

**What types of products
or samples can be
investigated using CT?**



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Liquid suspensions

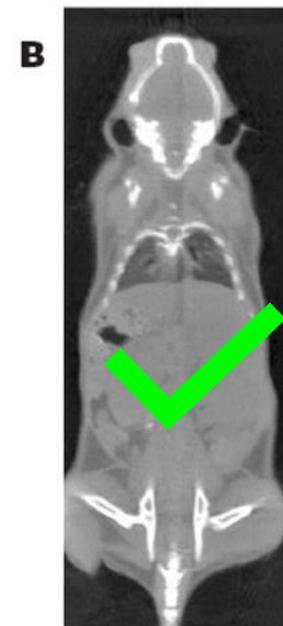


Difficulties due to Brownian motion and often times sub-resolution features

Solids and semi-solids



Small animal imaging



<https://www.nature.com/articles/labam0304-28>

<https://www.coriolis-pharma.com/manufacturing-services>

What types of products or samples can be investigated using CT?

Solids and semi-solids



Oral solid dosage forms



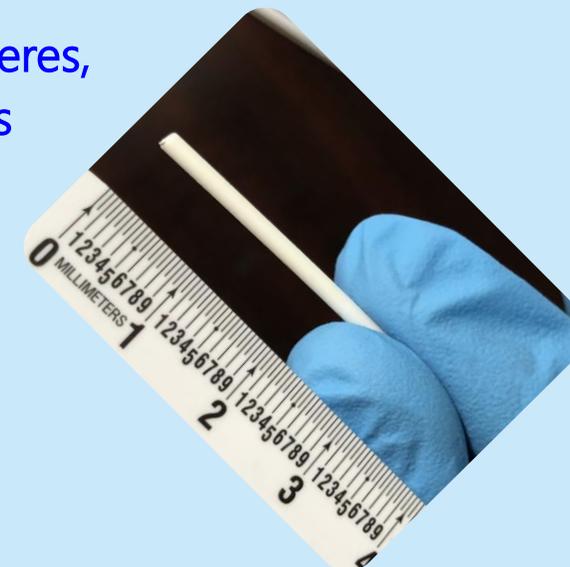
Lyophilized materials



Devices and their powders



Implants, microspheres, ointments

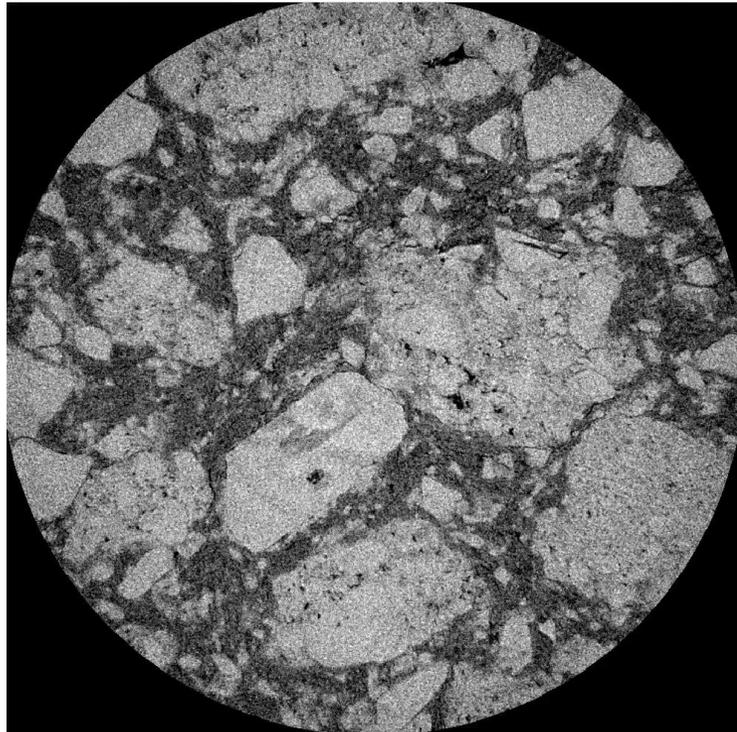


What types of products or samples can be investigated using CT?

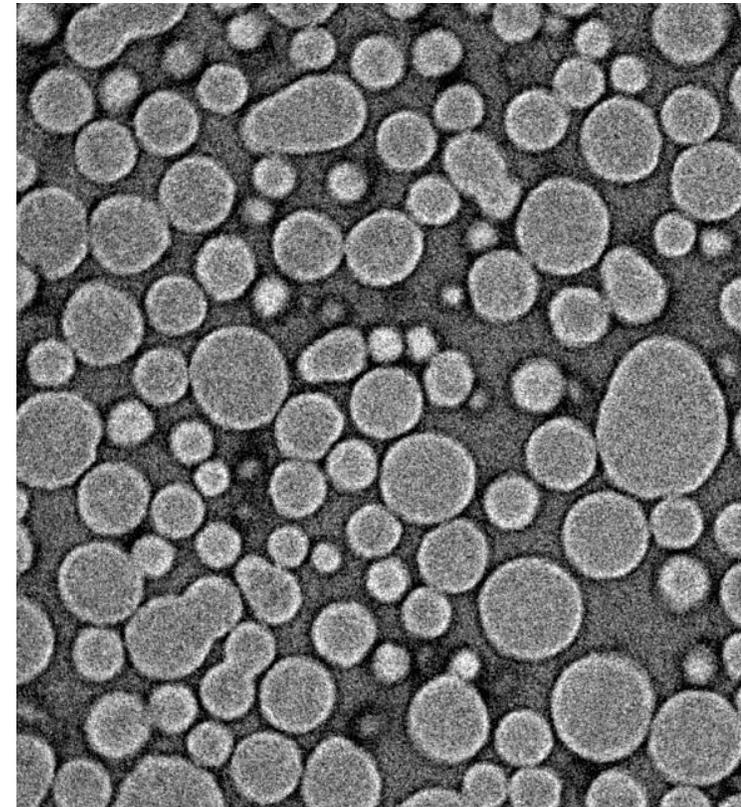
Typical tablet scan

D0000657: Glucophage M03
Slice 0000
04/19/2022 12:19

400.0um



Typical microsphere scan

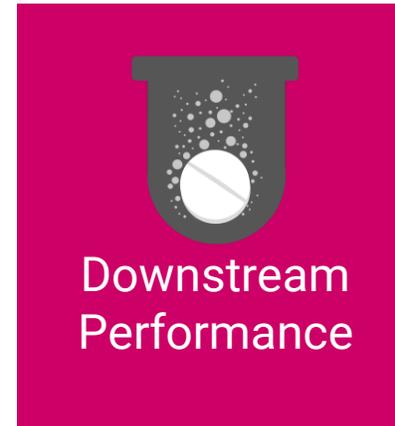


**What development challenges
can be addressed by CT?**



What development challenges can be addressed by CT?

