Particles in WFI

Detecting Foreign Particulate in Water for Injection

The Application of Dynamic Imaging to Detect Particles in Sterile Water

Andrew Short

CANTY PROCESS TECHNOLOGY

In Water for Injection (WFI) or Sterile Water applications it is vital to measure and quantify the amount of foreign particles such as solids, rouge, droplets, or biofilm in a given volume to ensure the product meets certain purification standards. USP 788 / 1788 is the accepted set of guidelines for testing and concentration limits for particulate matter in injectables.

Analyzing these particles continuously produces particle count and concentration data which can better inform decisions for downstream purification or upstream process control. This paper explores the application of CANTY's InFlow™ analyzer, a dynamic imaging technology that measures the solids, droplets, gas, and foreign materials if any, passing through an inline flow cell.

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Introduction

Dynamic imaging involves flowing process material through an analyzer that takes microscopic images of the fluid and analyzes those images to detect the presence of "particles." These particles could range from droplets to gas to solid materials. Since the acquired images are 2-dimensional and there is a physical difference in the appearance of these types of materials, dynamic imaging analyzers are capable of simultaneously detecting, sizing, and measuring concentrations of all of these materials independently from one another.

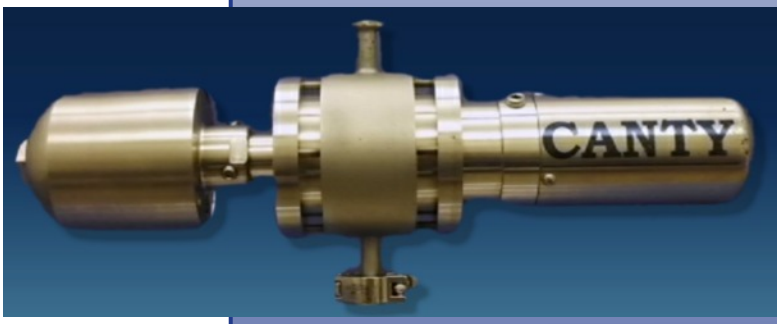
When a CANTY InFlow™ is installed inline of a WFI process tank outlet, the analyzer will be able to pick up on solid particles at a size of 1 micron and above. When detected, the analyzer can output a signal indicating the size, count, and concentration of particles detected.

These outputs allow a control system to automate a response far earlier and faster than a detection via other common methods, like laser light obscuration, turbidity meters, fluorescence or by Sampling. By detecting these particles in real time as they flow past an inline microscope, a representative determination of whether a stream of WFI has been properly treated, filtered, or distilled can be made without requiring a sample to be taken. Due to low particle concentrations, sampling can often lead to uncertainty in measurements. Also, a small sample volume creates additional risk for contamination from other sources such as the sample container. The information can also be used to determine when a line needs to be cleaned or de-rouged. The measurements taken by the CANTY Inflow are vital to optimize and detect contamination in the sterile water stream.

Overview of WFI

Water for Injection is typically produced through distillation or reverse osmosis, often with downstream filtration to ensure purity. Generally, the best methods are Vapor Compression Distillation or Multiple Effect Distillation which use evaporation and steam energy to create a pure product. Reverse Osmosis can produce a pure product without heating by using techniques such as UV treatment and multiple filtration methods to high quality feed water. This method has a lower energy requirement compared to Distillation, but it requires continuous efficiency control and monitoring of filters, cleaning, and validation. [1]

Two common methods to detect and measure particulate matter in WFI are specified in USP 788/1788. They are (1) Light Obscuration Particle Count Test and (2) Microscopic Particle Count Test. Method 1 uses laser obscuration to determine particle size range and concentration. There are problems with this technique in cases of reduced clarity, increased viscosity, or products that produce or contain air or gas bubbles, which lasers cannot differentiate from particles. In these cases, USP 788/1788 suggests using Method 2 which is a manual, time-consuming process that requires counting the number of particles in a Petri dish and comparing the size visually to reference circles. Both methods require sampling, which is not desirable because one sample is not representative of the random release of particles in WFI streams. A sample maybe be absent of particles or have a high particle count depending on the time of sampling. Sampling low particle concentration WFI streams may not be optimal because external sources of contamination such as a not perfectly particle-free container can skew results.

