: 0.00 Distance: 32.50
GONIOMETER:
Omega: 14.07 Theta: 38.87 Kappa: 0.00 Phi: 0.00 Distance: 32.50
0:00
Dose time
0:17
Structure
0:30
START/STOP
Shutter Closed
CAM
CRYO
X-RAY
STATUS
CCD GOING TO 52.719 55.469 0.000 0.000
32.500
RED Ready
SM Screening
Screening
Mount
Stop
PEAKS
UB fit with 38 obs out of 38 (100.0%)
UNIT CELL (CSD: install)
PG: mmm orthorhombic P
5.981(7) 8.968(19) 18.42(3)
90.30(14) 90.16(12) 90.25(15)
V = 988(3)
QUALITY
Resolution(A) N I/sig I/sigo
inf - 1.15 40 52.5 55.2
1.24- 1.15(last) 4 13.4 13.4
Well diffracting sample
Diff. limit: beyond 1.15 (theta res. limit) for I/sig=2.0
Mosaicity: e1=1.0, e2=1.0, e3=1.3 (deg), Iso=1.08 (deg)
Experiment - Complete data for publication
Name: exp_159
Detector=34.0mm, Res. = 0.837Ang, I/sig.=15.0, width=0.5deg, Movie, cryo off, Strategy: Complete data (default mode), Exposure: 0.5s 2.0s
Exposure time:
0.5 s
What is this?
Pre-Exp. (1 m)
Edit
Goniometer
Omega Theta Kappa Phi Distance
16.7 41.5 0.0 0.0 32.5
Generator
kV mA
40.0 30.00
Rigaku
oxford diffraction
CrysAlis PRO SM
Structure Explorer
OLEX2
Auto Chem
Im/Export
Image list
CCD

Crystal quality can vary a lot according to:

1. Tightness of crystal packing



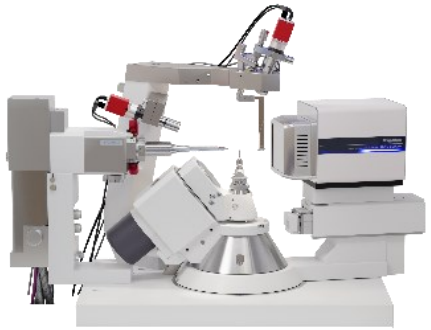
2. Size of the crystal



X-ray diffraction

Electron diffraction

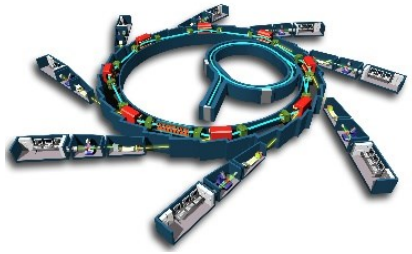
500-100 µm

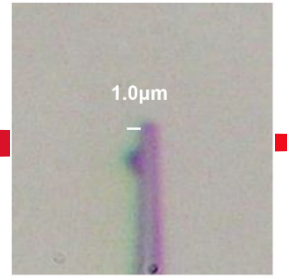


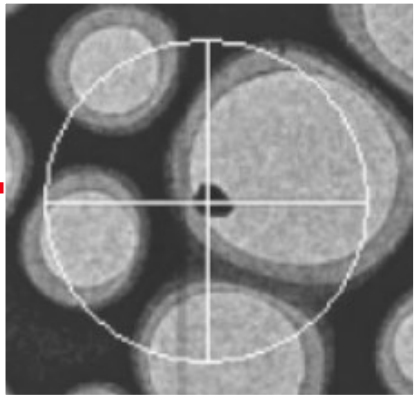
100-20 µm

20 ~ 1 µm

~1 micron







Decreasing sample size

~1 µm

3. One step further with electron diffraction

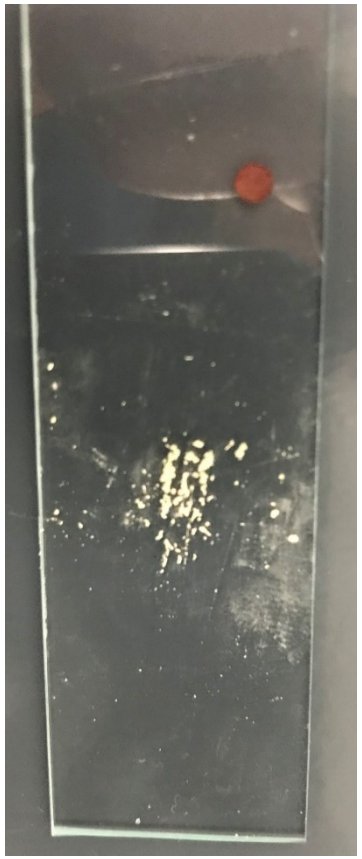
Key advantages of electron diffraction

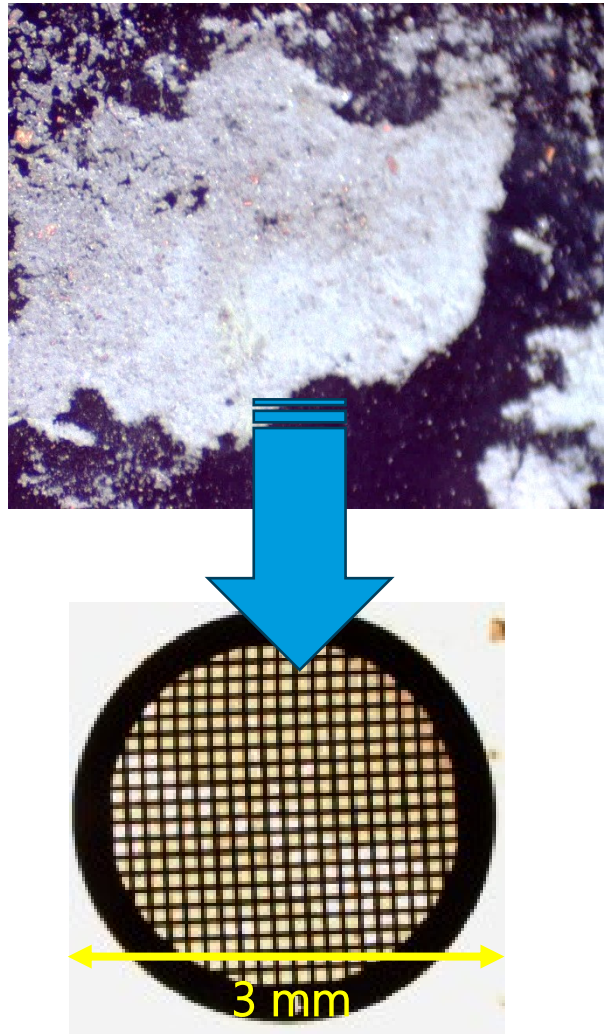
1. Crystal size:

   Submicron crystals i.e., crystalline powder.