Many of these challenge areas are applicable to other industries, from batteries to filters



Snack Break





Process Development



Downstream Performance



Formulation Selection



CMC and Stability

Snack Break



Consumer Experience

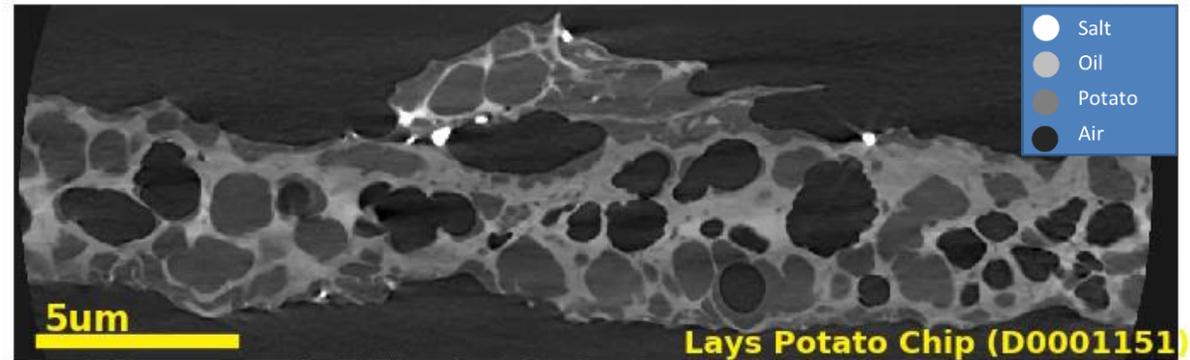
Taste

Mouthfeel

Smell

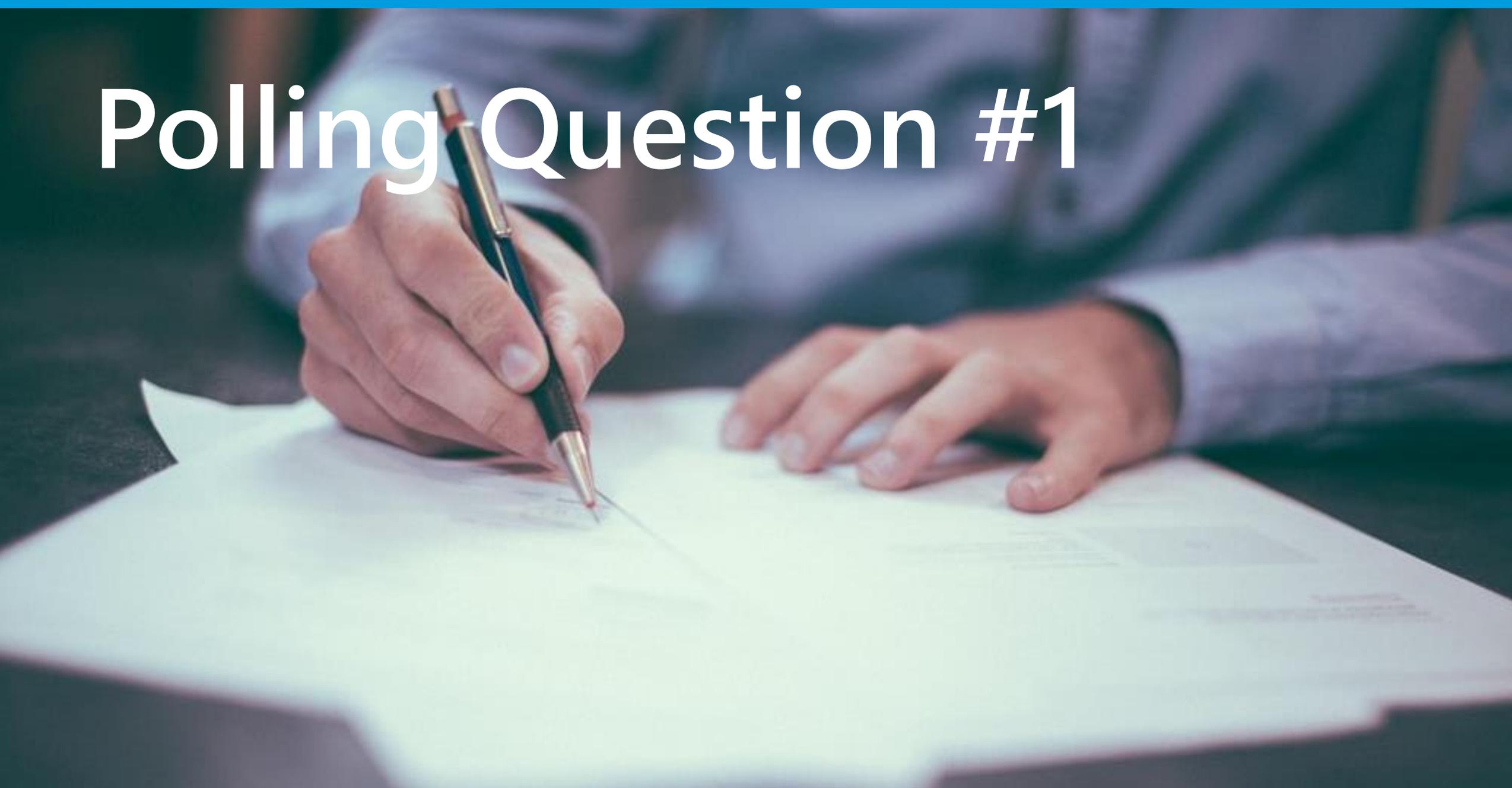
Shelf-life

Bowl Life



CT usage in the R&D space not exclusive to pharma!

Polling Question #1

A close-up photograph of a person's hands writing on a document. The person is wearing a light blue button-down shirt. They are holding a black and gold pen in their right hand, writing on a white sheet of paper. Their left hand is resting on the paper. The background is blurred, showing more of the person's shirt and a dark surface.

What is the typical design of an experiment when using CT data to support development?



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What do we want to quantify?



- Interaction of ingredients
- Distribution of ingredients
- Internal particle size
- Porosity, voids, fractures
- Particle morphology
- Uniformity within and across batches

What is the typical design of an experiment when using CT data to support development?

Sample size and region of interest?



Determines the field of view

Feature size?



Determines the needed resolution

Ingredients and their densities?



Guides expected contrasts and their correlation to each domain

**At what stage of development
should we consider using CT?**



At what stage of development should we consider using CT?

