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Without measurement there is no control

A Few of My Favorite FDA 483s and Warning Letters related to Aseptic Processes and Environmental Monitoring

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Even Congress Can "Bend" The Truth

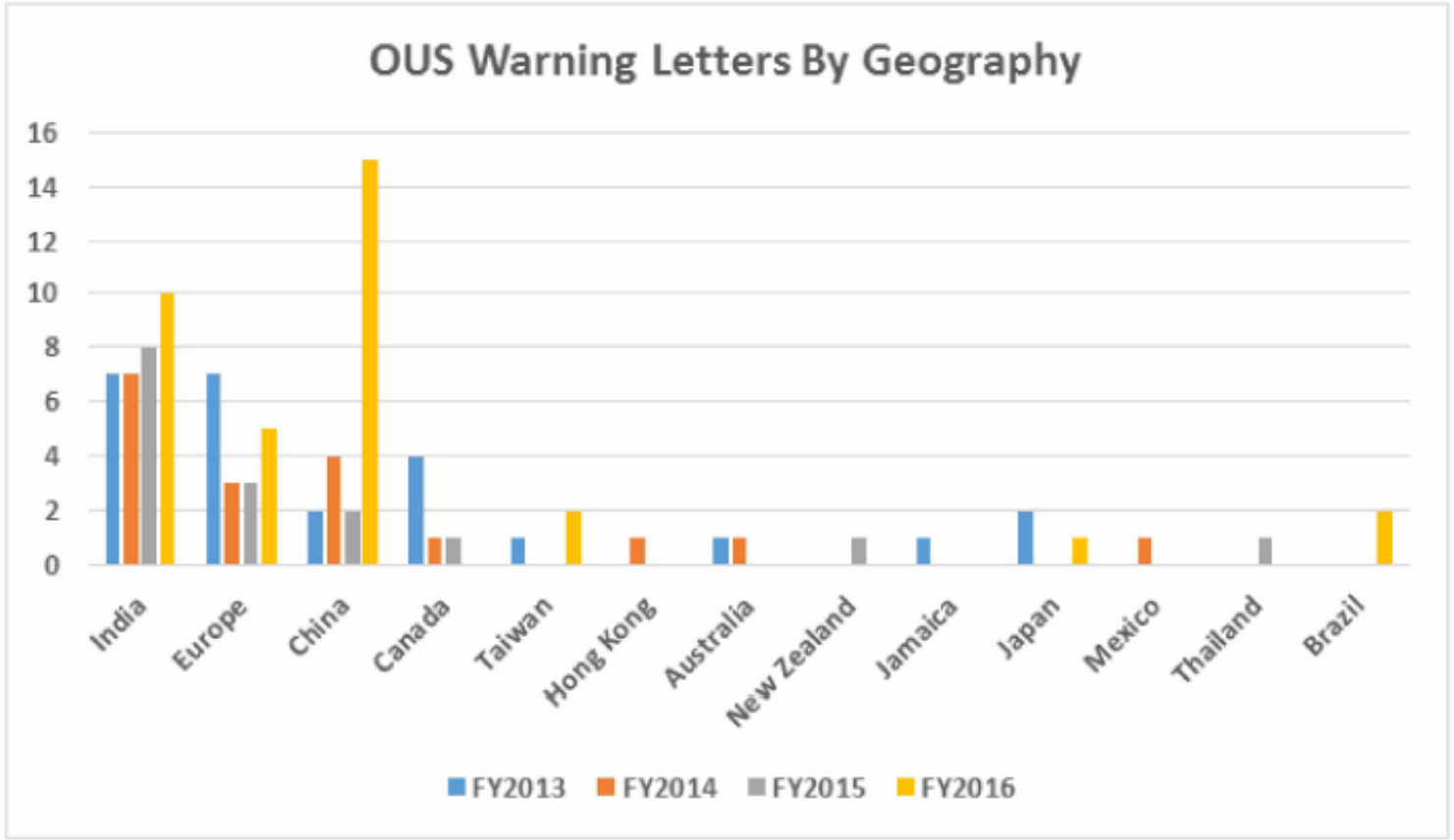
- FDA Committee indicated that Warning Letters had increased dramatically
- "Clearly show a dramatic change in FDA's regulatory approach"
- Increased Warning Letter referred to "Data Integrity" and "Sterility Assurance" (included Environmental Monitoring)

Warning Letter

Table 2: Drug GMP Warning Letters Regarding Sites Outside the U.S.

Country / Geography	FY2013	FY2014	FY2015	FY2016	Total
India	7	7	8	10	32
China	2	4	2	15	23
Europe	7	3	3	5	18
Canada	4	1	1		6
Taiwan	1			2	3
Japan	2			1	3
Hong Kong		1			1
Australia	1	1			2
Brazil				2	2
New Zealand			1		1
Jamaica	1				1
Mexico		1			1
Thailand			1		1

