Process Analytical Technologies for Continuous Manufacturing in Pharmaceuticals

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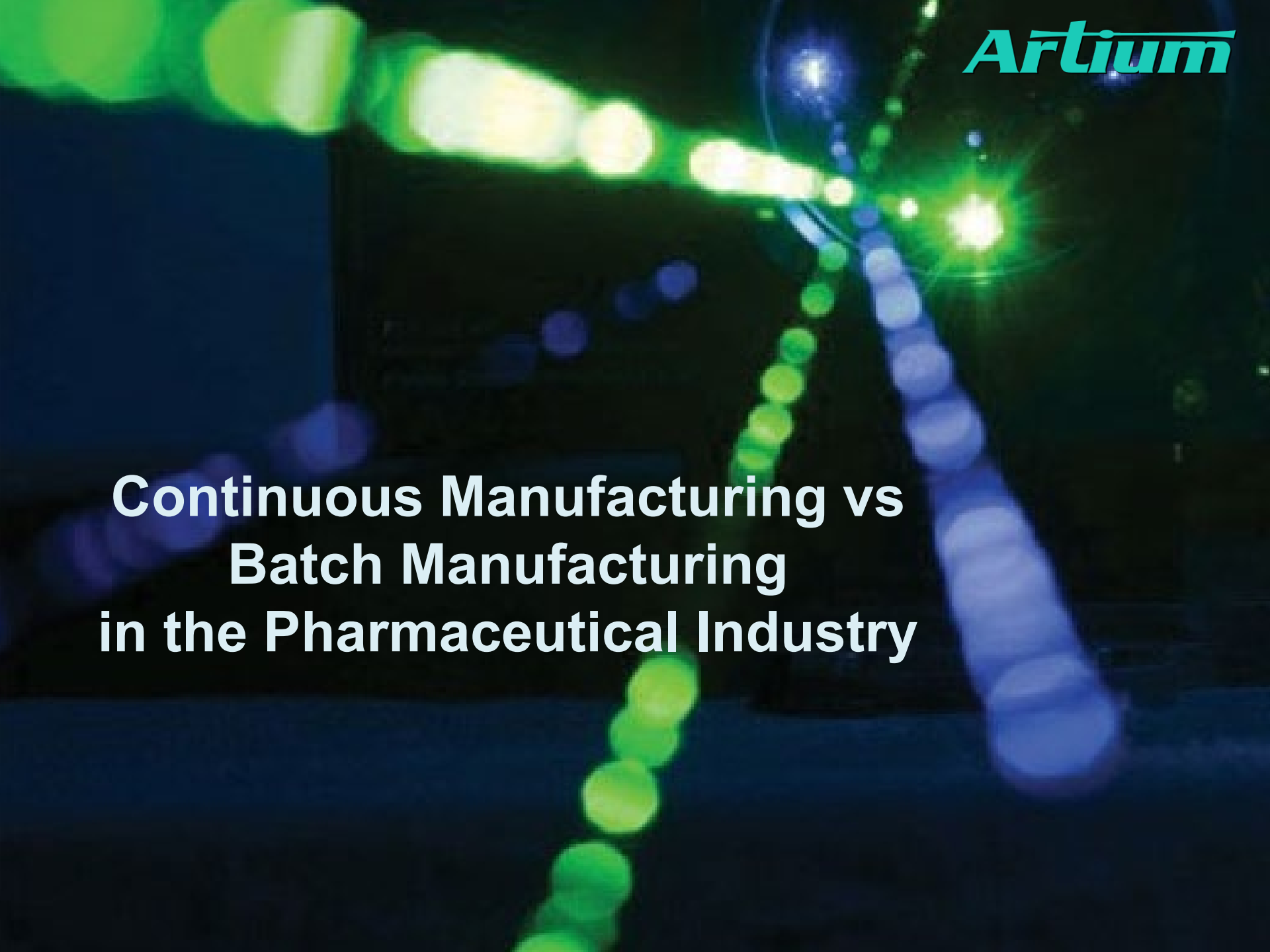
January 2020


Artium
Continuous Manufacturing vs
Batch Manufacturing
in the Pharmaceutical Industry

Traditionally, batch processing has been used in the pharmaceutical industry for drug production.

More recently, the FDA has been encouraging the industry to transition from batch manufacturing to continuous manufacturing because of the associated benefits.

Continuous Manufacturing allows for

- lower costs
- shorter process and development times
- improved process control,
  and most importantly
- the ability to assess the quality, on-line, for every product that is manufactured.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Benefits of Continuous Manufacturing

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Continuous flow of material vs. step by step processing		**Shorter production lead times, more flexible manufacture**
No scale-up or technology transfers		**Shorter development times**
Smaller footprint; decreased waste, energy consumption, and raw material use		**Reduced costs and environmental burden**
Better process understanding by in-line monitoring		**Enhanced process robustness and product quality**
Potential for real-time releases		**Reduced analytical costs**

Source: Orion Pharma

The FDA clearly recognizes that continuous manufacturing is an emerging technology that has the potential to deliver benefits to both industry and patients.

FEDERAL REGISTER

The Daily Journal of the United States Government

Notice

Quality Considerations for Continuous Manufacturing; Draft Guidance for Industry; Availability

A Notice by the Food and Drug Administration on 02/27/2019

PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Notice of availability.

SUMMARY:

The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Quality Considerations for Continuous Manufacturing." This draft guidance provides information regarding FDA's current thinking on the quality considerations for continuous manufacturing of small molecule, solid oral drug products that are regulated by the Center for Drug Evaluation and Research (CDER). The draft guidance describes several key quality considerations and provides recommendations for how applicants should address these considerations in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental NDAs and ANDAs, for small molecule, solid oral drug products that are produced via a continuous manufacturing process. FDA supports the development and implementation of continuous manufacturing for drug substances and all finished dosage forms where appropriate, including those submitted in NDAs, ANDAs, drug master files, biologics license applications (BLAs), nonapplication over the counter products. Soli

Agencies:
Food and Drug Administration

Dates:
Submit either electronic or written

Comments Close:
05/28/2019

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Notice

Document Citation:
84 FR 6403

Page:

Towards this end, the FDA released its guidance on the "Quality Considerations for Continuous Manufacturing" earlier in 2019.

Continuous manufacturing is expected to improve the quality of drugs produced and eliminate shortages while also lowering drug prices.

https://www.fda.gov/media/121314/download

Contains Nonbinding Recommendations

Draft — Not for Implementation

Quality Considerations for Continuous Manufacturing Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information regard
considerations for continuous manufacturi
regulated by the Center for Drug Evaluati
several key quality considerations and pro
address these considerations in new drug a
applications (ANDAs), and supplemental
products that are produced via a continuou
development and implementation of conti
finished dosage forms where appropriate,
master files (DMFs), biologics license app
(OTC) products. Scientific principles described in this guidance
continuous manufacturing technologies used for these drugs. B
intended to provide recommendations specific to continuous
for biological products under a BLA.

For purposes of this guidance, FDA considers "continuous manufacturing" to be a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system.[2] Although this description can be applied to individual unit operations or a manufacturing process consisting of a series of unit operations, as described in this guidance, continuous manufacturing is an integrated process that consists of a series of two or more unit operations.

This guidance focuses on scientific and regulatory considerations that are specific or unique to continuous manufacturing. These considerations include process dynamics, batch definition, control strategy, pharmaceutical quality system, scale-up, stability, and bridging of existing batch manufacturing to continuous manufacturing. Recommendations broadly applicable to both

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] "The system" is the integrated process that consists of a series of two or more unit operations.

FDA considers "continuous manufacturing" to be a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system.