The earlier the better! Save time and resources during

Pre-clinical

- Advanced understanding of active ingredient mechanical properties and interaction with excipients
- Guide formulation decision making through structural connection to release behavior

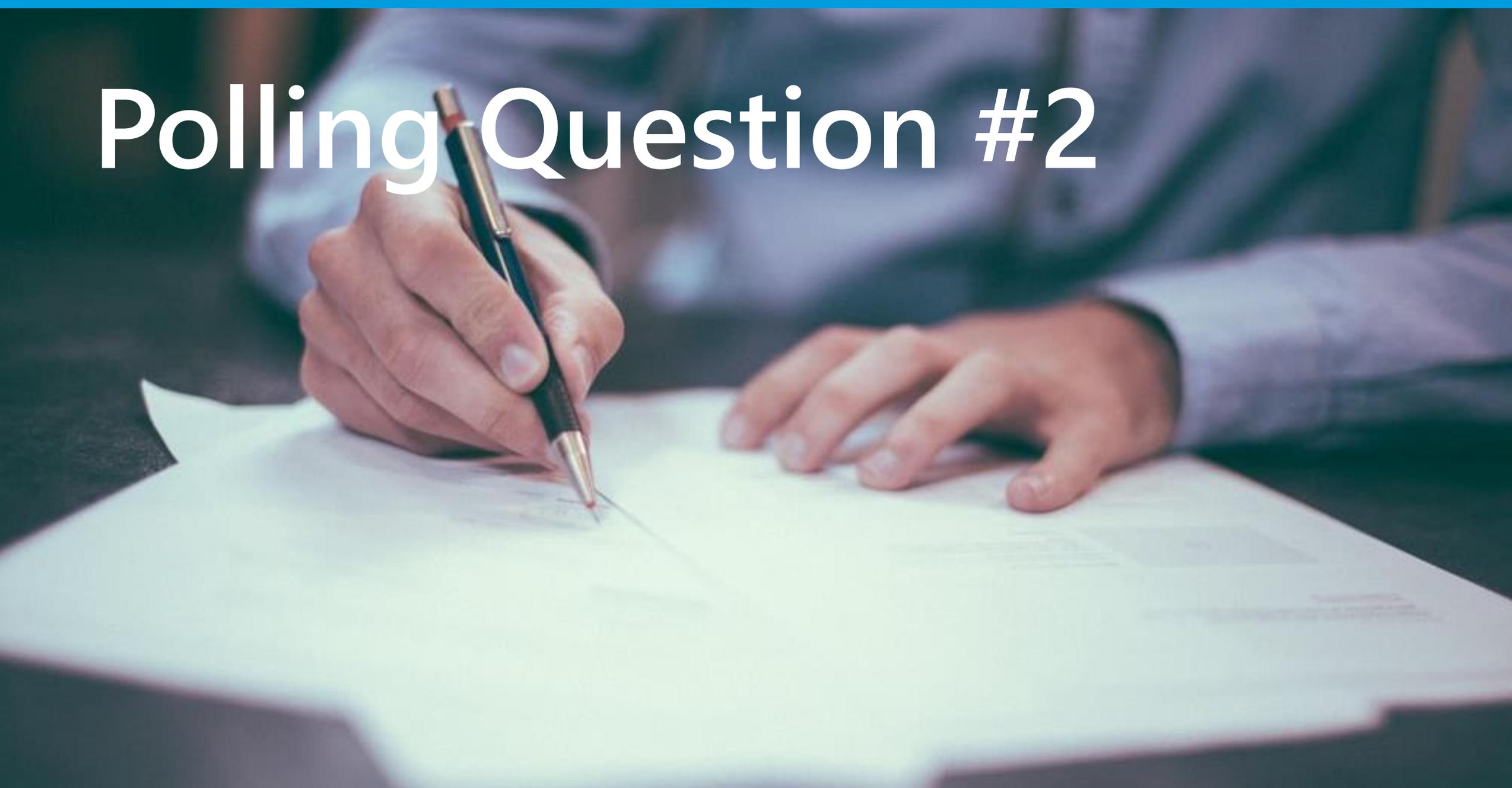
Clinical

- Optimize manufacturing techniques and process parameters rapidly
- Troubleshoot performance variability and reduce issues upon scale up

Post-approval

- SUPAC changes to manufacturing process and sites
- Enhance future development through a knowledge database

Polling Question #2

A close-up photograph of a person's hands writing on a document. The person is wearing a light blue button-down shirt. They are holding a black and gold pen in their right hand, writing on a white sheet of paper. Their left hand is resting on the paper. The background is blurred, showing more of the person's shirt and a dark surface.

Are there ways that CT data can support regulatory filing?



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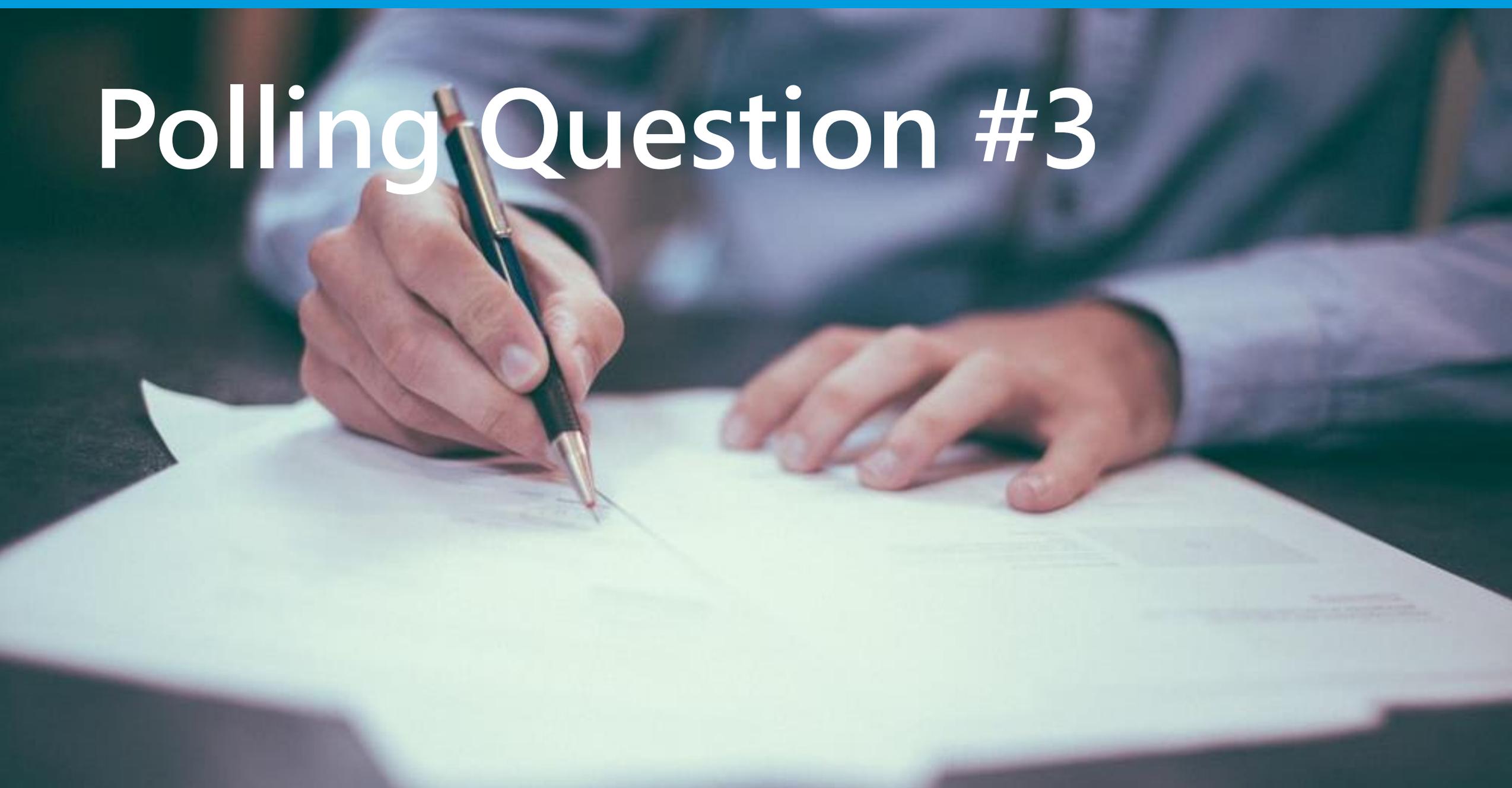
Yes it can!

