LYOhub.org

Advanced Lyophilization Technology Consortium

Annual Report

2020

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Directors' Message

"May you live in interesting times".

Sir Austen Chamberlain, British statesman and Nobel laureate, ca 1936

As this 2020 LyoHUB Annual Report goes to press, we are in the midst of the Covid-19 global pandemic. More than a million cases have been reported worldwide and more than 70,000 people have lost their lives. Lockdown and shelter-in-place orders are in place in many countries, and many of us are house-bound. Businesses are closed, universities have gone online, and travel has come to a standstill. The implications for the world economy are staggering and just beginning to be felt. We fear for our health, our families, our jobs and our future in ways unimaginable just a few months ago.

There are threads of hope in the midst of this – from small acts of kindness, to the dedication of medical personnel, to examples of inspired leadership at a national level. Woven together, these threads are strong stuff, a new social fabric still on the loom. As part of this fabric, biopharmaceutical and medical device industries are mounting a response to the pandemic by developing new vaccines, testing and repurposing approved medicines, rolling out new point-of-care assays, and donating equipment and supplies to front line responders. Many of you are directly involved in these efforts, and many more belong to companies and organizations that are making this response possible.

Here at LyoHUB, we're honored to be a small part of the broader scientific ecosystem that surrounds you. Taken individually, the activities in this annual report may seem small and unimportant. Taken together, though, they are the work of a community of scientists who are advancing lyophilization technology - through training and education, with new computational tools, in scientific meetings, by disseminating best practices and with fundamental research. These activities create new knowledge, strengthen today's scientists and help prepare the next generation. All of that serves the broader goal of making quality medicines available to patients, faster and more affordably.

Thank you for your interest in LyoHUB. Special thanks to our member companies for partnering with us in this effort - we salute your commitment to improving human health and we are honored to stand with you. Thanks, too, to the Birck Nanotechnology Center for hosting our Demonstration facility, to the instructors who contributed to our new online Lyo101 course, and to our students and postdocs whose energy and enthusiasm are an inspiration. We are continually grateful to Jen Gray, our Operations Manager, who is the heart and soul of LyoHUB. We look forward to continuing to work with all of you to advance lyophilization technology.

With our gratitude and best wishes,

Alina Alexeenko and Liz Topp

Membership

IMA LIFE Freeze Drying Solutions — *Member Since 2014*

Pfizer — *Member Since 2014*

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson — *Member Since 2015*

MILLROCK TECHNOLOGY INNOVATIVE BY DESIGN millrocktech.com — *Member Since 2015*

INFICON — *Member Since 2015*

SP SCIENTIFIC — *Member Since 2016*

Baxter — *Member Since 2016*

abbvie — *Member Since 2016*

Allergan — *Member Since 2016*

Roche — *Member Since 2016*

THE McCRONE GROUP — *Member Since 2016*

SIEMENS — *Member Since 2017*

FRESENIUS KABI — *Member Since 2017*

Bristol-Myers Squibb — *Member Since 2017*

Abbott — *Member Since 2018*

OPTIMA EXCELLENCE IN PHARMA — *Member Since 2018*

AMGEN® — *Member Since 2018*

Greene Tweed — *Member Since 2018*

Merck KGaA, EMD Serano — *Member Since 2019*

AstraZeneca — *Member Since 2019*

EVONIK POWER TO CREATE — *Member Since 2019*

Daiichi-Sankyo — *Member Since 2019*

COOK® BIOTECH — *Member Since 2019*

CORNING — *Member Since 2020*

LyoHUB Online Lyophilization Short Course

NOW AVAILABLE TO ALL!

- Online Lyophilization Short Course
- Featuring eight online lyophilization 101 learning modules, together with assessment tools and instructions for a virtual laboratory exercise
- There is no cost to take the course.

- Eight video modules presenting an introduction to pharmaceutical lyophilization (Lyo 101)
  - ◊ Introduction to pharmaceutical lyophilization
  - ◊ Overview of the lyophilization process
  - ◊ Production lyophilizers
  - ◊ Quality attributes of lyophilized products
  - ◊ Glass transition temperature
  - ◊ Freezing
  - ◊ Primary and secondary drying
  - ◊ Graphical design space.
- Virtual laboratory exercise in pharmaceutical lyophilization
- Assessment tools that evaluate student performance and quality of course content.

120 individuals have taken this course since January, 2020

https://pharmahub.org/courses/lyo101

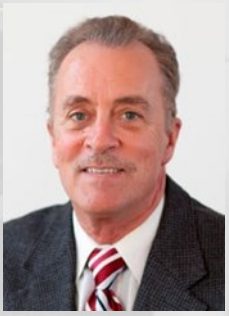
LyoHUB Inaugural Scientific Advisory Board

- Three year term
- Nominated by industry members
- Chosen based on nominations and need based on current research/interest
- Roles/Responsibilities
    - Monthly call participation
    - Annual meeting participation
    - Advise on specific topics as needed
    - Provide input on training, agenda if requested
    - Reach out to special speakers/presenters if requested
    - Can offer advice but have no voting rights
- Compensation
    - LyoHUB will compensate SAB members for LyoHUB travel expenses and meeting registration

LyoHUB Scientific Board
at the 2019 LyoHUB Annual Meeting

Robin Bogner
Professor of Pharmaceutics
University of Connecticut
Director, Kildsig Center for Pharmaceutical Processing Research (CPPR)
Current Research Interests:
- Freeze Drying Process Development and Characterization
- Reconstitution of Lyophilized Highly Concentrated Protein Therapeutics
- Characterization of Lyophilized Solids
- Prediction of Product Quality Variation based on Formulation and Process Variation

Other Expertise:
- Pharmaceutical Compounding
- Dissolution Enhancement of Poorly Soluble Drugs
- Characterization of the Amorphous State of Drugs



Steve Nail
Principle Scientist, Baxter Biopharma
Adjunct Professor, Purdue University
Leadership, LyoHUB
- Professor at Purdue for courses including parenteral pharmaceutical products (undergrad) and graduate courses in pharmaceutical processing.