Batch Manufacturing

- Multiple rooms
- Manual material handling & transportation
- Time and resource consuming
- Post-processing analytics

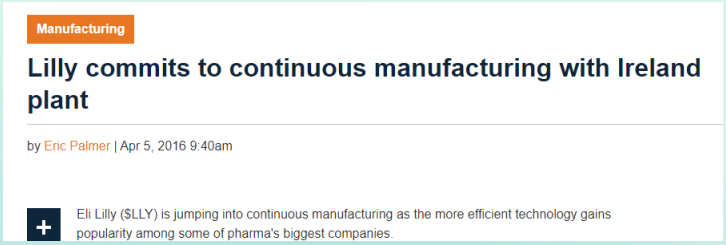
Continuous Manufacturing

- **One room**
- **Automatic material handling & transportation**
- **Real-time analytics; Process Analytical Technology (PAT)**

Continuous manufacturing is a **production** method used to manufacture, produce, or process materials **without interruption**

Source: Orion Pharma

In 2015, the U.S. Food and Drug Administration approved the first finished-dose drug, a cystic fibrosis medication called Orkambi, produced by Vertex Pharmaceuticals, made by an entirely continuous tableting process.



Since then, Janssen, Eli Lilly and Company, and Pfizer have received approvals for drugs made by continuous processes.

Many companies are now turning their attention to the continuous production of active pharmaceutical ingredients (API), which have proven more challenging than finished-dose tablets.

Synthesizing the ingredients with continuous technologies, such as processes that incorporate photochemistry, cryogenic/exothermic chemistry and other techniques, offers capabilities not readily available in batch processes.

Companies like GlaxoSmithKline (GSK), GEA Pharma Systems, and Siemens have also partnered together to provide a proof of feasibility for a continuous manufacturing unit.

Siemens, GEA Team Up for Continuous Manufacturing

The system integrates Siemens' process analytic technology with GEA's continuous tableting line providing a complete continuous manufacturing system for the pharmaceutical industry.

Jan 9th, 2017

In this project, funded by the UK Government, the team was able to prove that continuous manufacturing can reduce the process development time tremendously; it took them less than two weeks to develop a process for a new tablet.


Artium
Process Analytical Technology
(PAT)

The implementation of Process Analytical Technology (PAT) for real-time product quality monitoring is an integral part of Continuous Manufacturing and is consistent with the FDA's initiative on PAT which was released in 2004. This initiative is transforming approaches to quality assurance in the pharmaceutical industry.

U.S. FOOD & DRUG ADMINISTRATION

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GUIDANCE DOCUMENT

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Guidance for Industry

SEPTEMBER 2004

Issued by: Center for Veterinary Medicine
Office of Regulatory Affairs
Center for Drug Evaluation and Research

This guidance is intended to describe a regulatory framework (Process Analytical Technology, PAT) that will encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. Working with existing regulations, the Agency has developed an innovative approach for helping the pharmaceutical industry address anticipated technical and regulatory issues and questions.

Content current as of:
08/24/2018

Regulated Product(s)
Drugs

Topic(s)
Pharmaceutical Quality
Current Good Manufacturing Practices (CGMP)

The FDA considers PAT to be a system of designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pat-framework-innovative-pharmaceutical-development-manufacturing-and-quality-assurance

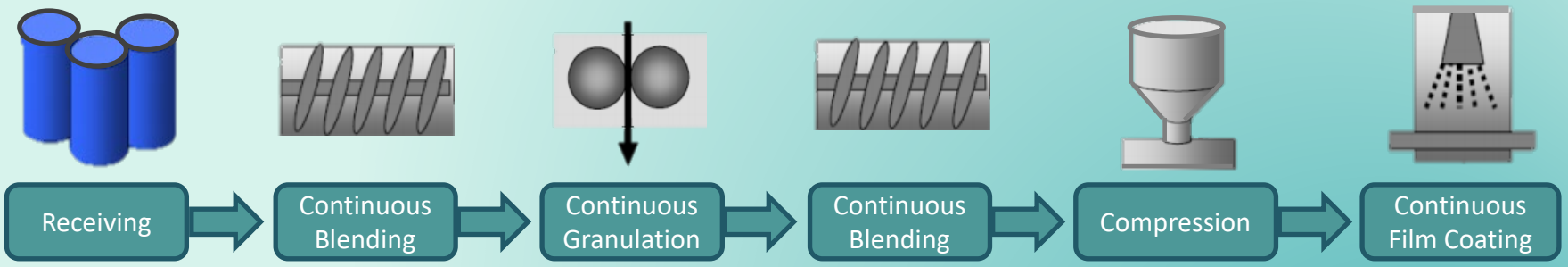
PAT is intended to enhance understanding and control of the manufacturing process, which is consistent with FDA's current drug quality system:

Quality cannot be tested into products; it should be built-in or by design.

The FDA considers PAT to be a system of

designing, analyzing, and controlling manufacturing

through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.



Source: Moore, FDA, 2011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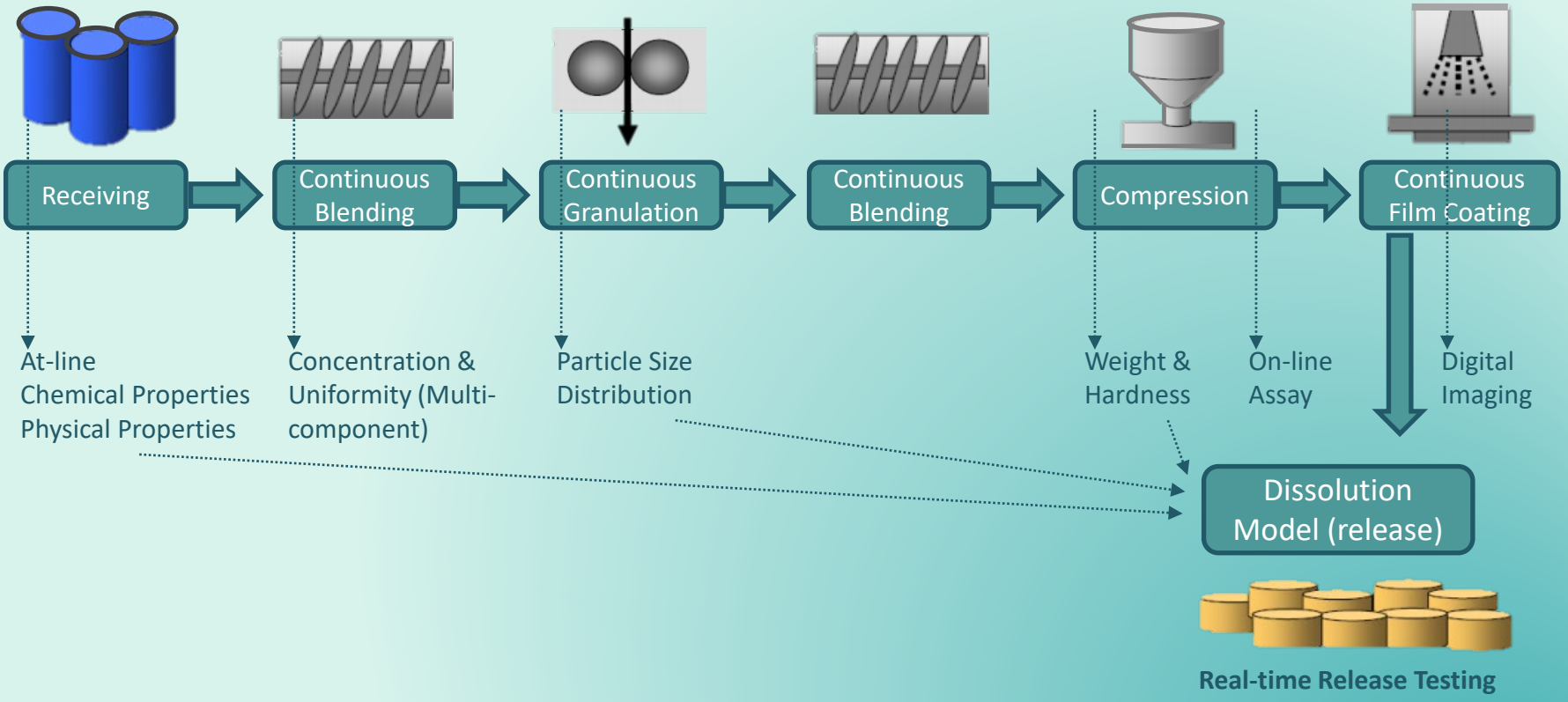
Real Time Release Testing
(RTRT)

Real Time Release Testing (RTRT) is the ability to evaluate and ensure the quality of in-process and/or final product based on process data.