- Direct visualization and quantification of drug domain size within the drug product → non-destructively!
- Assist in a variety of regulatory requests on physicochemical properties, such as porosity
- For generic developers: demonstrate structural sameness with the reference listed drug
- For specific generic products: use of Q3 bioequivalence as a biowaiver for further testing



Lightning Round

Polling Question #3



How does CT data and simulation support dissolution analysis?



How does CT data and simulation support dissolution analysis?

Case Study 1 – Scale up dissolution performance troubleshooting (With Eli Lilly)

Challenge - different dissolution profiles for GMP and R&D batches root cause analysis

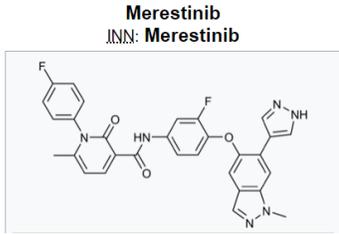


CMC and
Stability



Downstream
Performance

How does CT data and simulation support dissolution analysis?

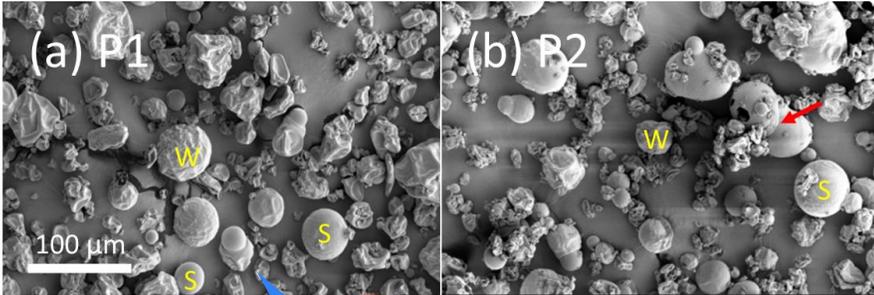


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)
European Journal of Pharmaceutical Sciences
journal homepage: www.elsevier.com/locate/ejps

Characterizing the Impact of Spray Dried Particle Morphology on Tablet Dissolution Using Quantitative X-Ray Microscopy

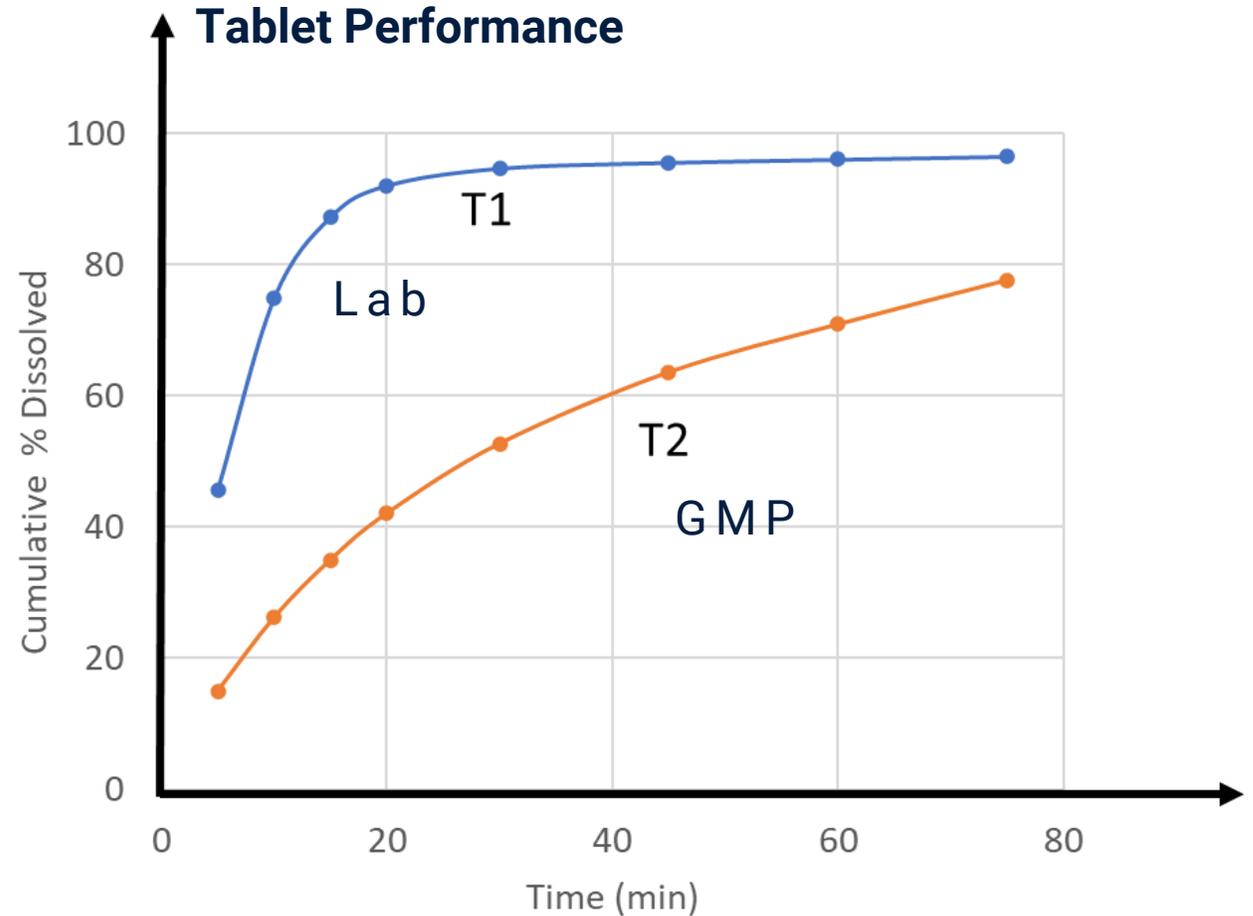
Lab

GMP



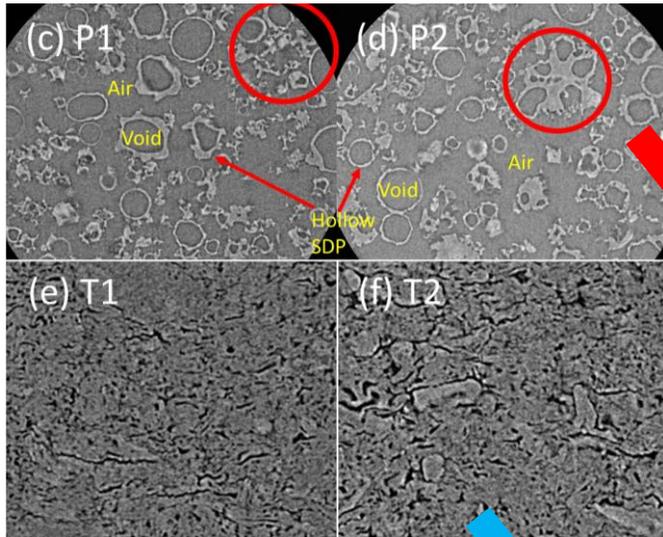
P1 and P2 powders compacted with excipients to form respective tablets T1 and T2

