ISPE
Connecting a World of Pharmaceutical Knowledge

Carolina-South Atlantic Chapter

CaSA News

Volume 22 • Number 2

April 2015

President's Message

Heather Denny

Spring has arrived and as the trees and flowers come back to life so do all the activities that pull us in so many different directions. Work, family, sports, and the lists go on..... Hopefully, you have been able to carve out some time spend with ISPE CaSA.

On behalf of the board, I would like to thank Mike Putnam, the Technology Conference Committee, speakers, exhibitors, sponsors and attendees for a record breaking event. With sold out exhibitor space and a solid line up of educational speakers our attendance exceptional. This year's conference is behind us and Amy Lineberry is already focused on planning for 2016; if you are a planner, executor, interested in continuing to build upon current success I urge you to get involved now. While you see a one day event there is a year-long cycle to create the vision and plan.

Your next opportunity to show up is the 21st Annual Golf Tournament at Prestonwood Country Club on May 18th. Registration and sponsorship are now open through www.ispe-casa.org. Don't miss out on what will be an enjoyable day to network with peers.

The Education Committee is working on our first education event in Georgia. For those that may reside or work in that area, please reach out to Jim Hubbard if you have interest in helping with the event. Watch for details about the date and topic.

It is amazing how time flies. Once again it is time for a **Call for Nominations** as we begin to look to the new CaSA year and selecting new board members. This is your chapter and as you receive the email do not just hit delete. Maybe you are interested in becoming involved, maybe not. Maybe you know someone you would like to nominate, maybe not. What you all have is the opportunity to provide input or at least your vote of confidence for the upcoming board. Your board puts in many hours to create and plan events through the year that provide you with opportunities for education and networking.

With that I would like to thank all of the current board and committee members for your time and efforts. We are not done yet so watch for other upcoming events.

Now go outside and enjoy the day.

Heather Denny
President, ISPE CaSA Chapter

Featured Sponsors

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Upcoming Events

Golf Event - May 18, 2015 - Prestonwood, Cary, NC

Membership Corner

$40 DISCOUNT NOW AVAILABLE FOR NEW INDUSTRY MEMBERSHIPS!

By Terence Morrison, P.E., CAP, LEED AP BD+C, ISA 84 SFS

$40 DISCOUNT NOW AVAILABLE FOR NEW INDUSTRY MEMBERSHIPS! Applications can be made online at www.ispe.org/join, click on Join Now under Industry Membership, and enter CASA2015 in the promotion code box. Please remember ISPE's Refer-A-Friend Program! Earn one free month of membership for every friend you refer. All the details are available at http://www.ispe.org/membership-referral-program

Join ISPE by 31 May 2015 and you will get a Double Bonus worth $685. Your bonus includes a free copy of Good Engineering Practice (pdf version), a $435 value, and a $250 conference discount certificate. Get more details or join today using promo code BONUSLINK.

This discount is not applicable to Students, Young Professionals, Academics, and Regulatory Authority / Government as these all hold discounted memberships already.

If you have any question about ISPE or the CaSA Chapter, please contact me at membership@ispecasa.org.

Industry
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Join Now

Welcome New Members

New Members who joined February 10, 2015 through April 10, 2015

Aaron Rice
Adam Stearns
Andrew Argo
Anthony Moore
Ashley M. Phy
Benjamin T. Harper
Bill Migirditch
Brandon C. Cook
Brian Xzavior Brown
Brian Foster
Caryle S. Vann, PE, PMP
Chris Gullette, PMP
Chris Mullins
Christopher S. Preslar
Cori Sandy
Courtney Rose
Dave C. Miller
Del Ponder
Diana M. Owens
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Greg Smith
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Harry Gill
Heather A. Black
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John Brabender
Joshua A. Rouse
Josue Rivera
Mrs. Julianna Forsythe
Julianne Tajuba
Mrs. Julie C. Christian
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Kris A. Lemerond
Lakshmi Sravya Kompalli
Lawresa T. Shoffner
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Mark P. Whitson
Martin F. Ceiler, Jr.
Maryam Unnisa
Matthew Truong
Matthew Meyer
Matthew Emerson Bauder
Michael Shane Bailey
Michael Muth
Miranda Daughtry
Nicholas C. McNamara
Olivia Oliver
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Jeff Wurch
Rich Danner
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Roger Wong
Ryan Pridgen

Membership Corner

To All Members: Time for Board Nominations

By Matt Gilson, CaSA Immediate Past President 2015 CaSA Nominations Committee

Dear ISPE-CaSA member - now is the time to nominate members for roles on the ISPE-CaSA Board of Directors. The Board is composed of executive members (President, Vice President, Treasurer, Secretary, and Past President), committee chairs (Tech Conference,Newsletter, Student Affairs, Networking, Membership, Education, IT Communications (Social Media), and Young Professionals), and at-large Directors.

Of these positions, for the 2015-16 term, the following are open: President; Vice President; Treasurer; Secretary; Committee Chairs for Technology Conference, Networking, Student Activities, and IT Communications (Social Media); and At-Large Director. If you or a member you know are interested in any of these positions, please send a nomination via email by April 30th to nominations@ispecasa.org by downloading the fill-in 2015 Nominations Form.

(Hint: You may have to select "Open with a different viewer" to access the Fill-In Adobe PDF. Save and download form, complete the form, then save your completed form to attach and email directly to nominations@ispecasa.org. DO NOT USE the "Submit" feature, because that will send the form to the CaSA staff. Alternately, you may print the form, scan, and email to nominations@ispecasa.org.)

Members must be in good standing as defined by the Election Policy as follows: Any member of the CaSA Chapter is considered to be in good standing if dues are up-to-date, with neither a pending nor historical disciplinary action, and is willing to sign a Volunteer Code Of Conduct.

Recent Events Hosted by the Young Professionals Committee

Leadership Symposium

By Leanna Pearson

In past years, the Leadership Symposium has provided educational and networking opportunities for students and young professionals. This year, the event was moved to the Technology Conference as the Student/Young Professionals Educational Track.

The morning educational session, entitled “Designing for Your Career” focused on professional etiquette, mentoring, and career development. The afternoon session, entitled “Pulling Back the Curtain on Project Management”, provided attendees with insight into project management techniques and attributes shared by successful project managers. At each session, there was a great turn out by students, young professionals and professionals alike.

The Young Professionals Committee is interested in keeping this track in years to come and would love to know what entry level subjects you would like to see. Please send your requests for particular topics to info@ispe-casa.com with *YP Leadership Topics* in the subject line.

Billiards and Brews

By Rich Stanfield

On February 23, the Young Professional Committee hosted a Billiards and Brews networking event at Buck’s Billiards and Sports Bar in Raleigh. Although the event had been postponed a week due to snow and ice, turnout was great, with about 25 people attending.

Students and Industry Professionals tried their hand at the billiard table while enjoying each other’s company and engaging conversations, good food and beverages.

Many thanks to Buck’s and the ISPE CaSA Young Professionals!

Membership Corner

22nd Annual ISPE-CaSA Technology Conference Special Feature
Wrap up & Thank You

By Mike Putnam, ISPE CaSA Technology Conference Committee Chair

If you attended the ISPE CaSA Technology Conference in March, you undoubtedly observed the momentum this event has gained as an opportunity to bring drug manufacturers, support companies and industry professionals together. At the center of the event was the new 'CaSA Pavilion Area' where the largest drug and device manufacturers in the southeast exhibited alongside product and service providers to discuss current initiatives to improve the delivery of life-saving drugs to patients worldwide. Thank you Biogen, bioMerieux, Fuji Diosynth, Hospira, Novo Nordisk, Novartis and Catalent. A special thanks also goes to each of the corporate sponsors. Without you, this conference would not be possible. We sincerely appreciate your support. Thank all of the attendees that chose to spend the day at the Technology Conference. As CaSA's largest event of the year, your support is vital to the continued success of the chapter.

The morning began with an opening message from Scott Billman, Director of Manufacturing Engineering at Biogen and Past President of ISPE CaSA. Scott welcomed attendees to Raleigh and reinforced the value of ISPE membership and involvement.

