aaps PharmSci 360 OCT 16-19 2022

# Development of Reentry Vehicles and Payloads for In-Orbit Drug Development

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Jordan Croom

VARDA SPACE INDUSTRIES

# Session Description and Objectives

- Microgravity brings many advantages for drug development and manufacturing. Researchers have demonstrated that the absence of buoyancy, sedimentation, and convection improves control over particle size distributions, polymorphism, and the kinetics of crystallization. This talk discusses the development of an unmanned orbital reentry vehicle for in-orbit drug development. Developed antisolvent and melt/quench hardware, strategies for operating within the constraints of spacecraft design, and unique considerations for hardware in microgravity will be presented.

Learning objectives:

- Understand the benefits of microgravity for small molecule polymorph discovery, form isolation, and manufacturing.
- Understand the constraints and capabilities of autonomous antisolvent and melt/quench microgravity payloads.
- Understand how to leverage microgravity pharmaceutical development equipment for various drug development and manufacturing applications.

# Biography and Contact Information

Varda Space Industries is developing in-space platforms for novel pharmaceutical form discovery, isolation, and scaled manufacturing using conditions impossible to replicate on Earth.

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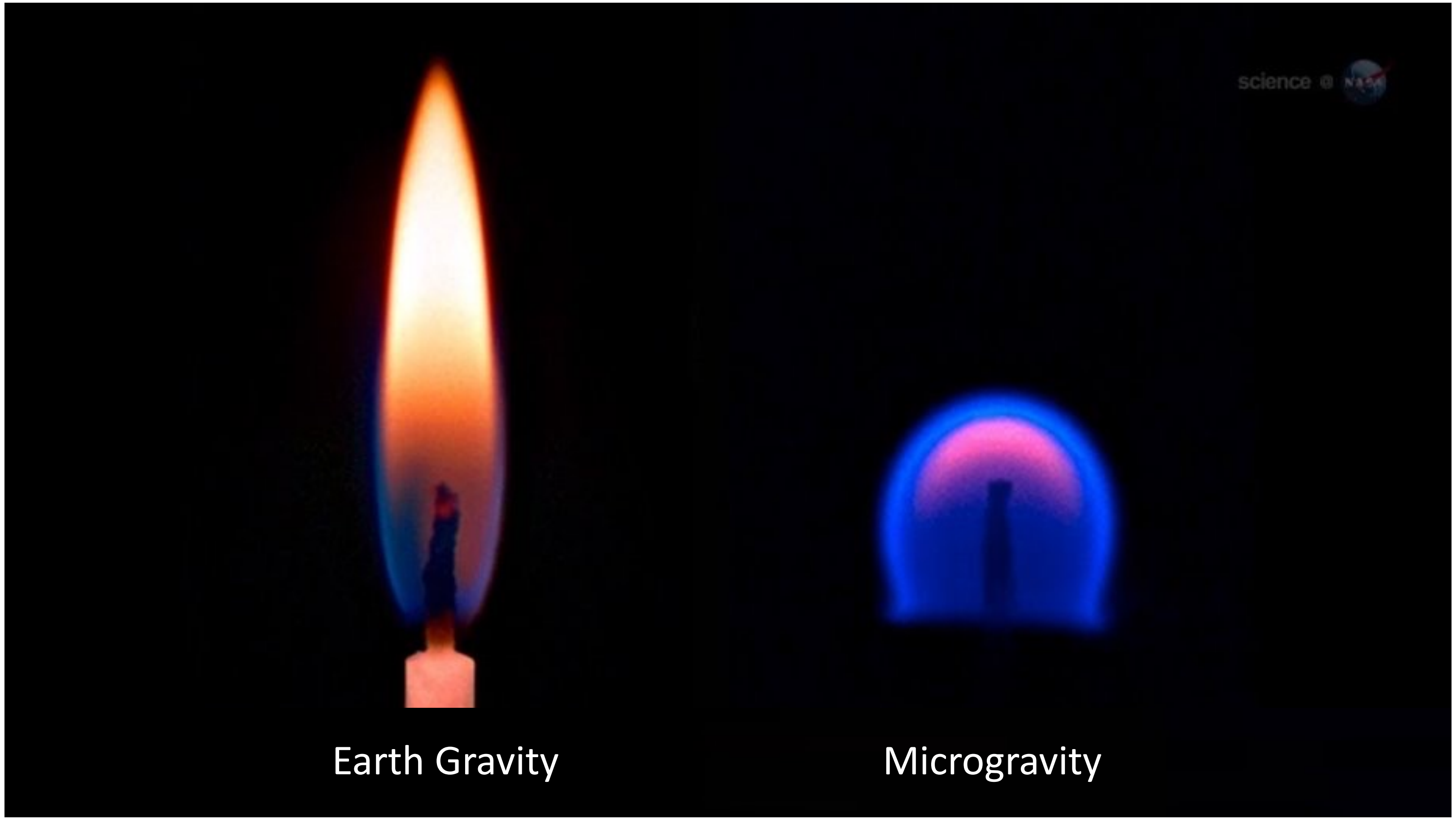
# Unique Behavior of Chemical Systems in Microgravity



