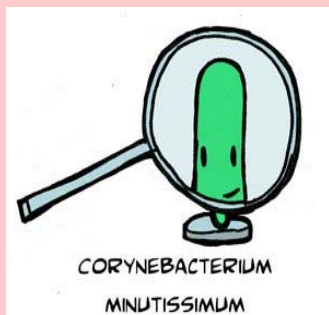




Environmental Monitoring: A New Look at an Old Topic

Jeanne Moldenhauer
Excellent Pharma Consulting

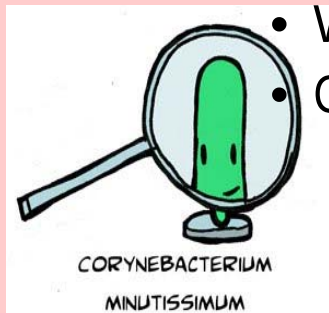


(c) Jeanne Moldenhauer 2008



Regulatory Interest

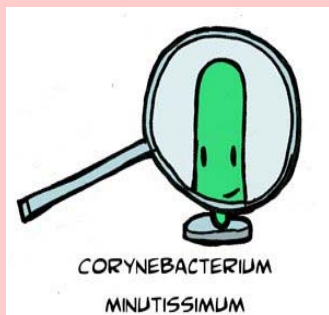
- EM has been a topic of increased interest by regulators since the early 1990's
- Highlighted in regulatory documents and inspection findings reports
 - ISO 14644-1
 - EU Annex 1 revised 2008
 - FDA's Aseptic Guidance 2004
 - Japanese Aseptic Guidance 2005
 - WHO 823
 - Compendial Requirements





Global Business

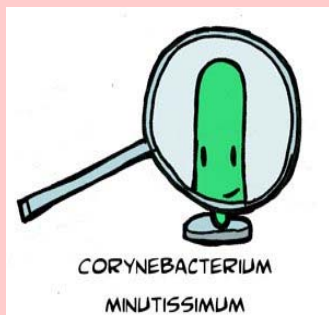
- Which regulations do I have to follow?
- How do I piece the requirements together to develop a cohesive program?
- How do I keep current on the changes to these requirements?





ISO 14644-1

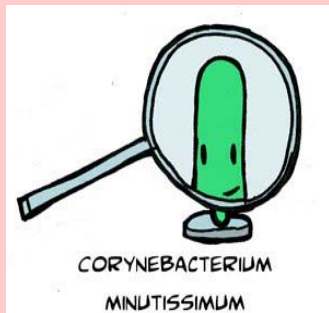
- Provides requirements for viables and non-viables
- While accepted by regulators, many companies have not standardized to these classifications
- Based upon area classifications





EU Annex 1 Revised 2008

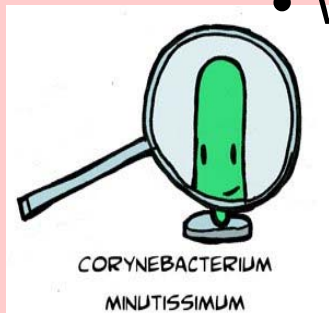
- Specifies requirements for microbial and particulate counts based upon room classification
- Limits kept for 5 μm particles, in spite of industry comments and proposals to remove requirements





FDA's Aseptic Guidance – September 2004

- Most detailed regulatory listing of environmental monitoring requirements
 - Includes requirements for SOPs
 - Philosophical Approach expected
 - Why did you use specific equipment
 - How did you set the limits
 - When do you test



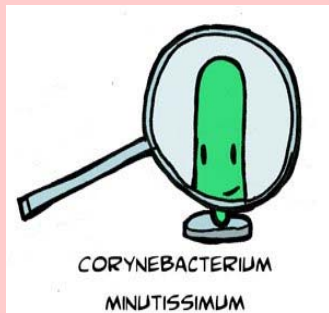
Validation
Trending

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FDA's Aseptic Guidance - 2004

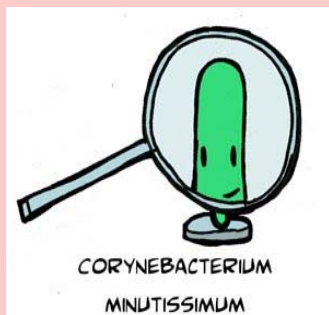
- While it is known that testing needs to be done at static conditions, limits are for dynamic conditions.





Japanese Aseptic Guidance 2005

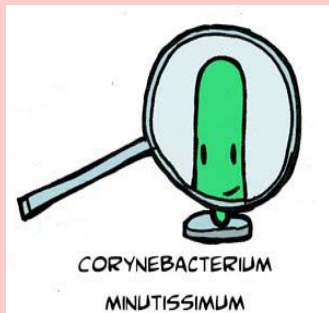
- Similar to USA Guidance, but with less detail for the program and SOPs required
- Tables of requirements for both static and dynamic testing