After Scott's opening remarks, conference guests were introduced to Me Fine Foundation, the featured charity of the 2015 Technology Conference. Me Fine Foundation Executive Director Joey Powell educated attendees on the mission of the organization and how attendees could make a difference in the lives of critically ill children in North Carolina. Raffle sales, donations from attendees, and contributions from ISPE CaSA resulted in approximately $6,000 being contributed to Me Fine Foundation. Six tracks of morning and afternoon educational sessions followed the opening ceremonies with topics ranging from 'Best Automation Practices in a Greenfield Startup' to 'Facilities of the Future'. Over 20 companies were represented by educational speakers including many leading drug manufacturers. During the lunch hour, conference attendees packed the ballroom to hear keynote speaker John Cox (Executive VP, Pharmaceutical Operations & Technology for Biogen) deliver a captivating presentation on Biogen's innovative approach to delivering a global biopharmaceutical portfolio. Afternoon product demonstrations followed the keynote session with novel technologies showcased on the main ballroom stage.

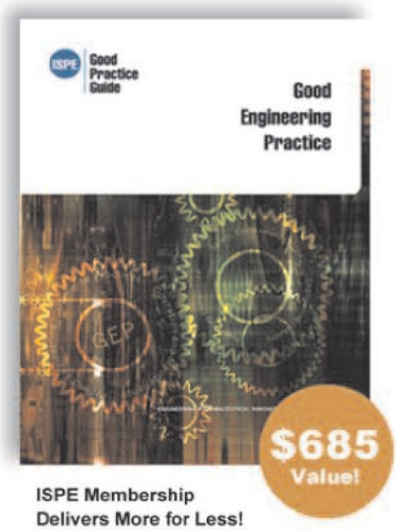
Closing ceremonies featured ISPE member recognition awards presented to Wes Robbins and Eric Mayer. These gentlemen have been instrumental to the success of the Technology Conference and ISPE CaSA Chapter over the years. Thank you Wes and Eric! As conference activities concluded, the party was just getting started at the networking reception which boasted a casino-night theme. Outfitted with a red carpet entrance and flashing paparazzi, the networking reception entertained attendees into the night. Gourmet carving stations and succulent desert selections framed a ballroom with 30 authentic gaming tables offering everything from roulette to Caribbean stud poker. It was a great day of education, networking, and collaboration between industry. Our hope is that this event continues to grow and spark new and innovative technologies that make a difference in the lives of patients around the world. As you can imagine, the

(continued next page)

Membership Corner

Technology Conference requires a tremendous amount of planning and our committee has already begun efforts to ensure the 2016 event builds from the momentum this year. Mark your calendars for March 31, 2016 and please email techconference@ispecasa.org if you would like to become more involved with conference planning.

Thanks and I look forward to seeing you at a CaSA event soon.



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Free Affiliate/Chapter Membership	**$95**
TOTAL VALUE	**$1,204**
TOTAL COST TO YOU (Annual Membership Dues)	**$279**

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1 *Good Engineering Practice* - ISPE Good Practice Guide

Both a primer and master reference, this 169-page ISPE best seller covers the complete lifecycle of engineering from concept to retirement. It provides advice on good engineering practices, explains underlying technical principles and suggests solutions in areas where no single answer is correct and where several outcomes may be possible. The Guide divides activity into three sections:

- Project Engineering including infrastructure, organization, value analysis, planning and monitoring, design review and handover
- Common Practices including standards and procedures, documentation practices, change management and innovation and continuous improvement
- Operation and Maintenance including engineering manuals and records, breakdown maintenance, internal audit and equipment decommissioning and retirement

(Downloadable PDF)

2 *$250 Conference Discount Certificate*

From aseptic processing technologies to meeting with regulators to a showcase of the latest solutions for the pharmaceutical lifecycle, chances are ISPE's conferences cover topics that meet your needs. Use this discount certificate and save big $$$ on the industry's most significant events.

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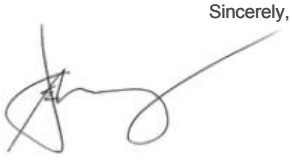
Sincerely,



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*Offer applies only to full dues-paying Industry Members, and cannot be used for dues renewals.

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Technology Corner

FOUR ELEMENTS OF CLEANROOM DESIGN

By Emil Bordelon, AM Technical Solutions

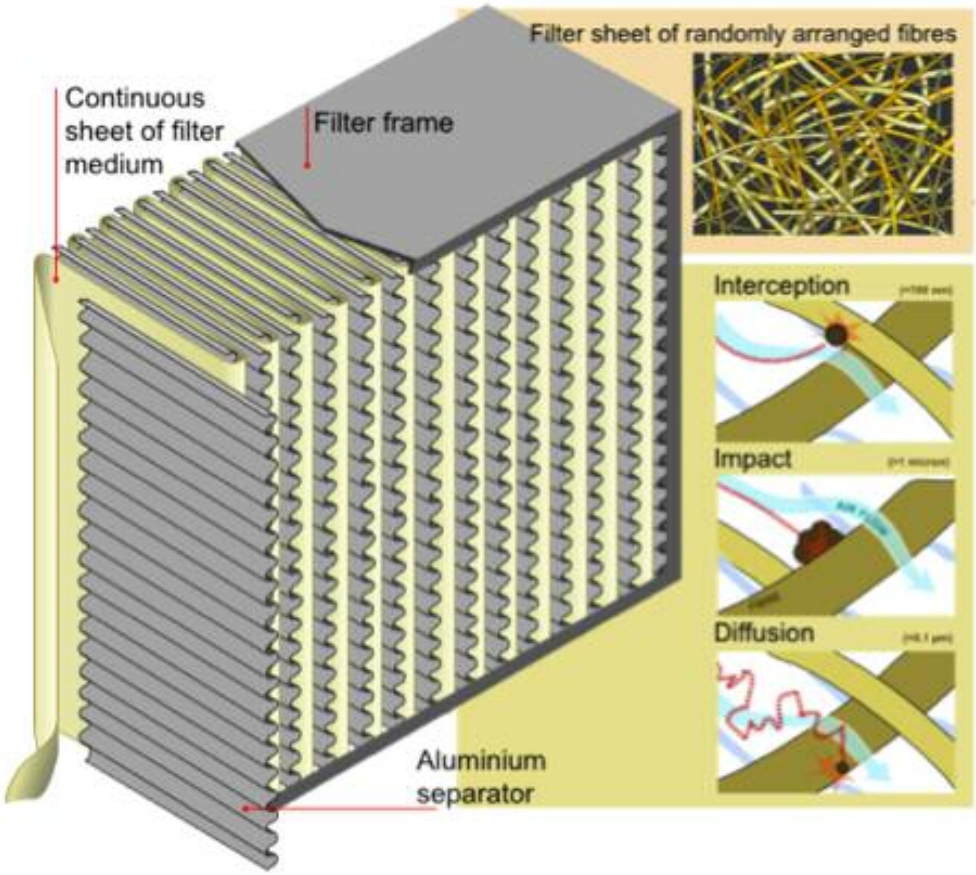
The 4 elements of Cleanroom Design are:
1. HEPA/ ULPA filters
2. Airflow
3. Cleanroom Classification
4. Room Pressure