# Microgravity Enables Improved Pharmaceuticals

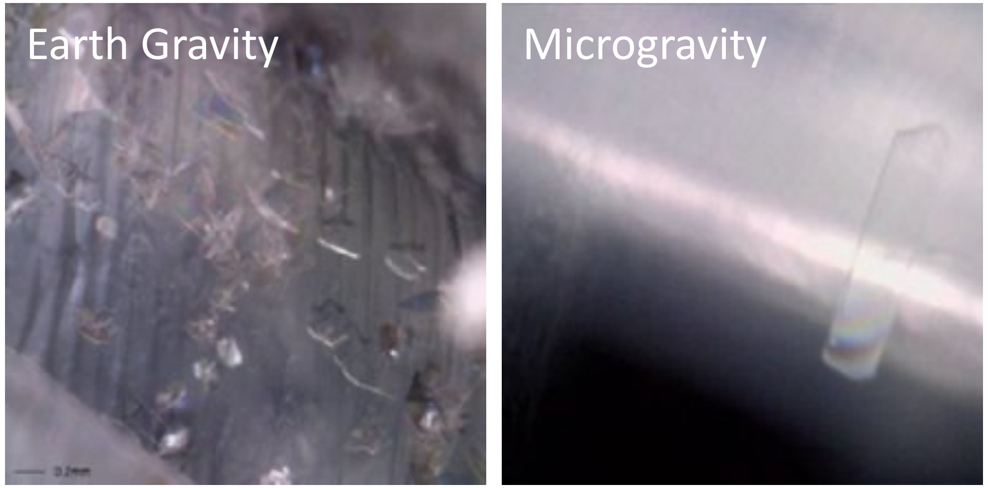
Elimination of buoyancy, natural convection, sedimentation, phase separation drives significant differences in transport-driven phenomena.

| Microgravity Results |
| --- |
| Controllable, uniform crystal size |
| Isolation of stable forms |
| More ordered crystals |
| Larger or smaller crystals |
| Novel crystal structures or morphologies |

→

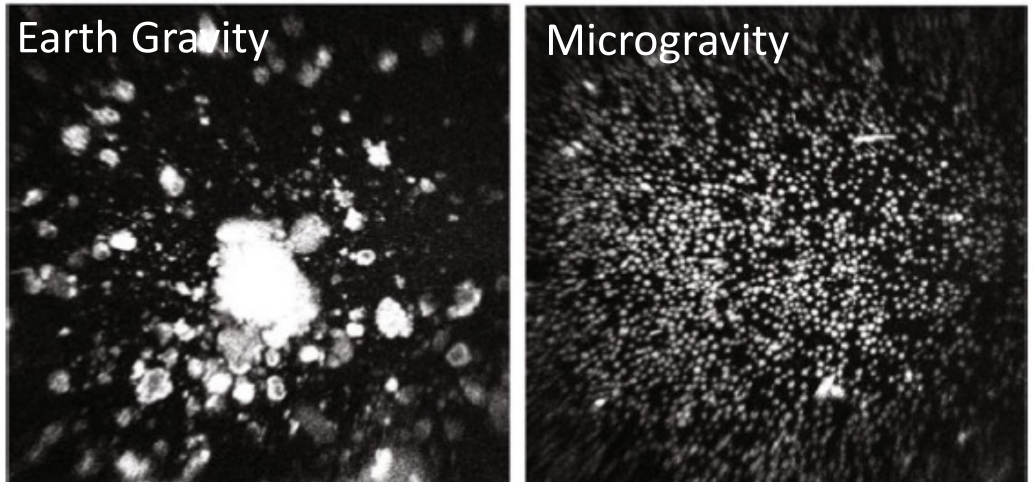
| Range of Formulation Benefits |
| --- |
| Enable new routes of administration |
| Improved bioavailability and solubility |
| Reduced side effects and toxicology |
| Extended shelf life |
| Novel form discovery |

# Experimentally Demonstrated Microgravity Effects




Different polymorphs of L-histidine are produced in microgravity than by the same process on Earth.