WHO 823/923 TR2

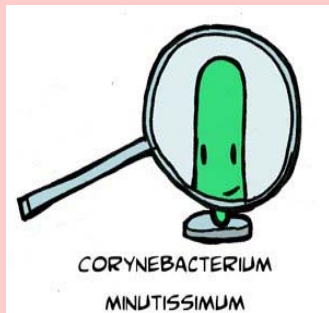
- Requirements for Environmental Monitoring and Control
- Primarily related to air flows and non-viable particulates
- Includes some specific types of tests and parameters to meet





Compendial Requirements

- USP <1116> Requirements for Cleanrooms
- JP § 8 Requirements both for at rest and dynamic conditions

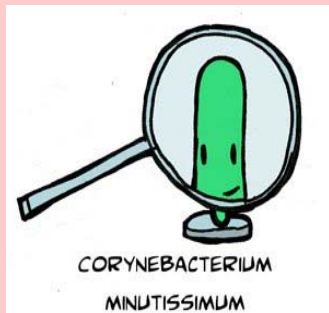




Warning Letters

- Across product types
 - Sterile
 - Non-Sterile
- Tend to apply similar requirements to aseptic
 - Lack of appropriate control programs
 - No trending
 - Limits not justified

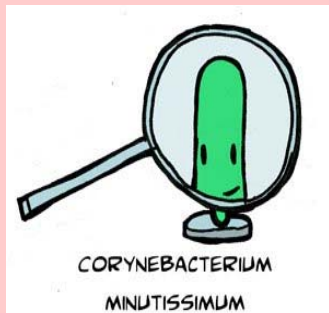
Etc.





What's Required?

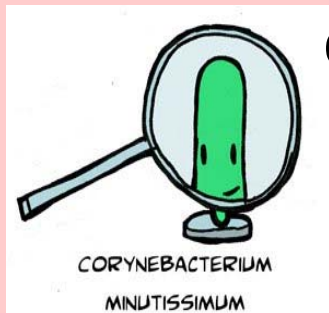
- General written program
 - Well defined, scientifically sound
 - All shifts,
 - Air, surfaces and personnel monitoring
 - List locations to be sampled
 - Sample timing, frequency, location included in program





What's Required?

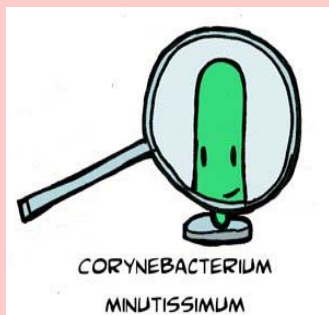
- General written program
 - Take samples throughout the **classified areas of aseptic facility**
 - Scientifically sound, sampling procedures, standards and limits
 - Sample sizes optimize detection of contaminants





What's Required?

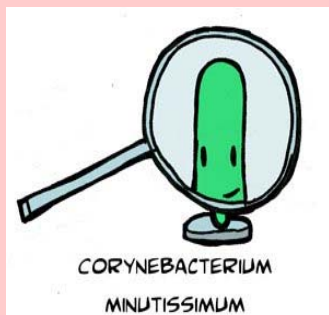
- Locations based upon microbiological risk assessment
- Critical surfaces should be sterile
- Air and surface samples to be taken at the actual working site and locations where significant activities take place, e.g., door handles, etc.





What's Required?

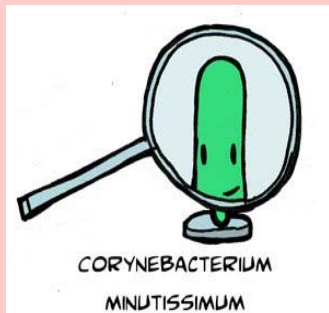
- Contamination on a critical site should not necessarily result in batch rejection
- Adverse trends are more than just consecutive counts, due to potential for false negatives





What's Required?

- Remedial actions to unfavorable trends
- Exceeding in absence of adverse trend, single exceeded action level should trigger investigation
- SOPs include:
 - frequency of sampling
 - Location
 - when samples are taken
 - duration of sampling
 - sample size
 - specific equipment used
 - alert and action levels and responses to deviations

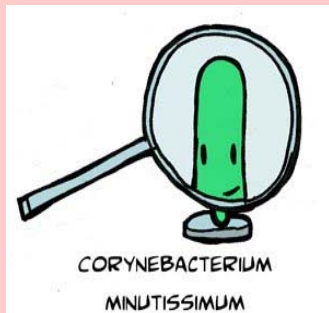


(c) Jeanne Moldenhauer 2008



What's Required?

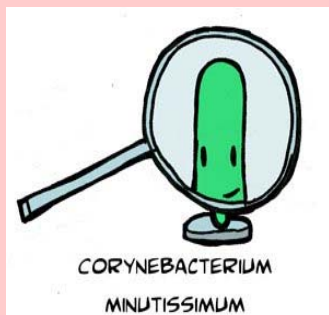
- Environmental Monitoring – Establishing a Trending Program
 - Detailed procedures for review of results, frequency of review, identification of contaminants, actions to be taken, routine QC oversight, daily, weekly, monthly, quarterly and long term trends





What's Required?