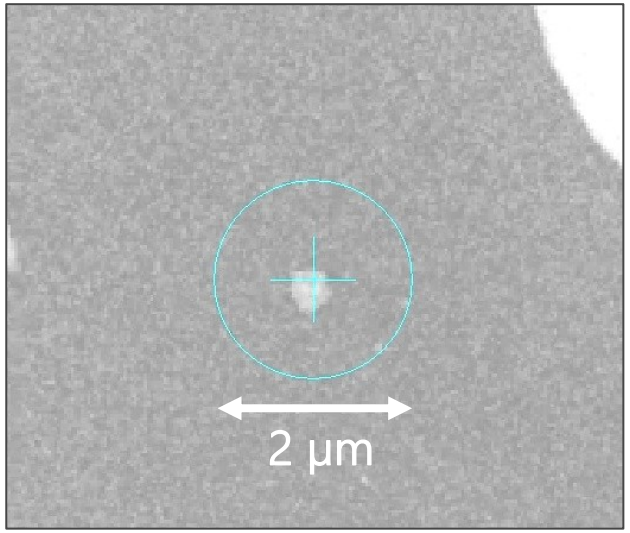
2. Sample amount:

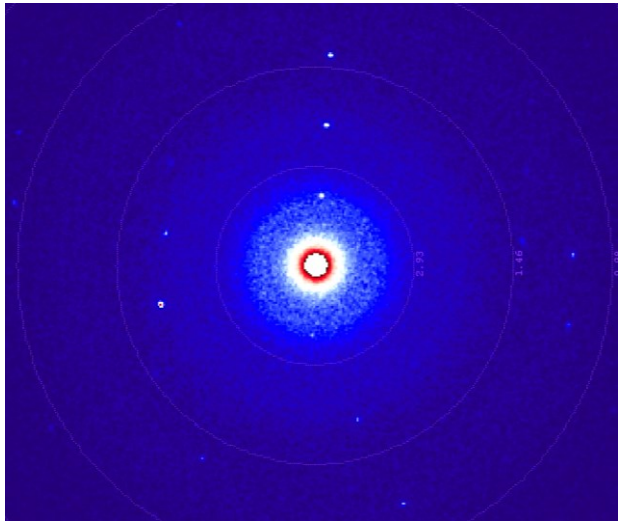
   Nanograms of powder.

