

Comparison of IMD-A® 300 and 350 Models

Introduction

Azbil BioVigilant's Instantaneous Microbial Detection™ technology gives users the ability to continuously detect and report in real-time the presence of airborne microbes and total particles. This technology platform couples an optically-based detection module with PharmaMaster® software to provide these results instantaneously in a user-friendly interface without requiring any culturing, staining, or reagents. Azbil BioVigilant currently offers two different instruments that utilize the same revolutionary technology:

- The IMD-A 300 system with a sample airflow rate of 1.15 liters per minute (LPM)
- The IMD-A 350 system with a sample airflow rate of 28.3 LPM

This bulletin explains the similarities and differences between the two instruments, and helps guide selection of the most appropriate model for a range of applications in pharmaceutical, medical device, compounding pharmacy, and food and beverage industries.

Common Features Between Models

The IMD-A 300 and 350 systems are almost identical in appearance (shown in Figure 1) and utilize the same core detection module for microbial and particle counting and sizing as shown in Figure 2. Table 1 highlights some of the key features that are common to both models.

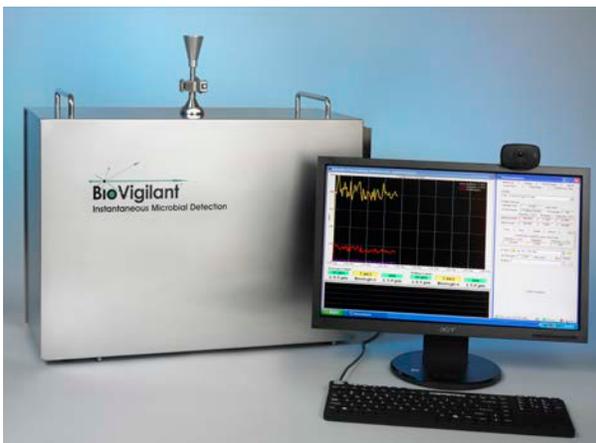


Figure 1: IMD-A System.

Optical Detection	Simultaneous Mie Scatter and fluorescence
Real-time Reporting	Particle counts, particle size, biologic status
Microbial Sensitivity	1 biologic (single-cell microbe)
Particle Size Range	≥ 0.5 to >10 µm
Software	PharmaMaster software with Profiles, Events, Markers, Video, and Historical Playback
Sample Modes	Continuous or by programmable volume/time
Networking Options	<ul style="list-style-type: none"> – Standalone – Wireless or wired connection to local computer – Networked with remote control
Compliance	<ul style="list-style-type: none"> – 21 CFR Part 11 – USP <1223>, Drug Master Files with FDA for each model – EP 5.1.6 – CE TUV

Table 1: Common Feature Set.

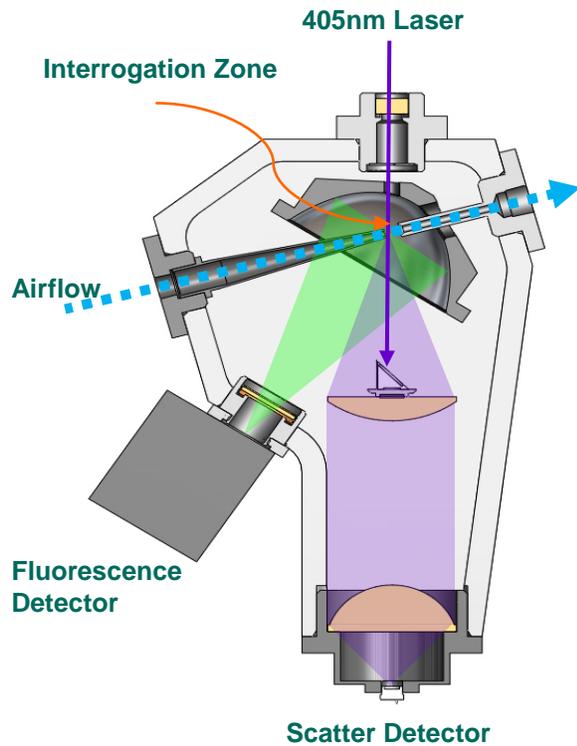
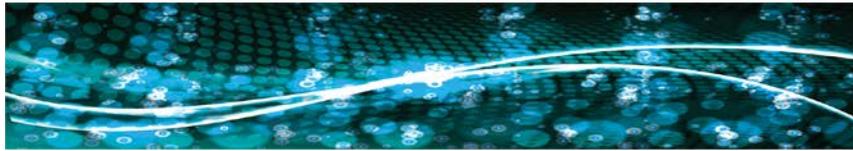


Figure 2. Detail of optical detection system for IMD-A 300 / 350 systems.