Source: Moore, FDA, 2011

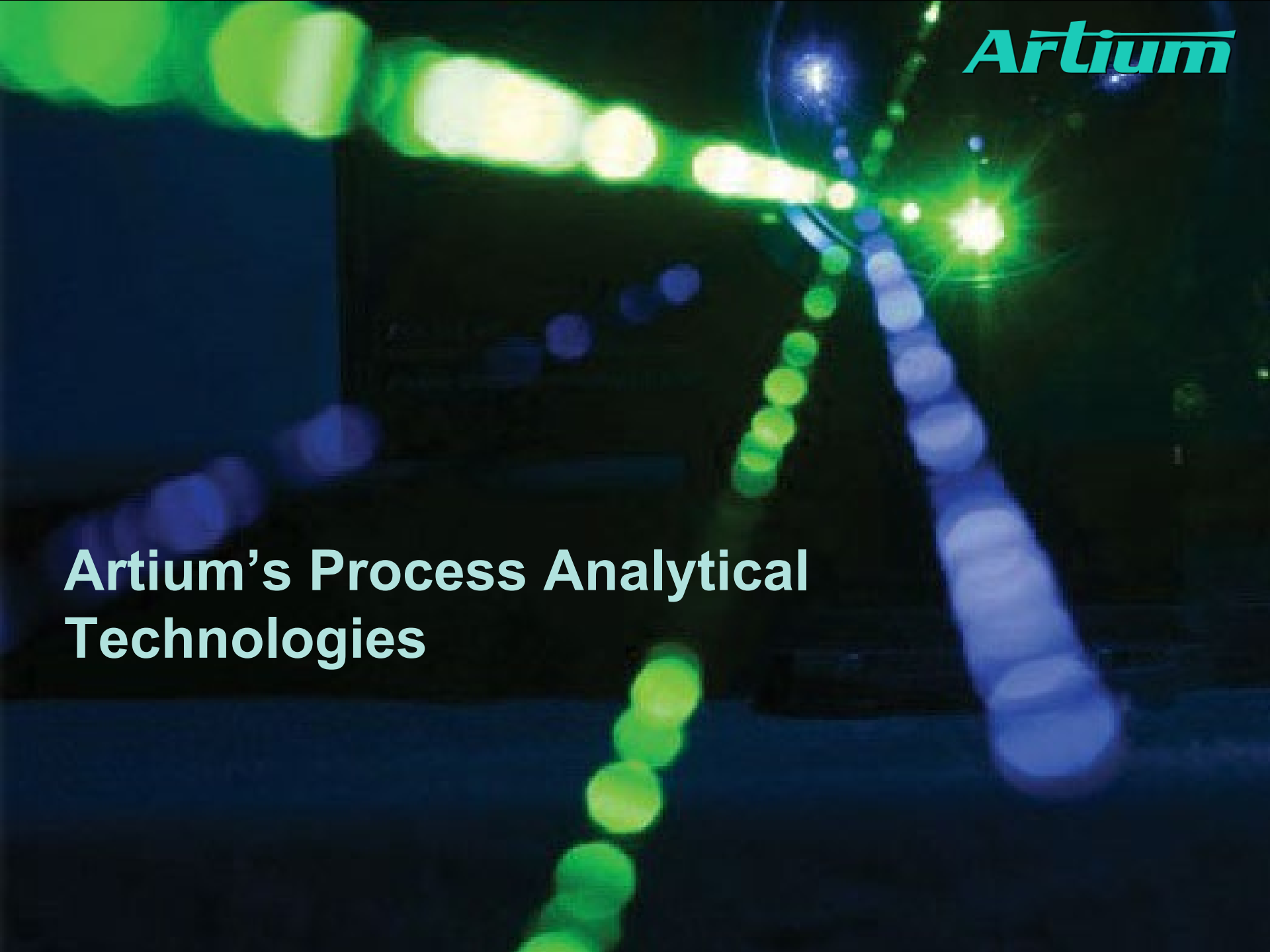
Real Time Release Testing in Continuous Manufacturing

Benefits:

- Provides increased assurance of quality – more data and better understanding
- Increased manufacturing flexibility and efficiency
  - Shorter cycle time
  - Reduced inventory
  - Reduction in ‘at release’ testing
  - Reduction of manufacturing cost
- Allows leveraging of enhanced process understanding – corrective actions may be implemented in real time → amount of waste decreases

Examples:

- On-line or in-line measure of particle size after granulation or milling
- Measurement of droplet size generated by a liquid dispense system for delivering the API on to tablets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Artium's Process Analytical Technologies

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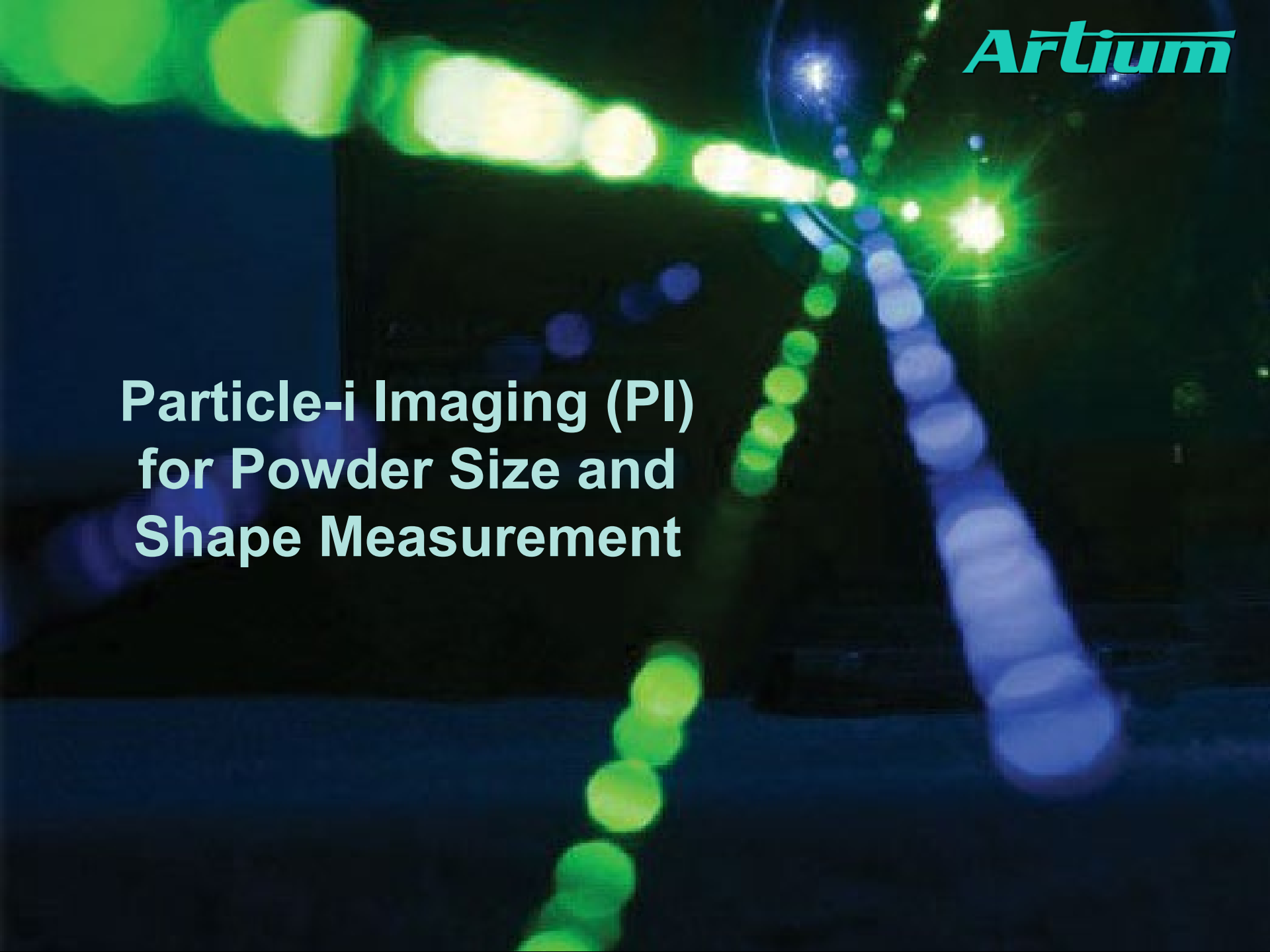
Artium's measurement technologies are suited for direct application in the continuous manufacturing line.