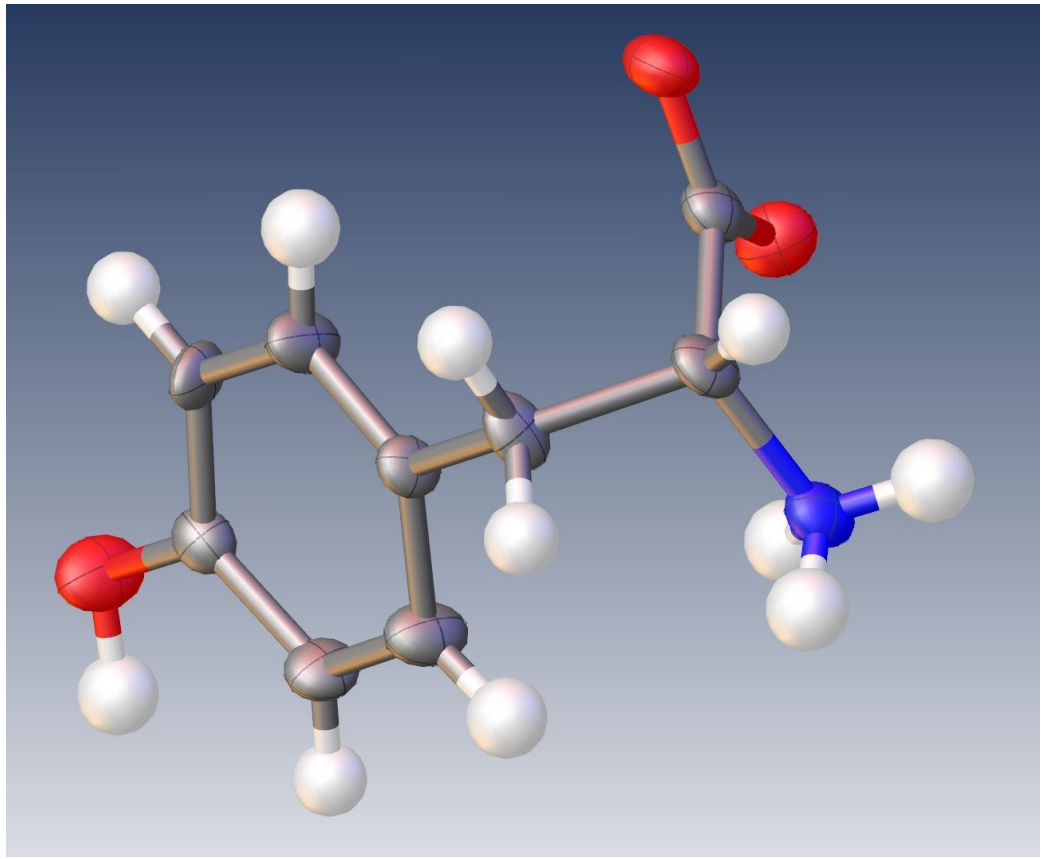




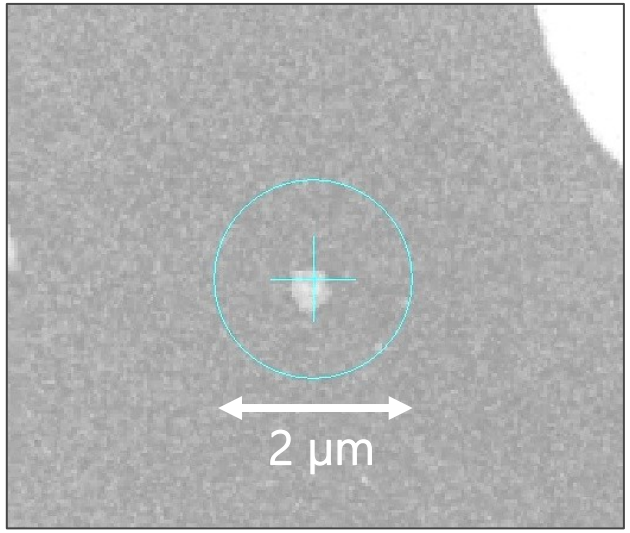
Tyrosine Organic co-crystal MOF: ZIF-8/Ni Grid preparation

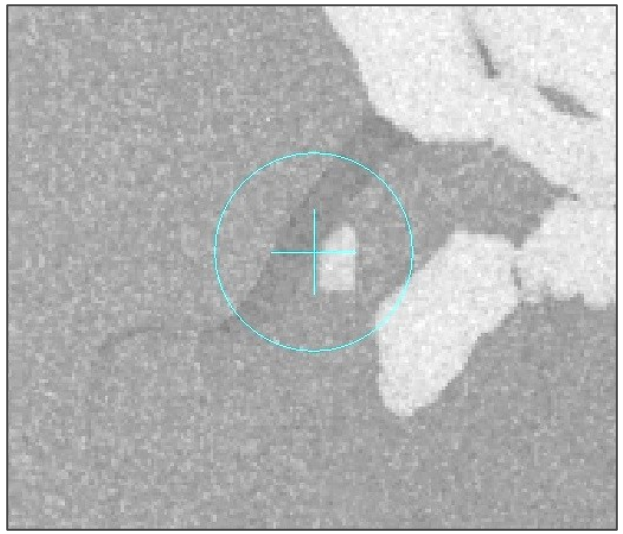


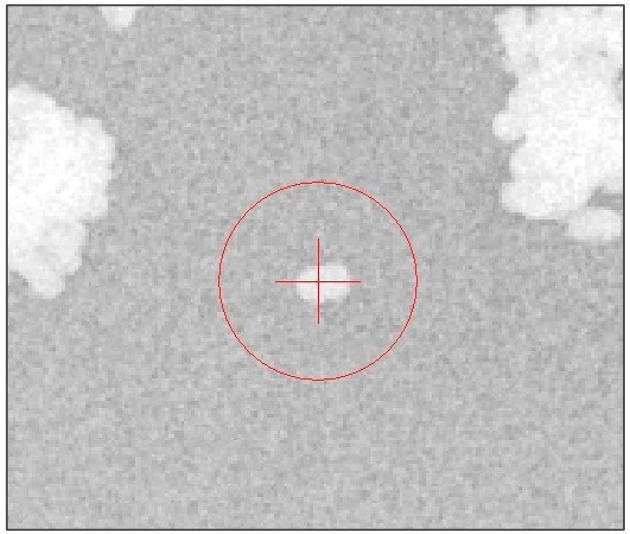


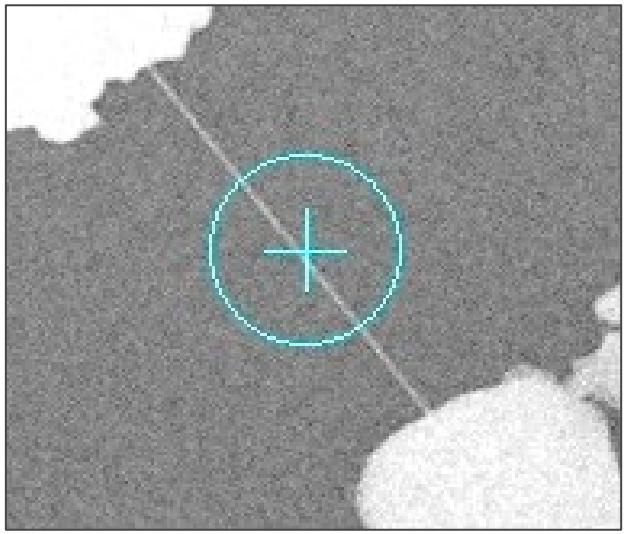


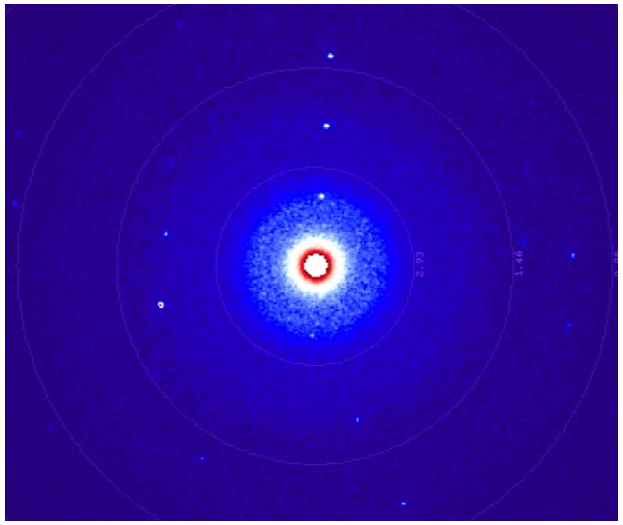
1 image from a series of rotational images