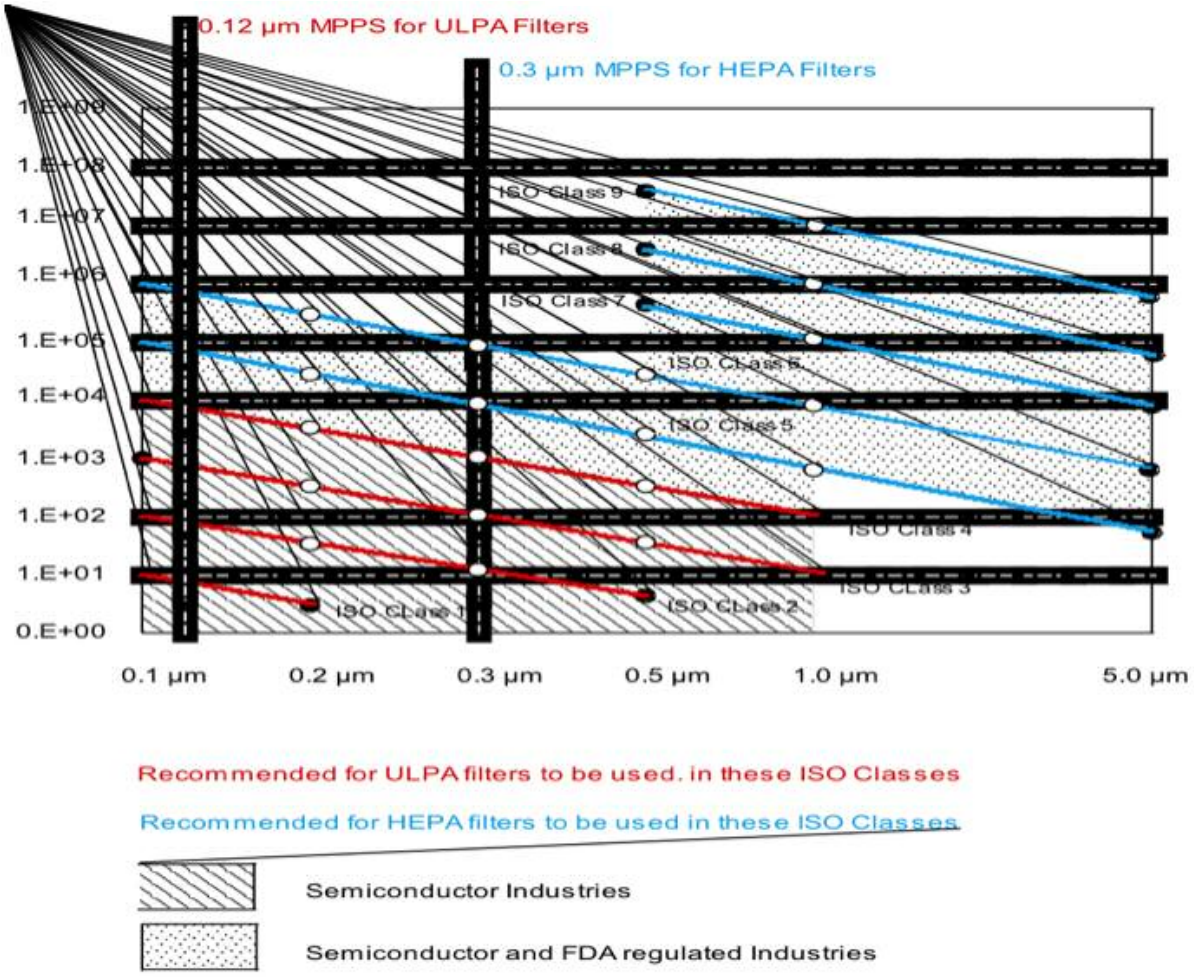
PART 1:

Types of HEPA / ULPA Filters
The first decision that is made during the design phase is the cleanliness class critical for the process or product being manufactured or handled in the cleanroom. To that end there are two types of filters that are used in the different cleanliness classification.

HEPA (High Efficiency Particulate Air) filters have minimum efficiency of 99.97% at 0.3 µm the Most Penetrating Particle Size (MPPS). This type of filter is usually used in ISO Class 5 (100) to ISO Class 8 (100,000). The types of industries that use this type of filter are FDA regulated facilities (drug manufacturers, medical device manufacturers and food and beverage manufacturers), hospital operating rooms and pharmacies and semiconductor (chip manufacturers, circuit board manufacturers, hard drive manufacturers and flash memory manufacturers) and companies that provide materials to the semiconductor companies.
ULPA (Ultra Low Penetration Air) filters have a minimum efficiency of 99.9997 at 0.12 µm MPPS. This type of filter is usually used in ISO Class 4(10) to ISO Class 1. THE ULPA filters are more costly than the HEPA filters which preclude using them in all cleanroom cleanliness classes. This type of filter is used where the smaller size particles are critical to their process or product – mainly in the semiconductor industry.

Most HEPA / ULPA filters media are made of boron silicate microfibers with binding and water proofing agents. These materials tend to off gas. With the new stringent process this off gassing creates difficulties and often contaminates these processes leading to product loss. The industry is moving to low off gassing filters. One type of filter is made of ePFTE (expanded Polytetrafluoroethylene – also called Teflon or Gore-Tex filters), and is becoming increasingly popular. It is corrosion resistant so can be used in highly corrosive areas like a wet benches or chemical manufacturers. It is also water resistant which makes it more suitable with the wet process. Additionally, with lower pressure drop it saves money on utilities and has very low off-gassing properties.





Importance of Leak Testing

In the certification phase it is highly recommended that newly installed HEPA / ULPA filters should be leak tested. Every HEPA / ULPA filter is scan tested at the factory but most damages to the HEPA / ULPA filters comes from transportation and installation. Filter leak testing after installing HEPA / ULPA filters is the only way to find these damages. For operating cleanrooms ISO 14644-2 Annex A recommends they be tested every 2 years. FDA requires all FDA regulated facilities must be tested every year or at the interval specified in their Current Good Manufacturing Practices (cGMP).

There are two different methods for leak testing HEPA/ ULPA filters. For FDA regulated facilities a photometer is used with an oil base aerosol to challenge the HEPA/ ULPA filter. This is an FDA requirement. For other facilities where the oil aerosol would damage their product or process (especially the semiconductor industry) a particle counter is used with Polystyrene Latex Spheres (PSL). One benefit of using PSL is you can challenge the HEPA/ ULPA filter at the MPPS for the HEPA/ ULPA filter or use a specific particle size that is critical to the process.

HEPA/ ULPA filter leaks are reported in percentages of upstream concentration. A .01% leak is a significant leak and needs to be repaired or the filter replaced. Sometimes the percentage of the leak (the size of the leak) is confused with efficiency of the filter. Filter leak testing is not efficiency testing. Efficiency testing is only performed at the filter manufacturer under strict conditions that cannot be reproduced in the field.

A HEPA / ULPA filter with a significant leak 0.1% and an upstream concentration of 1,000,000 particles at 0.1 µm per cubic foot of air would leak 100 particles at 0.1 µm per cubic feet of air. If you took a 1 Sq. Ft. area directly below the leak and the airflow from the filter was 100 feet per minute the area would be expose to 100 cubic feet of air per minute which would mean 10,000 particles at 0.1 µm per minute or 600,000 particles per hour. As you see even the smallest leak could have a large impact on the process or product.

The Importance of Cleanroom Filter Maintenance

In the maintenance phase the pressure drop of the HEPA/ ULPA filters is critical. As the pressure drop increases the airflow of the HEPA/ ULPA filter starts to be comprised. As the airflow starts dropping off it will reach a point where it is affecting the cleanroom cleanliness class affecting the process or product. It is recommend that the HEPA/ ULPA filter should be change out at double the initial pressure drop or 1 inch of water gauge. One key to prolonging this change out is the pre-filtration of the air going to the HEPA/ ULPA filters. A schedule for the regular change out of the pre-filters should be made. One way to determine if the pre-filters need to change is to measure the pressure drop across the pre-filters. Manufacturers of pre-filters have a max pressure drop for when the pre-filters have to be change. Regular monitoring of the HEPA / ULPA filters pressure drop should be considered. This testing can be included in the cleanroom certification.