Artium's advanced process analytical technologies

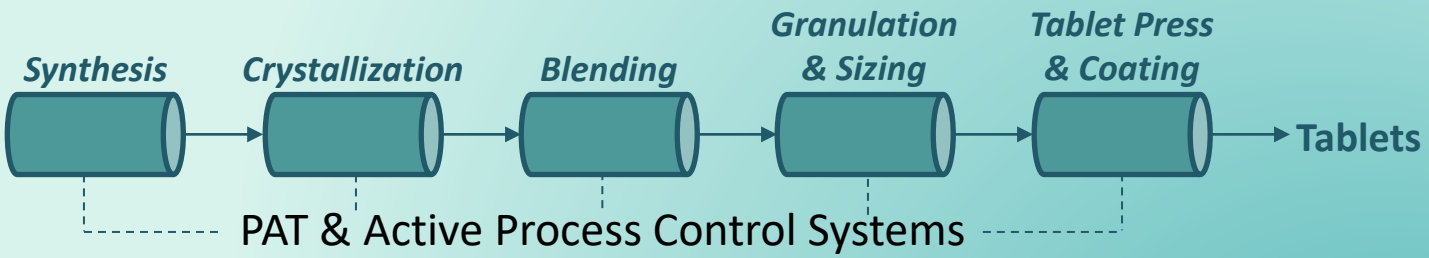
Particle-i Imaging (PI)

Phase Doppler Interferometry (PDI)


Artium
Particle-i Imaging (PI)
for Powder Size and
Shape Measurement

In continuous pharmaceutical manufacturing, input material is continuously added through a feeder system over the duration of the production run.

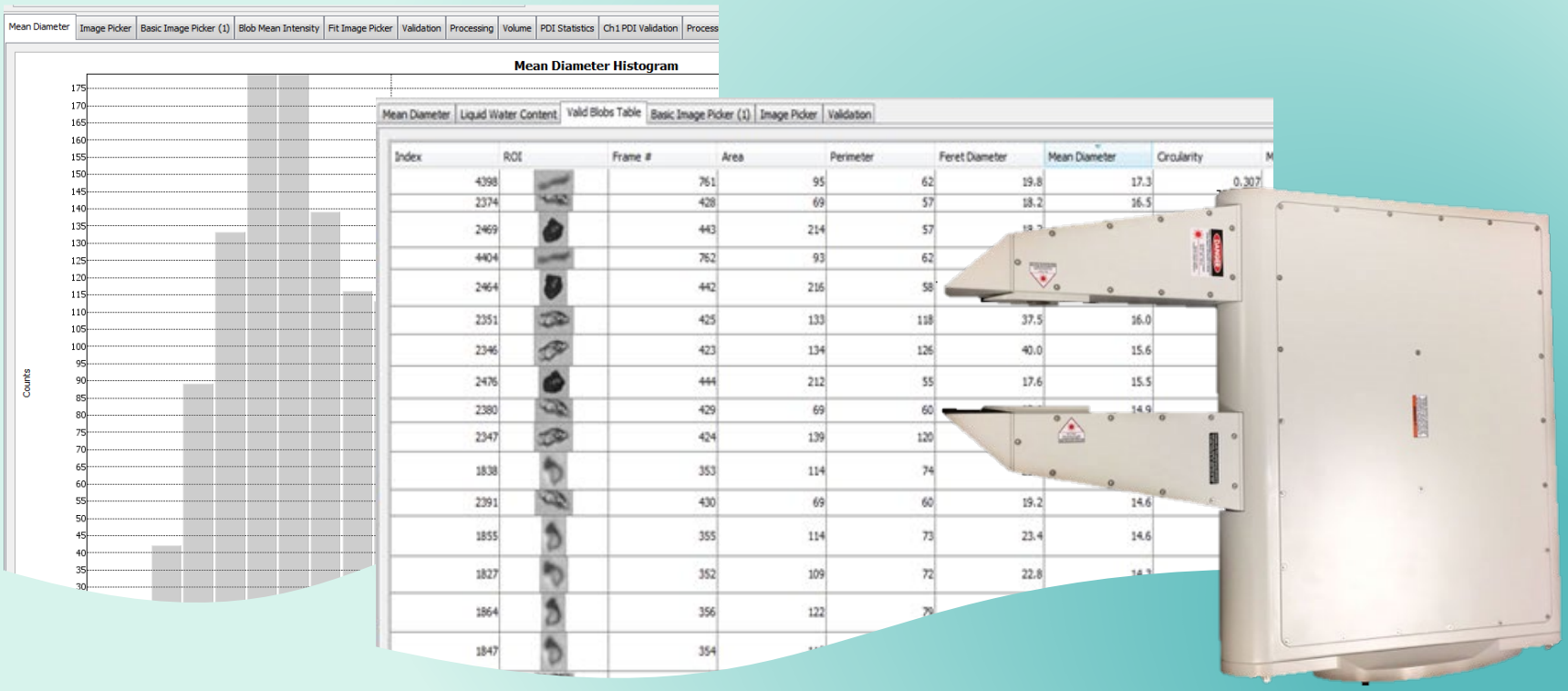
- Different batches of input material can be introduced to the system at different time points.
- Variability in input material attributes could affect feeding and potentially affect finished product quality.



Graph Source: US FDA

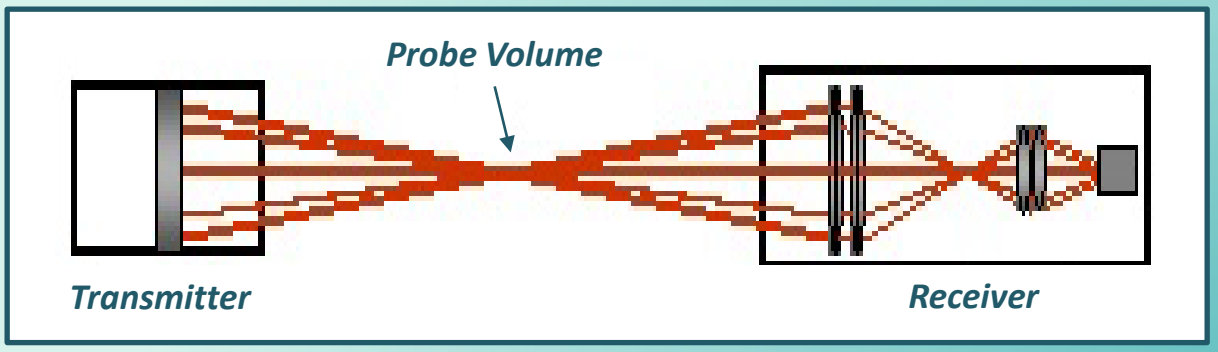
Real-time measurement and control of the input material is essential.