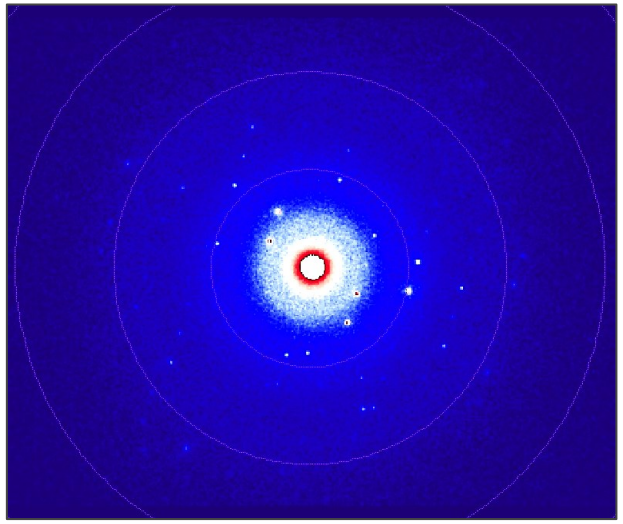


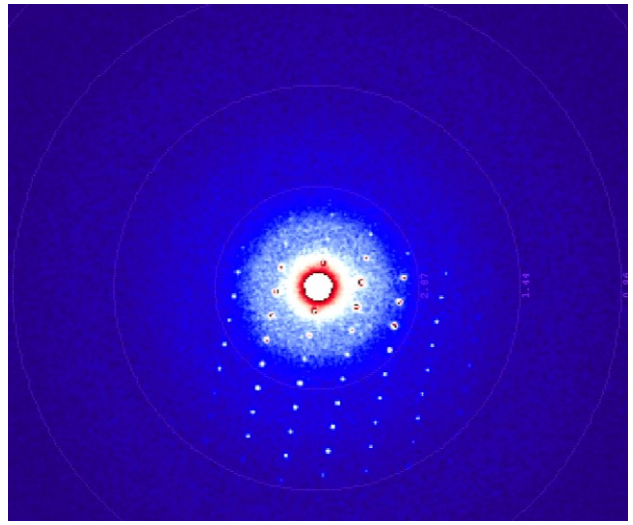


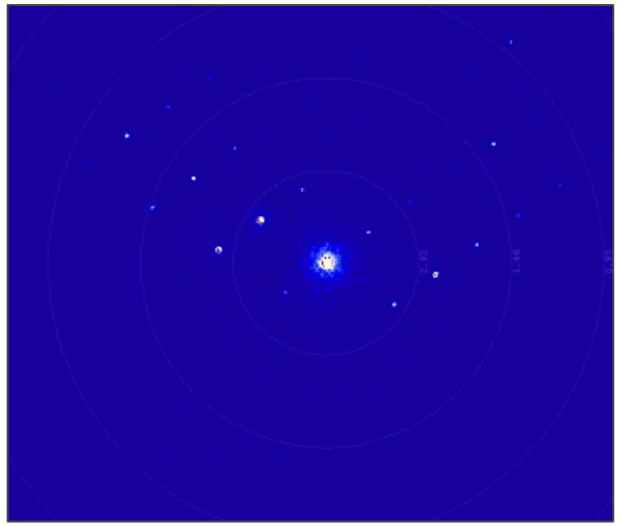












Tyrosine

Organic co-crystal

MOF: ZIF-8/Ni

Zr complex

Key advantages of electron diffraction

1. Crystal size:

   Submicron crystals i.e., crystalline powder.

2. Sample amount:

   Nanograms of powder.

3. Multitude of crystals at once:

   High-throughput screening of polymorphs on powders.

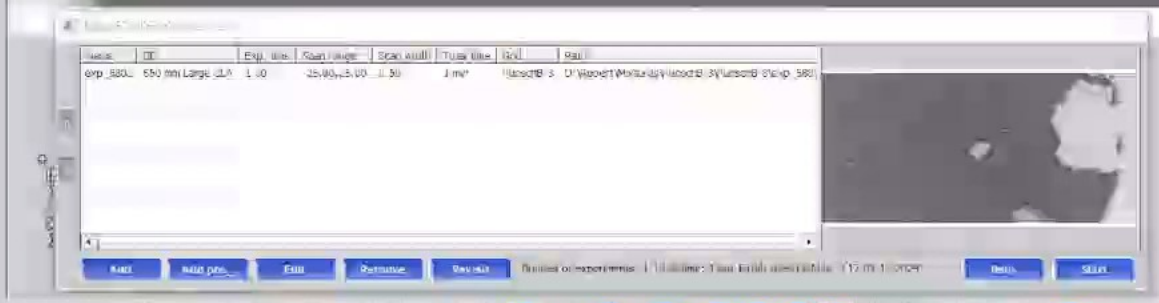
https://www.mdpi.com/2073-8994/15/8/1555