As illustrated in Figure 2, the common detection platform samples environmental air from the inlet through the interrogation zone. All particles in the air intersect a 405nm laser beam. Mie scatter is generated for each particle, represented by the shaded purple region, and focused on the scatter detector. Mie scatter is widely used among particle counters, whereby the amount of light detected is used to calculate the particle size. Simultaneously, if the particle contains the endogenous metabolic fluorophores NADH or Riboflavin (or dipicolinic acid in the case of endospores), intrinsic fluorescence will be generated. This light, represented by the shaded green region, is directed onto the fluorescence detector. Signals from the two detectors are analyzed simultaneously and displayed in real time by the PharmaMaster software. One major benefit of simultaneous scatter and fluorescence detection (as opposed to detecting these signals at different times/locations) is the signals are generated on a particle-by-particle basis, and thus, directly coupled. In turn, every particle that passes through the interrogation zone is deterministically counted, sized (from 0.5 μm to $>10 \mu\text{m}$) and classified as either biologic or inert.

Both the IMD-A 300 and IMD-A 350 systems were subject to rigorous testing and validation, both demonstrating single microbial cell detection. Validation was performed to standards including USP<1223> and EP 5.1.6, and a Drug Master File has been filed with the FDA for each system. Details of this validation effort and data are covered in a separate fact sheet.¹

Differences Between Models

Although the detection technology is identical for both systems, each model has been tailored to meet different customer requirements. Table 2 shows some of the key differences between the two systems.

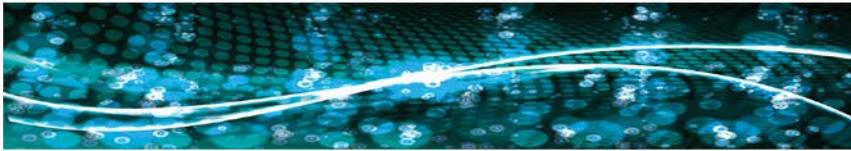
	IMD-A 300	IMD-A 350
Sample Flow Rate	1.15 LPM	28.3 LPM
Flow Concentration	None (100% interrogation)	Via virtual impaction ($D_{50} \leq 2\mu\text{m}$)
Particle Detection Performance	Meets ISO 21501-4	Meets ISO21501-4 except Counting Efficiency

Table 2: Key Differences.

The major distinction between the IMD-A 300 and IMD-A 350 systems is the sample flow rate. The IMD-A 300 system has a sample flow rate at 1.15 LPM, as compared to the IMD-A 350 system at 28.3 LPM. With the IMD-A 300 system, 100% of the sample flow passes through the detection module and thus all particles are measured.

To enable sampling at a higher flow rate without sacrificing the sensitivity to detect small amounts of fluorescence from single microbial cells, the IMD-A 350 uses a virtual impaction method to concentrate particles, analogous to that of most air samplers found in pharmaceutical environmental monitoring. Using an internal aerosol concentrator, the IMD-A 350 draws in air at a high flow rate that is concentrated into a 1.15 LPM air stream of enriched particles.

¹ Azbil BioVigilant, USP<1223> and EP 5.1.6 Validation Testing of IMD-A 300/350 Systems, LI-007.



This enriched air stream passes through the interrogation zone at 1.15 LPM where the individual particles are measured. The remaining particle-depleted airflow is exhausted out of the system. Figure 3 shows a comparison of the IMD-A 350 concentrator and a traditional air sampler. In both cases, sampling efficiency is less than 100%, as a proportion of the particles in the sampled air will invariably be lost through the exhaust. A commonly used metric to characterize this efficiency is the D_{50} value; the particle size at which at least 50% of the particles sampled are interrogated. IMD-A 350 tests put the D_{50} value at just under $2\mu\text{m}$, which is similar or superior to many of the common air samplers used today.^{2,3}

It should be noted that because of the concentrator design, the IMD-A 350 system does not meet the Counting Efficiency specification within the ISO 21501-4⁴ standard for particle counters, and so is not suitable for *certification* of cleanrooms to ISO 14644-1⁵, etc. The IMD-A 300 system does meet this Counting Efficiency metric in addition to all remaining ISO 21501-4 metrics for particle detection performance.