- Size and shape of the API particles can affect product:
  - bulk properties
  - performance
  - processability
  - stability
  - appearance
- Artium's Particle-i Imaging (PI) technology provides both size and shape of particles, simultaneously, in on-line or in-line analysis modes.

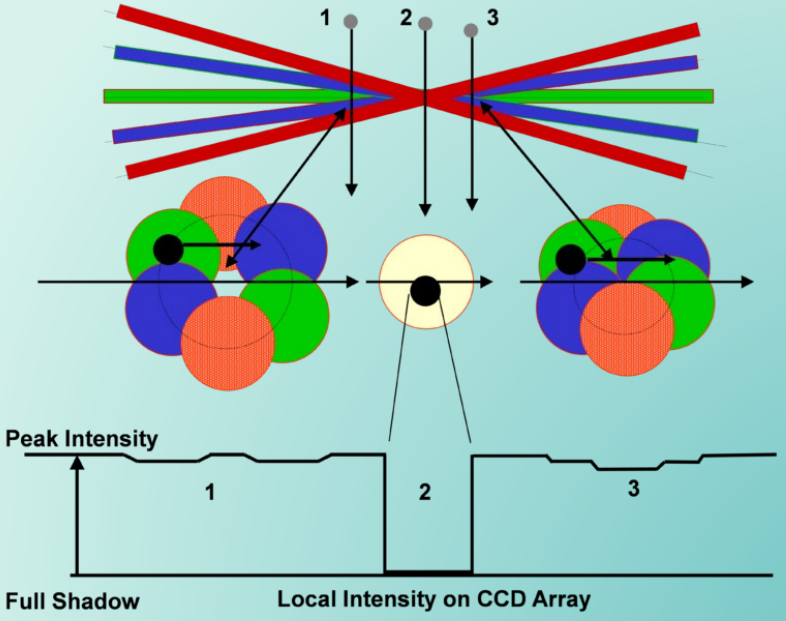


The PI is a high-speed particle imaging system that takes advantage of the latest advances in CMOS sensing technology combined with an innovative particle illumination method to deliver precise measurements of particulate size and shape.

The PI consists of transmitter and receiver optics. Multiple pulsed laser beams cross at the same point to form a measurement volume where a particle is probed when its presence is detected. Each beam is produced by its own laser source in the transmitter and is therefore optically incoherent with respect to other beams.



The intersection of multiple laser beams provides an intense uniform illumination in the sample volume. Since each laser beam takes a different path from the transmitter optics to the sample volume, particles that may momentarily block parts of any one beam will not, at the same time, block any of the other beams.

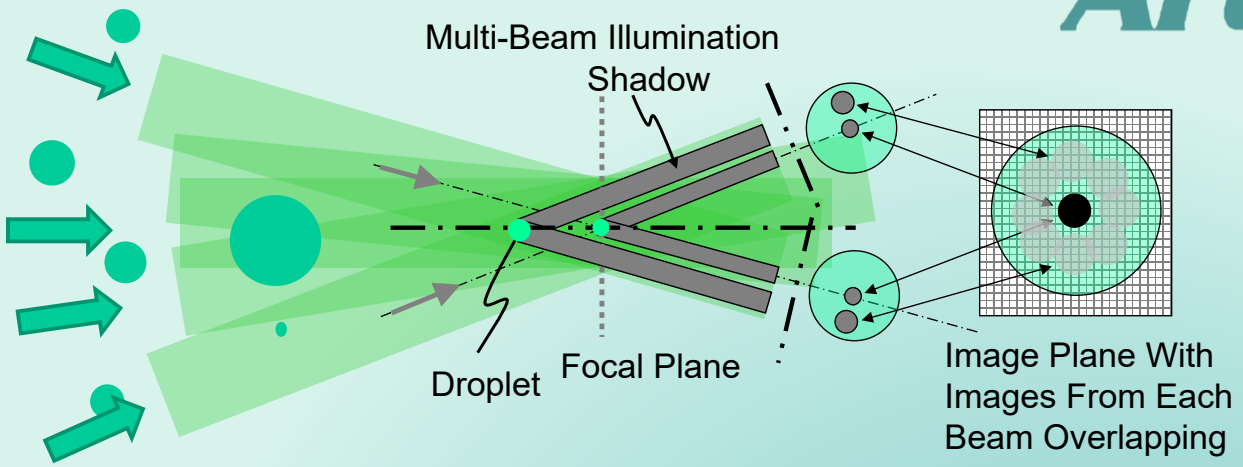


As a result, the illumination profile at the sample volume of the PI system does not lose uniformity at any time. The transmitted laser beams are re-focused onto a fast frame rate imaging sensor where a shadow of the particle is cast. The images are processed in real-time by the system software to extract various size and shape parameters.

The biggest advantage of Artium's PI technology is its ability to deal with the depth-of-field issue that is typical when imaging approaches are applied in a polydisperse particulate environment.

Depth of field as used in the field of optics refers to the range over which an optical instrument produces a sharp image of an object. Particles detected outside of the depth of field of the receiver optics cause a significant increase in measurement error since the sizes of the unfocused particle images will appear to be different from the true values.

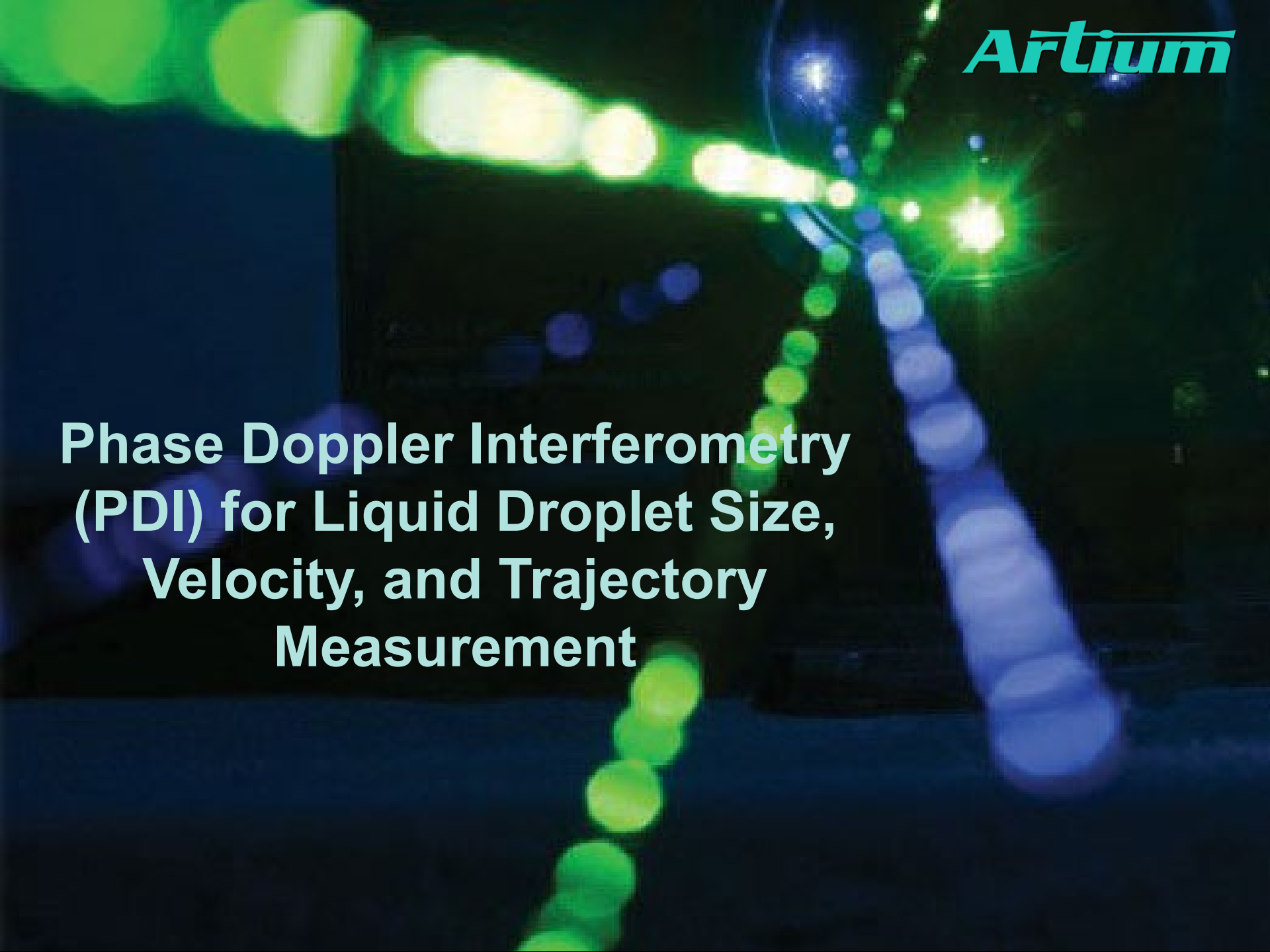
In addition, automated image processing systems need to determine when the images are in focus based on such criteria as depth of shadow and shadow edge gradients. Dependence of the object size measured with an imaging system follows a nearly monotonic variation with distance from the object plane.