Warning Letter

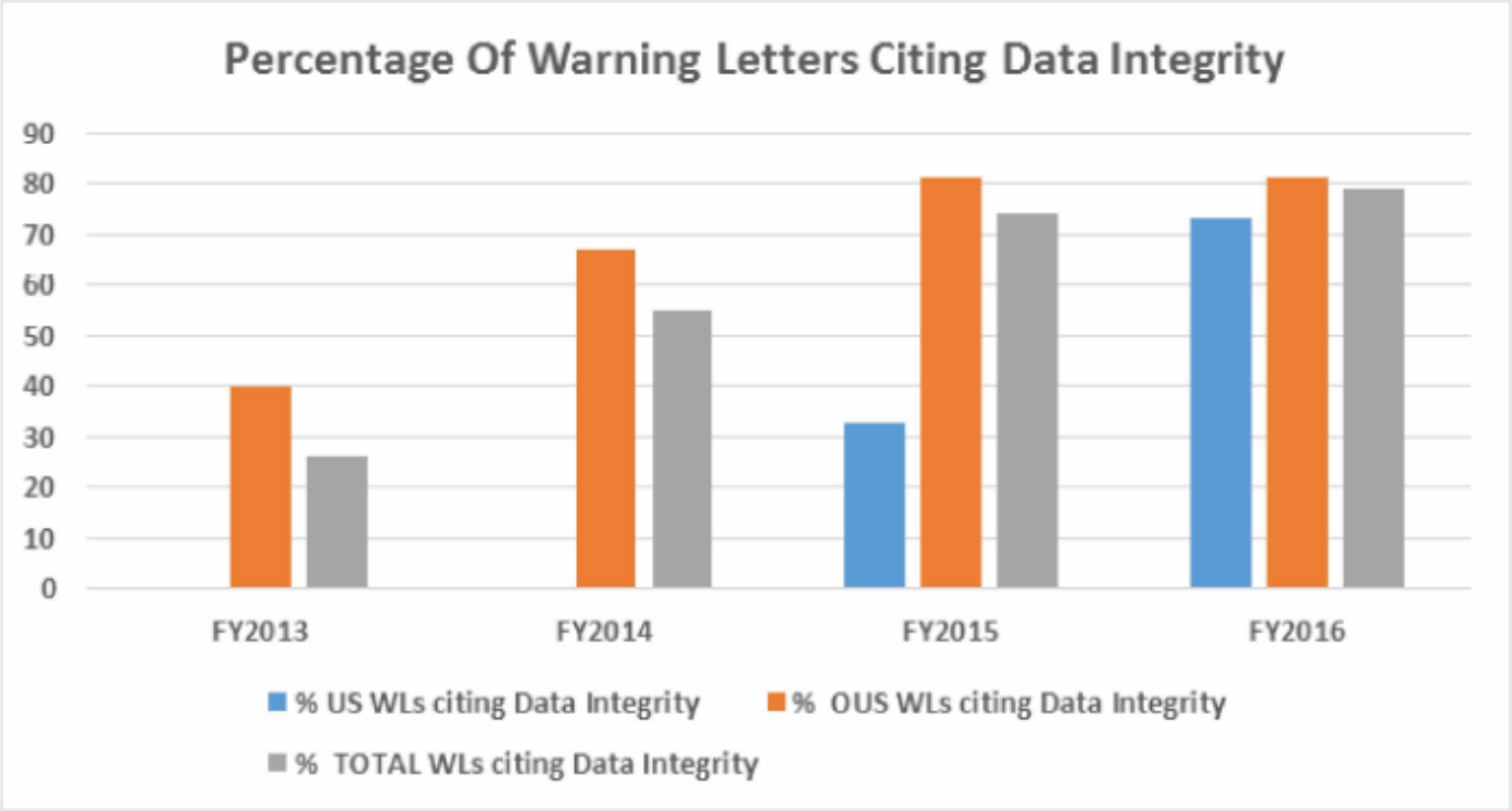


Warning Letter

Table 4: Warning Letters Citing Data Integrity Deficiencies (Excluding Compounding Pharmacies)

	FY2013	FY2014	FY2015	FY2016
Total warning letters	38	22	19	46
U.S. warning letter sites with data integrity citations	0 of 13 (0%)	0 of 4 (0%)	1 of 3 (33%)	8 of 11 (73%)
OUS sites with data integrity citations	10 of 25 (40%)	12 of 18 (67%)	13 of 16 (81%)	29 of 35 (81%)
Total number of warning letters citing data integrity	10 of 48 (26%)	12 of 22 (55%)	14 of 19 (74%)	37 of 46 (79%)

Warning Letter



Control of Microbiological Contamination 21 CFR 211.113(b)

- The FDA expect that the product bioburden be assessed and evaluated
- 211.113 Control of Microbiological Contamination
  - 21 CFR 211.113(b) provides for “appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed”. Such procedures shall include validation of all aseptic and sterilization processes.

Specified Microorganisms

- A “specified” microorganism has several elements that requires evaluation on a case by case basis for each drug manufacturer
- The primary meaning refers to microbial contaminants that, based on microbial species, number of microorganisms, dosage form, intended use, patient population and route of administration would adversely affect product safety
- Most “specified” microorganisms would pose a threat of patient infection or mortality

Infupharma, LLC Warning Letter (7/30/12)

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

Formatech Inc.
Warning Letter 2/10/11

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. §211.192]. For example,

   a) Your firm has routinely failed to thoroughly investigate and identify root causes when environmental monitoring data exceeds the action limit.

In your response, your firm states that you have hired a consultant to assess the environmental data and subsequently, repaired the facility.

Formatech Inc. Warning Letter 2/10/11 (con't)

- Your response, however, is inadequate because your firm failed to investigate adequacy of your disinfectant procedures, frequencies, and preparation as part of your investigation for environmental samples that exceeded action levels in the critical and supporting clean areas. For example, your firm's disinfection program included insufficient use of sporicidal agents. It is essential that environmental control is continually maintained throughout your aseptic processing facility.

Formatech Inc. Warning Letter 2/10/11 (con't)

- Furthermore, we evaluated your environmental data from 2008 to 2010 and are concerned with the lack of comprehensive investigations when mold and bacteria were identified in your aseptic filling facility that exceeded action levels. Your aseptic process relies on manual manipulations and interventions where personnel are in close proximity to open product, and poor environmental control poses a significant risk of contamination.

Dakota Labs
Warning Letter 3/17/11

- Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, as per 21 CFR 211.192. For example,
- a. You failed to investigate environmental monitoring data recorded in your aseptic processing suite, which failed to meet your established limits.
- Your response states that you have revised your environmental monitoring form to allow space for explanation when needed; however, your response is not adequate.

Dakota Labs

Warning Letter 3/17/11 (con't)

- You have not investigated the cause of the environmental monitoring results that exceeded the limits on your "Performance Qualification Data HVAC Validation" and "Routine Environmental Monitoring" worksheets, nor have you justified your assessment of the product impact caused by those excursions.

