SurFACTS in Biomaterials

SUMMER 2020
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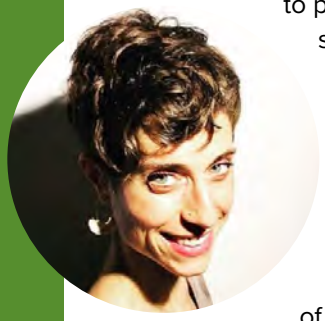
INSIDE THIS ISSUE

From President Angela DiCiccio



I am humbled and excited to present the 2020 summer edition of SURFACTs. The articles in this feature and their contributing authors highlight why I became a member of the Surfaces in Biomaterials Foundation and I am thrilled to help foster and grow our membership, our impact, and our mission. For me, this community represents a welcoming, passionate, and brilliant collection of technical experts and creative minds looking to motivate positive change and fluid knowledge sharing related to critical advances in biotechnology. As we forge into the second half of 2020, I'm curious to hear what motivates your Surfaces membership (or what you're looking for to join).

In tune with embracing change, we opened this quarter by quickly pivoting our annual Open House into a virtual symposium at the beginning of May. With the support of Nelson Laboratories and energetic collaboration with the American Physical Society, we hosted over 100 attendees for a stimulating two-hour learning session. Via Crowdcast and chatroom, Martell Winters of Nelson Laboratories and Mallika Kamarajugadda of Medtronic each shared advances in disinfection technologies, including COVID-related efforts and discoveries. Continuing the conversation from our session that afternoon, Martell and Mallika are featured authors in this edition of SURFACTs, providing an overview of their talks, diving deeper into questions from our attendees and offering updates.

In line with the intention of our community to cultivate collaboration, communication and recognition of emerging new technologies, we were excited to hear from an enthusiastic participant from the Open House, Tony Eisenhurst of NovaSterilis, who described the journey of fostering and growing a company and technological platform during a time of unmet need. We are thrilled to hear Tony and the Novasterilis team just received an EUA from the FDA for use of their technology by healthcare providers for N95 PPE decontamination and reuse!

Continuing with the theme of growth and future connections,

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Virtual Open House

The first Virtual Spring Open House held by Surfaces in Biomaterials Foundation and American Preclinical Services was a big success! Held on June 10, the event featured a webinar from two leaders in the medical device field on medical device sterilization alternatives to EtO and novel approaches/challenges to sterile processing of non-traditional materials (PPE) due to the COVID-19 pandemic. The event was sponsored by Nelson Labs and accrued nearly 100 attendees.

Additional Speakers and Presentations Included:

Dr. Mallika Kamarajugadda, Sr. Principal Scientist, Medtronic Corporate Science and Technology who presented on ethylene oxide (EtO) sterilization alternatives for medical device applications.

Martell Winters, Director of Scientific Competency, Nelson Labs, presented information on the decontamination and sterile reprocessing of personal protective equipment (PPE)—traditional and nontraditional methods.

Virtual attendees were able to post questions for the speakers and interact online with a live chat feature.

SIBF Board President Angie DiCiccio and Open House Event Chairperson Bill Theilacker hosted the event and included a trivia quiz challenging attendees' knowledge about SIBF's history that attendees could participate in while viewing the open house.

Our Trivia Quiz Winners:

Yelena Gorlin
Yongxing Qiu
Sebastian Riano
Benjamin Tang

Congratulations! Each won a $25 Amazon gift card.

For those who couldn't attend the event live, you can register to view the recording at our website: **www.surfaces.org**.

Thanks to our Open House Committee and special thanks to our generous sponsors.

Thanks to all who attended, we hope to see you at the Virtual Biointerface Conference beginning Thursday, October 1, 2020.

APS
AMERICAN PRECLINICAL SERVICES

Nelson Labs.
A Sotera Health company

From President Angela DiCiccio

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this feature reveals our new structure for the 2020 Virtual Workshop and Symposium. Throughout the month of October we will host mini technical sessions that will be supported by our interactive app developed with Socio, designed to enable unique and meaningful networking and collaborations. I am incredibly proud and excited by our speaker line up for this October and sincerely hope that you will join.

As I reflect in my improvised home office about my experiences this year, COVID is the umbrella that colored this journey. However, from this unexpected event matriculates recurring themes of breakthrough collective knowledge, unprecedented collaboration, and transparent communication. While this season marks a time of rapid adaptation and challenging convention, while feeling stuck in the middle of uncertain rapid change, I am confident and find comfort in knowing that change will come from discoveries made by the collective, creative, and empowered expert minds of the members of our Foundation. Thank you all for joining the conversation, tuning in to learn, and sharing your knowledge and passion. I look forward to growing together.