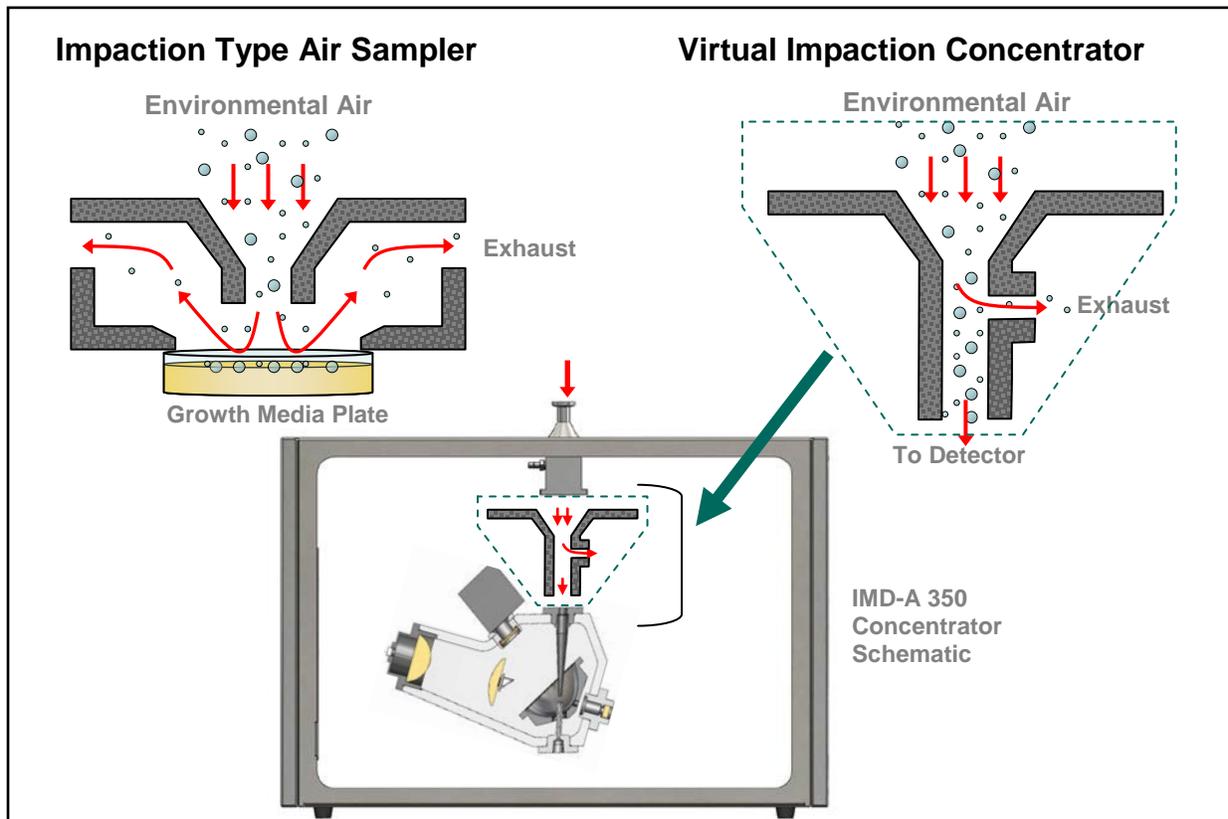


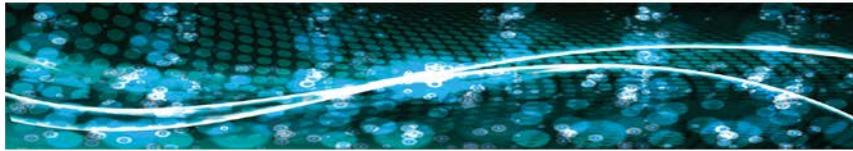
Figure 3: Comparison of traditional and virtual impaction, with IMD-A implementation.

² Jensen, P et. al. (1992) Evaluation of Eight Bioaerosol Samplers Challenged with Aerosols of Free Bacteria. Journal of American Industrial Hygiene Association, 53, 10, 660-667.