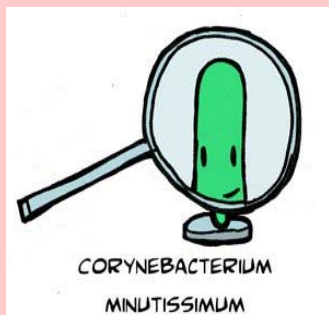
- Environmental Monitoring – Establishing a Trending Program
 - Reports generated by location, shift, lot, room, operator, or other parameters, ability to find an isolate throughout facility, etc.
 - Changes in microbial flora
 - Procedures to involve management, and inform them of trends





What's Required?

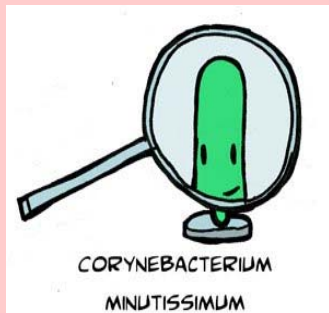
- Monitoring Methods
 - Surfaces: product contact surfaces, floors, walls, ceilings and equipment
 - Air: active and passive methods (active air samplers) Assess suitability of system chosen





What's Required?

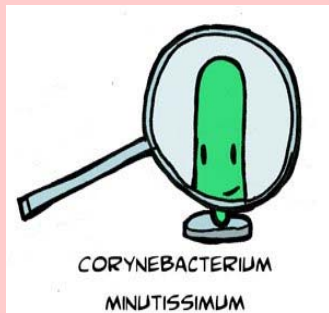
- Monitoring Methods
 - Evaluate media for passive air samples for exposure time/drying and growth promotion





What's Required?

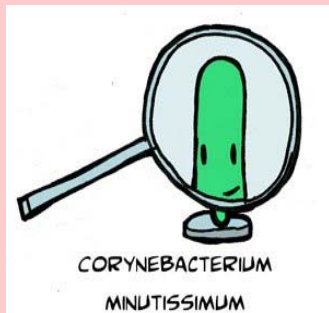
- Particulate Monitoring
 - Investigate in accordance with severity of excursion
 - Basis concept is that this directly correlates to potential product contamination





What's Required?

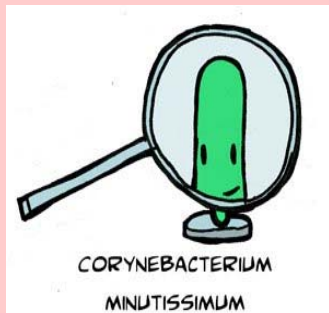
- Particulate Monitoring
 - Provides no guidance for continuous monitoring systems and the potential for excursions during cleaning, etc.





PDA Task Force Formed

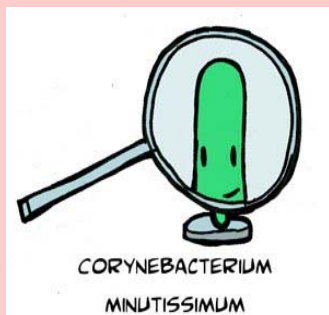
- Due to numerous regulatory changes
 - Set up task force
 - Implement changes from regulatory documents into the TR 13 (rev 1)
 - Represents companies across the world
 - Incorporates international requirements





PDA Task Force Formed

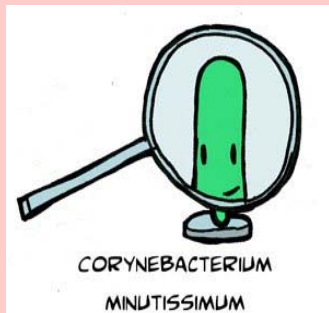
- Updated the document
- New features:
 - Represents updated regulatory documents
 - More emphasis on risk assessment
 - Represents the new sciences and technologies being used, e.g., both growth and viability based





PDA Task Force Formed

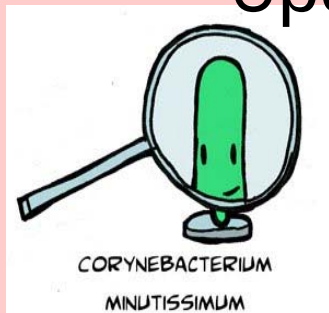
- New Features
 - Replaced details descriptions for each type of sampler with sampler names and associated website addresses
 - Updated the validation requirements for the support systems, like utilities
 - Where new PDA technical reports have similar information, referenced the new tech reports





PDA Task Force Formed

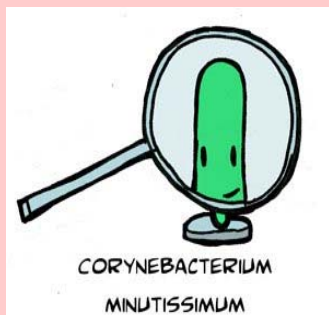
- New Features
 - Adds information on analytical method variability
 - Describes the scientific basis for variability
 - Cites literature that describes the actual variability present by type of test
 - Updated bibliography





PDA Task Force Formed

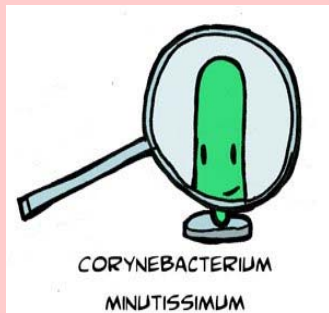
- The document is “first draft finished”
 - After “re-writing” of technical writer, comments are being addressed by the task force
 - Then eventually to SAB for review/approval, hopefully before the end of this year





What's New in EM?