Expertise:
- Physical chemistry of freezing and freeze-drying
- Characterization of frozen systems and freeze-dried solids
- Stability of proteins as freeze-dried products
- Pharmaceutical thermal analysis
- Pharmaceutical applications of supercritical fluid technology

Raj Suryanarayanan
Professor of Pharmaceutics
University of Minnesota
Site-Director, Kildsig Center for Pharmaceutical Processing Research (CPPR)
- Studying optimization of the freeze-drying cycles of protein pharmaceuticals. Simultaneous quantification of reactant, product, and intermediate phases of very rapid reactions using high intensity X-rays.
- Use of a microdiffractometer to map tablet surfaces and also to characterize specific regions of a powder bed (or of a tablet).
- Identify new excipients or modify the physical state of current excipients with the object of expanding their utility in freeze-dried formulations.

Standards and Best Practices for Pharmaceutical Lyophilization Meeting

In September 2019, LyoHUB held a meeting at the National Institute of Standards and Technology (NIST) titled***, Standards and Best Practices for Pharmaceutical Lyophilization***. Talks included **Use of Modeling and Simulation in Drug/Device Development and Regulatory Evaluation** by Tina Morrison (FDA), **Analytical Technologies for Product Quality Measurements** by John Schiel (NIST), **Drug Substance Manufacturing** by Scott Lute (FDA) and **Regulatory Review Perspective on Lyophliization** by Steve Rhieu (FDA). The day also included a panel on the **"Use of Standards in Validation for Lyophilization and other Pharmaceutical Processes"** and one featuring organizations working in lyophilization.

LyoHUB members can access the presentation slides at https://pharmahub.org/groups/lyo/wiki/LyoGroupMeetings

Panel participants

Dr. Scott Lute presentation

Dr. Steve Rhieu presentation

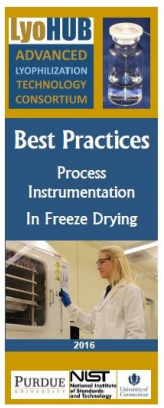
Dr. Alina Alexeenko introduces Dr. Tina Morrison

Q&A Session with Meeting Participants

Organizations working in lyophilization

- **ASTM (American Society for Testing and Materials):** Arnab Ganguly (IMA Life)
- **Center for Pharmaceutical Development (CPD):** Eric Munson (Purdue University)
- **Dane O. Kildsig Center for Pharmaceutical Processing Research (CPPR):** Sajal Patel (AstraZeneca)
- **National Institute for Innovation in Manufacturing (NIIMBL):** Kelley Rogers (NIST/NIIMBL)
- **National Institute for Pharmaceutical Technology & Education (NIPTE):** Vadim Gurvich (University of Minnesota)

Best Practices



LyoHUB published our first lyophilization best practices paper, **"*Recommended Best Practices in Instrumentation Process Monitoring in Pharmaceutical Freeze Drying*"** in 2017**.** It is available with open access and as of March 2019 has been downloaded over 11,000 times!

http://link.springer.com/article/10.1208/s12249-017-0733-1

Best Practices Papers in Progress:

Scale Up and Tech Transfer

Led by Serguei Tchessalov and Bakul Bhatnagar (Pfizer)

Equipment Performance Qualification

Led by Arnab Ganguly (IMA Life)

Submitted to AAPS PharmSciTech Jan. 17, 2019

A Practical Guide for Validation of Pharmaceutical Lyophilization

Led by Feroz Jameel (AbbVie)

Lyophilization Formulation Best Practices

Led by Elizabeth Topp (LyoHUB) and Greg Sacha (Baxter)

Lyophilization Modeling Presentation to the FDA

On February 25, 2020, Elizabeth Topp and Alina Alexeenko provided an information session to 32 FDA representatives from various groups, as well as countless more through a conference call. The presentation was on Modeling for Lyophilization and included an overview of resources available through LyoHUB, current modeling for primary drying and primary drying model applications in lyophilization.

LyoHUB members can access the presentation slides at https://pharmahub.org/groups/lyo/wiki/LyoGroupMeetings

Left, LyoHUB presentation to the FDA.

Right, Elizabeth Topp (far left) and Alina Alexeenko (far right) with FDA participants.

Awards/Grants

Improving Lyophilization of Recombinant Proteins with ssHDX-MS

- Funded by NIIMBL
- $450,000 over 18 months
- **Goal:** Evaluate solid-state hydrogen deuterium exchange with mass spectrometric analysis (ssHDX-MS) as a method to test stability of proteins in solid powders.
- **Investigators:** Lokesh Kumar (Genentech), Ben Walters (Genentech), Andrea Allmendinger (Roche), Deborah Bitterfield (Lindy Biosciences), Michael Doherty (Lindy Biosciences)

PFI-RP: Sensors, Computational Modeling, and Bioanalytical Technologies for Closed-Loop Lyophilization

- Funded by NSF, Partnership for Innovation program
- $750,000 over 3 years
- **Goal:** (i) Noninvasive product temperature monitoring using wireless probes that are compatible with aseptic processing requirements; (ii) Accelerated biomolecule stability analytics by solid-state hydrogen-deuterium exchange mass spectrometry; and (iii) Real-time lyophilization rate measurement and closed-loop process control based on distributed wireless probes and computational modeling of the heat and mass transfer in the product, container and the lyophilizer equipment.
- **Investigators:** Alina Alexeenko (PI, Purdue/AAE), Timothy Peoples (Co-PI, Purdue Foundry), Elizabeth Topp (Co-PI, Purdue/IPPH), Dimitrios Peroulis (Co-PI, Purdue/ECE)
- **Industry Partner:** Millrock Technology

Software and Hardware Tools for Pharmaceutical Lyophilization and Scale Up

- Funded by NIIMBL
- **Goal:** Develop and test hardware and software tools that will harmonize pharmaceutical lyophilization process development and scale-up.
- **Industry Partners:** Physical Sciences, Inc., Genentech, Merck, University of Massachusetts Lowell, NIPTE-University of Connecticut, Purdue University, Massachusetts Life Sciences Center