PART 2:

Airflow Design

There are 3 different types of airflow in a cleanroom:

Unidirectional Airflow (Figure A):

Unidirectional airflow is defined in ISO 14644-4 as “Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines”. It is also specified as ≤ 14º form perpendicular when performing airflow parallelism. In IEST RP-CC006.2 it is recommended that a unidirectional airflow cleanroom have at less 80% filter coverage. ISO Class 1 through 5 are recommended to be unidirectional airflow designs (see ISO 14644-4 table B.2 below). Below is an example of a unidirectional airflow cleanroom:

Non-Unidirectional Airflow (Figure B):

Non-unidirectional airflow is defined in ISO 14644-4 as “Air distribution where the supply air entering the clean zone mixes with the internal air by means of induction”. ISO Class 6 through 9 are recommended to be non- unidirectional airflow designs (see ISO 14644-4 table B.2 below). Below is an example of a non-unidirectional airflow cleanroom:

Mixed Airflow (Figure C):

Mixed airflow is defined in ISO 14644-4 as “A combination of both Unidirectional and Non-Unidirectional airflows”. Below is an example of a mixed airflow cleanroom:

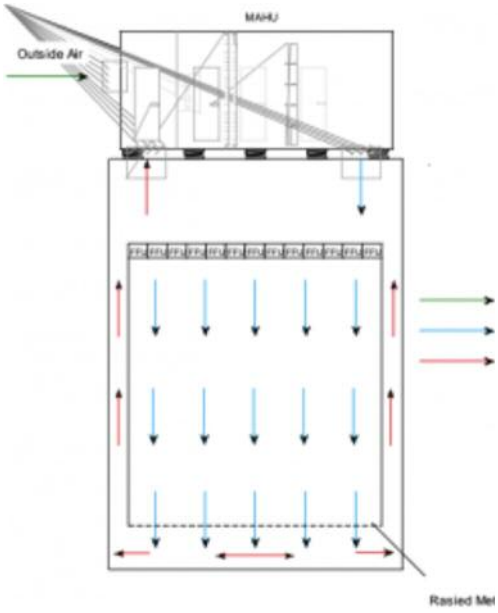


Figure A

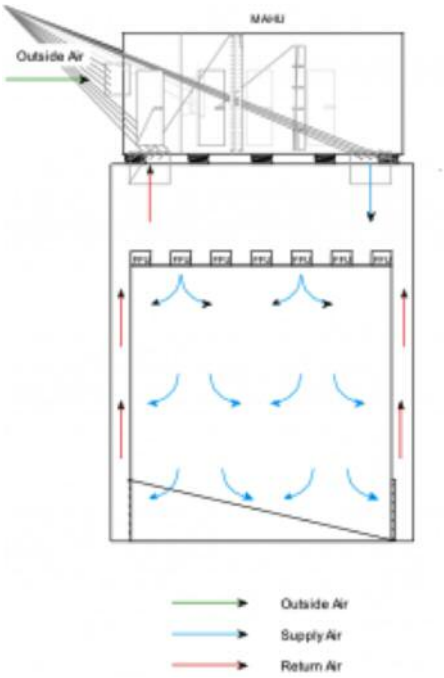


Figure B

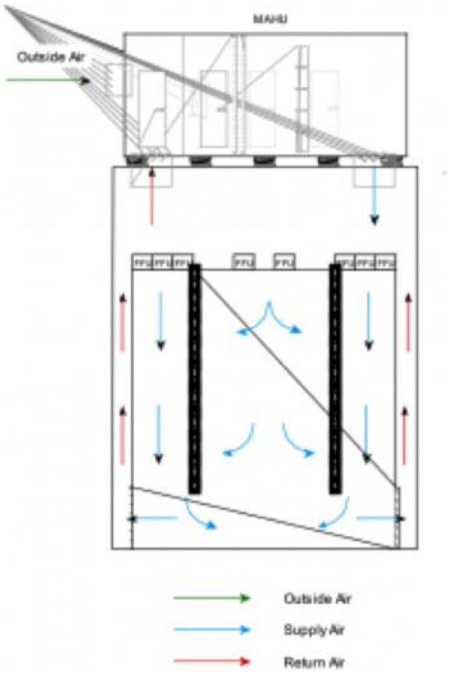


Figure C

Table B.2 — Examples for microelectronic cleanrooms

Air cleanliness class[a] (ISO Class) in operation	Airflow type[b]	Average, airflow velocity[c] m/s	Air changes per hour[d] $m^3/m^2 \cdot h$	Examples of applications
2	U	0,3 to 0,5	na	Photolithography, semiconductor processing zone[e]
3	U	0,3 to 0,5	na	Work zones, semiconductor processing zone
4	U	0,3 to 0,5	na	Work zones, multilayer masks processing, fabrication of compact discs, semiconductor service zone, utility zones
5	U	0,2 to 0,5	na	Work zones, multilayer masks processing, fabrication of compact discs, semiconductor service zone, utility zones
6	N or M[f]	na	70 to 160	Utility zones, multilayer processing, semiconductor service zones
7	N or M	na	30 to 70	Service zones, surface treatment
8	N or M	na	10 to 20	Service zones

NOTE na = not applicable

[a] Occupancy states associated with the ISO Class should be defined and agreed in advance of establishing optimum design conditions.

[b] When airflow type is listed, it represents the airflow characteristics for cleanrooms of that class: U = unidirectional; N = non-unidirectional; M = mixed (combination of U and N).

[c] Average airflow velocity is the way that unidirectional airflow in cleanrooms usually is specified. The requirement on unidirectional airflow velocity will depend on local parameters such as geometry and thermals. It is not necessarily the filter face velocity.

[d] Air changes per hour is the way that non-unidirectional and mixed airflow is specified. The suggested air changes are related to a room height of 3,0 meter.

[e] Impervious barrier techniques should be considered.

[f] With effective separation between contamination source and zones to be protected. Could be a physical or airflow barrier.

Airflow Testing:

There are two methods for measuring airflow depending on the type of airflow used.

Unidirectional Airflow:

The airflow velocity method is used in unidirectional airflow cleanroom. A test instrument is used to measure the speed of

the air as it exits the HEPA / ULPA filter. There should be a uniformed airflow speed of ± 15 %. In some cases a tighter specification is called for. The speed is measure in feet per minute or meters per second. In ISO 14644-4 Table B.2 it gives a range of the room airflow velocity for each ISO Class 1 through 3. This is the room airflow velocity not the HEPA / ULPA filter. They can be different depending on filter coverage and ceiling height.

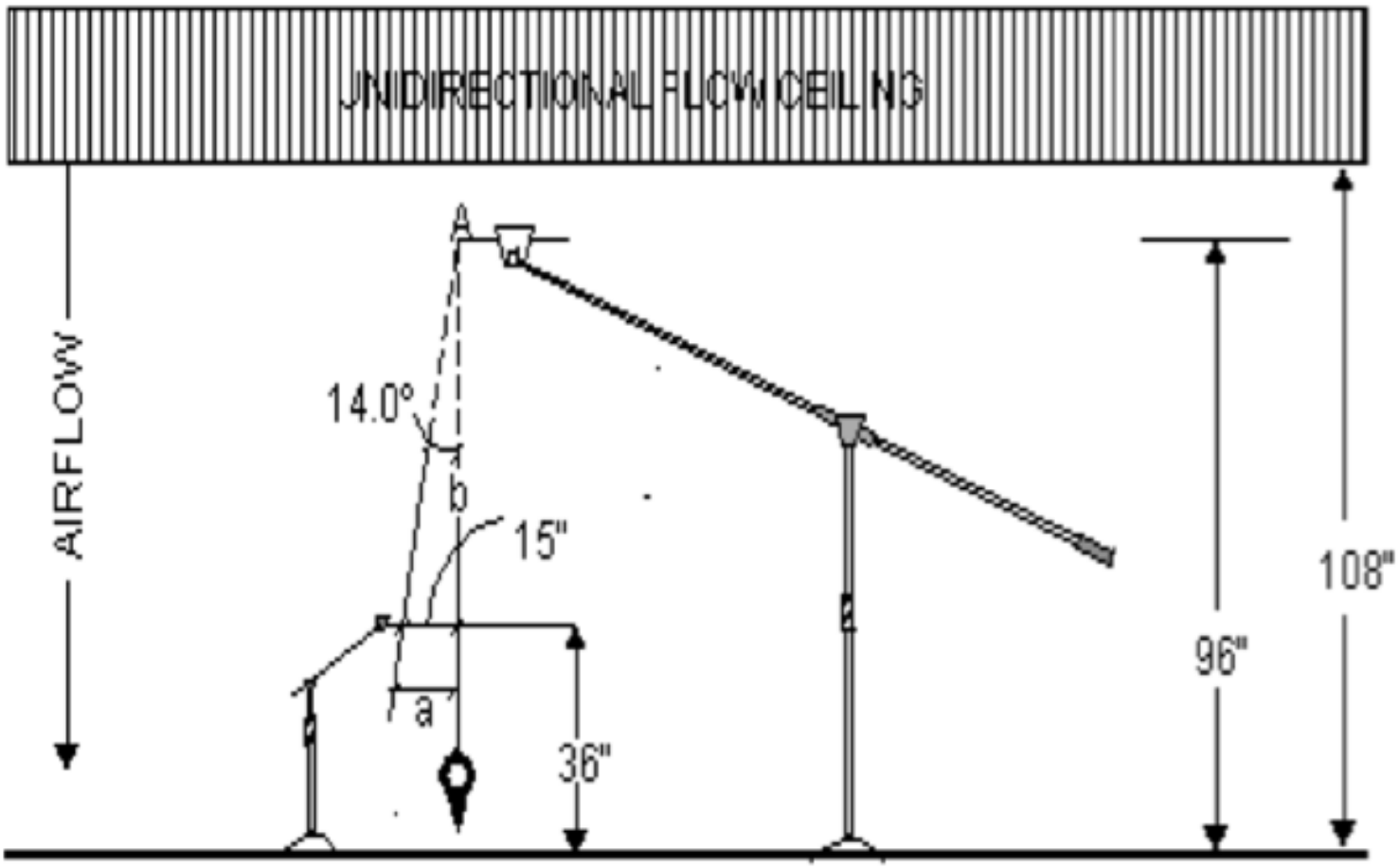
Non-Unidirectional and Mixed Airflow:

The airflow volume method is used in non-unidirectional and mixed airflow cleanrooms. A capture hood is used to measure the volume of air exiting the HEPA / ULPA filter. The test results are reported in cubic feet per minute or liters per second. The total airflow for the room is divided by the room volume to calculate the room air change rate per hour. In ISO 14644-4 Table B.2 it gives a range of air changes per hour for each ISO Class 6 through 9.

Airflow Visualization:

There are two methods for airflow visualization measurement.

Parallelism:
Airflow parallelism is used in unidirectional airflow cleanrooms to visualize airflow. Using a plum bob and a non-shedding thread that has high surface area to weight ratio (flow viz) to measure the angle of deflection of the airstream from perpendicular. Below is example of a parallelism test stand.



Airflow Directional Test:

Airflow directional test is used in non-unidirectional airflow cleanrooms. This test involves using visible vapor to visualize the direction of the airflow and the effects of process equipment to the airflow. The pharmaceutical industry uses this method for both unidirectional and non-unidirectional airflow cleanrooms for this reason. Below is an example of an airflow directional test stand.

Cleanroom Design:

Utilizing ISO 14644-4 Table B.2 air change rates and room velocities the basic airflow design for a cleanroom can be made. Below are two examples of cleanrooms one unidirectional and the other non-unidirectional.

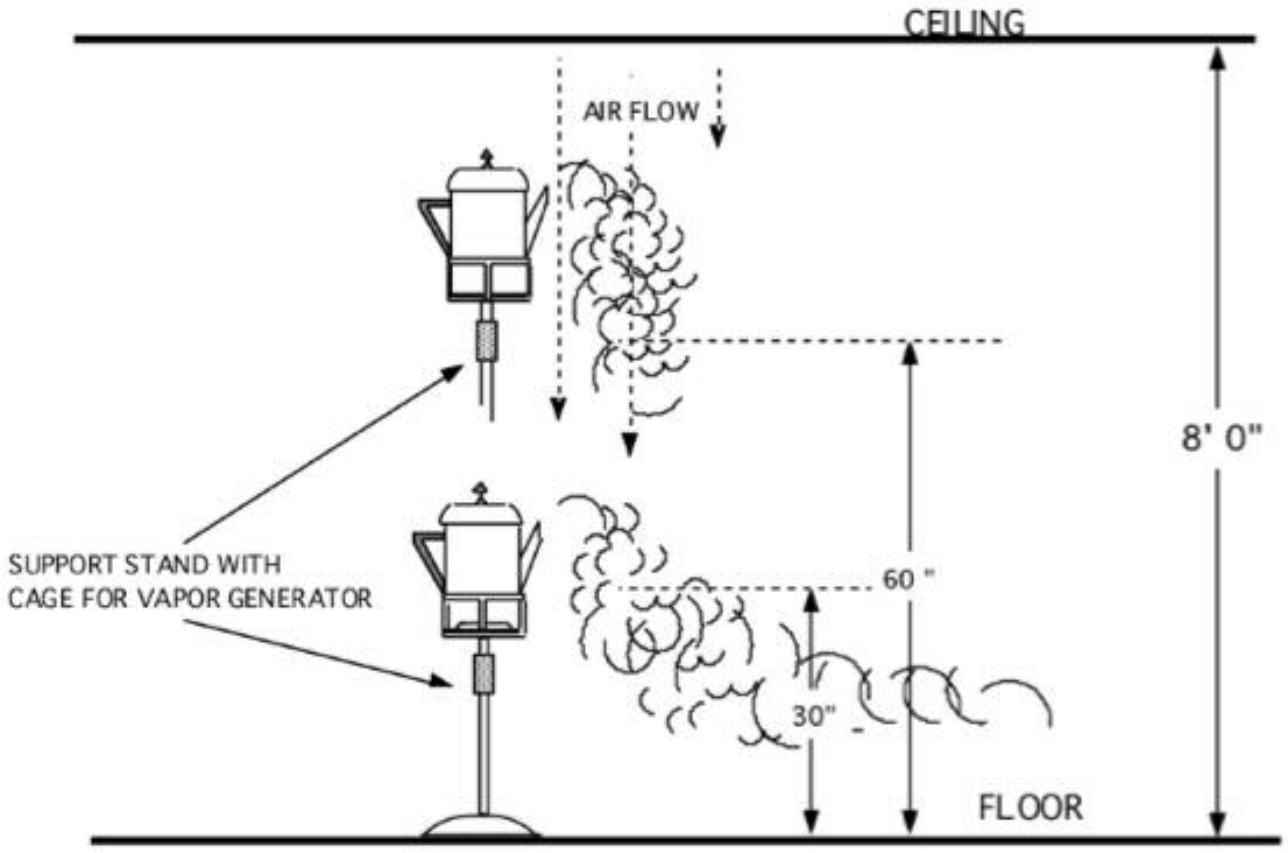
Non-Unidirectional Design:

This example is an ISO class 6 cleanroom 20' by 20' with 10' ceilings. The room volume is 4,000 cubic feet. The recommended air change rate range by ISO 14644-4 for class 6 is 70 to 160 per hour. Selecting the mid range of 115 air changes per hour the total volume per hour need is 460,000 cubic feet per hour (4,000 x 115). Divide the total volume per hour by 60 will give us 7,667 cubic feet per minute. Using the specified 720 cubic feet per minute per filter we divide 7,667 by 720 we get 10.6 round it up to 11 filters. This would equate out to 1.98 changes per minute or 118 changes per hour. This room would have a filter coverage of22%.

Unidirectional Design:

This example is an ISO class 4 cleanroom 20' by 20' with 10' ceilings. The room volume is 4,000 cubic feet. The recommended room velocity by ISO 14644-4 for class 4 is 0.3 is 0.5 meters per second (59 to 98 feet per minute). Selecting the mid range of 75 feet per minute the total volume need is 30,000 cubic feet per minute (4,000 x 75). Using the specified 720 cubic feet per minute per filter we divide 30,000 by 720 we get 41.6 round it up to 42 filters. This would equate out to 75.6 feet per minute. This room would have a filter coverage of 84%.
Utilizing ISO 14644-4 Table B.2 a very basic airflow design can be made but other factors will need to consider before a final cleanroom design is made. Some of these factors are; exhaust air, make up air, manufacturing process, type of filters to be used, etc. but by understanding the principle of airflow design these choice should be easier.

AIR FLOW DIRECTIONAL
TEST APPARATUS



PART 3:

Cleanroom Specifications:

In November, 2001, the GSA cancelled the cleanroom certification standard, Federal Standard 209E (FS) and replaced it with ISO 14644-1. In the last 13 years, Federal Standard 209E has not been an active specification but its terminology is still around. If a customer is asked, "What is the classification of your cleanroom?" 8 out of 10 times they will use a FS 209 E classification even if the cleanroom is being certified to ISO 14644-1.