Connecting the Dots from **Particle Intermediate** to **Downstream Performance**



How does CT data and simulation support dissolution analysis?

Connecting the Dots from **Particle Intermediate** to **Downstream Performance**



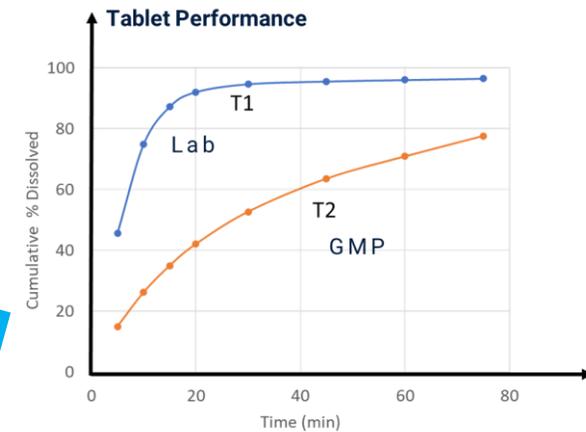
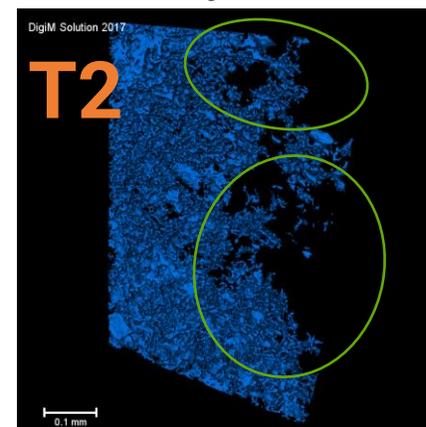
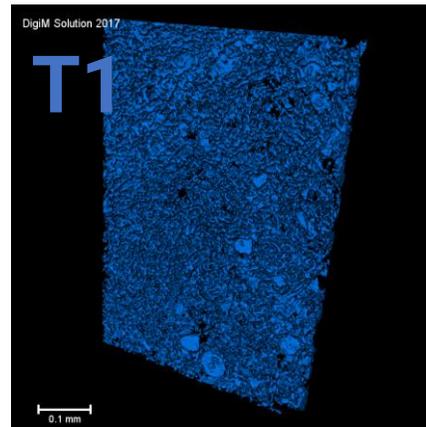
Spray Dried Particle CQAs

Sample ID	P1	P2
Resolution (μm^3)	0.5	0.5
D10 (μm)	15	20
D50 (μm)	31	34
D90 (μm)	48	59
Wall thickness T90 (μm)	6.1	8.4
Exterior surface area per unit ($1 \mu\text{m}^3$ drug volume)	0.54	0.33

Particle attributes directly drive compaction behavior and dissolution

CQAs

Visualization of Connected Porosity in Tablets



Large clusters of disconnected pores

How does CT data and simulation support dissolution analysis?

Case Study 2 – Next generation bioresorbable injectable contraceptive implants (With Innocore)

Challenges

1. Reducing the need for long *in vitro* testing cycles
2. Understanding of the release mechanism and erosion/degradation behavior of a novel polymer
3. Correlating *in vitro* and *in vivo* release



Mechanism of LNG release

1. Monolithic release

- Diffusion driven (through pre-existing LNG network)

2. Monolithic release with initial erosion influence

- Highly porous outer ring is formed
- Fractures formed inside inner core
- Constant release rate obtained

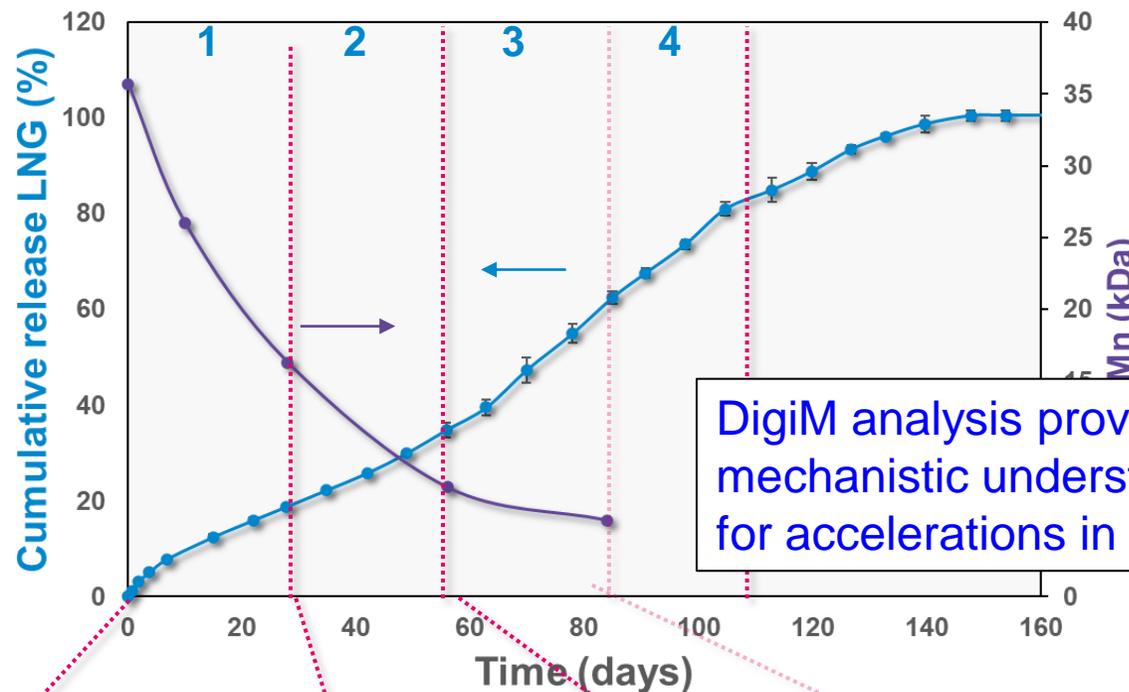
3. Degradation (fracture) driven release