Multi-beam illumination scheme for reducing depth-of-field measurement errors

For particle sizing, the acceptable size uncertainty usually sets the depth of field of the imaging system. Observations of larger structures generally will allow a larger circle of confusion and hence, a greater depth of field for the imaging system. For single beam illumination, the shadow remains as a single image, in this case a circle, but will go out of focus as indicated by blurred edges.

With multibeam illumination, the images will both blur and separate. In the design of the PI system, the beam intersection angle is set so that the separation of images is slower than the blur due to depth of field. In our application of image processing, this information is used to aid in the determination of when the images are in adequate focus or are unacceptably out of focus.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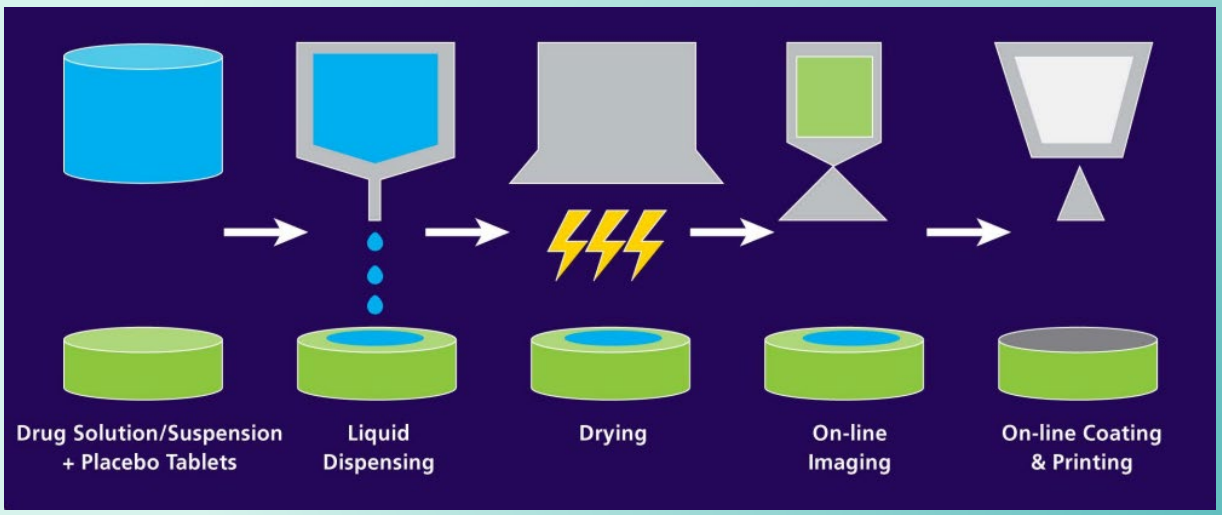
Phase Doppler Interferometry (PDI) for Liquid Droplet Size, Velocity, and Trajectory Measurement

Liquid dispensing technology can be used for rapid development and manufacture of low-dose and/or high potent tablets. The drug product, active pharmaceutical ingredient (API), is prepared in a liquid form and then applied to placebo tablets.

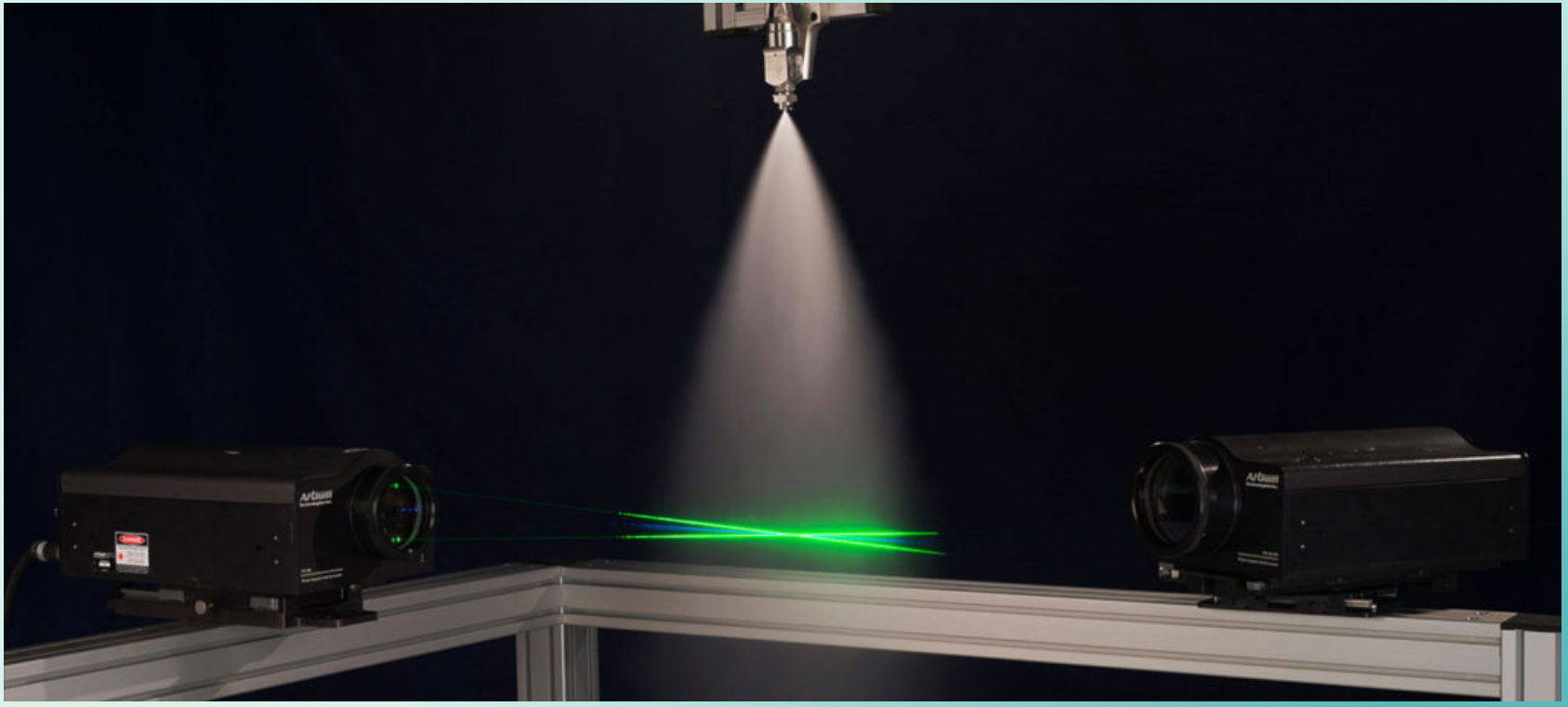
While different methods are available for dispensing the droplets precisely on to the tablet, the size and trajectory of the liquid droplet being dispensed are critical parameters that influence the amount of drug that is actually delivered to the tablet, and therefore, measuring and controlling these parameters in real-time are essential to the consistency in tablet production.