Sanofi Aventis Deutschland GmbH Warning Letter 2/11/11

2. Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during aseptic processing. [21 C.F.R. §211.42(c)]. For example,

b) Your environmental monitoring program does not give assurance that environmental contaminants are reliably detected. Your practice of collecting samples from the gloves of operators, from left and right hands on alternate days is unacceptable. In addition, your SOP fails to include instructions for the location and duration of samples collected in the critical aseptic processing area

Sanofi Aventis Deutschland GmbH Warning Letter 2/11/11 (con't)

- An adequate environmental monitoring program should be established by your firm. It should capture meaningful data and act as an early warning system to detect possible environmental contaminants that may impact the sterility of drug products manufactured at your facility that purport to be sterile.

Zyfine, Division of Cadilla (6/21/11) Warning Letter

1. Your firm's laboratory records fail to include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 C.F.R. § 211. 194].

For example,

a. Your microbiologists reported the MA 5 and MA 6 microbiological plates as "nil" while each plate contained one (1) colony forming unit (CFU).

Zyfine, Division of Cadilla (6/21/11) Warning Letter (con't)

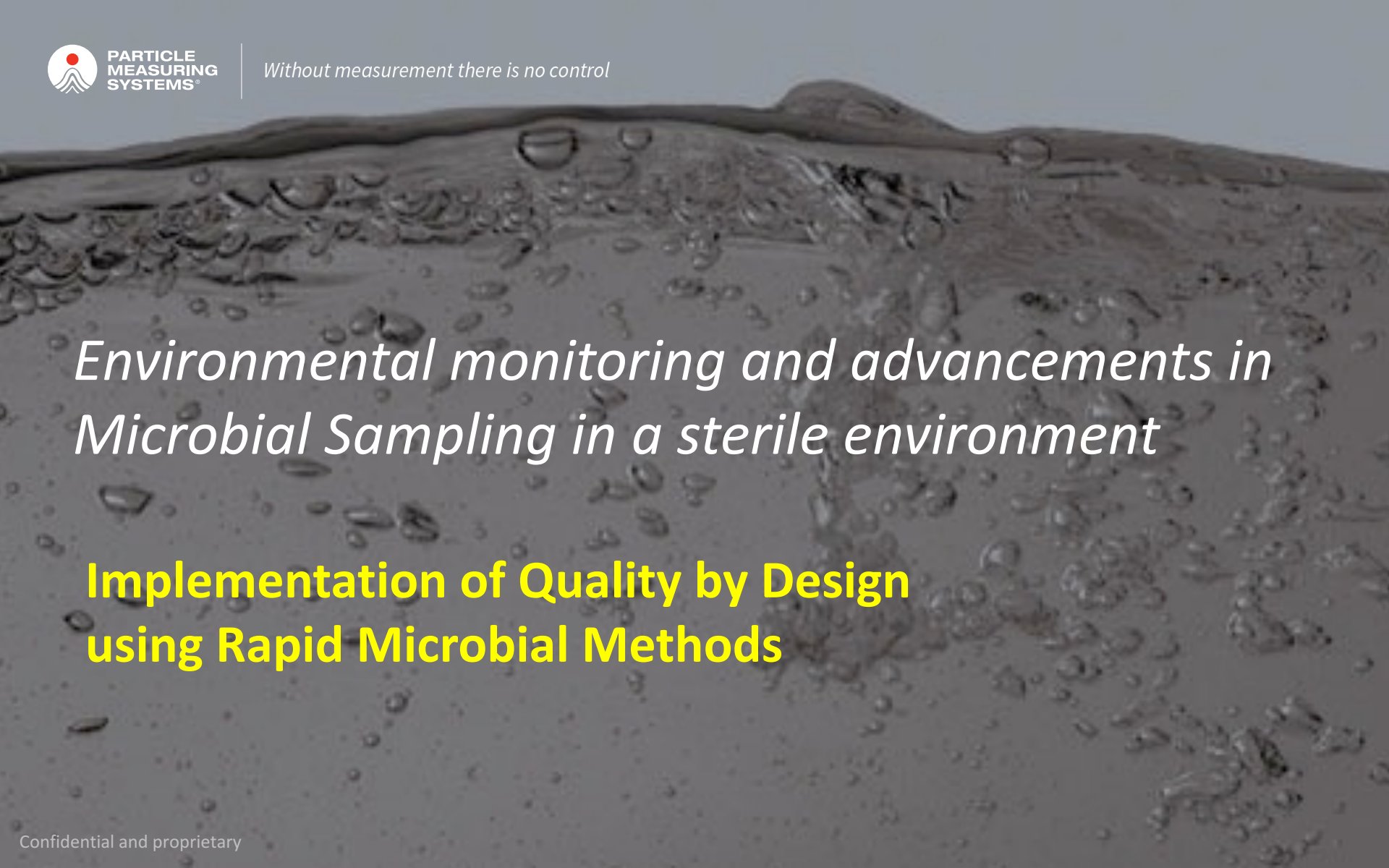
On January 21, 2011, the FDA investigator observed the microbiological plates, MA 5 and MA 6, from air sampling locations in the Class 100/Grade A laminar air flow cabinet in the Microbiology Lab. Each microbiological plate contained one (1) CFU/m^3. Your microbiologists reported these microbiological plates as "nil" on your form FM/QC/252-9 Quality Control Department Record of Environmental Monitoring of Microbiology Laboratory.

Zyfine, Division of Cadilla (6/21/11) Warning Letter (con't)

However, the action limit for these sample locations is 1 CFU/m^3 which requires an investigation per your procedure SOP/QC/049 entitled Environment Monitoring of Aseptic Area by Settle Plate, Air Sampling, Surface Sampling (RODAC Plate) and Personnel Hygiene for Viable Count. The results as originally reported on your form FM/QC/252-9 would not have prompted an investigation.