Advanced Wireless Sensor (PAT) for Pharmaceutical Lyophilization

- Selected for funding by CESMII (The Smart Manufacturing Institute)
- **Goal:** To apply a real-time, non-invasive, process monitoring system for pharmaceutical lyophilization equipment based on a wireless network of vacuum and temperature sensors.
- **Industry Partners:** Baxter Healthcare, Purdue University

ASTM Lyophilization Standards

E55.05 Lyophilization subcommittee of E55 Committee on Manufacture of Pharmaceutical and Biopharmaceutical Products: https://www.astm.org/COMMITTEE/E55.htm

ASTM INTERNATIONAL

E55.05 CHAIRS

Dr. Arnab Ganguly
Chair
IMA Life

Dr. Serguei Tchessalov
Vice-Chair
Pfizer

Committee Progress in 2019-2020:

- *Standard Practice for Product Temperature Measurement and Equipment Pressure Instrumentation in Pharmaceutical Freeze Drying* was submitted to the subcommittee for ballot on August 22, 2019.
- After edits were made per recommendations from the subcommittee, the updated work item was resubmitted for ballot on February 10, 2020.
- The vote resulted in 30 affirmative votes, 1 negative and 35 abstains. Minor edits were recommended and will be incorporated into the standard before resubmitting to ballot in April 2020.

Industry Visits/Conferences

Industry Visits to LyoHUB:

- Pfizer, April 2019
- Roche/ Genentech, April 2019
- Mettler Toledo, June 2019
- Baxter, June 2019
- Egyptian Armament Authority, June 2019
- Micromeritics, July 2019
- Baxter, Abbvie, July 2019
- Lighthouse Instruments, July 2019
- Mettler Toledo, July 2019
- Sero Colombia, July 2019
- Eli Lilly, September 2019
- AbbVie, September 2019
- Eli Lilly, April 2019, December 2019
- Millrock, January 2020
- Merck, January 2020
- Elanco, February 2020

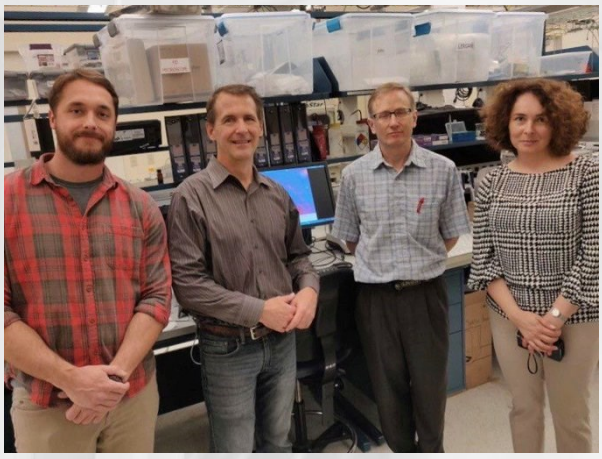
Conference Presentations or Posters:

- CPPR, May, 2019
- Biotech, Pharma, Cancer and Research Conference Conference, August 2019
- ISLFD Garmisch Conference, September 2018
- NIIMBL, September 2019
- ISL-FD Chicago, April 2019
- ISL-FD, East Coast, September 2019
- NIST, September 2019
- FDA, February 2020

LyoHUB Visits to Companies:

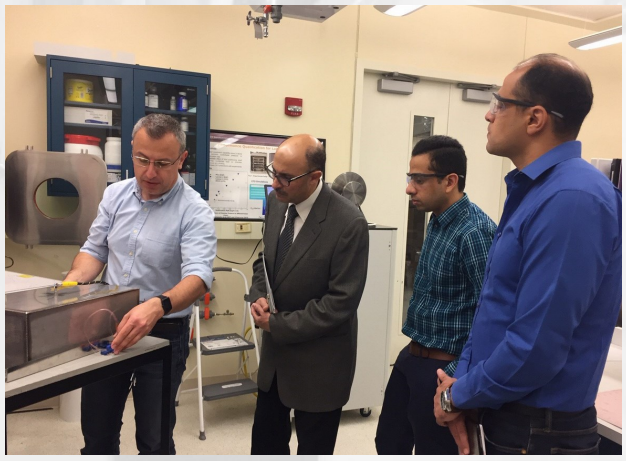
- AbbVie, June 2019
- Baxter, August 2019
- University of Massachusetts, February 2020

In July of 2019, (15) representatives from AbbVie, Baxter and Purdue met at Purdue to discuss the Vial Fogging Project.



Cellulose nanomaterials (CNM) project meeting with Dr Robert Moon and Gregory Schueneman from the US Forest Service.

LyoHUB hosted food freeze dry company, SERO Colombia and Doehler Dry Ingredients Solutions to the demonstration facility in July, 2019



Egyptian delegation representing the Egyptian Armament Authority visits the demonstration facility.

Education & Training

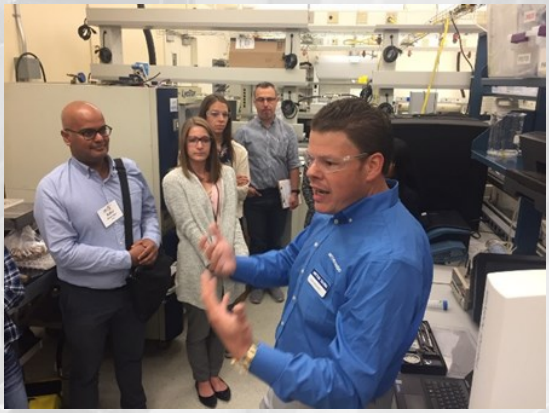
Liz Topp lectures about ssHDX-MS

Summer Lyo School 2019: Lyo201 Characterization of Lyophilized Solids
2 day workshop for Purdue and industry users
Participants:
•**15 students and postdocs**
•**10 industry participants:** Cook Biotech (3), Eli Lilly (1), Evonik (2), IMA Life (1), Pfizer (2), Singota (1)
•**Equipment demos:** Micromeritics (BET Surface Area Analysis), Mettler Toledo (DSC) and Lighthouse Instruments (Residual Moisture Analyzer)