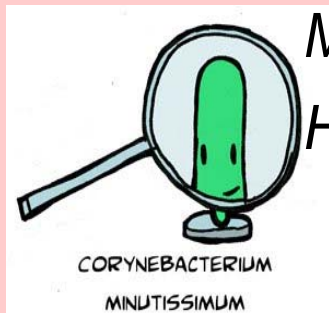
- Ways of doing business
 - Utilization of global best practices to reduce deviations and excursions
 - Alcon Presentation – Joe Lasich (PDA Annual 2008)
 - Evaluated practices at various sites
 - Determined the best practices
 - Implemented across sites
 - Saw a significant reduction in deviations and excursions





What's New in EM?

- Ways of doing business
 - Hazard Analysis and Critical Control Points (HACCP)
 - More focus on doing this analysis for environmental monitoring
 - Discussed in detail in a Book Chapter by Dilip Ashtekar (Amgen), in *Environmental*



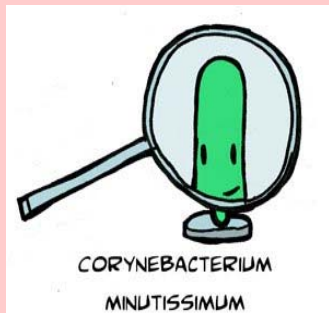
Monitoring: A Comprehensive Handbook

(c) Jeanne Moldenhauer 2008



What's New in EM?

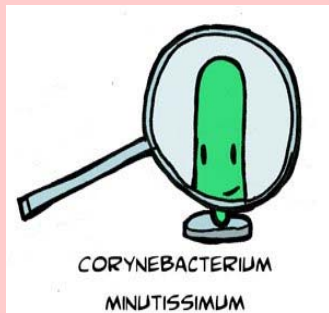
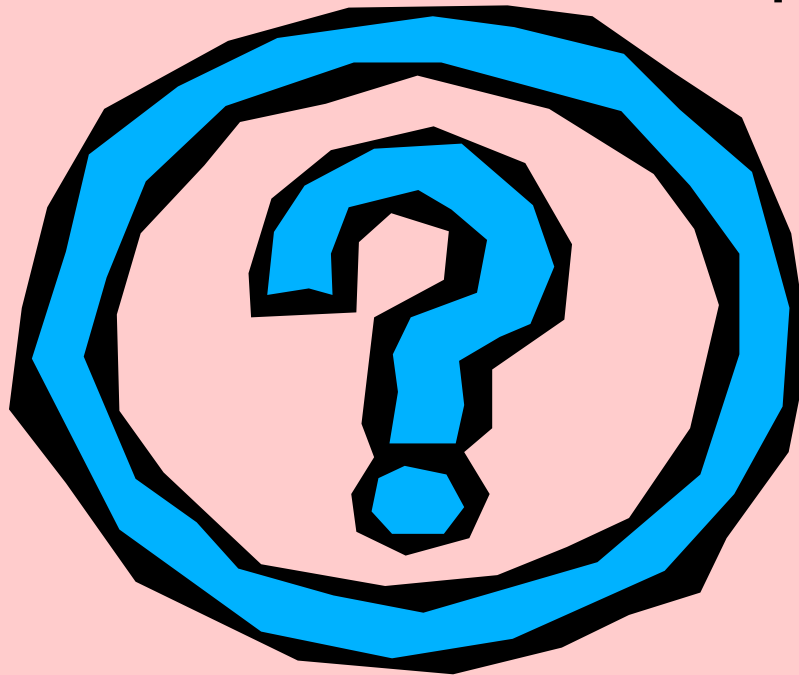
- Ways of doing business
 - Risk Analysis Methods
 - Grid Profiling is not enough
 - Sample site selection should be based upon risk assessment
 - Other risks should be incorporated into the program
 - More intensive manipulations
 - More interventions
 - increased monitoring expected





Dilemma

- At what level does environmental contamination result in unsafe product?

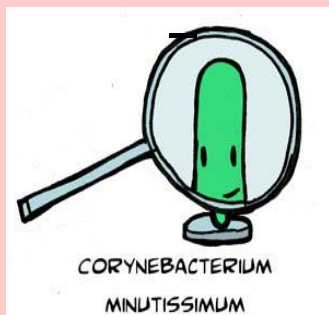


(c) Jeanne Moldenhauer 2008



The Unanswered Question

- This problem is not currently resolved.
- PDA-TRI data for media fills
 - Contamination doesn't guarantee you will see it in the final product
 - Gowning, or lack thereof, doesn't result in always affecting product

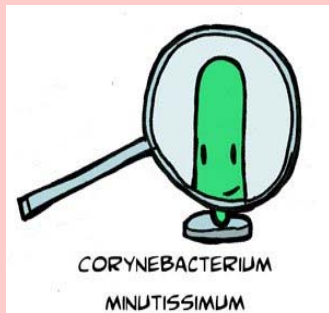


We still don't understand all that causes product contamination



What's New in EM?