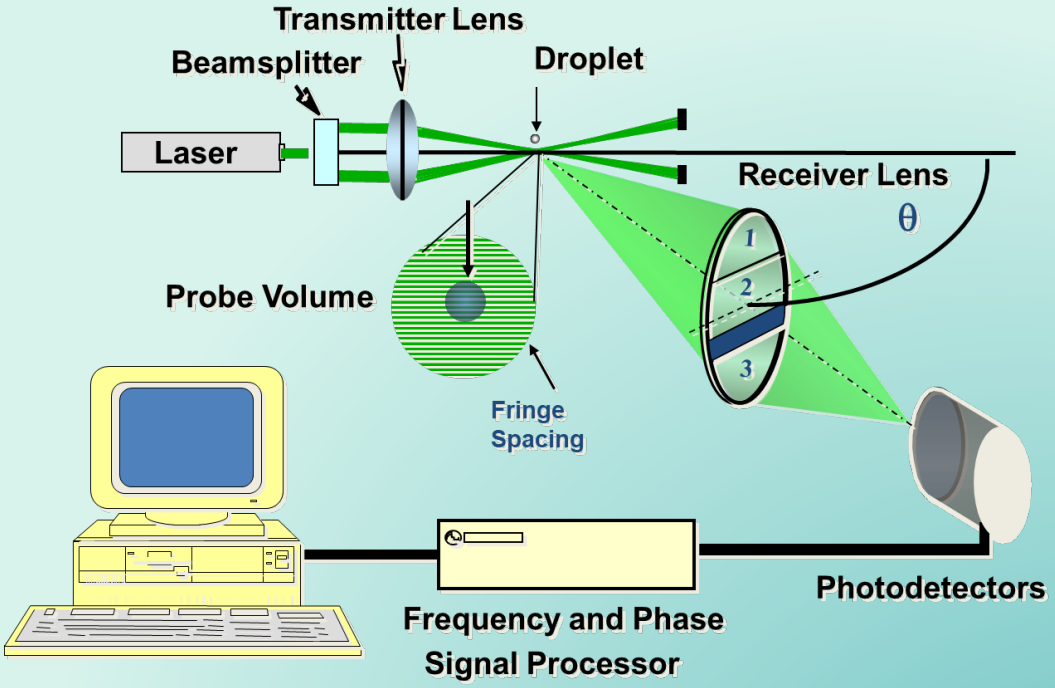


Liquid dispensing technology used for delivering the API to tablets

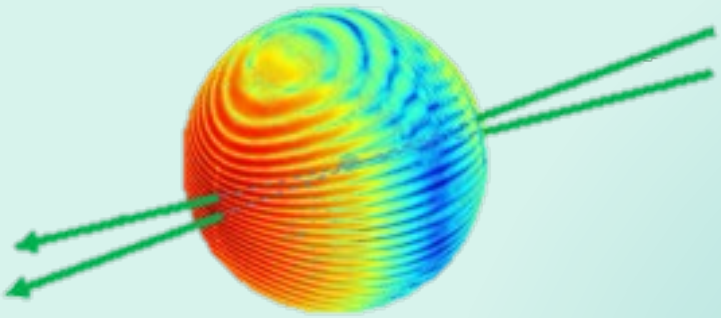
Graph Source: GSK

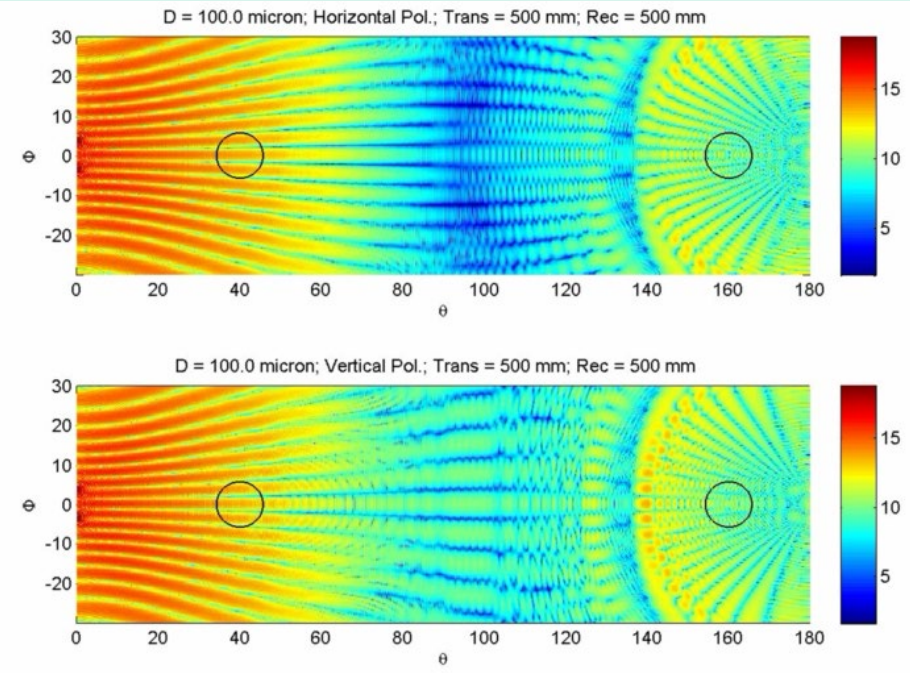
Traditionally, imaging methods have been used as a PAT tool for measuring the droplet size. However, Artium has developed the PDI, with several advantages over imaging methods, for precise measurement of the size and velocity of individual droplets. The method was invented in 1980 and developed by our engineers. It is recognized as the worldwide standard for spray droplet measurements.





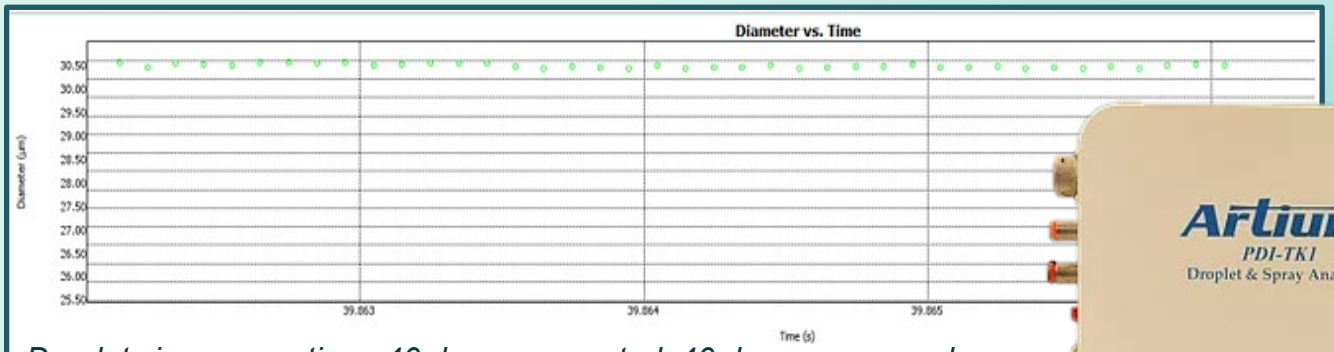
For the implementation of the PDI method, a laser beam is first split into two beams of equal intensity. The beams are then focused and made to intersect using a transmitter lens. Particles passing through the beam intersection region will scatter light that is collected by a receiver lens. A single aperture is used in the receiver to allow only light scattered by particles crossing a small region of the beam intersection to reach the photodetectors. The scattered light, which is Doppler frequency shifted, forms a moving interference fringe on the detector.