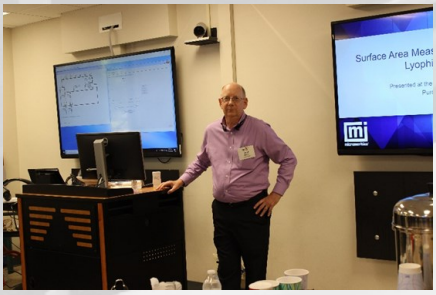
TOPICS:

- ssHDX-MS
- Lyo PRONTO
- ssNMR
- BET Surface Area Analysis
- Detecting Crystalline Impurities in Solids
- Introduction of DSC, New Innovations and their applications
- Residual Moisture Analysis
- Vapor Pro

A little Apollo 11, 50th Anniversary fun, too!



Caleb McDonald (Mettler Toledo) DSC demo



Paul Kester (Micromeritics) BET surface Area Analysis Demo

Talk by Garth Simpson (Purdue) on detecting crystalline impurities in solids

LyoHUB Demonstration Facility

In February 2016, LyoHUB opened the **Lyophilization Technology Demonstration Facility** located in the Birck Nanotechnology Center at Purdue Discovery Park. The facility, where collaboration on breakthrough technologies can be advanced with a goal of accelerating adoption and decreasing time to market, is equipped and supported by LyoHUB's industry members. The facility also offers various hands-on training opportunities for academic and industry users. Full equipment listings and capabilities can be found on the LyoHUB website at https://pharmahub.org/groups/lyo/demofacility

LyoHUB demo facility is located in Birck Nanotechnology Center, Room 2261.

Computrac® Vapor Pro ®

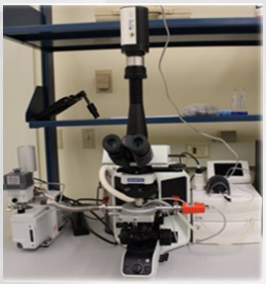
Donation from Baxter

Lighthouse FMS-1400 Headspace Pressure/ Moisture Analyzer

REVO lyophilizer with controlled nucleation and in-situ mass spectrometer.

LYOSTAR™ 3 Freeze-Dryer with controlled nucleation and mass flow meter

Development Freeze-Dryer/ Lyophilizer MICROFD



McCrone Freeze-Drying Microscope

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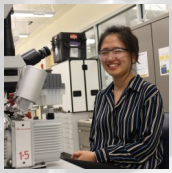

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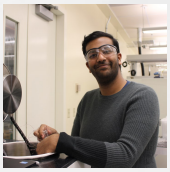

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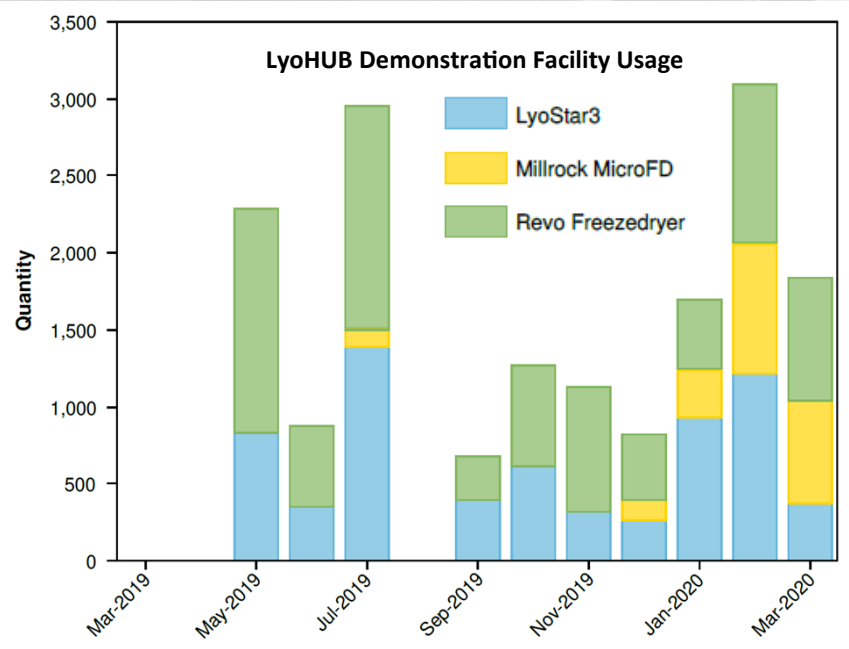
Demonstration Facility Usage



Total Number of Lyophilization Runs:
(2/26/16-3/26/17): **87**
(3/1/17-3/30/18): **178**
(4/1/18-3/27/19): **190**
(3/1/19-3/1/20): **421**

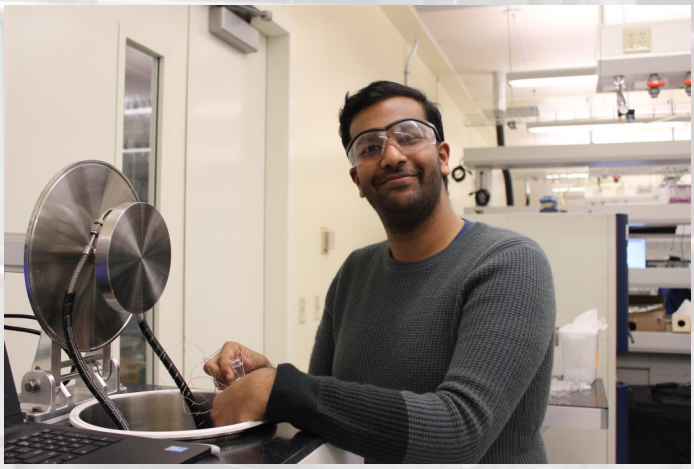
Average Time for Lyophilization Run (in hours):
(2/26/16-3/26/17): **33.25**
(3/1/17-3/30/18): **51.83**
(4/1/18-3/27/19): **73**
(3/1/19-3/1/20): **39**