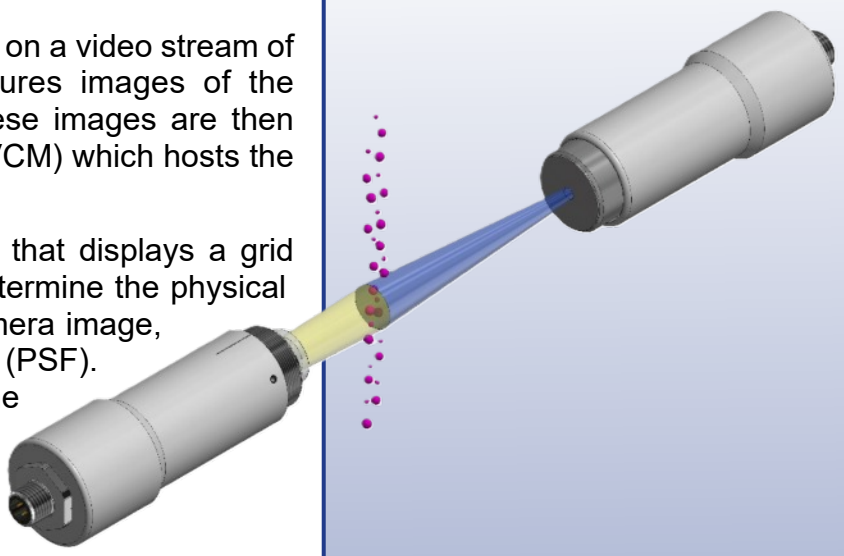


The Canty InFlow™ eliminates concerns of sampling inconsistency, streams with reduced clarity, increased viscosity, gas bubble interference. The analyzer can be applied directly in line or in a lab system, is fully automated, instantaneously captures data, and measures a particle's size, 2-D shape, and particle concentration. Integrating this technology inline eliminates the need for sampling, manual counting or observation to detect particles. By detecting these particles in real time as they flow past an inline microscope, a representative determination of whether a stream of WFI has been properly treated, filtered, or distilled can be made. The information can also be used to determine when a line needs to be cleaned or de-rouged, saving time and cost. The size and concentration data calculated by a CANTY InFlow™ can easily be compared to USP 788/1788 standards that are required for parenteral solutions. [2]

The Canty InFlow™ works on the premise of dynamic imaging. It is installed inline with process flowing through it. As particles are detected, the InFlow™ will quantify the size and concentration of the particles and output these values as tags to a control system. This system can then be set up to alert personnel if certain process parameters are out of spec and even begin measures to mitigate the situation.

How Dynamic Imaging Works

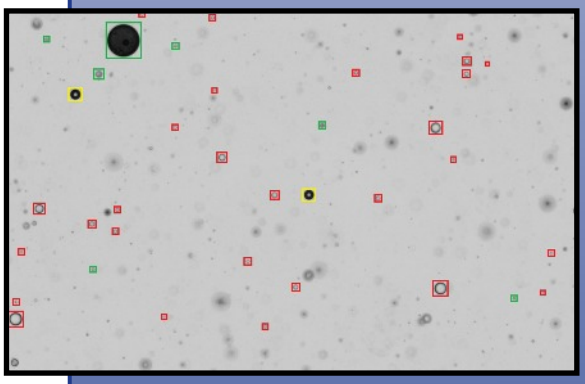
Dynamic imaging makes use of image analysis on a video stream of microscopic images. CANTY's InFlow™captures images of the process fluid and potential contaminants. These images are then transmitted back to a Vector Control Module (VCM) which hosts the software that performs the analysis.



The analyzer is calibrated by installing a tool that displays a grid pattern on the camera. This grid is used to determine the physical distance that each pixel represents on the camera image, what CANTY refers to as the pixel scale factor (PSF). This is typically reported in µm/pixel. Knowing the PSF, the 2-dimensional area of each frame can be calculated.

The lens utilized in an InFlow™ has a known depth of field (DOF). The DOF is a measurement of the depth in which subjects, such as the particles in a fluid, are in focus. This now allows CANTY to measure the volume of each image taken in which particles are in focus.

On each image, the CantyVision software determines what might be a "particle" from what is the background fluid. At this stage, the "particle" could be anything - a solid, rouge, biofilm, or bubble. After finding something that could be a particle, the software next makes a measurement that grades whether or not the particle is in focus. If it is in focus, then this particle is within the depth of field of the lens used. That means it should be included in the analysis. If a particle is not in focus, it is disregarded.