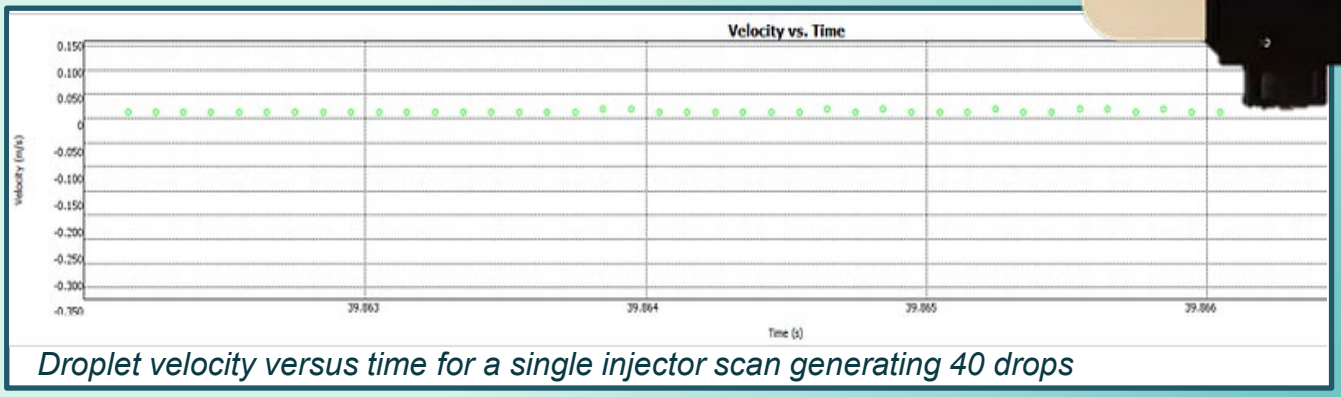


The spacing of the fringes is inversely proportional to the size of the droplet diameter. Measurement of the spacing of the interference fringes produced by the scattered light is accomplished in a straightforward manner using pairs of detectors which basically measures the phase shift between the two detector signals. In Artium's PDI, a third detector is used for redundancy and to increase the measurement size range without compromising the size resolution.

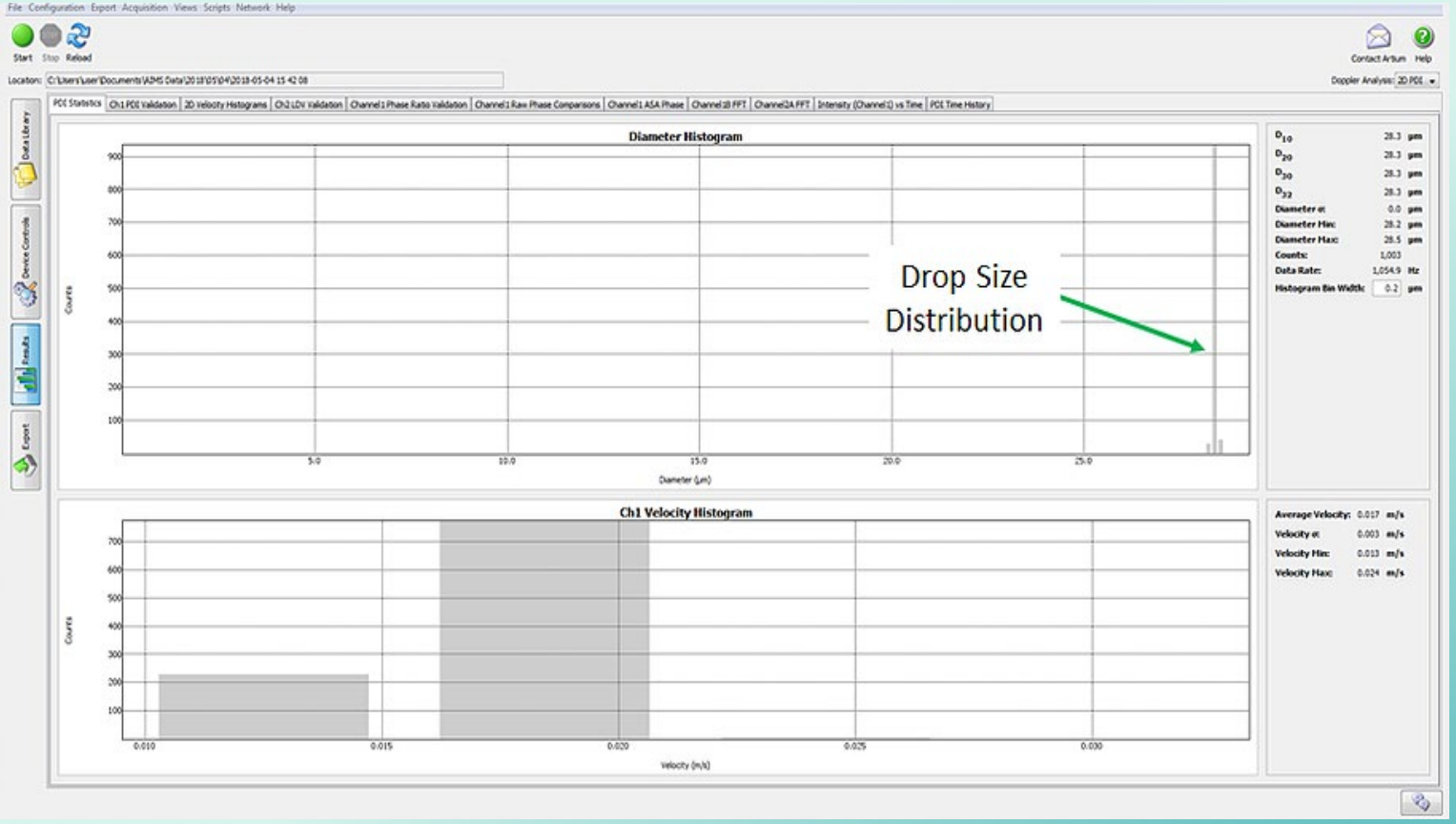
A compact and easy to use version of the PDI, namely the PDI-TK (turnkey), has been specifically developed for liquid dispense process monitoring applications such as inkjet printing. The TK is able to measure droplets as small as 1 um and with 0.1 um precision.



Droplet size versus time, 40 drops generated, 40 drops measured



Droplet velocity versus time for a single injector scan generating 40 drops



Droplet size and velocity distributions. Drop size standard deviation to less than 0.05 µm.

Process Analytical Technologies require real-time measurement and control of the input material:

- Artium's Particle-i Imaging (PI) technology provides both size and shape of particles, simultaneously, in on-line or in-line analysis modes.

- Artium's Turn-Key Phase Doppler Interferometer (PDI-TK) measures droplets as small as 1μm and with 0.1μm precision.

These proven technologies have been implemented in numerous applications spanning several industries, governmental agencies, and academic facilities.

These instruments are very useful in quality control procedures where the input material requirements are critical.


Artium
Technologies Inc.
High-precision measurement systems
for energy, environmental, and
industrial applications