Sanofi Pasteur Toronto, Canada FDA 483 (April 2012) (con't)

- B. There have been no less than 58 deviations relating to the isolation of mold within the aseptic operations areas of Building -(b)(4)- (Grade -(b)(4)-) including, but not limited to, ----------(b)(4)---------- filling, and freeze drying since August 2010. The samples were isolated from operator gloves and gowns, viable air sampling, and surface sampling. There is a lack of assurance that if this mold were to have an adverse effect on product, it would be detected using the current sterility test method…..



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Environmental monitoring and advancements in Microbial Sampling in a sterile environment

Implementation of Quality by Design using Rapid Microbial Methods

Aseptic processes cleanrooms

1. Traditional cleanroom production

Presence/interaction of people in grade A. The production must be done under grade A and grade A must be installed with a grade B surrounding environment.

2. RABs open systems

Physical separation of people from grade A but grade A air exhausted in grade B. The RABs must be installed in grade B surrounding environment.

3. cRABs close systems

Physical separation of people from grade A and grade A air recirculation inside cRABs. The cRABs must be installed in grade B surrounding environment.

4. Isolator systems

Complete physical separation of people from grade A and grade A air recirculation inside isolator. The isolator can be installed in grade C environment.

Pharmaceutical microbiology

- It is no longer possible to release products or monitor the processes (especially aseptically filled sterile products) using microbiological methodologies/techniques developed in the 20th century.
- The use of outdated microbiological analytical methods allows the detection of 1/3 of the microorganisms present in the product/process.
  - Therefore, it is not possible to completely identify areas of contamination in the production processes.
- Strategies and implementation of more sensitive and/or more reliable microbiological analytical methodologies that allow the identification of potential production processes problems and their resolution should be a priority.
- Improved detection results in improvement and therefore the increasing of microbiological quality.

This increase in microbiological quality and sensitivity must coincide proportionately with production costs

Such a challenge can be met

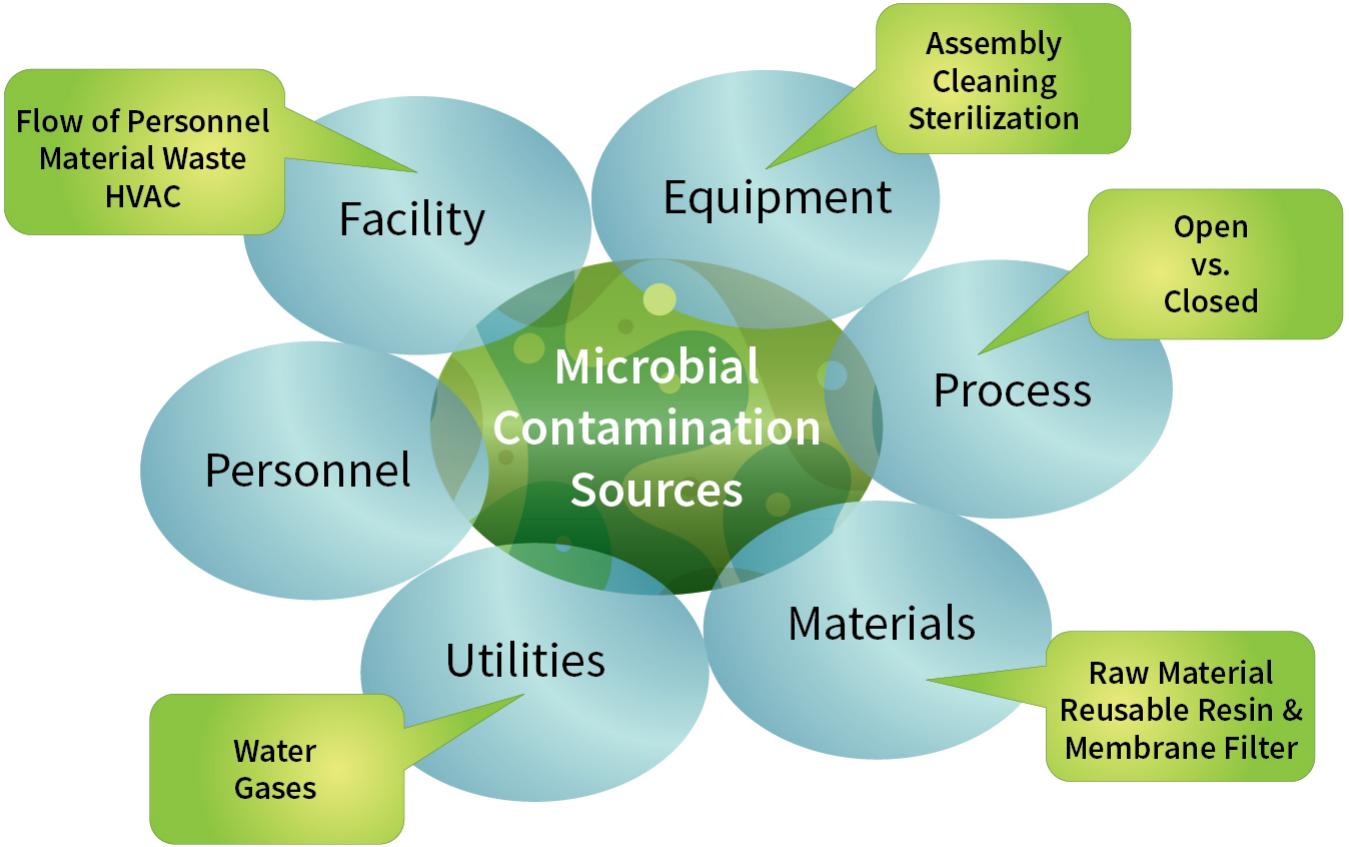
and

It is even probable to raise the microbiological quality with a significant reduction in production costs

How?