Total Lyo Run Time:
(2/26/16-3/26/17): **2,971.37 hours**
(3/1/17-3/30/18): **9,227.17 hours**
(4/1/18-3/27/19): **13,944 hours**
(3/1/19-3/1/20): **16,624 hours**

New Users Trained on Lyophilization Equipment from March 2019-2020

Name	Affiliation		Name	Affiliation
Brooke Davisson	Cook Biotech		**Iris Cho**	Purdue IPPH/Topp Lab
Sydney Hollingshead	Cook Biotech		**Siddhi Hate**	Purdue IPPH/Taylor Lab
Pravallika Kollipara	Cook Biotech		**Petr Kazarin**	Purdue AAE/Post Doc
Russell Miller	Eli Lilly & Co		**Rajashekar Kammari**	Purdue IPPH/Topp Lab
Harsh Patel	Evonik		**Tarun Mutukuri**	Purdue IPPH/Zhou Lab
Paritosh Pande	IMA Life		**Michael Sinanis**	Purdue/Electrical and Computer Engineering
Bakul Bhatnagar	Pfizer		**Cole Tower**	Purdue IPPH/Munson Lab
Vamsi Mudhivarthi	Pfizer		**Trae Carroll**	Singota
Lauren Markovich	Purdue ChemE/Chemical Engineering		**Ashley Lay-Fortenbery**	University of Kentucky
Dhawal Chobisa	Purdue IPPH/Yeo Lab		**Mehfouz Jalal**	Purdue/LyoHUB Associate Research Engineer
Ahmed Abdelraheem	Purdue Electrical and Computer Engineering		**Helen Corbat**	Purdue/Chemical Engineering
Sean Wainwright	Purdue/Aeronautics and Astronautics		**Caroline Alukkal**	Purdue/Agronomy
Yirang Park	Purdue/LyoHUB Associate Research Engineer		**Scott Griffin**	Purdue/Chemistry
Raj Khangura	Purdue/Biochemistry			

LyoHUB New Super Users



Mehfouz Jalal, Associate Research Engineer, LyoHUB Demo Facility

MEHFOUZ JALAL, Associate Research Engineer, LyoHUB

- Mehfouz received his BS in Chemical & Biomolecular Engineering from Georgia Tech in 2015 and a Professional Masters in Chemical Engineering from Purdue in 2019.
- His work experience includes working with offshore oil & gas procurement firms, polymers and plastics manufacturing
- Taught courses on acing college standardized tests.
- Mehfouz enjoys trips back to his hometown of Dubai and spending quality time with his family and friends. He is a self-professed foodie, movie lover, board game enthusiast and professional puzzle wrangler.
- Current LyoHUB project: applying lyophilization technology to different types and forms of crystalline nanocellulose materials in order to characterize the effects of freeze drying on their surface and overall structures.

YIRANG PARK, Associate Research Engineer, LyoHUB

- Yirang is from Daejeon, South Korea, but has lived in Korea, the Philippines, and China.
- She received her BS in Chemical Engineering at University of California, Berkeley in 2015 and a professional Master's degree in ChemE at Purdue in 2019
- Before Purdue, she worked in the Pharmaceutical Development group at AbbVie in Redwood City, CA for 2.5 years.
- She is excited to be working at LyoHUB, and hopes to become an expert in lyophilization technology from the experience.
- She is working on projects to characterize lyophilization of ammonium salt formulations and crystalline

Yirang Park, Associate Research Engineer, LyoHUB Demo Facility

Rishabh Tukra, LyoHUB Super User

RISHABH TUKRA, LyoHUB Super User

- Rishabh was born and raised in India and completed his bachelors degree in pharmacy from the University of Pune, India and his MS in pharmaceutical sciences from Creighton University, Nebraska.
- He is a PhD student under Dr. Elizabeth Topp in the department of Industrial and Physical Pharmacy, working on developing and understanding solid state hydrogen deuterium exchange-mass spectrometry and how it relates to protein stability in the solid state.
- Rishabh was able to explore the world of lyophilization in its true form while working with Drs. Greg Sacha and Steve Nail on an internship at Baxter. The internship got him interested in lyophilization. Since then, he has been involved with a couple LyoHUB projects and is excited to be a super user because "I get to work with incredible people and the diverse set of expertise they bring with them. I have been learning something new and exciting every week since and I look forward to more!"

Demonstration Facility Projects

LyoLaunchPad 2019-2020 Projects:

- Lyophilization of Cellulose Nanocrystals (US Forest Service and Georgian Tech)
- Application of residual gas analysis process gas composition measurement in lyophilization (Bristol Myers Squibb)
- Freeze drying of maize root tissue samples to be used for metabolite extractions. (Dr. Brian Dilkes, Department of Biochemistry, Purdue)
- Freeze drying of biosolids for the analysis of PFAS compounds, preserved to enable extended research. (Dr. Linda Lee, Agronomy, Purdue)
- Transforming hydrogel into aerogel using freeze drying (Wenzhou Wu, Industrial Engineering, Purdue)

Funded Projects:

- Wireless pressure and temperature sensor characterization (Purdue AAE/NSF project)
- Development of microwave assisted freeze drying (Purdue AAE/NSF project)
- Lyophilization Scale-Up Data Analysis and Modeling (NIIMBL project)
- Pyroglutamate formation project: (Astra-Zeneca/MedImmune; PhRMA Foundation fellowship to Lia Bersin)
- Antibody fragment project (Fab project, NIIMBL project)
- ssHDX-MS of proteins and ssHDX-MS under pressure of proteins (Purdue AAE/NSF project)
- ssHDX-MS: Generating a mechanistic understanding of solid state hydrogen deuterium exchange (ssHDX-MS) in lyophilized protein formulations. (Purdue AAE/NSF project)
- ssHDX-MS under pressure: Understanding the effects of pressure on the ssHDX-MS of lyophilized protein formulations. (Purdue AAE/NSF project)
- Wireless Sensor for Vial Headspace Pressure Monitoring During Controlled Ice Nucleation Process (Genentech)