- Detachment of porous ring from implant
- Accelerated crack formation increases the release rate

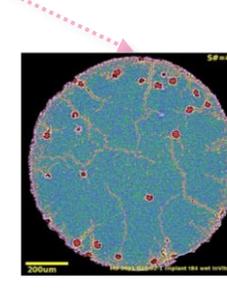
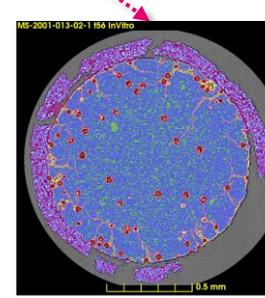
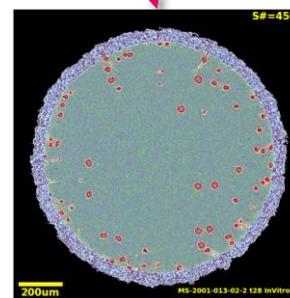
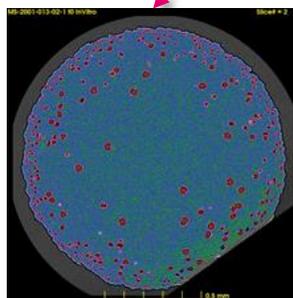
4. Monolithic release through cracks

- Reduced fracture growth and influence of erosion
- Release is governed by diffusion of LNG through preformed cracks

LNG release from implants
100 mM Phosphate buffer, 0.5% SDS, pH 7.4, 37°C



DigiM analysis provided a mechanistic understanding for accelerations in release



In vitro vs in vivo degradation and morphological differences

- **In vitro**

- Delamination of porous outer layer
- Crack formation
- outer implant diameter similar to full diameter of implant *in vivo*

- **In vivo**

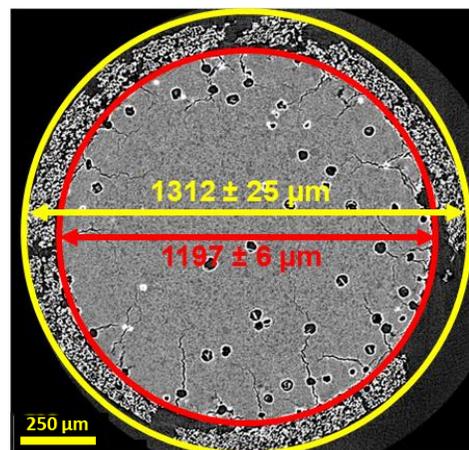
- no delamination layer
- No crack formation
- severally eroded implant at 240 days and outer layer with little to no porosity and a highly porous inner region

- **Degradation follows different trend *in vitro* vs. *in vivo***

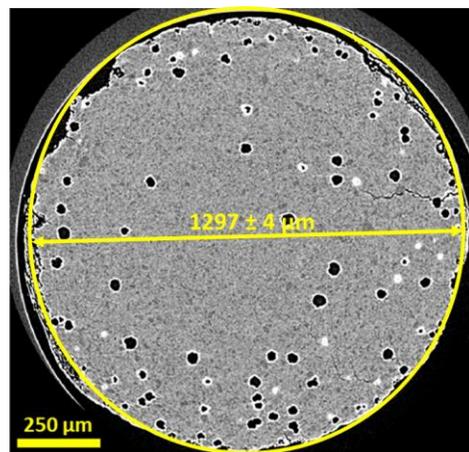
T = 56 days

T = 240 days

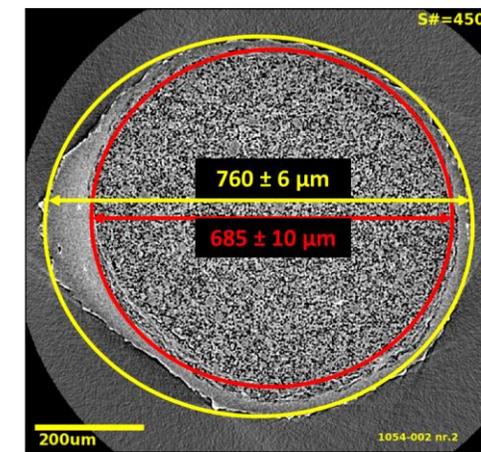
In vitro



In vivo

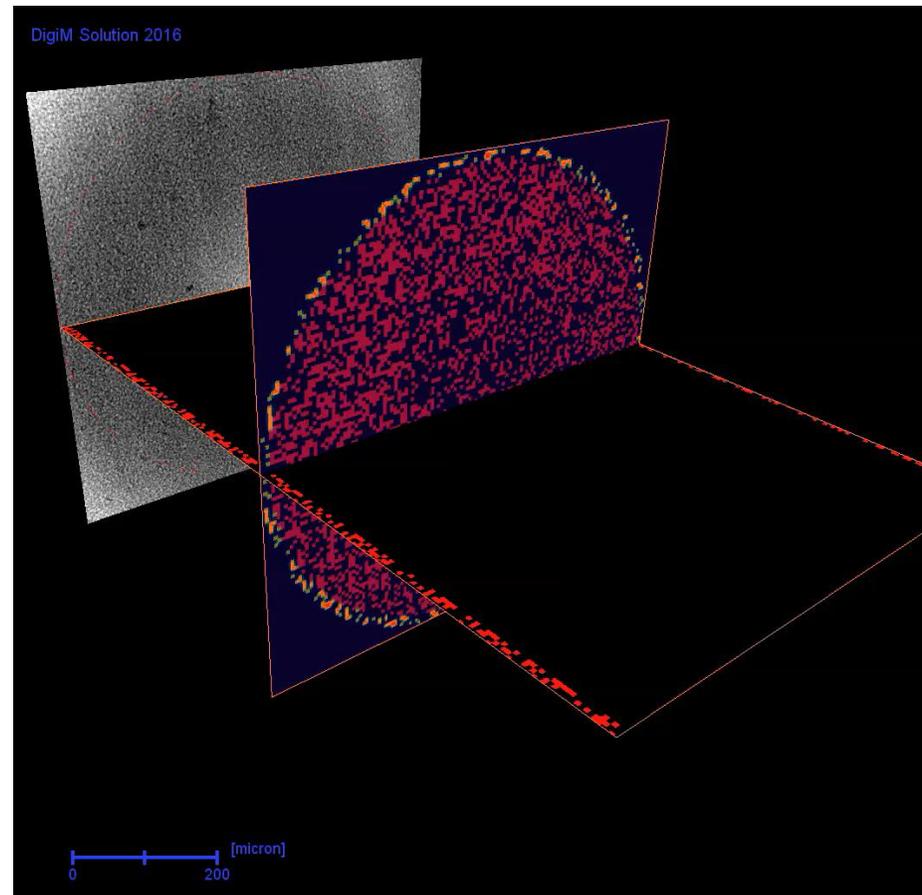


CT analysis can quantify polymer erosion and evaluate the post-release structures of *in vivo* vs *in vitro*



How does CT data and simulation support dissolution analysis?