³ Yao, M. and Mainelis, G. (2006) Investigation of Cutoff Sizes and Collection Efficiencies of Portable Microbial Samplers. Aerosol Science and Technology, 40: 595-606.

⁴ ISO (2007) ISO 21501-4: 2007 Determination of particle size distribution—Single particle light interaction methods—Part 4 Light scattering airborne particle counter for clean spaces.

⁵ ISO (1999) ISO 14644-1: 1999 Cleanrooms and associated controlled environments—Part 1 Classification of air cleanliness.



Application	IMD-A 300	IMD-A 350
Continuous Monitoring of Conventional Cleanrooms*	Yes, preferable for small rooms or critical areas	Yes, suitable for small and large rooms
Collection of 1 m ³ Point Samples	Yes	Yes, preferable
Continuous Monitoring of Fill Lines	Yes, preferable	Yes, if air flow disturbance is not problematic
RABS/ Aseptic Isolator Systems*	Yes	Yes, best-suited for large RABS/isolators or if air flow disturbance is not problematic
Monitoring of Compressed Gasses*	Yes, with high pressure diffuser	Yes, preferable, with high pressure diffuser
Monitoring During Media/Water Fills*	Yes, preferable	Yes
Investigations*	Yes	Yes, preferable
Operator Training*	Yes	Yes
HVAC/Energy Reduction Studies*	Yes	Yes
Monitoring of Manufacturing/ Maintenance Activities*	Yes	Yes, preferable for large rooms/areas
Risk Assessment*	Yes	Yes, preferable

Table 3: Recommended applications for IMD-A 300 and IMD-A 350 Systems.

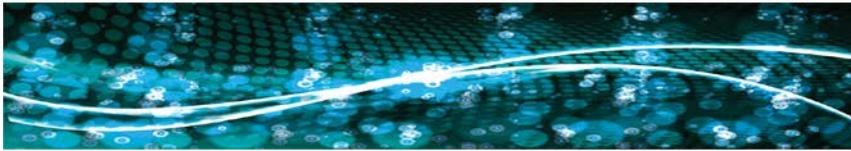
IMD-A Model Selection

When considering different applications, the user has a choice of IMD-A models depending on the tradeoff between sample flow rate and efficiency. The IMD-A 300 system has a low flow rate but high counting efficiency, and is well suited for applications where high efficiency and minimal disruption to the environmental flow dynamics are important. The IMD-A 350 system has the commonly-used sample flow rate of 28.3 LPM but with an efficiency tradeoff, and is often preferred by customers for applications where emphasis is on the ability to collect more data, faster.

Table 3 shows some of the common applications for IMD-A systems, with notes on the suitability of either the IMD-A 300 or IMD-A 350 system for each application. This is not a comprehensive list, but provides some general guidance. Asterisks (*) are placed next to applications for which published IMD-A literature, case study data, and/or Application Notes are available.

In addition, when selecting the most appropriate instrument for applications at your facility, it's wise to consider the following:

1. Size of sampling 'zone' to be evaluated
2. Discrete vs. continuous monitoring
3. Airflow conditions
4. How the data will be analyzed
5. Range of IMD-A applications



1. Size of sampling 'zone' to be evaluated

The sampling 'zone' is the floor space/air volume within a given environment intended to be measured. In a non-unidirectional flow environment, local airflow dynamics, particle settling velocity and sampler flow rate all affect the size of the 'zone' and how quickly a particle originating some distance away from the sampling instrument may be detected. The higher flow rate of the IMD-A 350 system creates a larger sampling 'zone' than the IMD-A 300. For example, microbe-generating activities on the other side of the room from an IMD-A 350 system would have a higher likelihood of detection and faster response time compared to the IMD-A 300 system (given equal sampling times). For this reason, Azbil BioVigilant generally recommends the IMD-A 350 for applications including conventional cleanroom monitoring, risk assessment, investigations, operator training, and monitoring of manufacturing/maintenance activities. The IMD-A 350 efficiency tradeoff is readily understood here in the context of being able to collect more data, faster.

For situations where monitoring of small, critical zones is required, the IMD-A 300 system may be the best choice, particularly if continuous monitoring is to be employed. In a low-count environment (i.e. very clean) where a critical area is sampled over long periods of time, the greater efficiency of the IMD-A 300 system may increase the chances of detecting any microbial particles that may be present.