McPherson, A., DeLucas, L. Microgravity protein crystallization. npj Microgravity 1, 15010 (2015). https://doi.org/10.1038/npjmgrav.2015.10



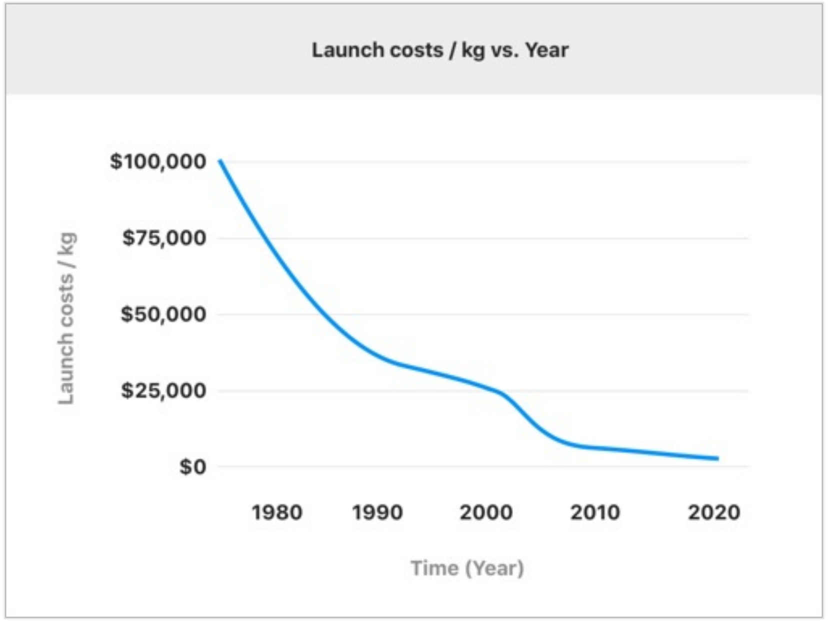

Keytruda produced in microgravity results in smaller, and more uniform crystallization than on Earth, theoretically enabling injectable rather than IV administration.

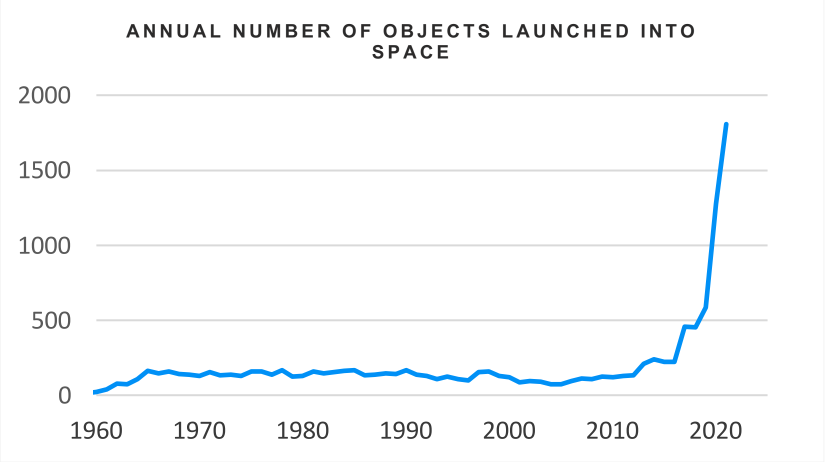
Reichert, P., et al., (2019). Pembrolizumab microgravity crystallization experimentation. *npj Microgravity*, *5*(1), 1-8.c