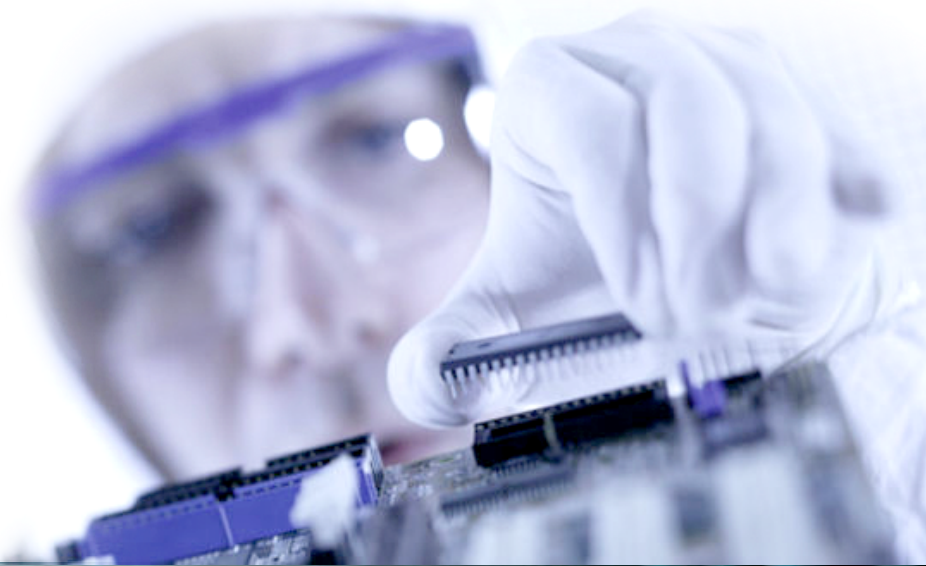
- Identify and calculate the costs of the so-called “poor quality”.
- Separate the operator from the aseptic process
  - There is a strong impact on the microbiological contamination caused by humans
  - There is a lack of difficultly in quantifying this impact caused by poor microbiological techniques/methods
- Increase Aseptic Processes Understanding and QbD
  - Regulatory authorities are leaning towards the introduction of RABS (Restricted Access Barrier Systems) or the use isolators systems.
  - I.e. Cooling zone of decontamination tunnel (grade A) not microbiologically monitored
- Introduction of new/alternative microbiological monitoring technologies

Microbial Contamination



Environmental Monitoring Systems

1. Important part of aseptic processing of sterile pharmaceuticals.
2. Process capable of controlling the presence, distribution, and survival of microorganisms.
3. Critical Areas
   - Process Waters (Deionized, RO and WFI)
   - Air/Compressed gases
   - Surface (included Personnel, Gloves and Equipments).



Limits of current controls

Because current microbiological methods are….

- Potential bottlenecks to product release
- Cannot deliver real-time results

there is a

- Reduced incentive to invest in real time chemical controls when finished products cannot be released

and consequently

- Current microbial controls represent a barrier to process understanding

FDA Initiatives - Innovation

In the beginning in 2002, the FDA recognized the need for the pharma industry to be more innovative. Therefore, it launched:

- A Critical Path Initiative
- Pharmaceutical Quality for the 21st Century – A Risk Based Approach
- Quality by Design (QbD)
- Process Analytical Technology (PAT)

The Goal of all is to modernize and improve the quality of pharmaceutical manufacturing processes – encourage industry to implement risk-based, continuous, real time quality assurance

How can we move forward?

- Look for different technologies
- Select the most suitable technologies for the purpose
- Define an appropriate strategy
- Follow the QbD approach

Improvements must encompass all areas of the process to achieve maximum benefits.

Desired attributes for a measuring system

- Sensitivity at single cell level
- Discrimination between viable and non viable microorganisms
- Able to detect viable microorganism but not culturable
- Rapid: as fast as possible (days vs. hours vs. minutes)
- Qualitative and quantitative capabilities
- Able to identify in case of contamination
- Cheap
- Easy to use and validate
- Robust
- Usable in the manufacturing environment

Products and processes define the technology

- Product and process requirements are paramount
- The technology must satisfy the product requirements and specifications
- Different technologies offer different attributes
- Understanding the process and product will dictate the best technology solution (risk analysis)
- Different technologies will have different implementation requirements

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Types of air monitoring – active and passive ……..towards innovation

Passive Monitoring

- Settling Plates (method without value for grade A/ISO5)

Active Monitoring

- Slit-to-Agar (STA) Air Sampler (Air through narrow slit, rotational agar plate)
- Sieve Impactors (Air through a perforated plate/s)
- Centrifugal Propeller Sampler (Agar coated strip)
- Filtration (Polycarbonate, cellulose acetate, gelatin filters)
- Impingers (use of liquid medium for particle collection)
- Real Time Laser-Induced Fluorescence Systems

Settling / fall-out plate

Advantages

- Ease of use
- Economical
- Small size allows for easy placement
- Can be useful in isolator systems
- No testing equipment required
- Continuous testing over a long period of time
- No electrical or vacuum source required

Disadvantages

- Minimum/maximum exposure time must be validated
- Results not correlated with air volume
- Many variables are associated with recovery rates such as temperature, humidity, air direction, and velocity
- Not validated as a method and not validatable

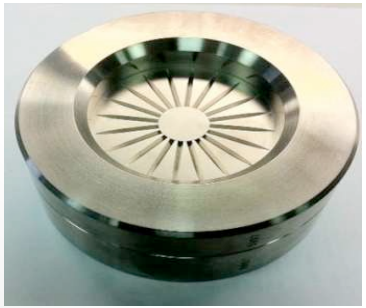
Viable active air monitoring

- Methods for sampling air in production areas for microbial content
- Samples a defined volume of air with units in cubic feet, cubic meters or liters
- Results defined as CFU/Volume of air
- Samples represent overall filling operations
- Required by all Regulatory Agencies
- Validated according ISO 14698
- Exhaust air HEPA filtered if used in ISO 5 environment