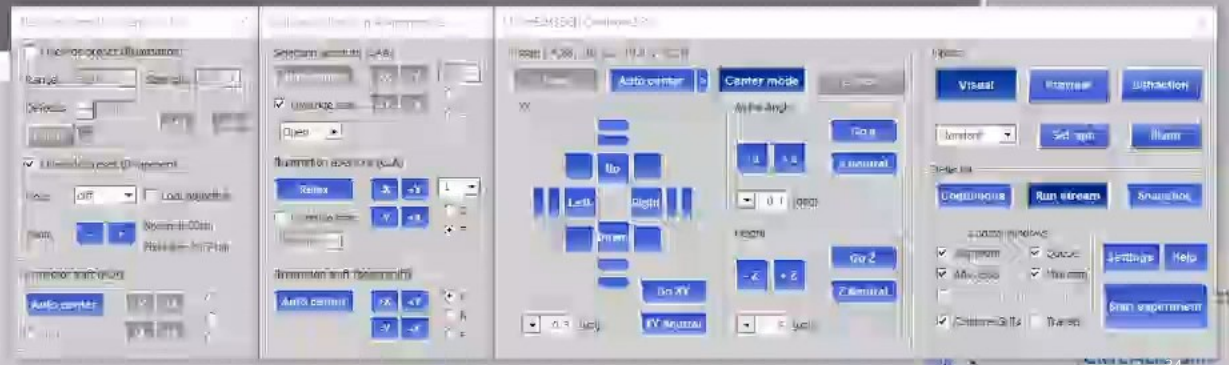
Auto-Screening

Automatic collection

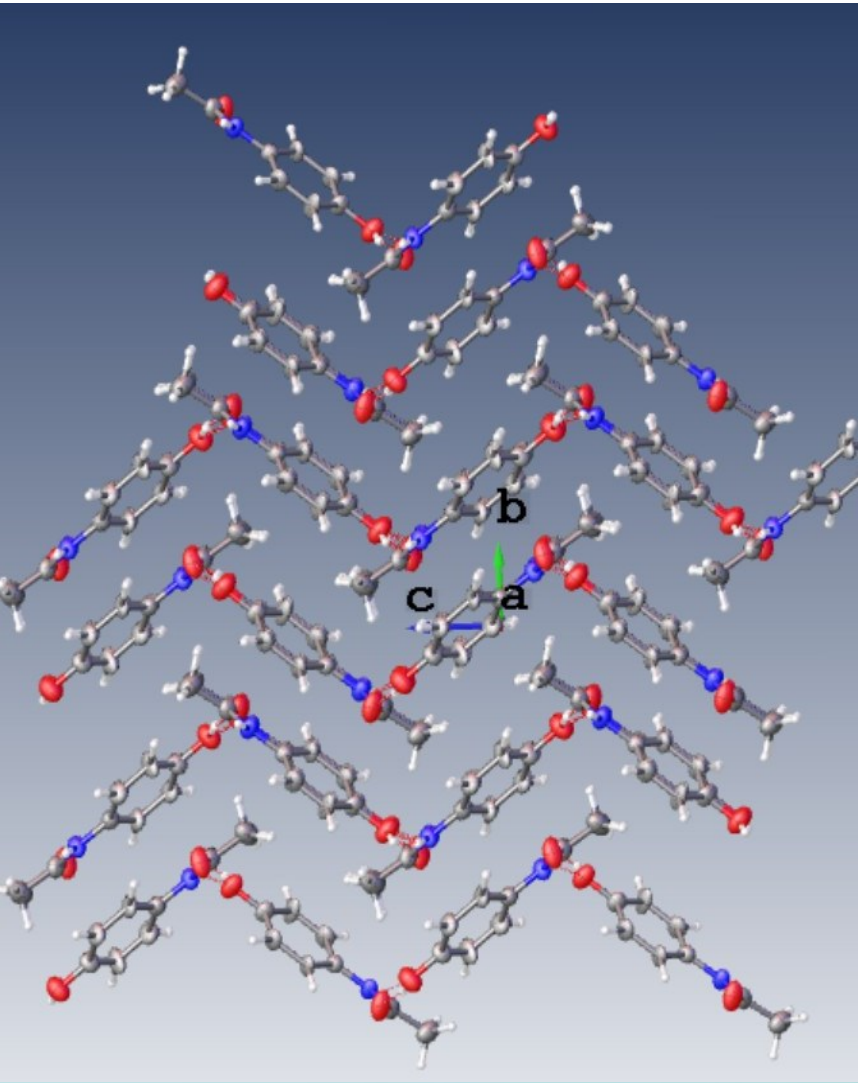
Grain selection

(without height adjustment)





4. Conclusion



Knowing the Crystal Structure mitigates time loss:

1. Unambiguous determination of molecular connectivity and crystal form
2. Hydrate? Solvate? Salt? Absolute configuration? Polymorphs?
3. Reduced pipeline time scale potentially by months

Questions?

2

Streamlining the Wet Lab: Best Practices for Managing Stock Solutions

presented by Amy Syverson

You will learn:

- 5 best practices for proper stock solution management
- How to implement stock solution management in your research workflow
- How to make liquid handling instruments a seamless and effective part of your lab

What is a stock solution?

Salts

Buffers

Precipitants

Prepared Reagent Solutions

How stock solutions keep your lab on track

- Faster turnaround
- Convenience
- Consistency

Specific Needs

- Concentrations
- Volumes
- Containers
- Specific times

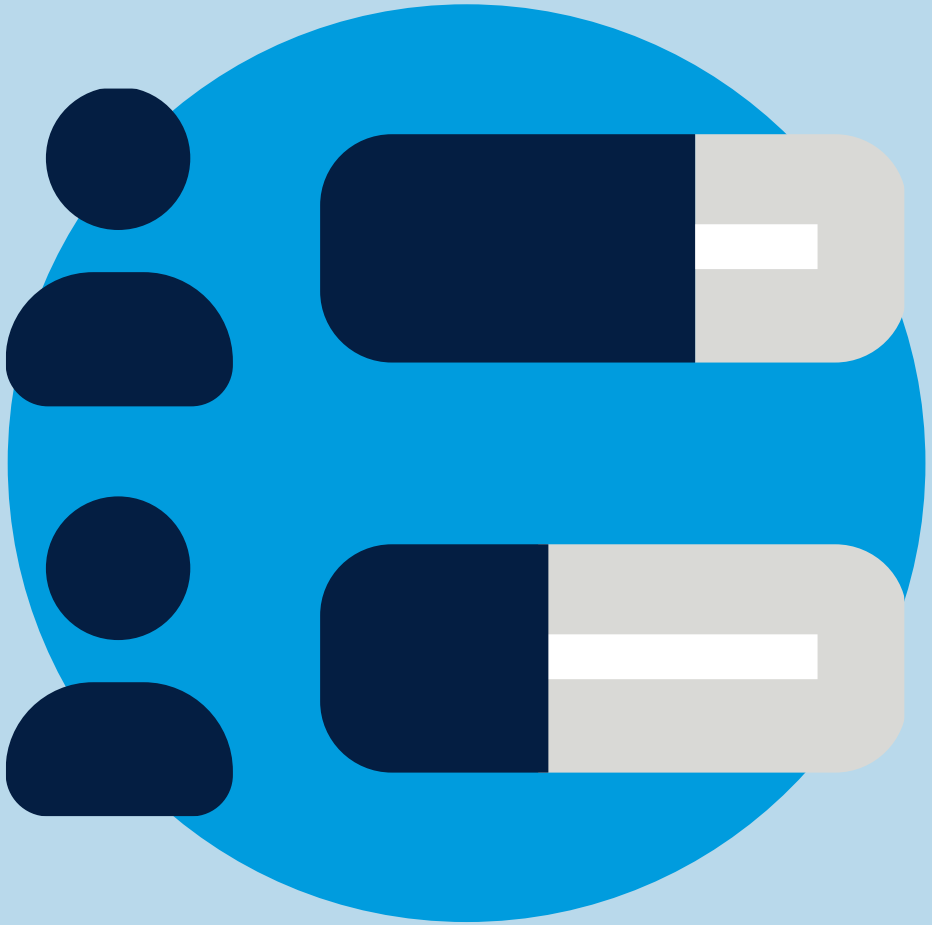
Is stock solution preparation creating chaos?