Resources Available on the LyoHUB Website

Tools available on Website:

- Lyo University Lyophilization Short Course https://pharmahub.org/courses/lyo101
- LyoPRONTO Lyophilization Process Optimization Tool http://www.lyopronto.org
- LyoHUB Training, July 2018: Freeze drying: https://pharmahub.org/resources/773
- LyoHUB Training, July 2018: CFD: https://pharmahub.org/resources/778
- LyoCalculator https://pharmahub.org/resources/lyocalculator
- Lyo Chamber Pressure Variation Calculator https://pharmahub.org/resources/pressurevar
- LyoHUB Best Practice Paper, Recommended Best Practices for Process Monitoring in Pharmaceutical Freeze Drying http://link.springer.com/article/10.1208/s12249-017-0733-1
- LyoHUB Lyophilization Technology Roadmap https://pharmahub.org/groups/lyo/lyohub_roadmapping
- Presentations, such as “Developing Transferable Freeze Drying Protocols using Accuflux® and a MicroFD®” https://pharmahub.org/groups/lyo/tools

Additional talks and tools available on the website under “tools”

https://pharmahub.org/groups/lyo/tools

LyoLaunchPad Residual Gas Analysis Application to Lyophilization Process Project

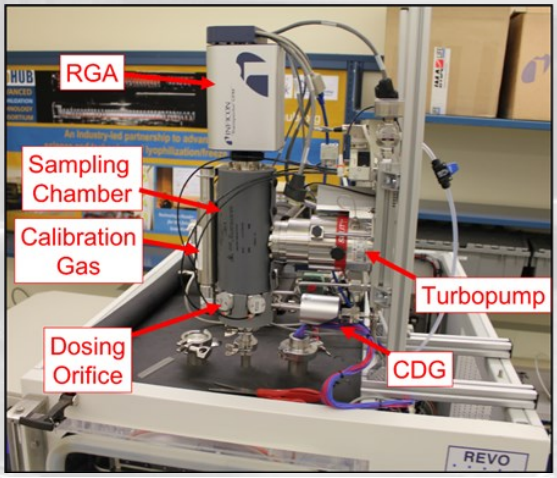


Figure 1. Residual gas analyzer (RGA) from INFICON and its components.

Figure 2. Lab-scale freeze dryer (REVO) with a residual gas analyzer (RGA) on top of the chamber.

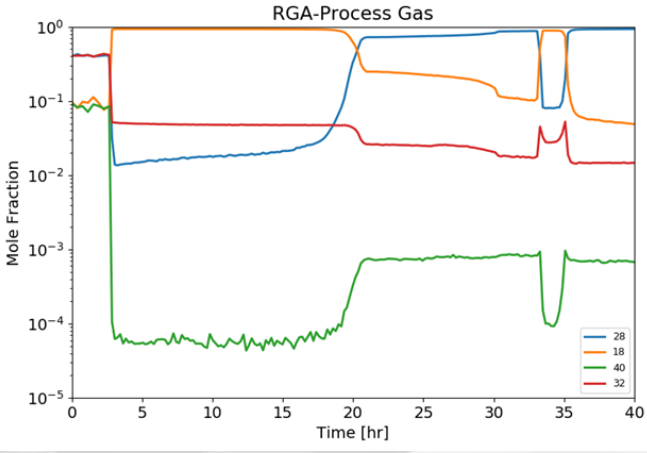


Figure 3. Mole fraction of processed RGA versus time graph. Legend on lower right corner indicates signal mass values, best representing the following gas species [28: N_2, 18: H_2O, 40: Ar, 32: O_2]. Argon signal likely results from minor impurity in the nitrogen ballast.

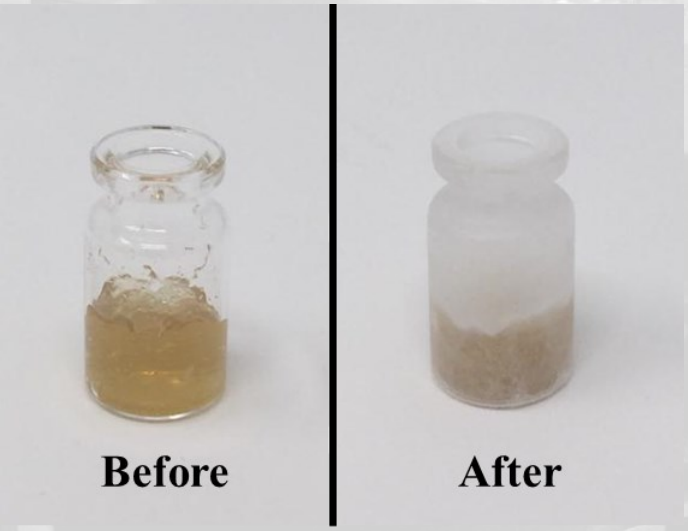
Residual gas analyzer (RGA) is a small mass spectrometer that is often used in semiconductor industry to check the integrity and quality of high vacuum systems for contamination and leakage at pressures typically lower than 10^{-4} Torr. When combined with a partial pressure reduction system (dosing orifice in Figure 1) that allows for measurements in higher pressure range of 10^{-3} Torr, it can be a powerful tool for monitoring the gas phase compositions in complex vacuum processes like lyophilization. This project leverages RGA's process gas monitoring capability to explore applications of the technology to freeze-drying process. A successful development of such application would provide a method to study numerous uncertain parameters such as off-gassing rates of co-solvents and compounds in the formulation or gaseous byproducts in the freeze-drying process that may not be present in the final lyophilized products.