Microbial Sieve Impactors - Remote & Mobile

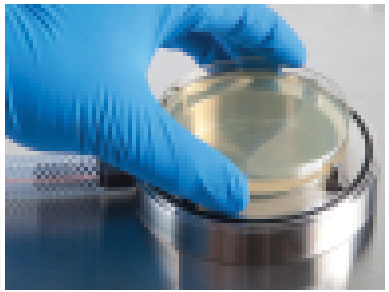
- Air is drawn through slits in the sampling head using an internal vacuum pump.
- The organisms are impacted on a 100 mm agar surface in the pattern on the sampling head.
- 25, 50, and 100 LPM units

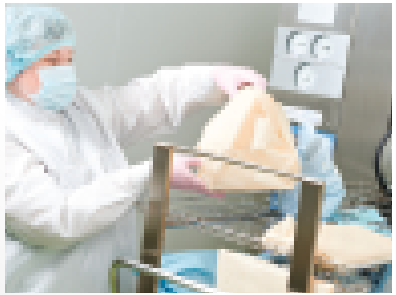
Disadvantages Using a Stainless Steel Sampling Head



Manipulations and Risk of False Positives

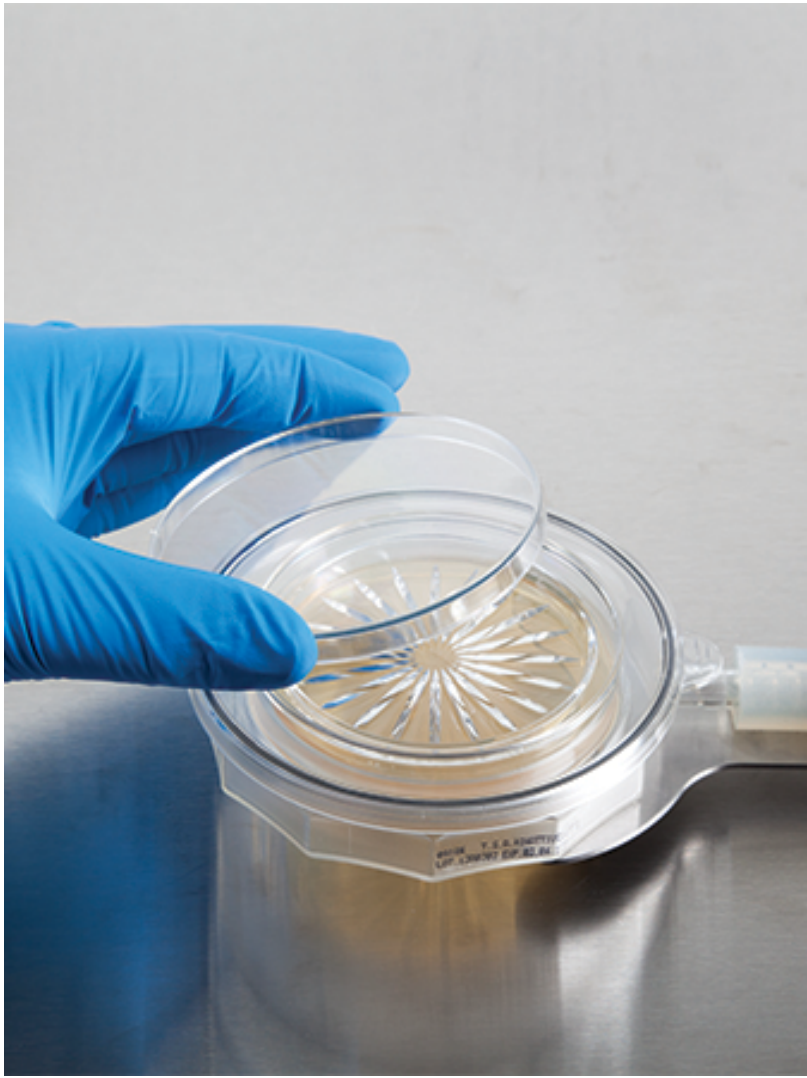
- Risk of microbial contamination during the manipulation by the operator.
- Disinfection between uses
- Sterilization of sampling head is time consuming
- Only max. 40 minutes sampling at 25 lpm





Solution: Single Use

- Minimizes media exposure
- Prevents direct operator contact with the media plate
- Reduces risk of contamination by improper handling
- Eliminates the need for traditional air sampler sterilization
- 2 hr. sampling in continuous at 25 LPM



Real-time air monitoring

- This system is based on laser-induced cell fluorescence
- Gives a quantitative result
- Viable organisms will fluoresce due to presence of NADH, riboflavin or dipicolinic acid in the cells
- Inert particles will not fluoresce
- Usually used in conjunction with active air monitoring
- Monitoring is continuous
  - In operations
  - At rest

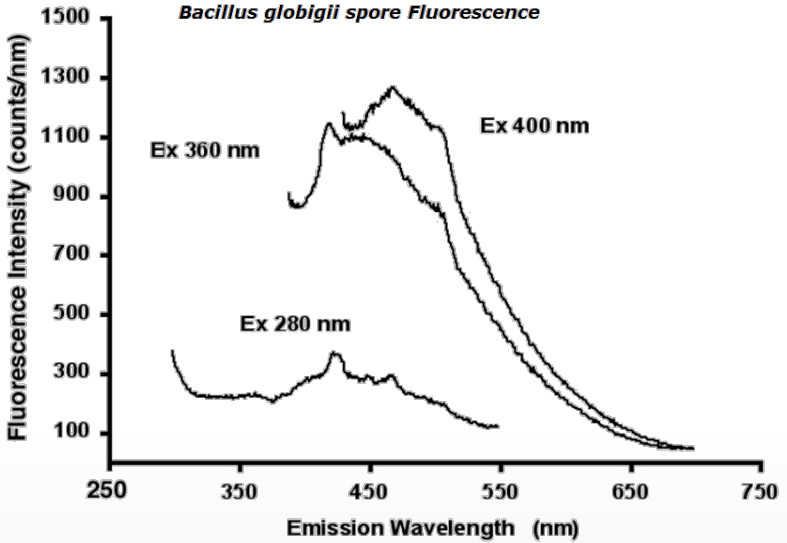
Real-time monitoring: Coenzymes

Many are derived from vitamins:

1. Niacin
   - NADH (Nicotinamide adenine dinucleotide)
2. Dipicolinic acid (spore wall)

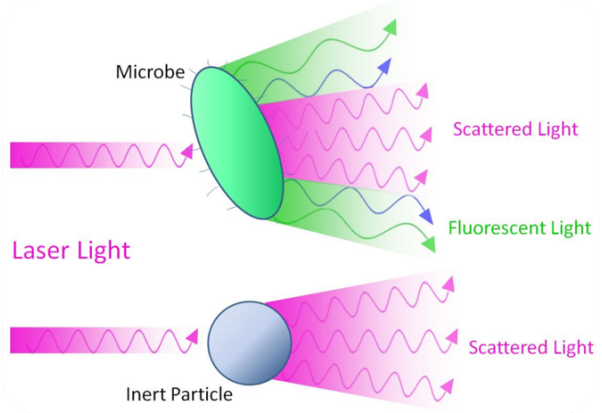
Cell Fluorescence

- NADH has a fluorescence of 460 nm when excited at 405 nm
- This fluorescence is a clear indicator of cell activity and is directly associated with “living” cells, i.e. those metabolizing.
- Other cell components also exhibit a fluorescent emission:
  - Riboflavin
  - Dipicolinic Acid (spores)



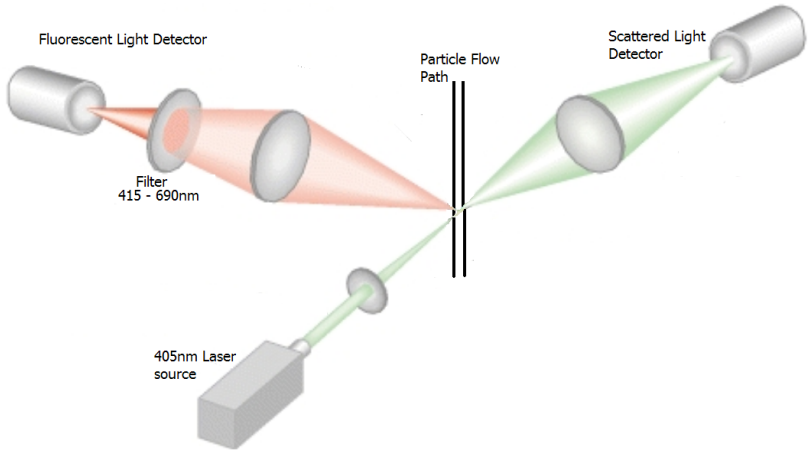
Real-time laser induced fluorescence technology

- Laser Induced Fluorescence (LIF) utilizes a high intensity light source, e.g., **~405 nm laser**, to induce light scatter and fluorescence resulting in real time detection of both inert particles and biologics like bacteria, yeasts, molds
- Fluorescence is derived from internal fluorophores (NADH, riboflavin, DPA) of microbes
- Detects and characterizes particles in the 0.5 to 50 micron range



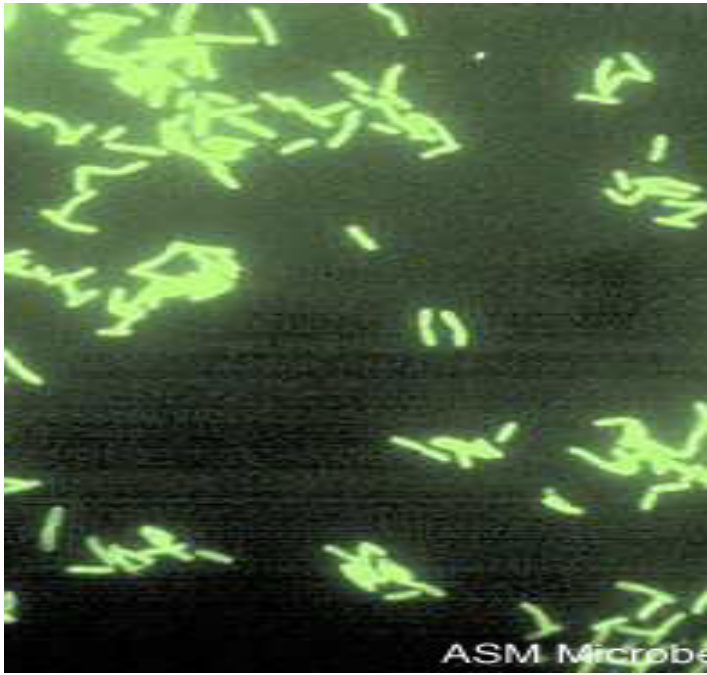
Optical Fundamentals

- The sample is pulled through the optical chamber and illuminated by the laser source.
- Elastic light scatter occurs when a particle enters a laser beam.
- The trigger from the elastic light scatter activates the fluorescence algorithm to detect any fluorescence from that particle at a wavelength shift.
- Filters ensure the active component of fluorescence is detected and the scattered light does not interfere with the signal.