Why after all this time is this still happening? One reason is the ISO 14644-1 cleanroom classification does not do much to identity the class. For example, an ISO Class 6 shows 35,200 particles at 0.5 µm per cubic meter of air, whereas the Federal Standard class 1,000 (which is the equivalent of ISO class 6) means 1,000 particles at 0.5 µm per cubic foot of air. The second reason is almost all particle counters have a one cubic foot of air per minute sample rate. The results are reported in cubic feet per minute which means you have to think of class limits in cubic feet which leads you back to the Federal Standard 209E classification. One cubic foot per minute sample must be multiplied by 35.315 to reach one cubic meter. ISO 14644-1 requires all the results to be reported in cubic meters.

There are major differences between the two specifications. The first is ISO 14644-1 is based on 0.1 µm whereas Federal Standard 209E was based on 0.5 µm thus the reason that the two specifications do not match up (see the chart below). Two cleaner classes, ISO Class 1 & 2, and one less clean class, ISO Class 9 (room air), were added. The ISO Class 1, 2 or 9 are rarely used.

Another major change is that ISO 14644-1 is not a standalone specification. It is one of 10 parts in the ISO 14644 series (see the list below). There are plans to add more parts – ISO 14644-11 and 12 are in draft form right now.

- Part 1: Classification of air cleanliness
- Part 2: Specification for monitoring to prove continued compliance with ISO 14644-1
- Part 3: Test methods
- Part 4: Design, construction and start-up
- Part 5: Operations
- Part 6: Vocabulary
- Part 7: Separative devices(clean air hoods, gloveboxes, isolators, and mini-environments
- Part 8: Classification of air cleanliness by chemical concentration
- Part 9: Classification of surface cleanliness by particle concentration
- Part 10: Classification of surface cleanliness by chemical concentration

Design:

As stated in Part 1 of this series, the dividing line between pharmaceutical and semiconductor cleanrooms is ISO Class 5. The majority of pharmaceutical cleanrooms are between ISO Class 5 and Class 8. The majority of semiconductor cleanrooms are between ISO Class 3 and Class 5. To determine the proper ISO Class the following requirements must be considered: 1) type of product and process 2) particle sizes and quantity that is detrimental to your product 3) choose an ISO Class that fits that parameters of 1 and 2.

The next step in the cleanroom design phase is compliance to ISO 14644-1 which means meeting the requirement in ISO 14644-2. There are different ways to stay compliant and the first step is to develop a monitoring program. ISO 14644-2 defines what cleanroom monitoring is and what intervals are allowed.

Monitoring: Observations made by measurements in accordance with a defined method and plan to provide evidence of the performance of an installation.

Below are listed the intervals:

- **Continuous:** updating that occurs constantly
- **Frequent**: updating that occurs at specified intervals not exceeding 60 minutes during operation
- **6 Months:** updating that occurs at an average interval not exceeding 183 days throughout periods of operational use, subject to no interval exceeding 190 days
- **12 Months:** updating that occurs at an average interval not exceeding 366 days throughout periods of operational use, subject to no interval exceeding 400 days
- **24 Months:** updating that occurs at an average interval not exceeding 731 days throughout periods of operational use, subject to no interval exceeding 800 days

In section 4 of ISO 14664-2 as stated below in 4.2.4 and 4.2.5, if the facility is equipped with monitoring instruments the testing in Table 1 and 2 can be extended. The most efficient way to install these monitoring instruments is during construction. It can be retrofitted after construction but will be more costly and may involve down time for the facility.

FED STD 209E			0.1µm		0.2µm		0.3µm		0.5µm		1µm		5µm	
			m3	ft3	m3	ft3	m3	ft3	m3	ft3	m3	ft3	m3	ft3
SI	ENG	ISO CLASS 1	10	0.28	2	0.056								
		ISO CLASS 2	100	2.8	24	0.67	10	0.28	4	0.1				
M1.5	1	ISO CLASS 3	1000	28	237	6.7	102	2.8	35	0.9	8	0.2		
M2.5	10	ISO CLASS 4	10000	283	2370	67	1020	28	352	9	83	2		
M3.5	100	ISO CLASS 5	100000	2831	23700	671	10200	288	3520	99	832	23	29	0.8
M4.5	1,000	ISO CLASS 6	1000000	28316	237000	6711	102000	2888	35200	996	8320	235	293	8
M5.5	10,000	ISO CLASS 7							352000	9967	83200	2355	2930	82
M6.5	100,000	ISO CLASS 8							3520000	99674	832000	23559	29300	829
		ISO CLASS 9							35200000	996743	8320000	235593	293000	8296

4.2.4 Where the installation is equipped with instrumentation for continuous or frequent monitoring of the airborne particle concentration, and air pressure difference, where applicable, the maximum time interval as stated in Table 1 may be extended, provided that the results of continuous or frequent monitoring remain within the specified limit(s).

4.2.5 In those installations that require additional tests, and where the installation is equipped with instrumentation for continuous or frequent monitoring of the test parameter applicable, the maximum time interval(s) as stated in Table 2 may be extended, provided that the results of continuous or frequent monitoring remain within the specified limit(s).

The second way to stay compliant is to have the facility certified semi-annual or yearly depending on the cleanliness classification. This may be a more cost efficient solution depending on the size of the facility and cost of the monitoring instrumentation. Testing in Table 1 and 2 must be performed at the stated time interval for the cleanliness classification.

Table 1- Schedule of testing to demonstrate compliance with particle concentration limits

Classification	Maximum time interval	Test method
≤ ISO Class 5	6 months	Annex B in ISO 14644-1:1999
> ISO Class 5	12 months	Annex B in ISO 14644-1:1999

NOTE: Particle count tests will normally be performed in the operational state, but may also beperformed in the at-rest state in accordance with the designated ISO classification.

Table 2 –Schedule of additional tests for all classes

Test Parameter	Maximum time interval	Test Procedure
Airflow volume[a] or airflow velocity	12 months	ISO 14644-3:-, Clause B.4
Air pressure difference [b]	12 months	ISO 14644-3:-, Clause B.5

NOTE: These tests may normally be performed in either the operational or at-rest state in accordance with the designatedISO classificationa

[a]Airflow volume may be determined by ether velocity or volume measurement techniques.[b] This test will not apply to clean zones which are not totally enclosed

Testing:

In Federal Standard 209E, the number of locations required to certify a cleanroom is based on cleanroom class and type of airflow design- unidirectional or non-unidirectional. In ISO 14644-1, the number of locations is solely based off the size of the cleanroom in square meters. The formula is the square root of the square meters of the cleanroom. A 100 square meter (1076 Sq. Ft.) cleanroom would have a minimum of 10 locations. The minimum number of locations is one with 3 samples or 3 locations. The locations should be evenly distributed throughout the cleanroom.

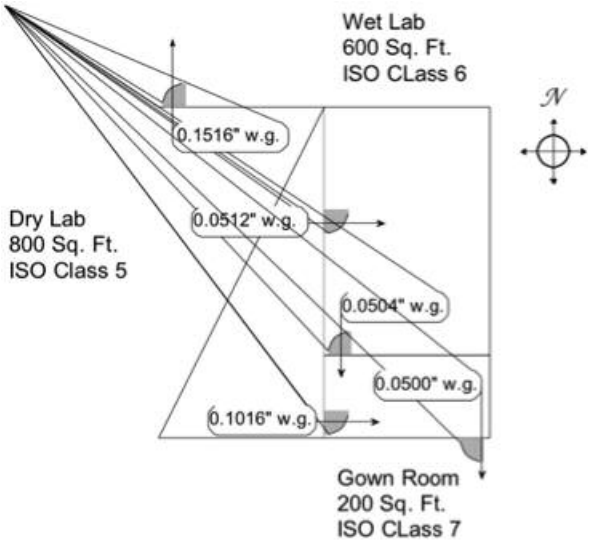
For the sample volume, you should sample a sufficient volume of air that a minimum of 20 particles would be detected if the particle concentration for the largest considered particle size were at the class limit for the designated class. For an ISO Class 1 cleanroom (10 particles @ 0.1 µm per cubic meter) the sample volume would be 2 cubic meters or 71 minutes with a 1 cubic foot per minute counter. The minimum sampling time is one minute.