- Dry chemicals: maintain range of different supplies
- Weigh out dry chemicals, bring into solution
- Labeling and storage

What can go wrong?

- Run out of chemicals
- Expired stock solutions
- Tools and inventory become inaccurate
- Contamination

Polling Question

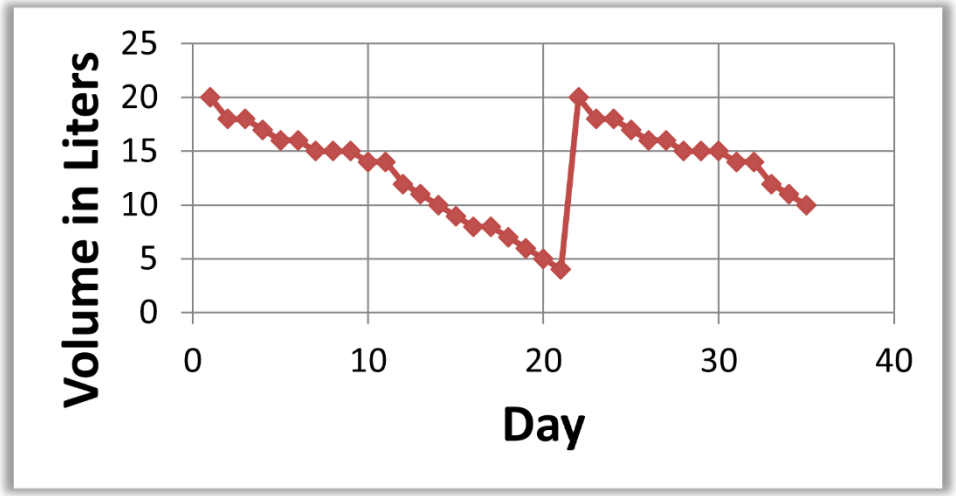


5 Best Practices to avoid such chaos

- Know consumption needs of your lab.
- Plan labs needs into the future.
- Monitor inventory regularly.
- Create standard recipe repository
- Teamwork. Embrace lab standards.

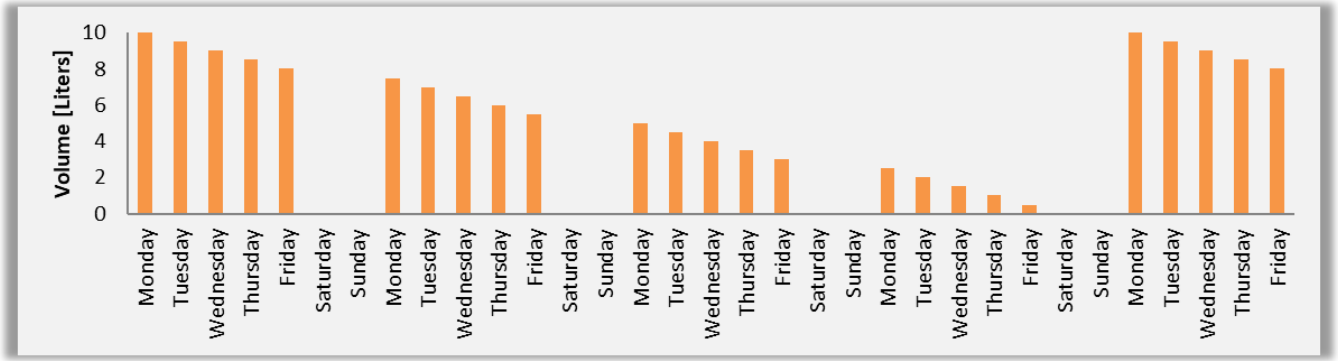
#1: Know consumption needs

- Track overall use over time for each instrument
  - Type of stock solution
  - Volume
  - Container
- Consumption fluctuations
- What does your lab consider empty?