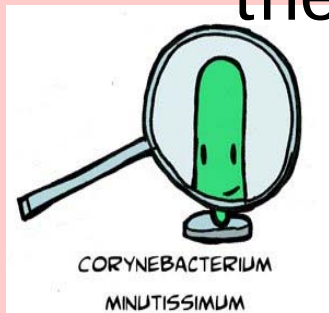
- New or Modified Technologies
 - Most of these slides are courtesy of the equipment vendors





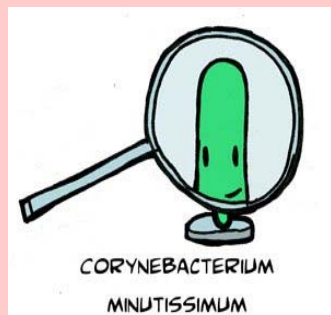
Automated Traditional Methods

- Growth Direct™
 - Rapid Micro Biosystems
 - Not a true alternative method, as only the incubation/detection times have changed
 - Traditional methods with automated computer imaging to enumerate growth in $\frac{1}{2}$ the time of a traditional test





Growth Direct™

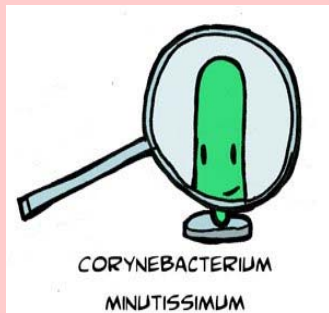


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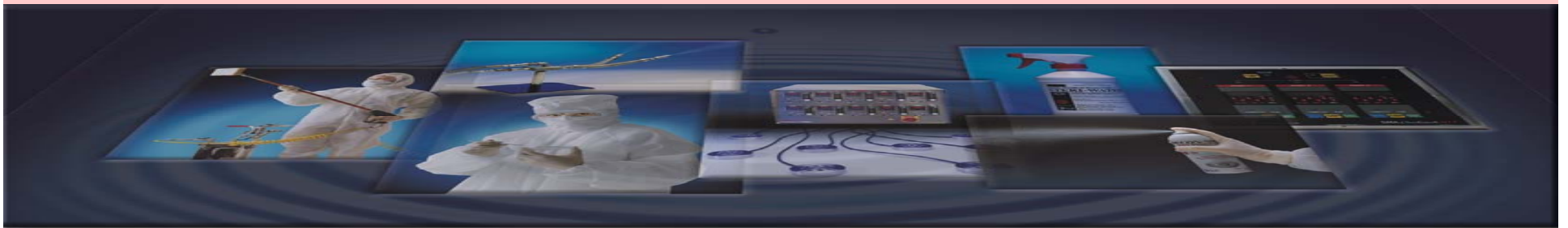
Growth Direct™

- Can be used for: airborne organisms, **surface** monitoring, and personnel monitoring
- Non-destructive testing
- Isolates available for identification testing





Future of Airborne Sampling



Art Vellutato, Jr.

V.P. Technical Support Operations

Veltek Associates, Inc.

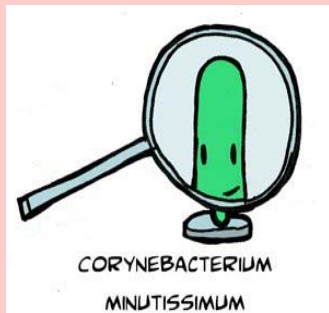
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Present Day Viable Sampling

- Method One: A sample is taken conventionally via a microbial air sampler SMA, STA, RCS, etc to a nutrient media plate, cultured and enumerated and then an ID performed if necessary. This is done via stationary, portable or installed fixed facility monitoring systems.
- Method Two: A sample is taken via a rapid method technology and the results enumerated and then an ID performed if possible or necessary.

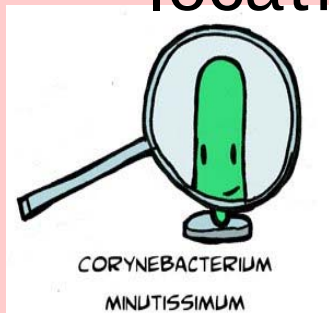


(c) Jeanne Moldenhauer 2008



Present Day Non-Viable Sampling

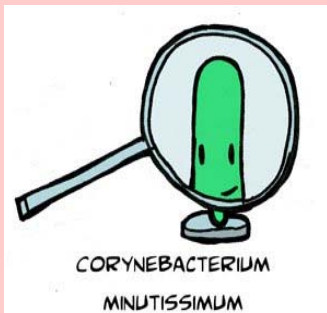
- Method One: A portable or stationary sampler is located at the point of sample and sampling conducted. Results are recorded either on paper (tape), downloaded routinely or downloaded directly from the device.
- Method Two: Centralized sampling systems routinely monitor air from installed fixed locations throughout the facility.





New Patented Technology

- Veltek Associates, Inc. has developed and patented through 14 different applied for (11 approved so far) and approved patents the ability to combine a majority of the functions.