Figure 2 shows the laboratory scale REVO freeze-dryer from Millrock that was used for this project. It is equipped with a RGA unit (Transpector Compact Process Monitor) from INFICON mounted on top as shown. Multiple on-going projects at LyoHUB utilize this unit for monitoring and identifying the volatile byproducts during the drying steps of lyophilization. The RGA unit can monitor the gas composition *in situ* in the mass range up to 200 amu with the detection threshold of 2-20 ppb. An example of processed RGA data is shown in Figure 3. The sensor output current signals are processed to calculate the mole fraction of gas species at select masses. For example, water vapors and N_2 gas in the chamber are best represented by signals at masses of 18 and 28 amu respectively. The decrease in signal 18 (water) and the simultaneous increase of signal 28 (N_2) near 19-hour mark indicate the end of primary drying step, followed by the sharp increase in signal 18 as the secondary drying step is initiated near 33-hour mark. The RGA has the capability of measuring the gases at sub-ppm levels, and if properly implemented, it could provide a method to study chemical changes during primary and secondary drying steps, and its data could further serve as additional scientific results to complement submissions to regulatory agencies.

While the potential benefits of augmenting process monitoring capability of freeze-drying process with RGA are clear, there are challenges that need to be overcome before its implementation would have any meaningful impact. In efforts to address such issues, the ongoing projects at LyoHUB focus on refining the data processing method, developing a precise quantitation process, and building a deconvolution technique for more complex gas compositions.

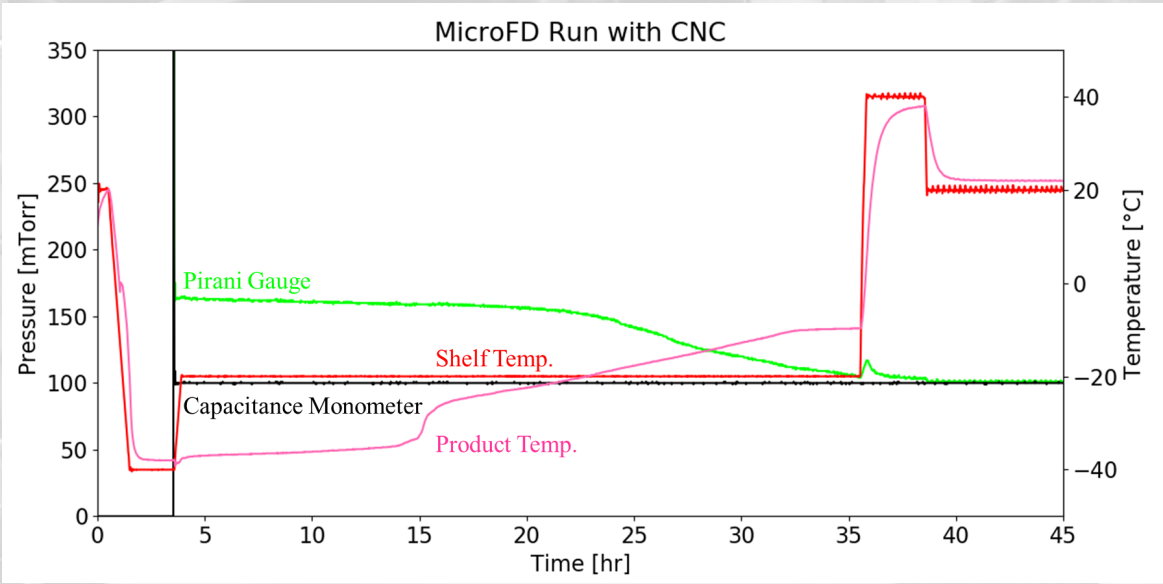
LyoLaunchPad Nanocellulose Project

Lyophilized CNC om various forms across different dilutions



CNC sample before and after being flash-frozen using liquid N_2

In collaboration with the Georgia Institute of Technology, LyoHUB has performed a set of lyophilization experiments on cellulose nanocrystals (CNC) using devices such as a freeze-drying microscope (FDM), an ultrasonic homogenizer (UH) and a micro-freezedryer (MicroFD) to name a few. Experiments have involved lyophilizing various types of CNC, like maleic acid-based or sulfate ester-based ones, under different conditions and states to determine the effects they have on their surface area. The surface area was studied by labs at Georgia Tech using Brunauer–Emmett–Teller (BET) specific area analysis and scanning electron microscope (SEM) imaging. The first step conducted at LyoHUB's facilities was to determine the collapse temperature (T_c) of the current formulation by using an FDM. A specialized camera captures the freeze-drying process of a few micrograms of the specified CNC samples to visually determine T_c. With the T_c known, a compatible recipe can be made for use in a MicroFD. Select CNC types were diluted with water prior to use with a UH which disturbs the water-CNC mixture with ultrasonic disruption delivered via a titanium tip. Once the samples are prepped, they are subjected to lyophilization. Most often, a MicroFD is used to go through all the steps of lyophilization, namely freezing, primary drying and secondary drying. However, some CNC samples were flash-frozen using liquid nitrogen and then placed in a MicroFD to continue with primary and secondary drying. CNC exposed to flash freezing was either frozen as a complete mass or as granules using syringes. Other CNC samples were subjected to post lyophilization experiments using a VaporPro which uses high temperatures to determine the level of moisture a sample contains. Here, it was used to find the moisture lyophilized CNC retakes when exposed to atmospheric conditions. Finally, the data obtained was analyzed to determine tweaks and adjustments that can made to the process as well as understand the freeze-drying process better for future implementation.



A graph depicting one of the lyophilization runs conducted with CNC using a MicroFD with freezing (hours 0-3.5), primary drying (hours 3.5-36) and secondary drying (hours 36-39)

Lyo PRONTO

Lyophilization at Variable Pressure and Temperature using Lyo PRONTO: An Open Source Lyophilization Process Optimization Tool

This work presents a new user-friendly lyophilization simulation and process optimization tool, freely available under the name LyoPRONTO. It is a new lyophilization simulation and process optimization tool. It includes freezing, primary drying modeling and optimization modules as well as the design space generator (Figure 1(b)). It can be used to model the lyophilization process and create more efficient cycles. Moreover, the tool is capable of determining the vial heat transfer parameters and product resistance characteristics, thus reducing the number of experiments.