# Why Now?

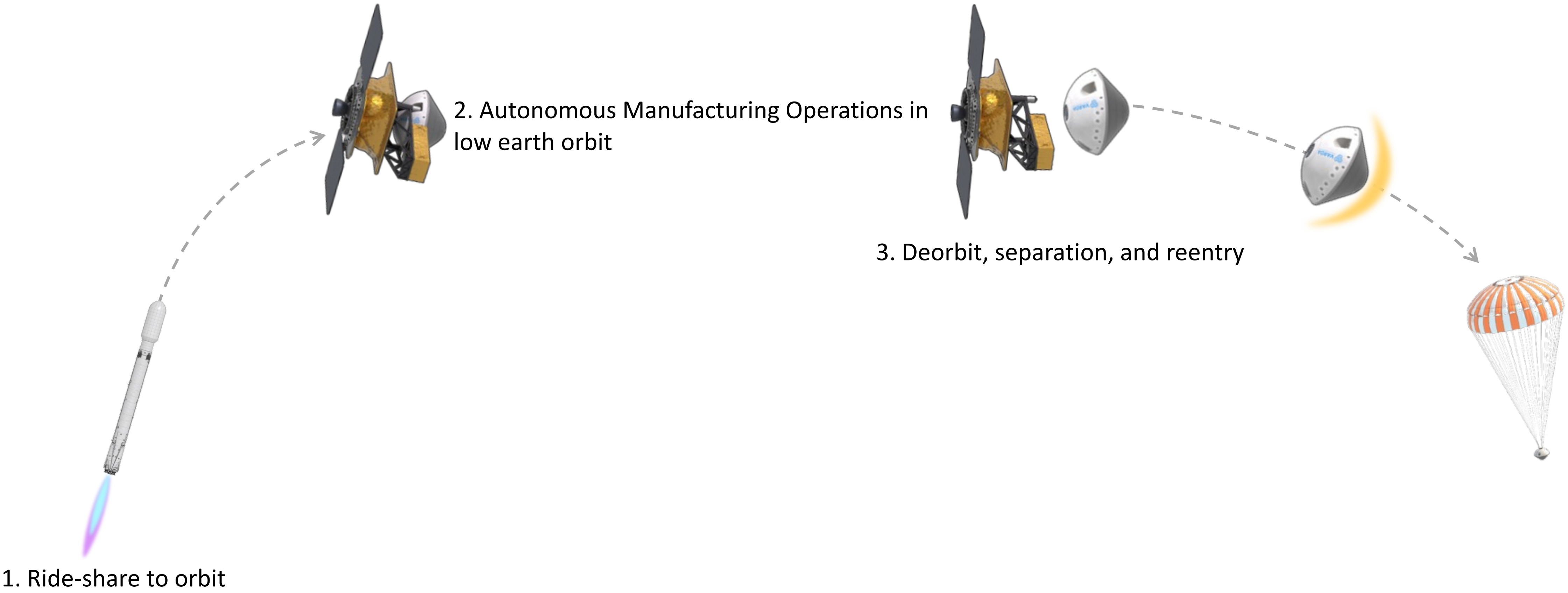
Significant progress from the commercial space industry makes building and launching spacecraft cheaper than ever.

Microgravity is now economically viable for pharmaceutical R&D and production.