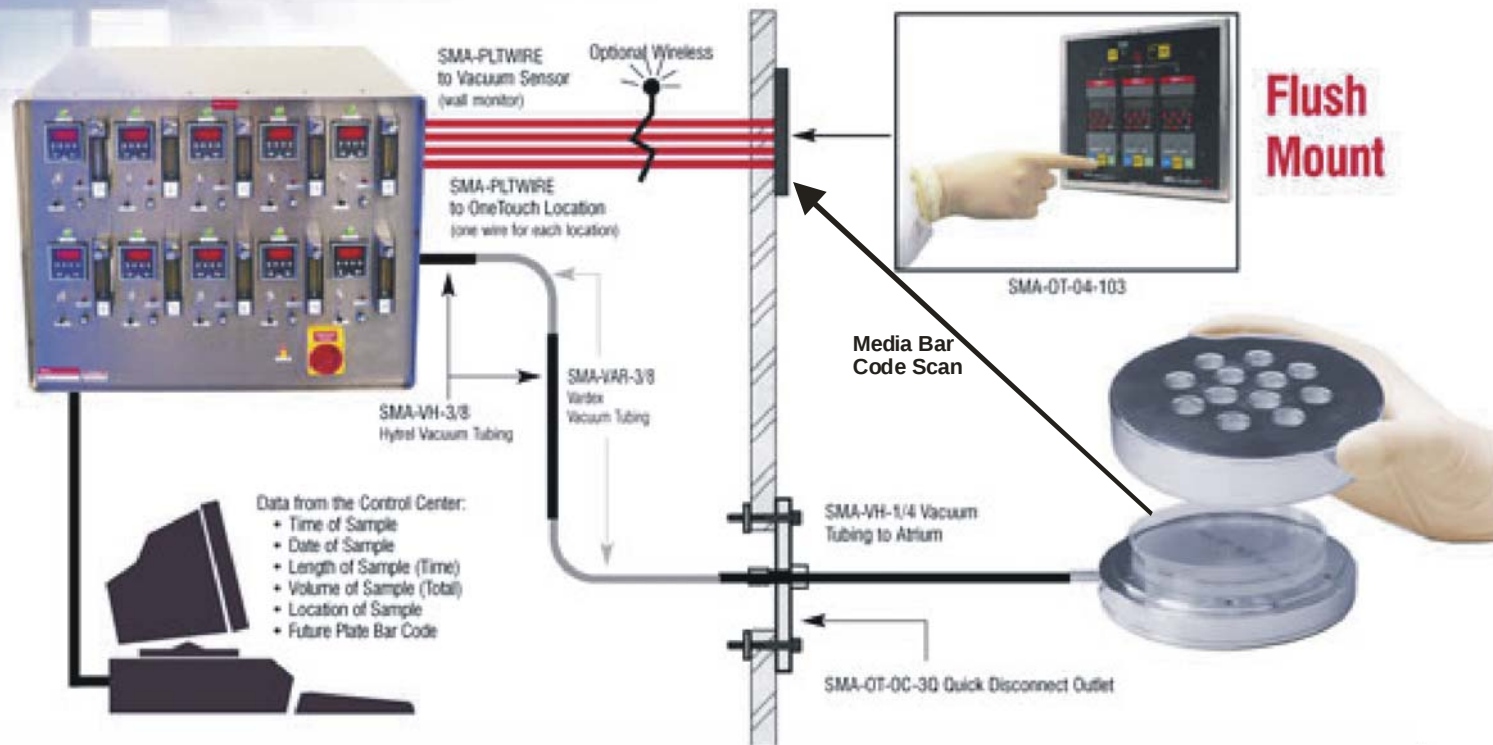




What is the Base Technology?

SMA ONETOUCH™ COMMAND SYSTEM

MICROBIAL AIR SAMPLING SYSTEM





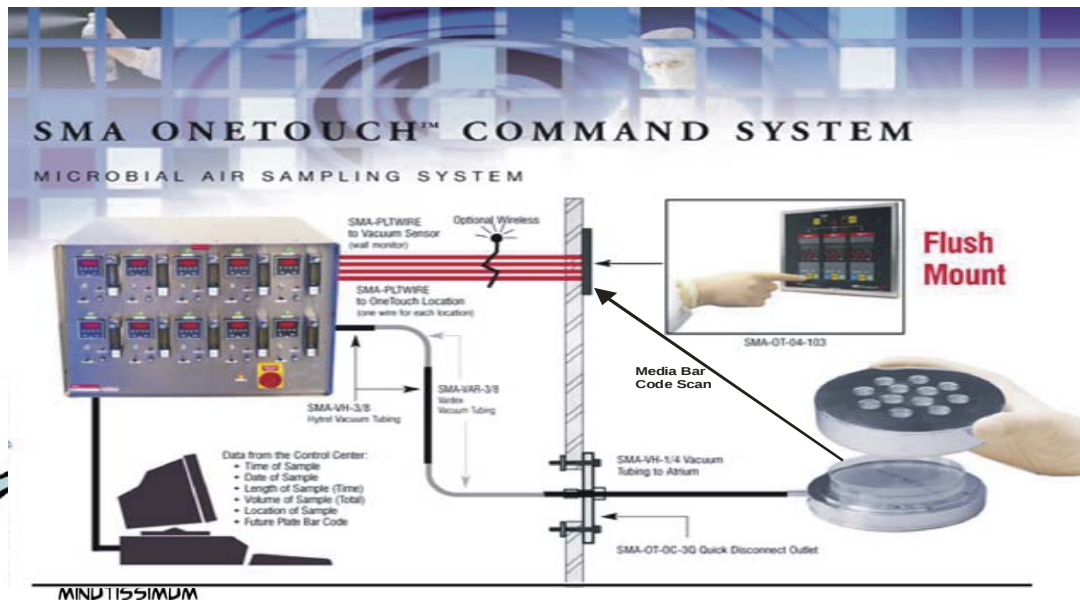
What is the System Technology?