The 0D lumped capacitance modeling approach is used in a freezing calculator to predict the product temperature variation with time and results in reasonably good agreement with experimental measurements. The primary drying calculator is based on 1D heat and mass transfer analysis (Figure 1(a)) in a vial and deviation from the experimental data is within 3% (Figure 1(d)).

The optimization tool enables acceleration of the primary drying cycle by 62% for 5% Mannitol (Figure 1(c)) and by 50% for sucrose solutions in comparison to traditional cycles. Thus, coupling with controllers and accurate sensors will allow creating self-driving lyophilizers.

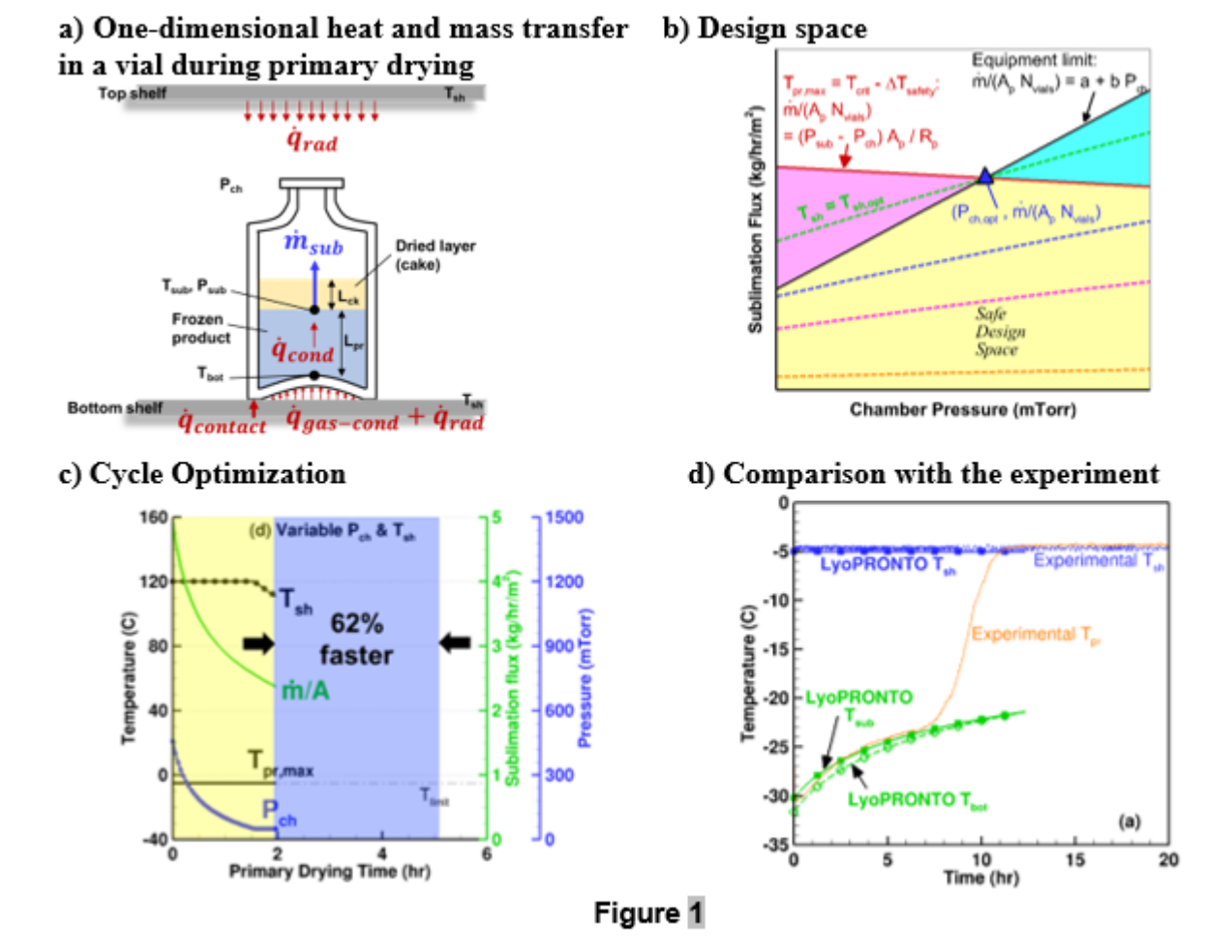
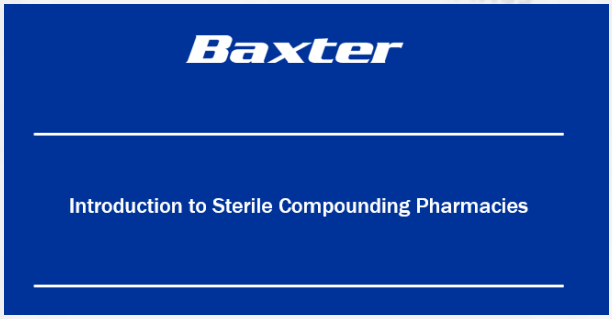


Figure 1

- Freely available (Python Source Code): lyopronto.org
- Online version with GUI: http://lyopronto.rcac.purdue.edu/

Special Presentations

Daniel Gunderud, IMA Life
August 2019



Gregory Sacha, January 2020

Quantitative Characterization of Lyophilized Solid Microstructures with 3D Micro-Imaging
Shawn Zhang, DigiM Solution

July, 2019
http://www.digimsolution.com

Vial Fogging – can we control it?
Rishabh Turka, Ph.D. Student, Topp Research Group

October, 2019

Joe Tort, October, 2019
http://recontherapeutics.com/

Scott Ross, W.L. Gore & Assoc. November, 2019
https://www.gore.com/

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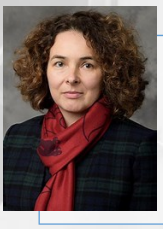

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Annual Member Meeting, April 2019, Chicago

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