Join us for Virtual Biointerface 2020

Join the Surfaces in Biomaterials Foundation community for a month of virtual lectures and networking opportunities via our new app designed to enable virtual connections, collaborations and communication.

Visit **surfaces.org/Biointerface-2020** for the complete October BioInterface program.

Dr. Robert Langer

Register online for an unlimited pass to all sessions. Early bird discount registration ends August 31.

Workshops and sessions include:

- Workshop: Entrepreneurship in Surface Solutions
- Surface Modifications and Coatings
- Interface of Biomaterials
- Drug Delivery
- Tissue Engineering and Regenerative Medicine
- Analytical Tools
- Point Counterpoint
- Student Competition

In addition to our talented speaker consortium, all participants will have the opportunity to meet this year's Excellence in Biomaterials Science Award winner, Dr. Robert Langer from the Massachusetts Institute of Technology (MIT) and hear from our keynote speaker Bob Ward from ExThera Medical.

We hope you will join for some or all of our live programs, on demand content, and networking opportunities as we grow as a digital community.

Open Volunteer Position: Social Media Communications Captain

The Surfaces in Biomaterials Foundation values the voice of each member of our community and seeks to leverage opportunities to promote networking, collaboration, innovation and share advances from our community. If this mission resonates with you and you have a passion for communication, please join us! We are looking for a skilled and enthusiastic social media communications captain to create and coordinate our communications platforms. If you are interested, please send your contact information and a short share about why this position caught your eye to **info@surfaces.org**. Please reach out with any questions!

Thank you,
Surfaces in Biomaterials Foundation Board of Directors

Follow the Surfaces in Biomaterials Foundation on Social Media!

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Visit our LinkedIn page here

Follow us on Twitter: click here

Decontaminating N95 Respirators in Response to the National Shortage

We are living through the most sustained and pressing crisis of our generation. As the SARS-CoV-2 virus was spreading globally in early March, we realized that our supercritical carbon dioxide sterilization (scCO2) technology could aid in the pandemic response. We will forgo the typical technical article and share how we quickly pivoted our business to focus on the decontamination of N95 respirators in response to a national shortage. By addressing this market need brought on by the COVID-19 pandemic, we were able to meaningfully improve our research activities, business operations and financial strength through the learnings of a time-sensitive project. NovaSterilis had substantial process and equipment expertise in the use of its scCO2 technology in the medical device manufacturing environment, but we had a knowledge gap as it related to the healthcare setting. NovaSterilis engaged lead partners iFyber, LLC as well as Drs. Geoffrey Coates and Richard Turner to close this gap and provide a solution less than 30 days.

NovaSterilis' scCO2 platform has been used globally for over 10 years to clean, decellularize and sterilize biomaterials and functionalize drug delivery devices. Over 300,000 allograft tissues have been processed with our technology and implanted in patients across North America, Australia, and Europe. The deep penetrating capability of scCO2 (it is a solvent with liquid-like density but gas-like diffusibility), low operating temperature (sub-37°C), and minimally reactive additive, make scCO2 technology ideal for sensitive materials, such as low Tg polymers, hydrogels, growth factors, small molecules, and biotherapeutics. The process is effective on liquid, lyophilized, hydrated, and submerged materials. In early March the closest we had come to operating in a healthcare setting was a project on sterilization of duodenoscopes. The question we posed on March 18 was two-fold—could scCO2 sterilization be used to decontaminate N95 respirators in a healthcare facility respecting current workflows and could this be achieved in under 30 days?

NovaSterilis has always taken a practical approach to technology development, starting from when the concept was spun out of Dr. Robert Langer's lab. Rather than focus on the sterilization of bioactive drug delivery devices, we targeted a lower risk, nearer term commercial opportunity in tissue banking : provide a Sterility Assurance Level 10-6 for soft tissues without damaging performance. The N95 respirator project would be different. It required a multi-pronged, aggressively staffed, "all-in" effort. If successful, this would not only generate broader market opportunities, but it would also provide a new paradigm for project execution for the company.