SMA Atrium is replaced with The SMA Plus 200.



SMA Plus 200 is a:

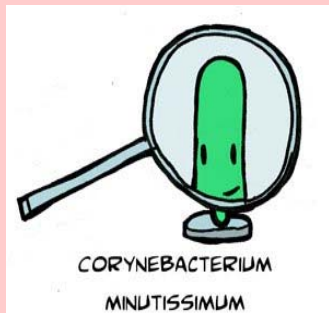
- Particle counter
 - Disposable micro sampler (via laser counting at 0.1 um)
 - Disposable rapid methods collection vehicle (via disposable phosphate buffer cartridge or Genomic Profile Cassettes)
4. Most Rapid Method Technologies can use the collection
 5. Particulate and Microbials are evaluated in the same volume of air and all data sent electronically to the same data system.
 6. Wireless data is sent from the SMA Plus 200 to the CC interface unit and then to the software package.





SMA Plus 200

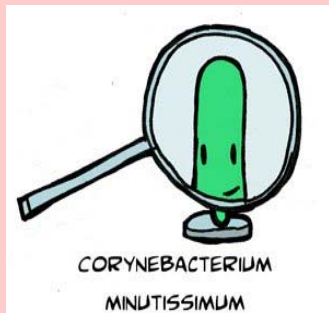
- Measures particles and viable cells (growth based)
- Allows for use with Growth Direct™
- Allows for use with viability based technologies – via liquid culture





IMD-A

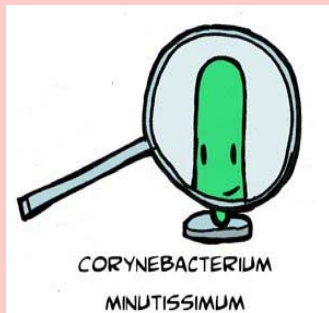
- Manufactured by BioVigilant, Inc.
- Developed as part of DOD grant for bioterrorism
- Consortium of about 15 companies evaluating the system





IMD-A

- Two basic models
 - IMD 200-1 viables, non-viables, not for use in clean rooms
 - IMD 220-4 viables, non-viables, for use in clean rooms (includes a concentrator for 1m³ of air sample)

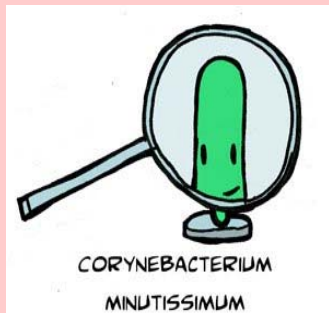




IMD-A

- Looks like a particle counter probe, and can enumerate both non-viables and viables
- Does not capture the microorganism (destructive test)
- Reviewed extensively with FDA
- True PAT application (in-line, real time)

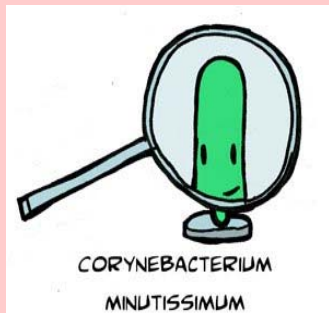
Validation has not yet been conducted





Surface Sampling ScanRDI

- Method developed by GSK
- Uses flocked swabs with ScanRDI, to get results for viable microorganisms present
- Takes about 90 minutes to get counts
- Method submitted for FDA approval



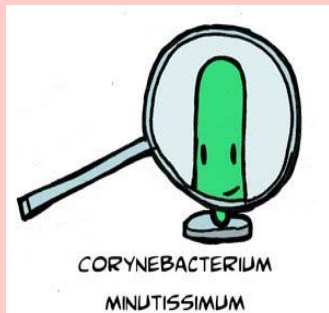


Flocked Swabs (Copan)

- Flocking is the process of applying a fiber directly onto a surface. The new flocked swab is a pre-shaped plastic applicator onto which a thin layer of nylon™ fiber is sprayed by flocking process perpendicularly.
- The nylon™ flocked swab displays significantly improved fluid dynamics in sample absorption by strong capillary action and releasing up to 95% of collected sample. Traditionally, wound fiber swabs (rayon™ or polyester swabs) trap a large percentage of the sample in the fiber matrix, retaining the sample resembling a mattress effect.