The particle counter industry has come out with some new particle counters with new features. One is the ability to normalize the count to 1 cubic meter. The counter will sample one cubic foot of air but would report the results in cubic meters which eliminates the need to multiply the results. The other is a 50 liter per minute counter which would allow a 20 minute sample time for a cubic meter.

PART 4:

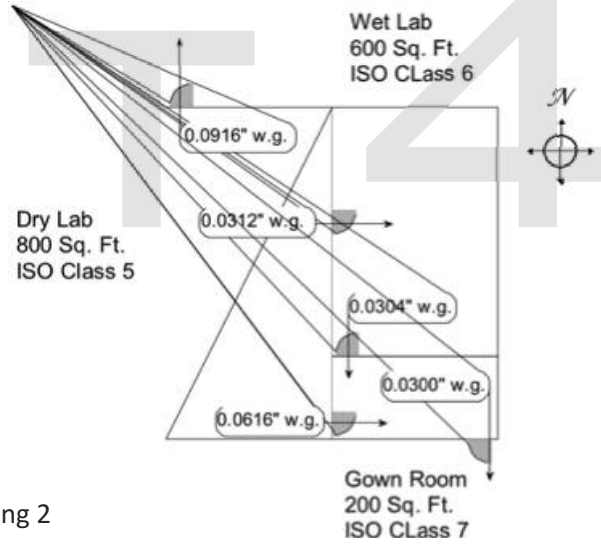
Room Pressure:

The main function of room pressure is to mitigate infiltration of particles from a less clean cleanroom to a cleaner cleanroom i.e. ISO Class 5 to ISO Class 4. The cleanest area in the fab should have the highest pressure cascading out to the less clean areas. In drawing 1, the cleanest room would be the Dry Lab ISO Class 5 then the Wet Lab ISO Class 6 and finally the Gown Room ISO Class 7 then outside of the cleanroom facility.



Drawing 1

In Fed. Std. 209B published in 1973 the minimum pressure requirement was 0.05 inches of water gauge (12 Pascal (Pa)). This requirement was removed from the later Fed. Std. 209 standards. The 0.05" w. g. (12 Pa) requirement was found to be on the high side due to the cascading requirement (see drawing 1) with a 3 room cascade the pressure from the cleanest room to the exterior would be 0.15" w. g. or higher (37 Pa) . This higher pressure causes some issues i.e. doors not closing correctly or hard to open, higher air leakage and high demands on the HVAC system. The requirement now was modified to 0.03" to 0.05" w. g. (7 to 12 Pa). With the lower pressure and the same 3 room cascade the pressure from the cleanest room to the exterior would be .09' w. g. (22 Pa) (see drawing 2). This is a reductionof the differential pressure by 0.06" w. g. (14 Pa). ISO 14644-4 has a recommendation of 5 to 20 Pascal (0.02" to 0.08" w. g.).



Drawing 2

DESIGN

Constructing a cleanroom facility is like constructing a building inside of a building. A cleanroom needs to have a separate HVAC system, lighting system, flooring and wall system and a differential pressure to the interior of the building. An exterior wall of a building should not be used as a cleanroom wall. Also there should never be a door from the cleanroom to the outside of the building. This is due to wind pressure – a 10 mile per hour wind has a wind pressure of .05 "w. g. (12.9 Pa). A 30 mile per hour wind has a wind pressure of .47 "w. g. (116.2 Pa). A 50 mile per hour wind has a wind pressure of 1.3" w. g. (322 Pa). Of course, the wind pressure can vary due to conditions such as temperature, air density, and altitude.

Pressurizing a cleanroom is like keeping a balloon inflated that has a leak in it. There should be a constant airflow with constricted air return to build the pressure. For example, the Wet Lab ISO Class 6 is 600 sq. ft. with a 10 foot ceiling equals a room volume of 6,000 cubic feet. The recommended air change rates for ISO Class 6 is 70 to 160 changes per hour mid-range would be 115 changes per hour. To meet this air change rate the airflow requirement is 11,700 cubic feet per minute (CFM). An air return flow rate of 450 feet per minute (FPM) through an 80% open grill with a 30% grill deflection will create a 0.062" w. g. (15.4 Pa) pressure. Dividing 11,700 CFM by 450 FPM will equal a return area of 26 Sq. Ft. To calculate the running feet of air return divide the return area required (26 sq. ft.) by the height of the air return(1.5') times the gill opening (80%) equals 22 running feet
(21.6 feet rounded up). It is recommended not to exceed 600 FPM air return flow rate as this will create higher noise levels and vibration in the return space.

A cleanroom should be built tight with very little air leakage but there are always leakages that cannot be stopped i.e. gaps around doors, loose fitting ceiling tiles, penetrations though walls. Also, every time a door opens in a positive room there is airflow from that room causing a loss of air. Also, there is the air loss through the exhaust system if one is installed. To combat these air losses,makeup air is supplied to the cleanroom. It also supplies fresh air to the cleanroom. The makeup air is filtered and usually supplied to the return side of the recirculation air handler which feeds the filters in the cleanroom.

CONTROLS

With today's advance control systems and pressure transducers, the monitoring and controlling of the cleanroom room pressures have been simplified. Gone are the days of an employee walking around checking magnehelic gauges and documenting the room pressures. Today room pressures are monitored on a computer screen with the data stored for later use with low and high pressure alarms. With makeup air handlers (MAHU) being equipped with variable frequency drives (VFD) pressure control is also mostlyautomatic. The one major problem is with a lot of traffic going in and out of the cleanroom, the MAHU may start to hunt (ramp up and down rapid). One fix is to program a delay into the VFD and another is to have a wider range of set points.

TESTING

For this test, an Air Data Meter (Electronic Micro Manometer) is used to measure pressure across a door or pass-throughs. The meter has two ports – one positive and one negative. A testing tube is placed under the door or across the pass-throughs to the other room. Connect the testing tube to the negative port of the meter. Take a reading – if the number is positive, the air is flowing away from you. If the number is negative, the air is flowing to you. Take the average of the four readings and document the result. The four readings should be similar – if there is a major difference, check for door openings or the MAHU hunting.

Emil Bordelon is a Certified National Environmental Balancing Bureau Professional in Cleanroom Performance Testing with 19 years in the cleanroom certification industry.
http://www.amts.com/services/cleanroom-services.

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ispeCaSAsac@gmail.com

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Student Corner

Connecting a World of Pharmaceutical Knowledge

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2015 ISPE CaSA Poster Competition

By Leanna Pearson and Diane Darlington

CASA's annual poster competition is a chance for students to gain valuable experience presenting their research to industry professionals. This year's event attracted four competitors from two local Universities. The Undergraduate Winner was Stephanie Nguyen and the Graduate Winner was Diana Wright, both from ECU. They will each go on to compete against other regional winners at the ISPE Annual Meeting this November. Abstracts from their presentation can be found on next page.

Student Corner

HTLV-1 encoded protein HBZ inhibits the transcriptional activity of the cellular factor GATA-4

Authors: Stephanie Nguyen, Kimson Hoang and Isabelle Lemasson

East Carolina University

Abstract:
Leukemia virus type 1 (HTLV-1) is a complex retrovirus that infects CD4+ T-cells. A certain subset of infected people will develop a deadly leukemia called adult T-cell leukemia (ATL). ATL is a very aggressive disease and when the patient is diagnosed with the acute clinical subtype, the median survival time is 6 months. We found that HTLV-1 infected cells and ATL cells abnormally express the transcription factor GATA-4. GATA-4 is from the GATA family of factors that contain a zinc finger DNA-binding domain that binds the consensus DNA site [(A/T)GATA(A/G)]. To activate transcription, GATA proteins recruit the coactivator p300 and its paralogue CBP to the DNA. GATA-4 regulates transcription of genes involved in embryogenesis and myocardial differentiation and function. Usually, GATA-4 is not expressed in T-cells, but GATA-3 is. Surprisingly, we found that the HTLV-1 infected cells and ATL cells do not express GATA-3. In an effort to understand the role of GATA-4 in HTLV-1 infected cells, we focused on the interaction between GATA-4 and p300/CBP. We found that GATA-4 binds to two domains of p300/CBP, the cysteine/histidine domain 3 (CH/3) and the histone acetyl transferase domain (HAT). One of the viral proteins produced by HTLV-1, known as the HTLV-1 basic leucine zipper factor (HBZ), also binds the CH/3 and HAT domains of p300/CBP. Using a biochemical assays, we found that GATA-4 and HBZ compete for binding to the CH/3 domain. In luciferase reporter assays, HBZ repressed transcription by GATA-4, which may mean that HBZ prevents GATA-4 from recruiting p300 to the DNA for the activation of transcription. We would like to extend our studies to HTLV-1 infected cells and determine whether a subset of GATA-4 can still bind p300 and activate transcription. There are several other viral proteins that are produced by HTLV-1, and GATA-4 may function with one of them at a different time during HTLV-1 infection.