We are a small, technology focused team with minimal regulatory experience. Filing an FDA Emergency Use Authorization (EUA) request required expertise in regulatory strategy, planning, and execution. We needed a regulatory partner that was nimble, multi-disciplinary, and willing to integrate into our team. iFyber was engaged because they provided immediate access to a multi-disciplinary team of Ph.D. scientists and utilize an "immersive" partnership approach. iFyber's technical expertise lies at the interface of microbiology,

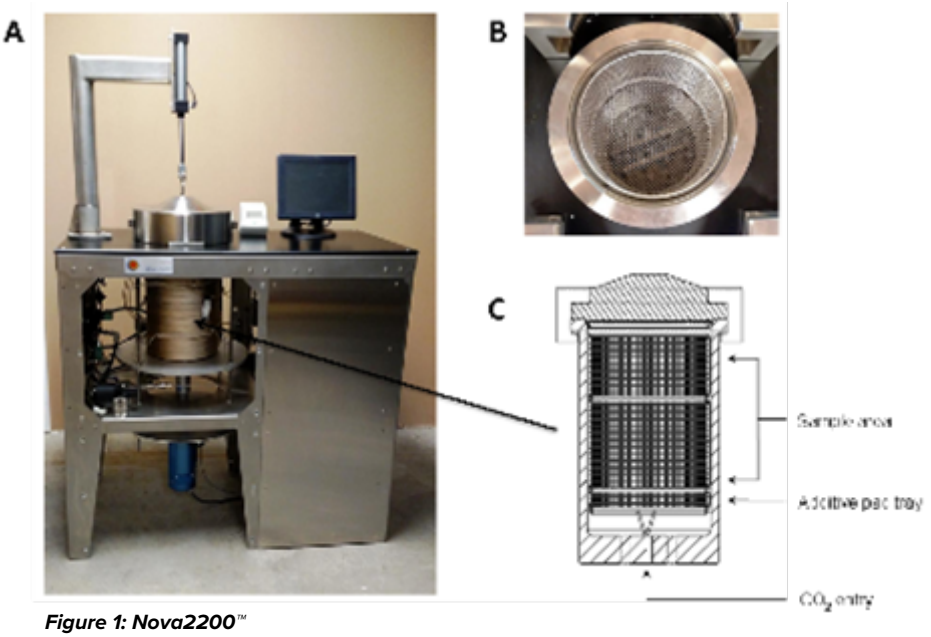

Figure 1: Nova2200™

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Decontamination and Sterile Processing of Personal Protective Equipment

Traditional and Nontraditional Methods

Martell Winters, B.S., RM/SM (NRCM), AAMI CISS (RAD) – Nelson Laboratories, a Sotera Health company
Janelle Bentz, M.S., Nelson Laboratories, a Sotera Health company
Aaron DeMent, B.S., Sterigenics, a Sotera Health company

When the COVID-19 pandemic hit, personal protective equipment (PPE), especially facemasks and respirators, were in short supply due to unforeseen, increased demand and shortages in raw materials and finished products. As can be imagined, the month of March 2020 brought a tremendous quantity of inquiries flowing into laboratories worldwide regarding validation of new masks and validation of processing masks for reuse (re-processing). Prior to the COVID-19 pandemic there was no standard, established process for validation of mask reuse. Particularly, the biggest concerns tended to be with the masks that were originally sold as N95 respirators, but which were being reprocessed in some form to allow for reuse of this rapidly-diminishing commodity. For purposes of this article the term "reprocessing" includes all forms of decontamination, disinfection, sterilization, etc. that are applied to PPE to allow it to be reused. Also, unless specifically called out, the general term "masks" will be used to represent both surgical masks and respirators.

Thus, a flurry of activity came from many stakeholders. The Food and Drug Administration (FDA) and other national regulatory bodies around the world, World Health Organization (WHO), Association of Perioperative Registered Nurses (AORN), Center for Disease Control (CDC), National Aeronautics and Space Administration (NASA), National Institute of Occupational Safety and Health (NIOSH), Global Center for Medical Innovation (GCMI), and hospitals around the world began work in an attempt to remedy the PPE shortage. On the industry front, work was being conducted by many existing medical device manufacturers, both US-based and global, and other manufacturers also got involved who had no previous experience in the health care industry.

Nelson Laboratories, Nordion and Sterigenics, all Sotera Health companies, developed in internal COVID-19 task force consisting of experts in PPE testing, sterilization and microbiology. Much of the information in this article is based on information gathered and discussed by this task force.

FDA Emergency Use Approvals

Fortunately for the industry, FDA and other national regulators quickly issued their emergency use approval processes for masks and reuse of masks. The FDA document released early during the COVID crisis is entitled Enforcement Policy for Face Masks and Respirators During the Coronavirus Disease (COVID-19) Public Health Emergency – Guidance for Industry and Food and Drug Administration Staff. This document specifically provides guidance to the industry regarding how to make more single use masks available to health care workers and to provide a framework around the minimum requirements FDA would expect for a submission for equipment or a process to allow reprocessing and reuse of masks in a health care setting.