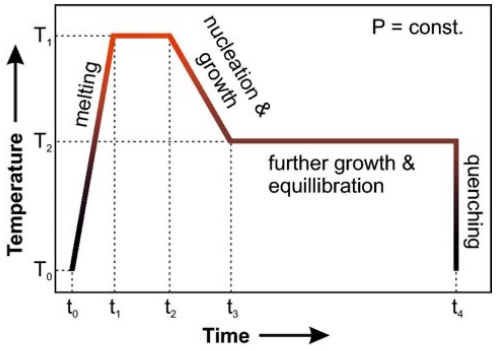


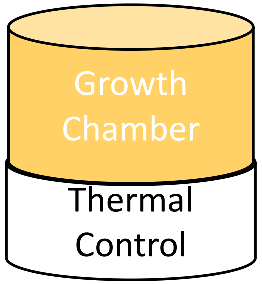



# Varda’s Orbital Manufacturing Platform

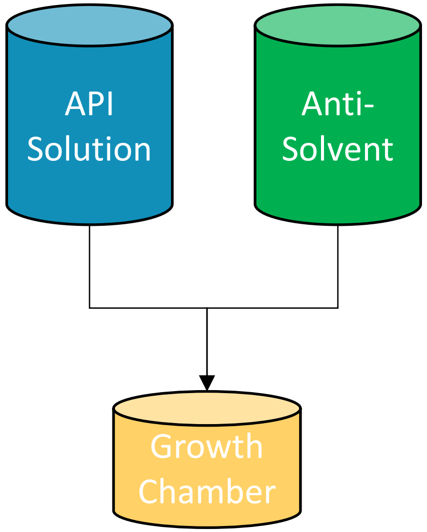


# High Level Processes Available




**Melt / Cool**
Amorphous Solid Dispersions
Cooling Crystallization



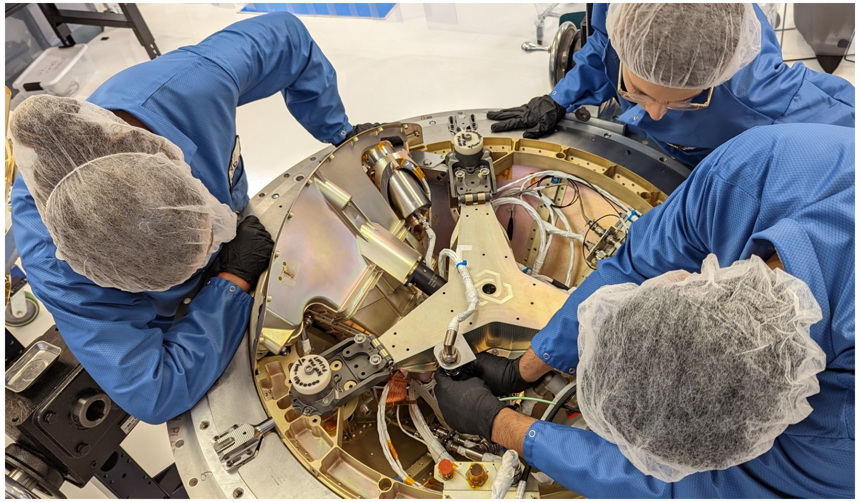

**Solvent / Antisolvent**
Antisolvent Crystallization
Slurry Crystallization
Cooling Crystallization
Evaporative Crystallization

# Melt/Cool Process Capabilities (Flights Starting 2023)

- Accommodates both amorphous and crystalline products for small molecule APIs
- Controllable temperature profiles including set points and ramp rates
- Key challenges: launch and space environment, power/thermal management

Runs on Less Power than a Single Incandescent Bulb

| Parameter | Payload Specification |
|---|---|
| Process Temp Profile Range (°C) | -10°C to 170°C |
| Pre-Process Storage Temp Range (°C) | 10-32°C |
| Volume per Sample | 0.1 to 1 mL |
| Unique Samples per Flight | Up to 100 |
| Returned Products | Solid Material |
| APIs Supported | Any Compatible with 316L Stainless Steel, PTFE |
| In-Situ Monitoring Capabilities | Temp, Acceleration<br>Future Work: Raman |



Melt/Cool Payload Currently Integrated into Flight 1 Capsule (Launching early 2023)

# Melt/Cool Results

- Ground based development testing on hardware revealed first new polymorph of Ritonavir characterized in 24 years
- Showed ability to isolate and grow “Form III” Ritonavir on flight hardware
- Results discussed in “Pharmaceutical Experiments for Microgravity” with Stephan Parent 3:15 on Wednesday and published in Chemrxiv (see ref below)
- Extending results to microgravity with first flight in early 2023

**Ritonavir Form III: Lighting strikes twice at the same time, 137 miles apart**

Stephan D. Parent[1], Pamela A. Smith[1], Dale K. Purcell[1], Daniel T. Smith[1], Susan J. Bogdanowich-Knipp[1], Ami S. Bhavsar[2], Larry R. Chan[2], Jordan M. Croom[2], Haley C. Bauser[2], Andrew McCalip[2], Stephen R. Byrn[1], Adrian Radocea[2]