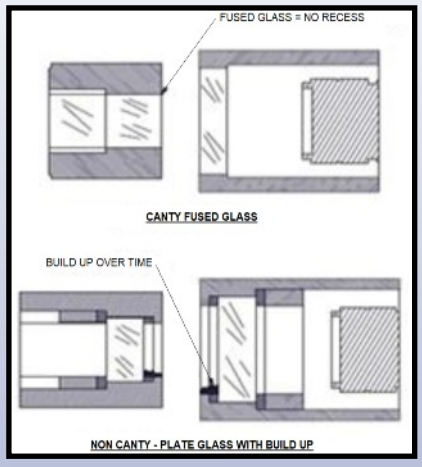
Each type of particle, solids, and bubbles, look morphologically different from one another. These differences are captured, numerically, in the various shape factors measured. The software is trained via AI to recognize the trends in these shape factors belonging to each type of particle. This is key because it allows CANTY to distinguish between different kinds of particles that were captured in the same analysis and quantify measurements for each class of particle differently.

After a particle has been sorted into its correct class, the software calculates a volume of that particle based on its class. Since we already have the volume of each image being analyzed, the concentration of any given class of particle can now be calculated on a volumetric basis and can be converted into a mass concentration using the bulk density of the particle class in question.

By averaging over hundreds of images, the InFlow™ is able to provide a representative concentration and particle size distribution for each particle class analyzed. Additionally, if there is ever skepticism about the reading, the images from the analyzer can be viewed live and/or saved as a recording for reference.

InFlow™ Hardware

The hardware involved in CANTY's InFlow™ includes 4 main key technologies: the flow cell, lighting, camera optics, and Vector Control Module (VCM).



The flow cell on an InFlow™ is designed to mount directly inline with standard sizes up to a pipe size of 3". (Note that custom units may be provided for line sizes greater than 3". Consult the factory for details). The flow cell is designed to orient particles such that the analyzer is always able to capture an image of the longest side of each particle. This is key to accurately sizing each particle seen. Critically, the flow cell seals the light and camera from the process using CANTY's fused glass technology. This fused glass barrier, unique to CANTY, can sustain extremely high temperatures and pressures while still allowing for a view into the process. Unlike with other analyzers, this fusion of metal to glass creates a hermetic seal and does not utilize gaskets or O-rings at the glass interface that the camera and light look and shine through. That smooth surface doesn't leave any crevices and makes it difficult for contaminants to stick to or build up on the surface of the glass which is extremely important for mining slurries.

CANTY always says that there are three keys to a perfect image: lighting, lighting, and lighting. CANTY has been leading the industry and innovating in process lighting since the 1970's and applies all of that knowledge in the InFlow™ analyzer. The LED light used is the brightest in the industry with a guaranteed lifetime of 5 years. Unlike many other analyzers, the light in the InFlow™ back-lights the process, resulting in sharp, crisp images of each in-focus particle.

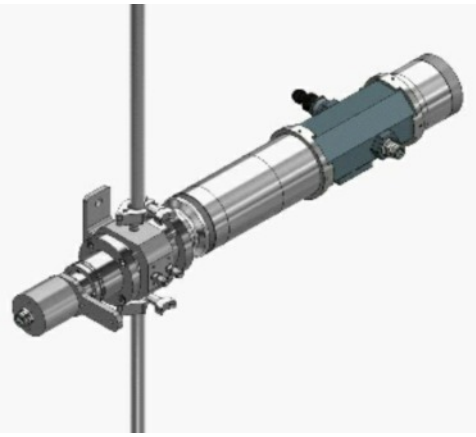
The camera optics used in each InFlow™ are high resolution gigabit Ethernet CCD's that undergo significant testing to ensure they will be robust for long-term use. Optics are always improving, so CANTY is constantly evaluating the latest and greatest cameras and lenses to provide the highest quality images without compromising on quality and reliability of the analyzer. Optics used in any given analyzer are picked according to the requirements of the application. The latest generation of optics used in the InFlow™ utilize a 4K resolution camera that can pick up on particles as small as 1µm.

Obtaining a high quality image of a process is only half of the battle. The magic happens when that image is processed on CANTY's VCM. The VCM platform is a series of powerful processors that host the CantyVision software. These machines are configured with the analyzers at the factory prior to shipping to make obtaining an image plug-and-play out of the box. In an age of remote connections, the VCM's have the ability for users to allow CANTY personnel to remotely access the unit to provide support and help troubleshoot the analyzers. These analyzers also provide the outputs to interface the data tags with a user's control system.