Image-based simulation can directly predict release profiles from the particle networks identified with CT → reduces major assumptions on structural arrangement because they have been visualized, and quantified!



Simulation of *in vivo* release HME monolithic LNG implants – SynBiosys

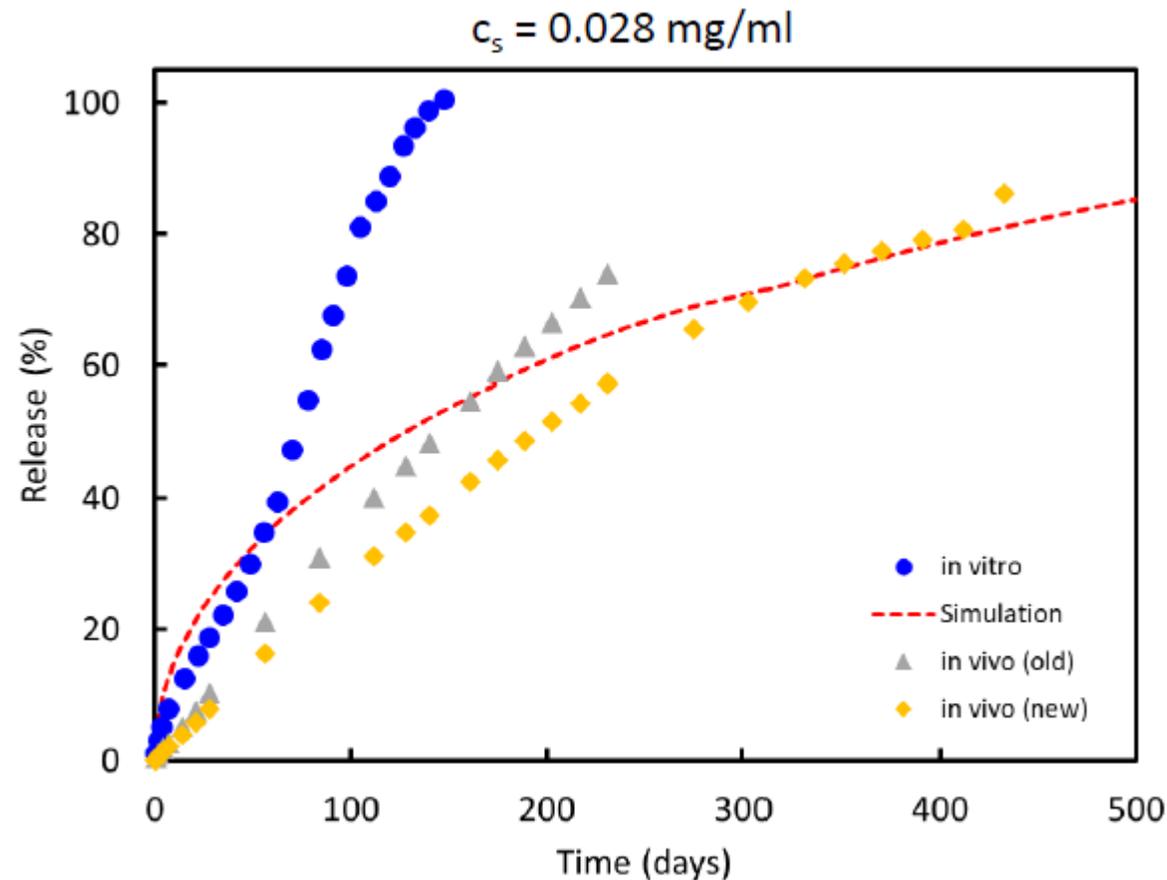
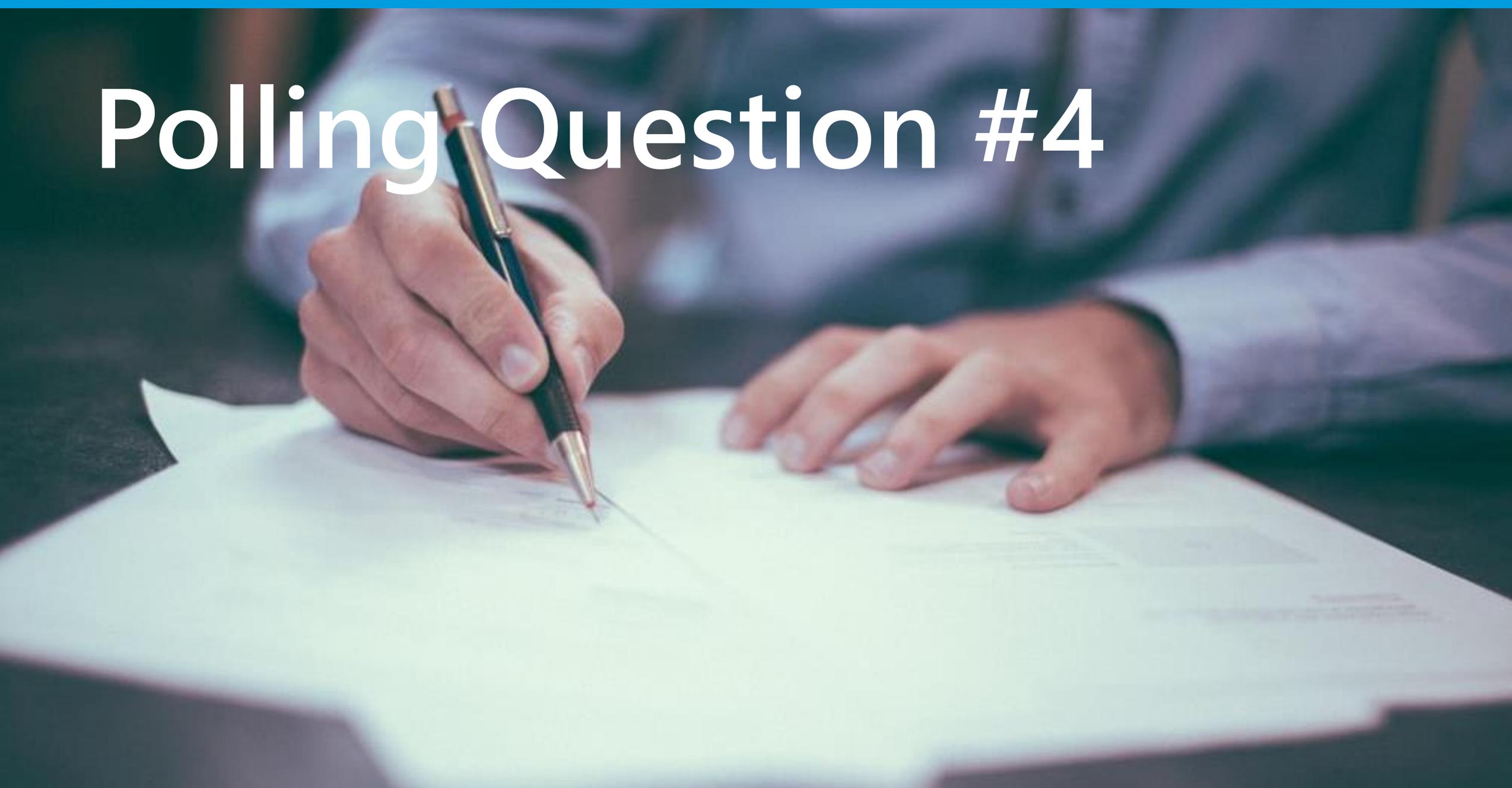