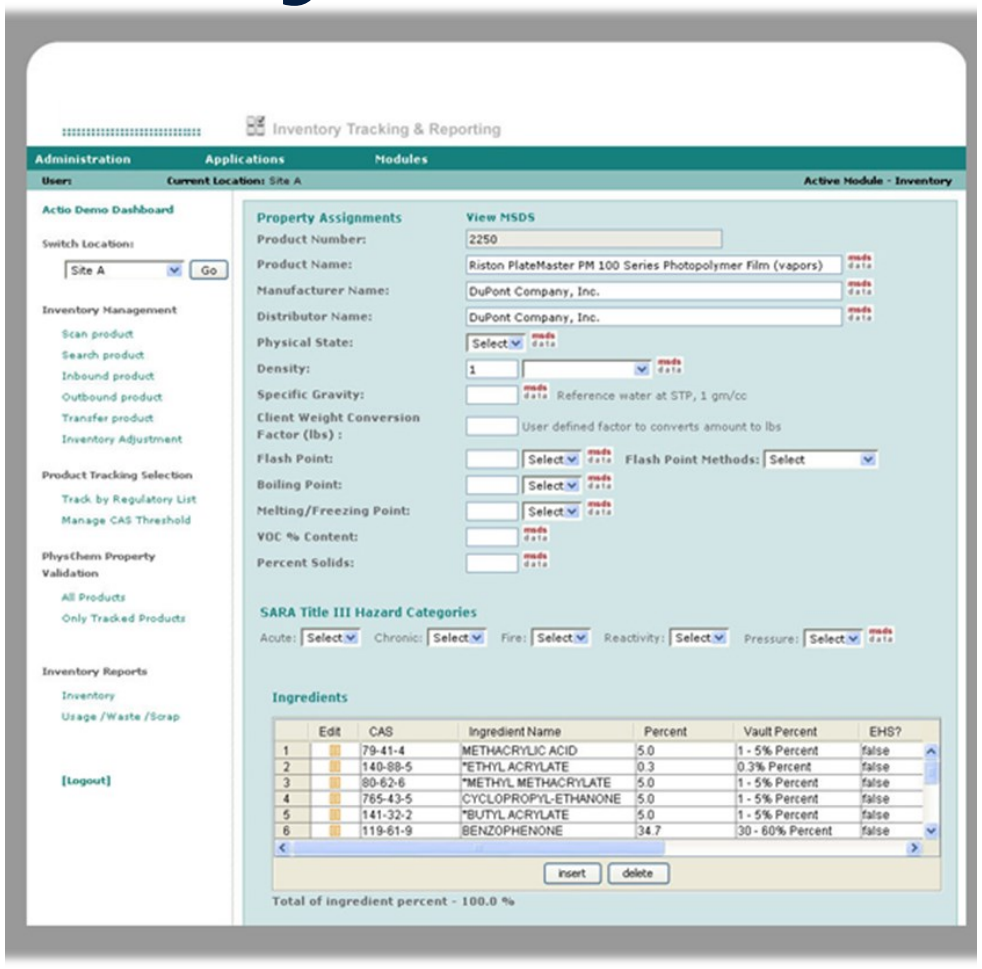


#2: Plan for lab's future needs

- Project use into the future for each instruments and each project
- Consolidate projections for multiple instruments

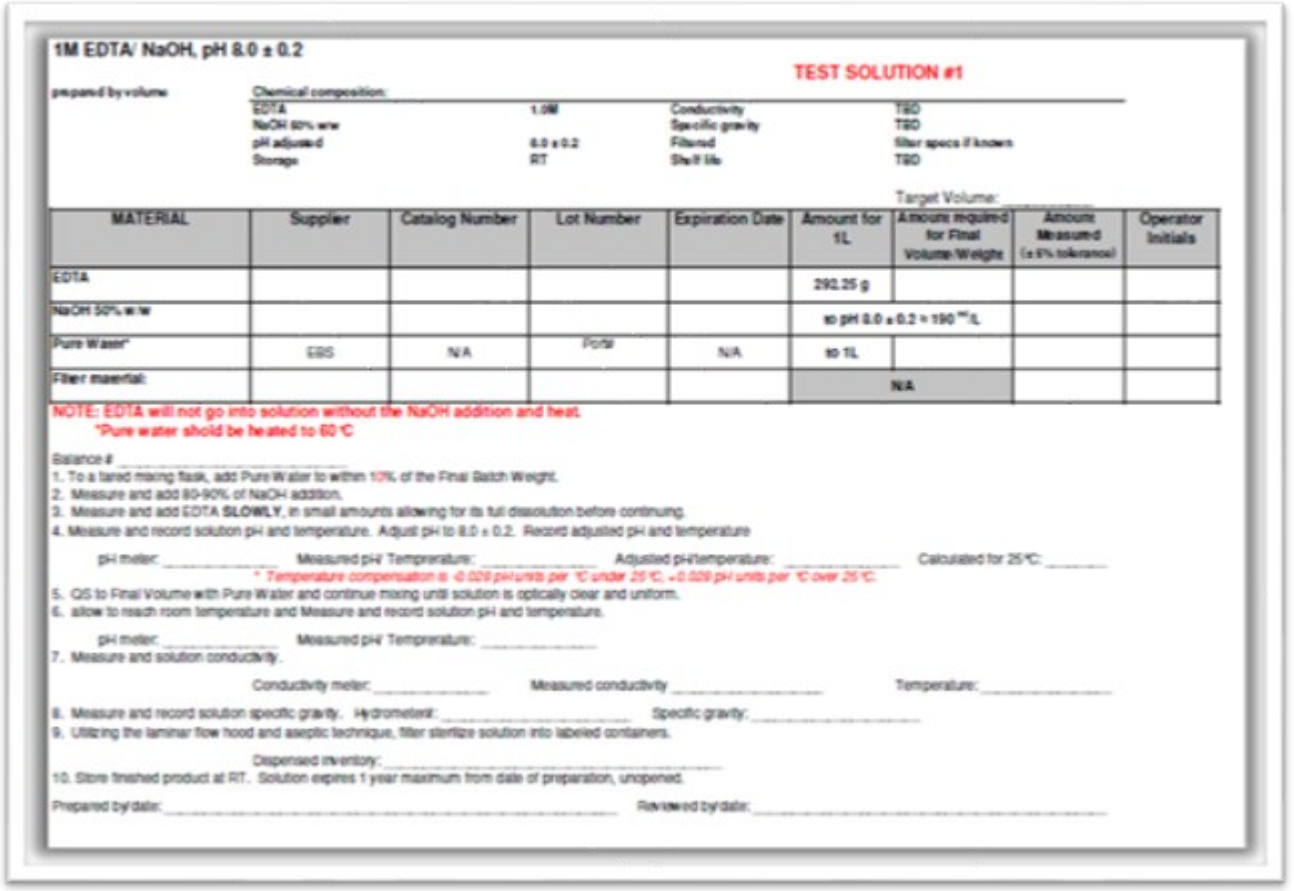


#3: Monitor inventory regularly



#4: Create standard recipe repository

Document special conditions for producing that solution so you will be better prepared for the next time!