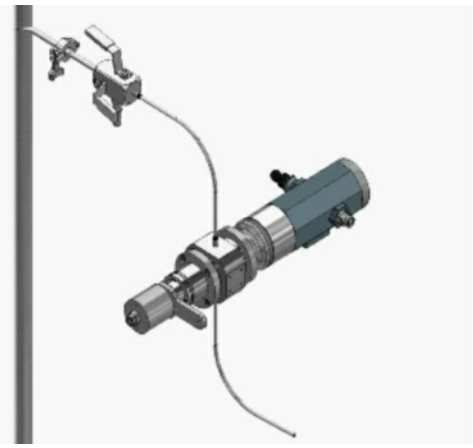
InFlow™ Hardware Cont'd & Configurations

CANTY InFlow™Analyzers can be configured multiple different ways, either in the field or in a laboratory environment. When mounted in the field the analyzer connects to two pieces of process tubing directly **inline or at-line** on a sample line. For either configuration vertical upward flow is preferred, flow rates and connection sizes determine if it is best to mount directly inline or on a sample line. Inline analyzer connection sizes range from 1/2" to 8" and the at-line system is a 1/2" sample line connection size.

Inline Unit

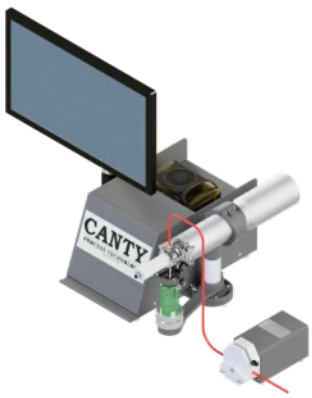


At-Line Unit



Although sampling is not recommended, these analyzers can also be configured for laboratory environments if a suitable location in the field can not be accommodated. The **Mini Lab InFlow™** can draw samples of fluid through the flow cell to analyze the sample and detect droplets, solids, rouge, or biofilm. Although sampling is not optimal, dynamic imaging is still being utilized which has many benefits above other methods such as laser light obscuration. Any lab configuration is fully automated, requiring limited operator intervention. When there are several streams that need to be tested and permanent installations on each may not be possible, the **Portable InFlow™** can be used. This system is easily moved from stream to stream to run short-term testing on each. This can also be a useful tool in situations where space is limited and monitoring is only needed occasionally.