The potential of Human T-cell leukemia virus type 1 bZIP factor (HBZ) as a multi-target treatment

Authors: Diana Wright, Nicholas Polakowski, Torsten Wurm, Stephanie Nguyen, Isabelle Lemasson

Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA

Abstract:
Human T-cell leukemia virus type 1 bZIP factor (HBZ) is a viral protein encoded by the retrovirus HTLV-1. We previously found that HBZ interacts with the histone acetyltransferase (HAT) domain of p300/CBP and inhibits acetyltransferase activity. At this time, we have evidence that proper acetylation of different substrates regulates development, cognitive and neurodegenerative disorders, cancer, and cardiovascular disease, and it is likely that as research develops acetylation will be linked to the regulation of several additional processes. Curcumin, a dietary pigment from Curcumin longa, is able to inhibit the HAT activity of p300/CBP and other coactivators. Curcumin is currently used for its antioxidant, anti-inflammatory, and anti-cancer properties. We have shown that HBZ-mediated inhibition of p300/CBP HAT activity is stronger than a known inhibitor, curcumin. We now demonstrate that HBZ is able to inhibit the HAT activity of multiple coactivators including p/CAF, HBO1, and MOZ, demonstrating that it has possible widespread use. We narrowed down the inhibiting domain of HBZ to a peptide, 33 amino acids long, and this peptide has the same inhibitory activity as the entire protein itself. Although full length HBZ is a viral protein with many harmful effects, synthetic creation of its inhibiting domains may be carefully used as a varied pharmaceutical treatment.

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Prestonwood Country Club
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Technology Corner

Calibrating Conductivity Sensors In Ultra-Pure Water System

By Bruce Bartlett, Consultant, PCI Consult

In pharmaceutical and biotechnical industries the need to properly monitor quality water systems is paramount to ensuring product quality and FDA compliance. The standards set by United States Pharmacopeia (USP) require Water for Injection (WFI) and Purified Water (PW) meet certain conductivity limits before it can be used to manufacture a product. In order to properly monitor these limits, conductivity-measurement-systems should be calibrated utilizing methods that will improve accuracy and provide dependable and accurate readings in purified water environments. It is well documented that a significant percentage of the error associated with a conductivity-measurement-system is attributed to the conductivity sensor. Conversely, the conductivity sensor should undergo a well-defined calibration process that enhances or improves the accuracy.

Conductivity is measured by placing two electrodes of known area (a) in a solution at a fixed distance apart (l). The ability of solution to conduct (conductivity) is measured by applying an alternating current (AC) to the electrodes and measuring how difficult (resistance) it is for the electrons to flow from one electrode to the other (current flow). A fixed area of 1 square centimeter and a distance of 1 centimeter were established to standardize conductivity measurements worldwide. Utilizing these standardized parameters defines the cell constant and normalizes conductivity measurements to a volumetric measurement of 1 cubic centimeter (see figure 1)[1]

$$K = \frac{\ell}{a}\left[\frac{cm}{cm^2}\right] = cm^{-1}$$

Figure 1

A complete measuring system consists of three basic components: measuring instrument (or analyzer), sensor or cell, and the cable linking the sensor and analyzer. Each of these components contributes to overall system accuracy. Modern sensors utilize a concentric design (see figure 2) which was developed to be more a robust solution than the theoretical cubed design (see figure 3). Located internally on the sensor is a 1000 ohm platinum (Pt1000) resistance temperature device (RTD) to accurately measure temperature.

[1]Braga, Victor M. (2004) Conductivity Sensor Calibrations to Meet Water Industry Requirements.

Analyzer calibration consists of applying known resistance values across all temperature and conductivity ranges to align the gain circuitry, optimizing the measured value. This is a relatively straight forward calibration process done through automated fixtures or resistance simulators traceable to the National Institute of Standards and Technology (NIST). The sensor, however, is calibrated by placing it in a known conductivity solution, traceable to national standards, and computing the cell constant and temperature multiplier values. The cell constant is a conversion factor used to convert the measured conductance to conductivity (Conductivity = Cell constant x Conductance). In order to provide the end user with better accuracies and a better defined cell constant the conductivity sensor is calibrated at the bottom of its range (18.18 Mohm-cm or 0.055µS/cm). Unfortunately, low level conductivity standards for Ultra-Pure Water (UPW) applications are not commercially available, nor can they be easily produced. To remedy this issue, sensors utilized in UPW environments are calibrated in a sealed, circulating Ultra-Pure water loop against a standard sensor that is calibrated and is traceable to ASTM International Standard D1125. The water loop circulates until the water quality reaches 18.18 Mohm-cm and the temperature is stabilized at 25°C. At this point, the sensor or unit under test (UUT) cell constant and temperature factors can be computed, which is annotated in the calibration report and affixed on the measuring equipment for easy reference.

Through traceability to ASTM International Standard D1125 and by utilizing an on-site closed Ultra-Pure Water system, Metrology Laboratories can now offer 17025 Accredited Service for conductivity sensors. Scopes of Accreditation express expanded measurement uncertainties as low as 0.27 Mohm-cm, further improving Test Uncertainty Ratio's (TUR) and the level of accuracy for the end user.

Figure 2

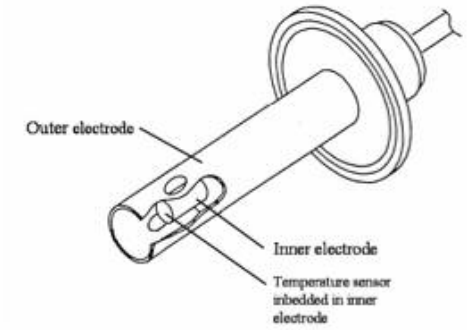
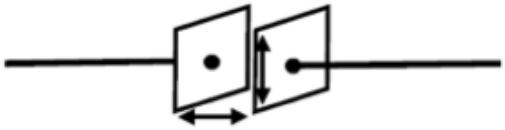


Figure 3



Questions or comments concerning this article can be emailed to Bruce Bartlett at bbartlett@pci-llc.com. Bruce Bartlett is a consultant with Pharmaceutical Calibrations and Instrumentation (PCI). Bruce has a combined 10 years of metrology experience in Aviation, Nuclear and Life Science Industries. Bruce has worked for PCI 3 years and is located in Raleigh, NC. PCI's 17025 Accredited Metrology Lab can offer a diverse scope of measurement disciples and has provided Life Science Industry clients across the nation with dependable, FDA compliant solutions.

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ISPE Carolina-South Atlantic Chapter Newsletter

1500 Sunday Drive, Suite 102, Raleigh, NC 27607
Tel: 1-919/573-5442 • Fax: 1-919/787-4916
rich.stanfield@cagents.com

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Articles should be written for technical professionals in the pharmaceutical, biotechnology, and medical device industries. The author is responsible for the accuracy and correctness of all statements contained in the manuscript (ISPE Carolina-South Atlantic Chapter assumes no liability.) Manuscripts should be forwarded to a Member of the Newsletter Committee at rich.stanfield@cagents.com for review 30 days prior to publication. A brief three to four sentence synopsis of the article, as well as a brief biographical statement about the author that includes educational background, title and job affiliation, job responsibilities and major areas of accomplishment must accompany the article.

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