[1] See <http://www.copaninnovation.com>

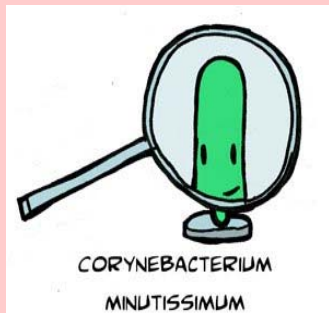
Information supplied by Gilberto Dalmasso, Ph.D.





Flock Swabs with ScanRDI

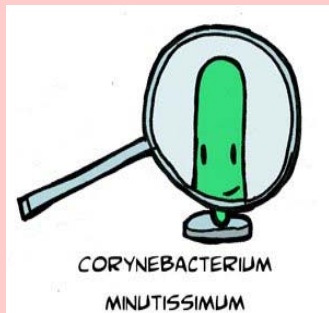
- Allows for use all surfaces
- Single cell detection has been approved with ScanRDI for sterility testing (Alcon)
- Counts viable cells present
- Methodology has already been submitted to FDA for approval





BeviStat™ Microbial Test System

- You can detect the presence of yeast and mold contamination down to **one cell per sample** in your raw materials, CIP rinse water and beverage samples in just 10 minutes for the majority of filterable samples.

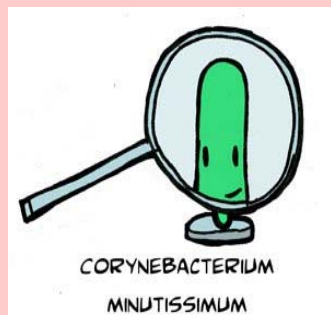




BeviStat™ Microbial Test System

Speed and Sensitivity

- Eliminate potential contamination earlier in your process
- Avoid costly corrective action
- Reduce product loss
- Process multiple batches without the risk of cross contamination
- Release product to market sooner
- Reduce storage and warehousing cost

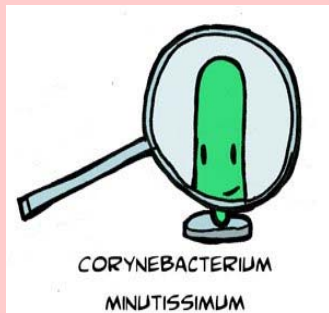




REBS

- Collects samples (air or liquid)
- Results in about 15 minutes
- Non-destructive
- Detects, enumerates, and identifies the contaminant

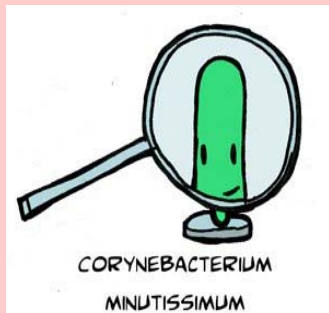
Saves the captured organism on a coupon for subsequent evaluations





REBS

- Final stages of development
- Not yet fully commercialized

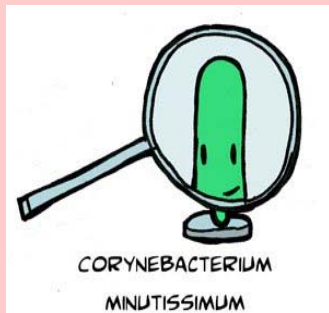


(c) Jeanne Moldenhauer 2008

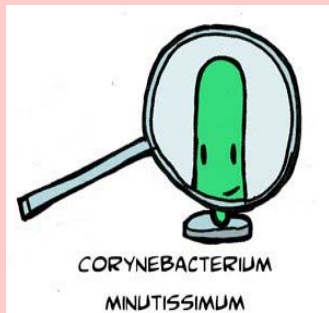


Other Applications

- PallCheck for surface monitoring
- ATP bioluminescence methods for water monitoring
- ScanRDI for water monitoring



Questions?

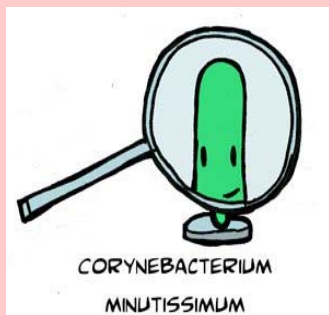


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Reference Info

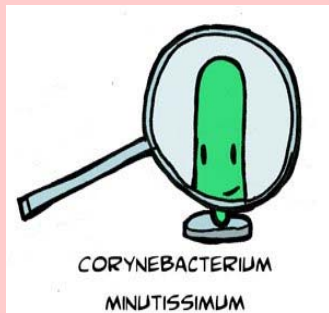
- See *Pharmaceutical Microbiology, 2nd Edition* edited by Richard Prince, PhD Chapter 16 for a side by side comparison of the limits/requirements for EM in the various regulatory documents





Acknowledgements

- Microorganism drawings are from www.adoptamicrobe.blogspot.com in the archives
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- PDA TR 13 Revision 2 Task Force Members

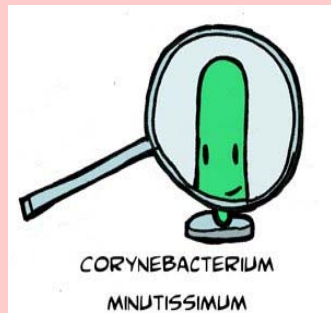




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