Mini Lab InFlow™

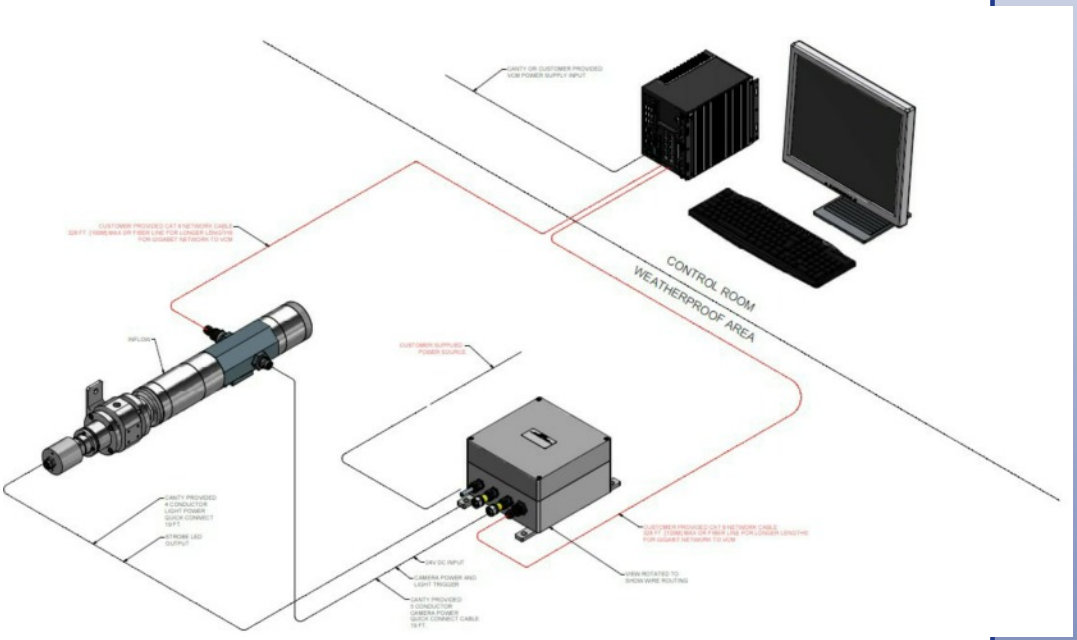


Portable InFlow™

Connectivity

Inline Connectivity

Due to the amount of data being transmitted between the InFlow™ and VCM, CANTY requires the use of CAT6 Ethernet running from the analyzer to it's power supply and from it's power supply back to the VCM. A typical layout of the components can be seen here. CAT6 Ethernet, however, has a distance limitation of 100m before there is signal loss that can interrupt analysis. In those situations, it is possible to convert the CAT6 Ethernet to fiber via CANTY's media converters. Refer to document TA11950-1024 if this situation applies.



Lab Connectivity

The Canty core unit powers and controls the analyzer. Once the Mini Lab InFlow™ and core unit are setup on a lab bench, connecting them is simple. There are unique pinned receptacles which only allow them to be connected one way with the provided cables allowing for easy straight forward wiring.

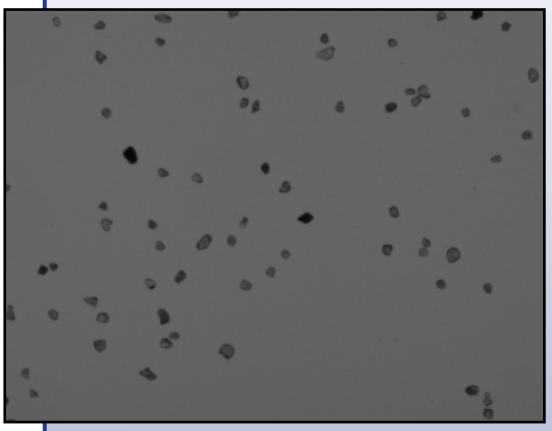
The Ethernet connections on the core unit and analyzer are connected to the VCM in the labeled Ethernet ports.

Connecting the USB from pumps in the Mini Lab InFlow™ system to any USB port on the VCM as well as connecting the USB dongle for the keyboard and mouse is simple.

The monitor comes pre wired from Canty's factory with the display cable and power cable wired through the mounting pole that slide into the core unit. Connecting the display cable to the VCM will allow for the CantyVision Software to be displayed on the monitor. Lastly, connecting the core unit and monitor to a standard wall outlet powers the system allowing for samples to be analyzed right away with data storing locally on the VCM.

Data Outputs For Particles in WFI

When a suspended solid is detected, it is critical that as much information as possible is learned as quickly as possible. The Canty InFlow™ will provide:



- Count of suspended solids/rouge, biofilm, and counts of bubbles per unit volume of process fluid