An exception to these guidelines is when sampling in unidirectional (laminar) flow. Best practice dictates the use of isokinetic probes when sampling such an environment. A properly designed isokinetic probe restricts the sample 'zone' to the vertical cylinder of air directly above the probe's opening. In this situation, any sampling instrument, regardless of flow rate, would not be able to detect particles or microbes from adjacent or remote locations.

2. Discrete vs. continuous monitoring

A key benefit of IMD-A technology is the user choice it enables of discrete or continuous sampling modes. A discrete sample volume/time is necessitated by traditional, growth-based air sampling methods, while continuous monitoring is a capability long-offered by standard particle counting instruments. Both methodologies are available to IMD-A users and can be optimally applied to the applications in Table 3. Applications often driven by discrete sampling include investigations, training, maintenance monitoring, and energy reduction, where multiple data points with different conditions or sample locations are key for analysis. Often, an IMD-A system is placed on a wheeled cart and can be easily moved between

locations in these cases. Given the samples are discrete, flow rate is a consideration to achieve a given sample volume in reasonable time, and many users opt for the IMD-A 350 systems accordingly.

However, applications focused on monitoring and control, such as media fill process support, can derive significant value from continuous data. Monitoring for microbes during an entire process is a paradigm-changing capability, as traditional approaches often yield data describing only a fraction of the process. Consider, for example, using a traditional air sampler to collect a single 1 m³ air sample during the beginning, middle, and end of an eight-hour aseptic filling campaign. These samples total 3 m³ of air from a critical sample point, and depending on flow rate, temporally represent about 6% of that eight-hour environment. Clearly, the IMD-A system's continuous monitoring capability can provide significant value, giving instantaneous data for 100% of the eight-hour operation. Similarly, Art Vellutato discusses continuous vs. discrete monitoring:

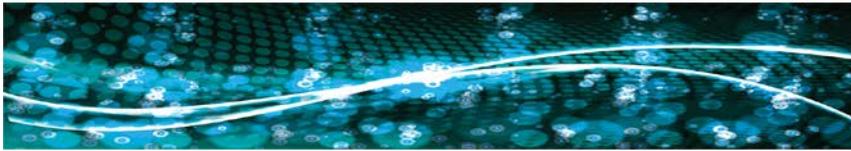
"In review of total sample volumes, some confusion arises ... from the perception that the idea is to monitor as fast as is possible, attain zeros and move on. This is incorrect thinking. The goal is to monitor as much of the process as is required to assure we have looked at every important factor before we release a product to the market. ...Seemingly, one would look to monitor for a longer time at a lower flow rate to attain data for a majority of the product run. This enables us to disseminate what is occurring in a longer time period in our operations. And thus, makes release a more calculated equation."⁶

Accordingly, the IMD-A 300 system may be an ideal instrument for fixed, continuous monitoring of critical areas.

3. Airflow conditions

Applications tied to process support or monitoring of controlled environments are typically related to manufacturing spaces with tightly controlled parameters. Environments within manufacturing fill lines and RABS often have specific airflow patterns (e.g. unidirectional/laminar) which have been validated, for example. The impact of an additional piece of environmental monitoring equipment should be carefully evaluated, and it is typically the case that a lower flow rate minimizes any potential disruption to these environmental flow dynamics. And of course,

⁶ Vellutato, A. (2005) "Sampling Equipment" Moldenhauer, J. (ed.) Environmental Monitoring—A Comprehensive Handbook, Volume 1, 2005.



the proper isokinetic probe should be selected to match the instrument's flow rate with the laminar flow rate (different isokinetic probes are offered for both the IMD-A 300 and 350 systems). The low flow rate IMD-A 300 system can be ideal for monitoring a 'critical point' with these constraints. Similarly, contained environments like RABS, and especially aseptic isolators, are kept at a positive pressure with respect to their surroundings to help preclude ingress of contamination. Pulling environmental air samples from these closed spaces should be considered, and the IMD-A 300 system can be preferable to maintain ideal pressure balances.

For sampling of compressed process gases, a high pressure diffuser (HPD) is typically needed upstream of the sampling instrument. While the IMD-A 350 has typically been used for this application, the important point is to ensure the output flow rate of the HPD is matched with that of the sampling instrument.