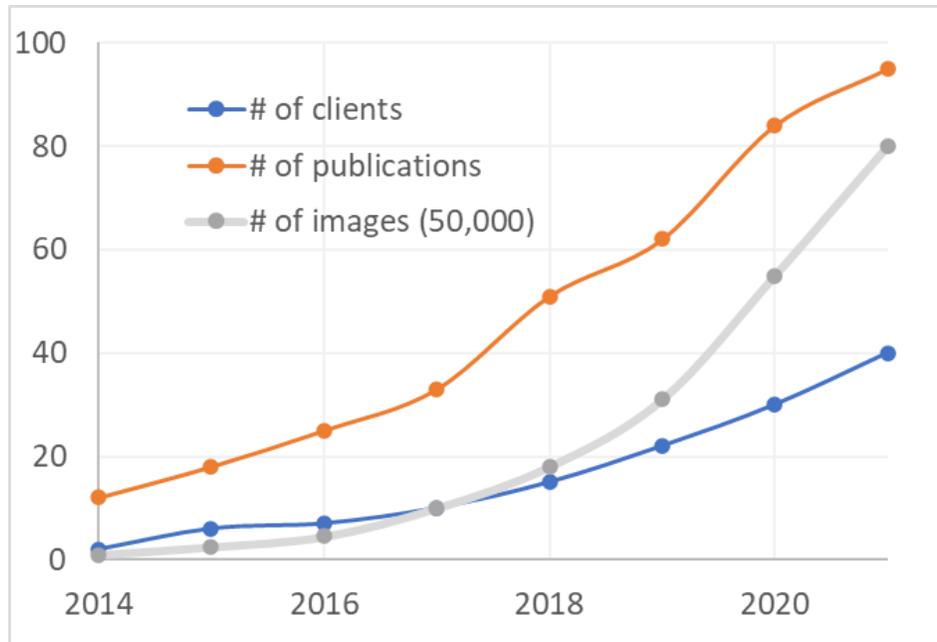
Image-based simulation can save significant time for lengthy *in vitro* and *in vivo* testing, allowing more rapid assessment of formulation and process design

Polling Question #4

A close-up photograph of a person's hands writing on a document. The person is wearing a light blue button-down shirt. Their right hand holds a black and gold pen, and their left hand rests on the paper. The document is white with some faint text and a grid-like structure. The background is blurred, showing more of the person's shirt and a dark surface.

What does do?

Technology leader for characterization-based solutions



- Founded in 2014
- HQ in Woburn, MA

DigiM Digital Transformation Team

Microscopists *Analysts*



Developers *Scientists*



Working hand-in-hand with clients to develop solutions



abbvie 

 Bristol Myers Squibb

Genentech 

 AstraZeneca 

Contract research to transform product development

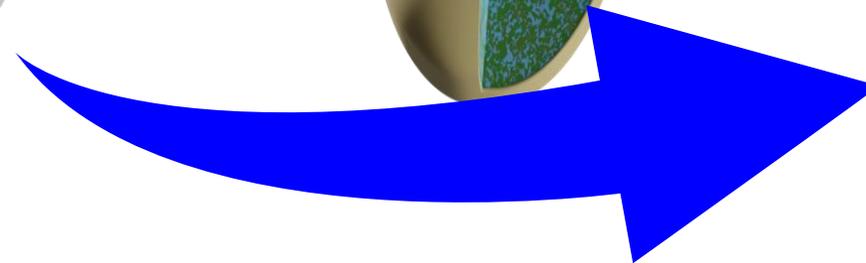
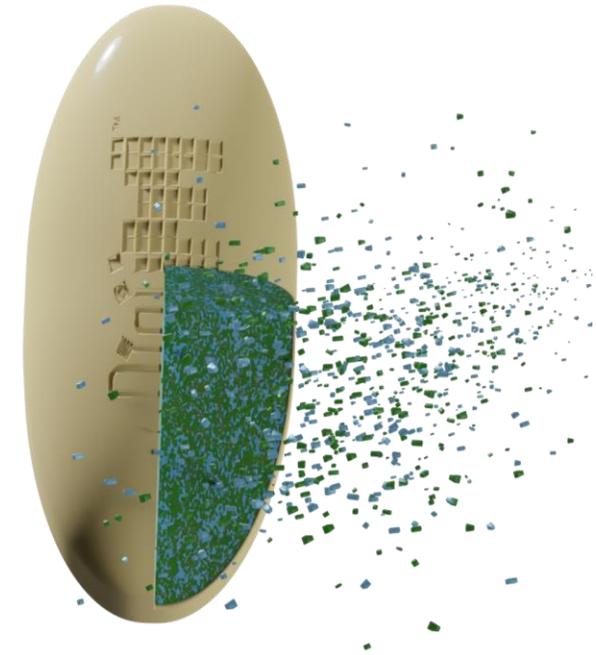
High-res imaging



AI analytics and CQAs



Image-based modeling



Software and analysis service for image analytics, prediction, and data management

The screenshot displays the DigiM Microstructure Library interface. On the left is a navigation sidebar with options: Dashboard, Data, Project, Image Processing, Computing, Chart Studio, Report, Search, and Documentation. The main content area is titled 'Data' and shows a grid of data entries under the heading 'ALL DATA'. The entries are sorted by 'Data ID' and include a 'MY' button and an 'ALL' button. Each entry consists of a thumbnail image, a title, a data ID, file size, date, and user name.

Thumbnail	Title	ID	Size	Date	User
	spray dried baby formula	D0003871	0B	12/19/2022	Lisa Ma
	Mangrove Roots	D0003870	56.8M	12/19/2022	Aidan Herbert
	nanoParticles-Inside-TEM	D0003795	17.2M	11/28/2022	Aiden Zhu
	Lipid-Nanoparticles	D0003793	8.8M	11/28/2022	Aiden Zhu
	mRNA-Lipid-Nanoparticles	D0003792	8.6M	11/28/2022	Aiden Zhu
	Zorpad shoe inserts	D0003790	0B	11/28/2022	Lisa Ma
	Self Adhesive Wrap	D0003737	14.5G	10/10/2022	Lisa Ma
	MCC and PMMA microspheres	D0003682	87.0G	09/02/2022	Lisa Ma
	Allergy Relief-D	D0003496	0B	05/17/2022	Lisa Ma



NEXT ON ASK THE EXPERT

Digital Rock Physics – When and How to Use It



With Dr. Arne Jacob

Wednesday, May 17, at 1 PM CDT