Solution: 405 nm laser technology

- 405 nm laser light illuminates sample air flow through the sensor
- All particles, viable and nonviable, scatter light
- NADH (nicotinamide adenine dinucleotide), Riboflavin and Dipicolinic Acid in biological particles will fluoresce
- The laser simultaneously detects both scattered light and fluorescence:
  - Non-Biological particles scatter light and do not culture
  - Biological particles scatter light, fluoresce and culture
  - VBNC (viable but not culturable) particles scatter light, fluoresce and do not culture
- 1 fluorescent particle represents 1 Bio-Count



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Types of Surface monitoring…….. ……..towards innovation

Surface Monitoring (included garments and gloves)

Standard Methods

- Rodac/Contact plates
- Swabs

Issues with standard methods

- Long incubation times
- Continuous manipulation
- Time-consuming procedures
- Low sensitivity (sampling and measuring)
- Results within 6–8 days

Solution: Rapid Swab approach

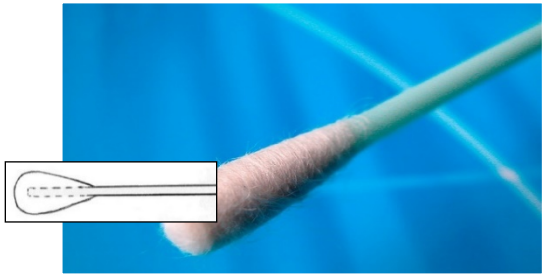
Swab solution for microbial monitoring of :

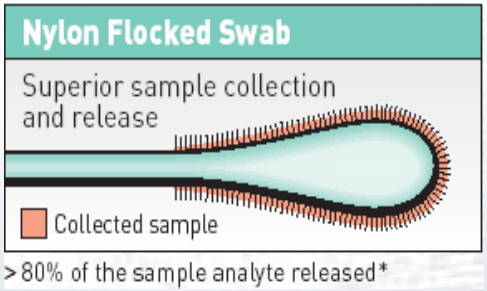
- Surfaces (even and uneven)
- Personnel garments
- Personnel gloves
- Equipment

Technology can detect microbial contamination based on measurements of oxygen depletion over time of incubation in a pharmacopoeial liquid broth, such as TSB. Non-destructive testing. The sample is available and intact for any further identification steps if required (if ID microbial species).

Rapid Swab approach: technology introduction

- Traditional fiber winded swabs trap the sample in the excessive fiber matrix and release maybe 20-22%. Only vigorous extraction will improve the release.
- Flocked swabs release more than 90% of the sample they absorbed. The thin layer of flocked fiber is highly absorbent as the perpendicular fibers display a strong hydraulic capillary action. The flocked device absorbs more sample very fast and holds the liquid close to the surface allowing easier elution.

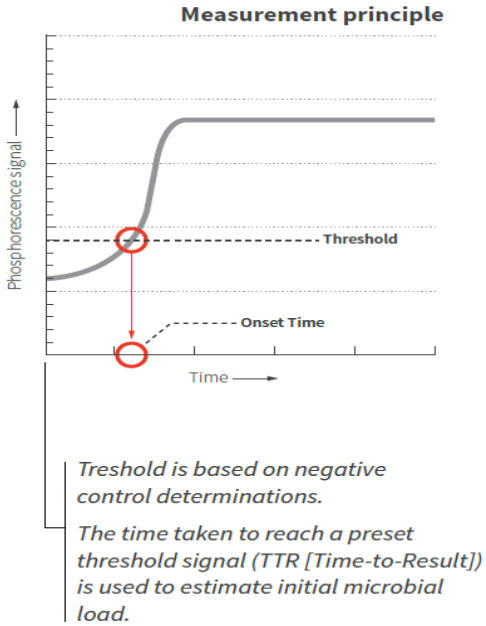




Rapid Swab approach: technology introduction

Basic principles of O_2 sensing:

- Fluorescent O_2 sensitive probe in each vial.
- O_2 causes a reversible decrease in phosphorescent signal.
- Respiration:
  $\downarrow O_2 = \uparrow$ Phosphorescent Signal.

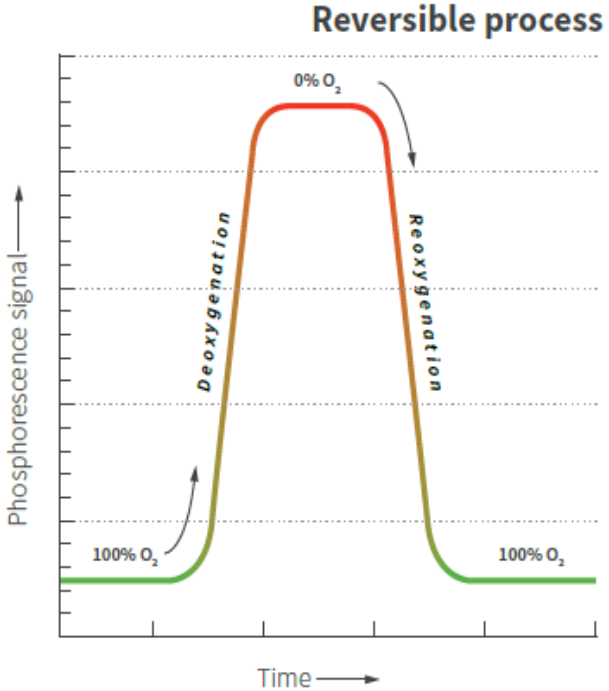


Treshold is based on negative control determinations.

The time taken to reach a preset threshold signal (TTR [Time-to-Result]) is used to estimate initial microbial load.

How O_2 sensing works

- The measure of the bacterial O_2 consumption is then equates to microbial load.
- As bacteria growth in a sample (into a vial) and consume dissolved O_2 , the polymer sensor attached to inside vial bottom, reacts to the O_2 depletion.
- The greater the initial microbial load the faster the time to result.



Y. Will, Hynes J. et al. - Nature Protocols, 2007, 1: 2563-2572.

Economical benefits of environmental surface monitoring

- Early evaluation of the surface, personnel and additional critical points of the aseptic manufacturing area and minimization of corrective action time
- Effect on product release
- Enhanced efficiency and productivity: labor and time
- Increased assay sensitivity
- Improved reproducibility
- Overall cost reduction after capital investment
- Data Integrity

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Final considerations

- Different sampling tools and measuring systems will offer flexibility in the application of the appropriate technology for each sampling point
- Specific methods will be registered for monitoring critical quality parameters and critical process parameters
- In the medium-long term, gained experience could form the basis for the Real Time Release (RTR) of drug products manufactured under conventional aseptic process with removal of sterility test
- Control verification needs to be defined in the overall strategy for RTR

My Board of Directors Say “Thank You”

Questions?

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