4. How the data will be analyzed

For most IMD-A applications, data from another instrument is used at some point for comparison or information synthesis. The IMD-A systems are designed first and foremost to be biologic detectors and so are often compared to traditional air samplers, but it is very common to compare IMD-A results to those obtained with a standard particle counter. Both IMD-A systems have demonstrated excellent correlation (R^2) with particle counters during both validation and customer field tests, often yielding coefficients of determination of $R^2 \geq 0.99^1$. For the IMD-A 350 system, the decreased sampling efficiency caused by the concentrator, as discussed earlier, may result in the volume-normalized number of particles counted by the 350 system to be lower than that obtained with an ISO 21501-4 compliant particle counter. The IMD-A 300 system, on the other hand, should show very similar counts.

Other considerations include how thresholds may be set and regulatory requirements. For continuous applications such as fill line monitoring, the ability to set automatic microbial alert and action level indicators through the PharmaMaster software is valuable. Traditionally, these alert and action levels are based on units of CFU/m³. The IMD-A 350 system would reach 1 m³ of sample volume in the shortest time, assuming a 1 m³ sample volume is truly required. Alternately, the units for alert and action levels could be scaled to smaller volumes, and some customers are even evaluating non-traditional approaches such as frequency-based limits instead of

limits based on magnitude. In these cases, the IMD-A 300 system can be very appropriate. The PharmaMaster software is capable of reporting results for a predefined sample interval (i.e. volume) on either a discrete average or rolling basis. This versatility makes setting process limits in PharmaMaster scalable depending on the flow rate of the IMD-A system used. In accordance, it is important to clearly understand any regulatory implications/requirements of how the data is used. For example, traditional EM microbial limits (e.g. Grade A ≤ 1 CFU/m³) are based upon the discrete sampling paradigm^{7,8}. As is discussed in Vellutato's quote earlier, continuous monitoring obviates this need to collect a certain volume as quickly as possible. Indeed, regulatory agencies have confirmed⁹ that continuous monitoring with low sampling rates can be applied to a traditionally discrete process by scientific adjustment of the limits structure. That is to say, a low-flow instrument such as the IMD-A 300 system can be appropriately applied to continuous monitoring applications.

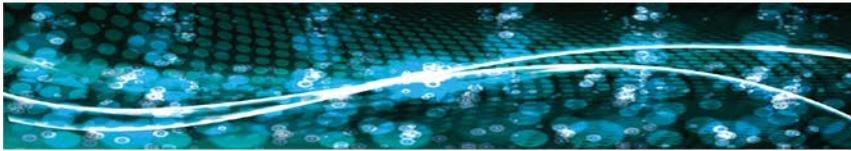
5. Range of IMD-A applications

The IMD-A system applications listed in Table 3 contain a mix of applications bearing regulatory requirements for formal testing and validation before implementation – sometimes termed “compendial” (e.g. environmental monitoring of pharmaceutical fill lines) and examples of applications for which you could leverage the benefits of instantaneous microbial detection immediately – “non compendial” (e.g. investigations). Ultimately, the specific application, intended use of IMD-A data, a customer's Quality structure, and the regulatory jurisdiction will guide the appropriate validation process and formality. For practical purposes, customers with a limited number of IMD-A systems often benefit from purchasing at least one IMD-A 350 system because of the greater application versatility. However, compendial applications typically require validation be performed with the model instrument which will ultimately be

⁷ European Commission (2008) EU Guidelines to Good Manufacturing Practice—Annex 1 Manufacture of Sterile Medicinal Products. Enduralex. European Union: Brussels, Belgium.

⁸ Food and Drug Administration (2004) Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice. U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD.

⁹ Azbil BioVigilant Fact Sheet: Minutes of Regulatory Roundtable, October 2011 US IMD Consortium Meeting. Available from www.biovigilant.com.



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used. In this case, validation goals should be considered when the initial IMD-A model is selected.

Summary

The considerations listed earlier can help guide the user in not only selecting the most appropriate IMD-A instrument for the desired applications, but also in executing and analyzing data from the application to yield the most value. Certain applications and evaluations can be complicated, and extend beyond the topics covered herein.

Support

Azbil BioVigilant has a team of expert Application Scientists who can help with everything from training, experimental design, and test execution, to data analysis and regulatory support. The Applications Team offers a full range of support services and documentation for various IMD-A applications. Please contact Azbil BioVigilant's Applications team or your sales executive to learn more.

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LI018 March 4, 2013



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