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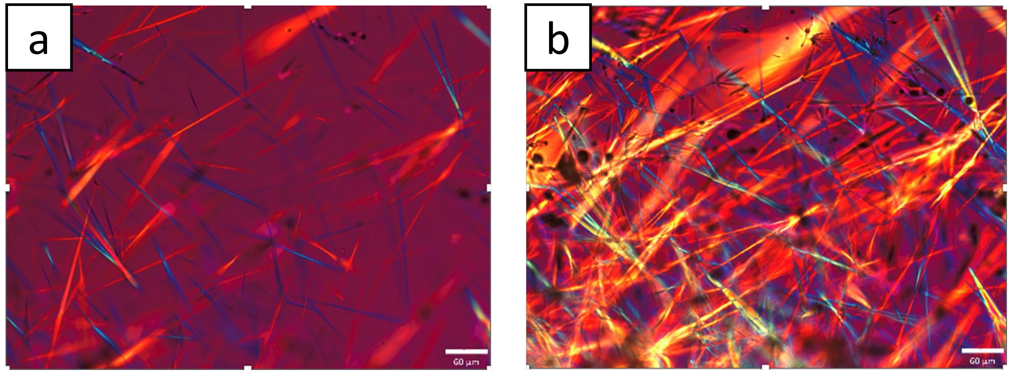



**Hot stage microscopy during growth at a) 5 hours and b) 8 hours**

# Solvent-Based Process Capabilities (Flights Starting 2024)

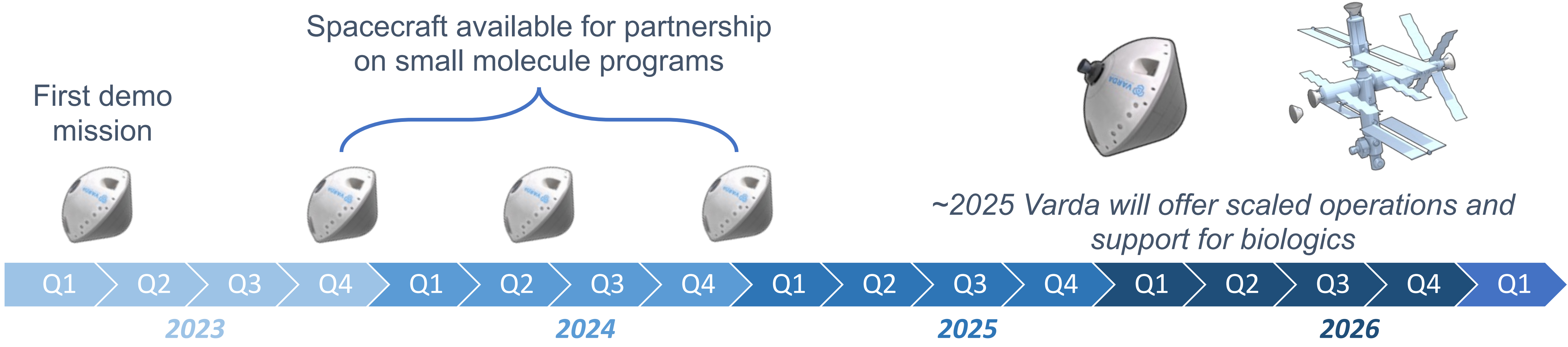
- Capable of antisolvent addition, cooling crystallization, evaporative crystallization, slurry crystallization of small molecule APIs
- Controllable temperature profiles including set points and ramp rates
- Key challenges: fluid location control, mixing, bubble removal

| Parameter | Payload Specification |
|---|---|
| Process Temp Profile Range (°C) | 0°C to 80°C |
| Pre-Process Storage Temp Range (°C) | 10-32°C |
| Volume per Sample | 20 mL Mixed Solution |
| Unique Samples per Flight | Up to 24 |
| Pre-Process API Storage | Dry Powder, Mixed In-situ |
| Returned Material | Solid Products, Mother Liquor |
| Solvents, APIs Supported | Any Compatible with 316L Stainless Steel, PTFE |
| In-Situ Monitoring Capabilities | Temp, Turbidity, Acceleration<br>Future Work: Raman, Microscope |

Bubbles in Zero G Do Not Coalesce in a Controlled Location

# Varda's Orbital Manufacturing Platform

- Offering solvent-based and melt/cool process on flights starting in early 2023
- Planning to support biologics in ~2025
- Can be quickly scaled as research moves to production
- Learn more about microgravity implications from "Pharmaceutical Experiments for Microgravity" with Stephan Parent at 3:15 on Wednesday



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# Acknowledgments


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Adrian Radocea

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# Questions

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