1M EDTA/ NaOH, pH 8.0 ± 0.2

TEST SOLUTION #1

prepared by volume

Chemical composition:

EDTA	1.0M	Conductivity	TBD
NaOH 50% w/w		Specific gravity	TBD
pH adjusted	8.0 ± 0.2	Filtered	filter specs if known
Storage	RT	Shelf life	TBD

Target Volume: _____

MATERIAL	Supplier	Catalog Number	Lot Number	Expiration Date	Amount for 1L	Amount required for Final Volume/Weight	Amount Measured (± 5% tolerance)	Operator Initials
EDTA					292.25 g			
NaOH 50% w/w					to pH 8.0 ± 0.2 ≈ 190 ᵐᴸ/L			
Pure Water*	EBS	N/A	Portal	N/A	to 1L			
Filter material:					N/A			

NOTE: EDTA will not go into solution without the NaOH addition and heat.
*Pure water should be heated to 60°C

Balance # _____

1. To a tared mixing flask, add Pure Water to within 10% of the Final Batch Weight.
2. Measure and add 80-90% of NaOH addition.
3. Measure and add EDTA **SLOWLY**, in small amounts allowing for its full dissolution before continuing.
4. Measure and record solution pH and temperature. Adjust pH to 8.0 ± 0.2. Record adjusted pH and temperature

pH meter: _____ Measured pH/ Temperature: _____ Adjusted pH/Temperature: _____ Calculated for 25°C: _____

** Temperature compensation is -0.029 pH units per °C under 25°C, +0.029 pH units per °C over 25°C.*

5. QS to Final Volume with Pure Water and continue mixing until solution is optically clear and uniform.
6. allow to reach room temperature and Measure and record solution pH and temperature.

pH meter: _____ Measured pH/ Temperature: _____

7. Measure and solution conductivity.

Conductivity meter: _____ Measured conductivity _____ Temperature: _____

8. Measure and record solution specific gravity. Hydrometer#: _____ Specific gravity: _____
9. Utilizing the laminar flow hood and aseptic technique, filter sterilize solution into labeled containers.

Dispensed inventory: _____

10. Store finished product at RT. Solution expires 1 year maximum from date of preparation, unopened.

Prepared by/date: _____ Reviewed by/date: _____

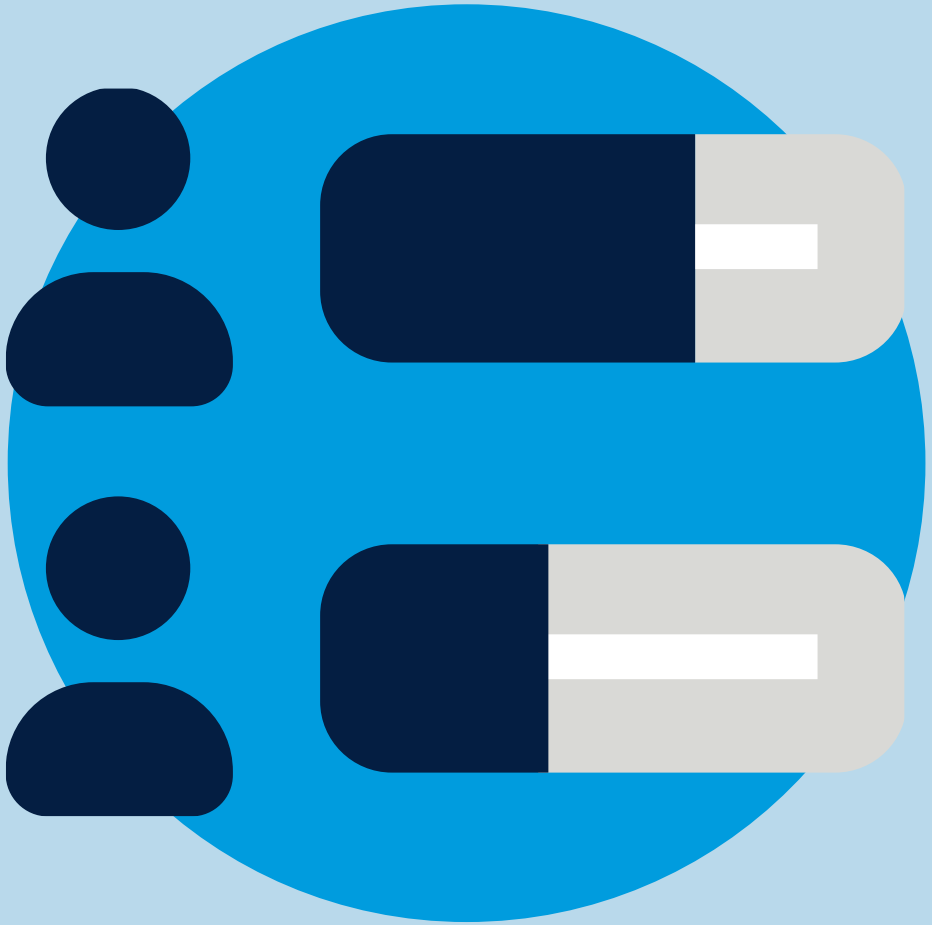
#5: Embrace team standards

- Document material requirements
- Project them months in advance
- Weekly scheduled inventory
- Recipe file system
- Teamwork: training on standards established

Rigaku Reagents' Stock Solutions

- This Stock Solution system works for us, it can work for you.
- We produce and inventory over 200 unique stock solutions in our manufacturing facility to use on our liquid handling instrumentation to produce the screens we offer.

Polling Question



Key Takeaways:

- Time Efficiency
- Faster Turnaround
- Convenience
- Precision and Consistency
- Confidence in Results

Questions?

We'll follow up with your questions.

Recording will be available tomorrow.

Register for seminar.

Rigaku

Webinar Series

Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 2 – Preclinical Development & Preformulation

1. **Thermal Analysis/Preclinical Development**
   Presenter: Genesis Infante, PhD
2. **Unlocking Drug Potential: The Role of X-Ray Powder Diffraction in Preformulation**
   Presenter: Akhilesh Tripathi, PhD

Starting Wednesday, April 16 at 1 pm CST

Don't forget to register for the next episode!