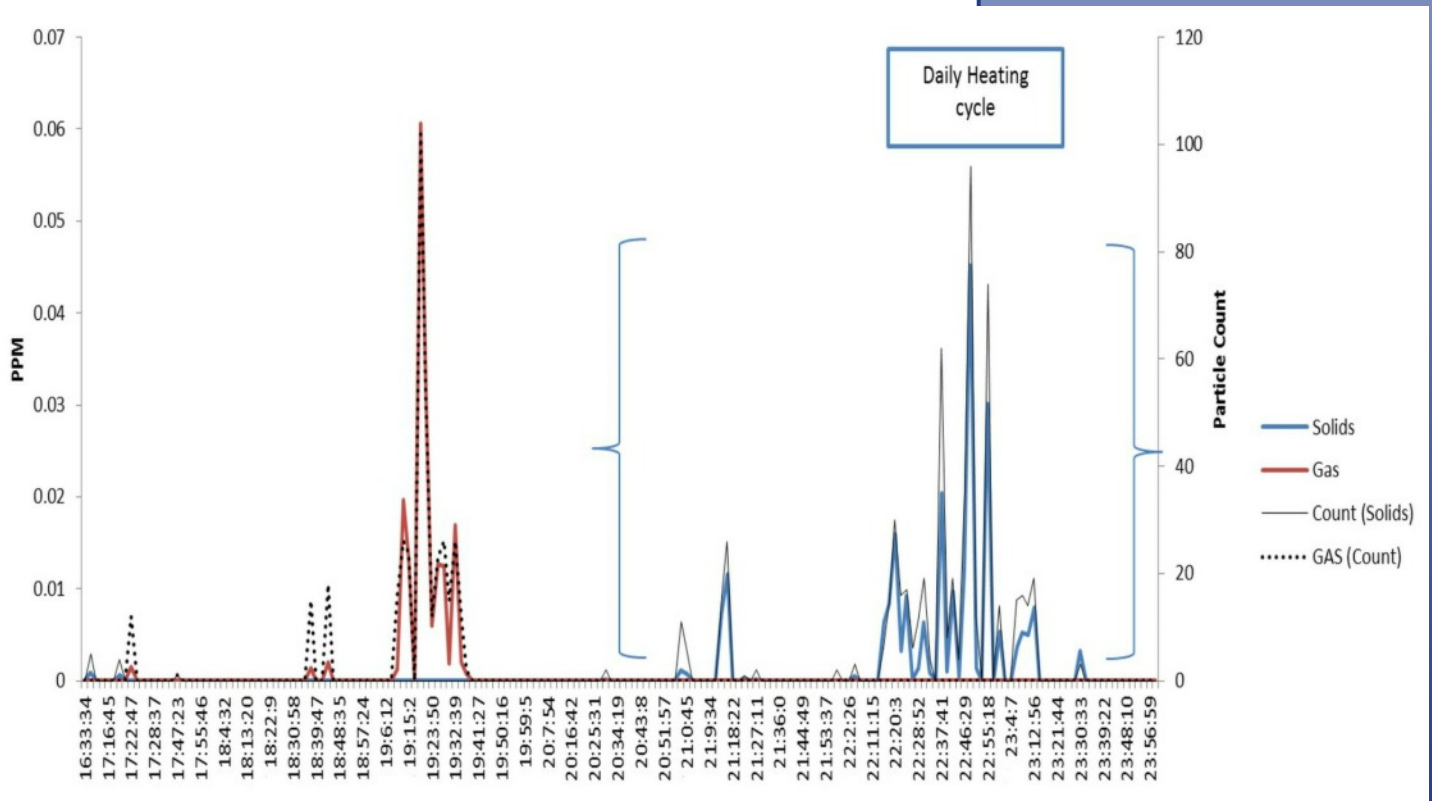
  Combined with size data, outputs of counts/mL in a size range output to match USP 788/1788.

- Shape and Size distribution of the solid particles

  The shape and size distribution of the suspended solids can give information on the type of solid and promote understanding of biological, chemical, and physical processes that form the solids.

These outputs are in addition to generic system health alarms that would indicate if there is a problem with the analyzer, such as camera temperature and communication signals.

Each of these outputs can be trended over time in a data historian to monitor contamination trends and effectiveness of filtering and distillation to provide historical context. To communicate between the analyzer and your control system, outputs including OPC UA, Modbus TCP/IP, Modbus RTU, and Analog (4-20mA) are available. Reference the VCM brochure, TA12100-1012, which outlines the available communication methods for each VCM.



Conclusion

CANTY's InFlow™ analyzer is an effective tool for the automatic detection and measurement of foreign particles in Water for Injection. It is installed directly inline which avoids misrepresentative sampling, can measure particles at very small sizes, and has multiple outputs that can help inform how well a filter or distillation process is operating. The analyzer provides a 2-D measurement while filtering out gas bubbles, resulting in more accurate and detailed data. The measurements taken by the CANTY InFlow™ is a robust method to confirm that Water for Injection meets purification standards specified in USP 788/1788.

Get more information!
Website: https://www.jmcanty.com

North America
JM Canty, Inc.
6100 Donner Road
Buffalo, NY, United States
+1 (716) 625-4227
sales@jmcanty.com
techsupport@jmcanty.com

EU & International
JM Canty International, Ltd.
Ballycoolin Business Park
Blanchardstown
Dublin 15, D15 KV02, Ireland
+353 (1) 882-9621
+353 (1) 882-9622
Sales.ie@jmcanty.com
Techsupport.ie@jmcanty.com

Thailand Office
JM Canty Thailand Office
Phuket, Thailand
+66 83 9689548
Sales.ie@jmcanty.com
Techsupport.ie@jmcanty.com

References

[1] *Methods of producing WFI - water for Injection*. Water for Injection Systems. (2023a, October 24). https://waterforinjection.com/pharmaceutical-water-for-injection-methods-to-produce-wfi

[2] <788> particulate matter in injections. (n.d.-a). https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisionGeneralChapter788.pdf