General EUA requirements: During this time FDA has proven willing and expeditious regarding talking to companies or people in industry and evaluating processes that allow reprocessing of masks. The general information required for a submission for emergency use approval (EUA) for reprocessing includes the following:

• A description of the process for disinfection or decontamination controls, such as the cycle parameters and the chemical indicator (CI) and biological indicator (BI) to be used to monitor the process.

• Validation data to support a bioburden reduction for reprocessing should generally achieve a ≥3-log reduction of virus (specifically coronavirus) and a ≥6-log reduction of Mycobacteria or spores. It must also be demonstrated that soils (for example makeup, blood, or dirt) can either be removed or do not interfere with the bioburden-reduction process.

• Demonstration of the ability to maintain chain of custody and to have safeguards in place to prevent exposure of contaminated masks to those who handle the masks before and during reprocessing. This becomes less of an issue if the wearer of the mask is performing their own disinfection process and if it will only be used by the same person after reprocessing.

• The bioburden reduction process must be shown to be compatible with the mask materials. Data must be available to demonstrate that the necessary fit and filtration efficacy are still met after the maximum number of disinfection processes.

• The process must be shown to not leave enough residues to cause a health hazard or deleterious effect.

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Decontamination and Sterile Processing of Personal Protective Equipment

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• Evidence to demonstrate that repeated exposure to decontamination cycles does not interfere with the filtration ability or breathability of the respirator. A method of tracking repeated exposures should be defined.

As interested stakeholders reviewed the guidance document, questions arose regarding how much flexibility could be permitted in meeting some of the requirements. On a conference call with representatives from the Sotera Health COVID-19 task force, others from the health care industry and the FDA, some questions were asked to better understand the intent behind the document. Following are some of the questions that were discussed. Note that this was an informal discussion with a small number of FDA representatives, and thus it reflects only their opinions, not necessarily the expectations of the FDA as a whole.

Sample size: A document commonly used in the medical face mask industry is EN 14683. In this document the sample size for some mask testing is commonly five. It was asked if this number would be considered acceptable for tests performed for an FDA submission when the standard test method does not specify a sample size. The representatives felt that the sample size of five was a reasonable, general number for the tests required in their guidance document.

BIs and CIs: It was mentioned that for some forms of reprocessing being investigated or proposed, BIs and CIs might not be readily available. For example some processes being investigated do not occur in a chamber, but might be applied in a room or a container of some sort. Because of this it could be difficult to obtain or develop a BI and CI in all situations. Thus the question was centered on the ability to authenticate the effectiveness of reprocessing based on verification that the required parameters were all met. This is often called parametric release in the sterilization industry. The representatives shared a desire that BIs and CIs be used to verify these cycles rather than relying on parametric release. This is a reasonable request as many of the processes being investigated are new to the industry, or at the very least are newly being applied to masks.

Testing of Mycobacteria and human coronavirus: The requirement to demonstrate a 6-log reduction for Mycobacteria is difficult from a timeline perspective, due to the lengthy amount of time required to allow many species of Mycobacteria to replicate. It is not uncommon to allow a two or three-week incubation time to allow Mycobacteria to replicate to a level where it can be used for a test or counted to know the number of survivors after a test. This incubation time compounds when several tests are needed and can result in several months of delay in order to gather appropriate data. It was asked whether it would be possible to use published literature instead of requiring empirical data for inactivation of Mycobacteria. Along these same lines, if it is known that the human coronavirus causing COVID-19 is less resistant to the disinfection process than another microorganism being evaluated, it seems justifiable to not require empirical data on the viral inactivation either.

In a second document released by FDA (*Enforcement Policy for Sterilizers, Disinfectant Devices, and Air Purifiers During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency – Guidance for Industry and Food and Drug Administration Staff)* the resistance scale for germicidal chemicals, which has been known and used in the industry for decades, was reproduced (see Figure 1). This resistance scale makes it clear that bacterial spores are at the top of the resistance scale with enveloped (lipid) viruses, such as coronavirus, at the bottom of the scale, meaning that coronaviruses are the least resistant to germicidal chemicals when compared to other types of microorganisms and when compared to nonenveloped (nonlipid) viruses. The FDA representatives felt that if appropriate literature were available to support the greater resistance of the microorganism being evaluated, the less resistant microorganisms could be eliminated from the empirical test plan.

Chemical residues and material functionality: Obtaining a high inactivation of Mycobacteria or spores usually requires fairly harsh chemicals. Use of these kinds of chemicals are likely not often feasible due to either residuals on the masks or material functionality loss after exposure. The idea was discussed of using a risk assessment to justify a

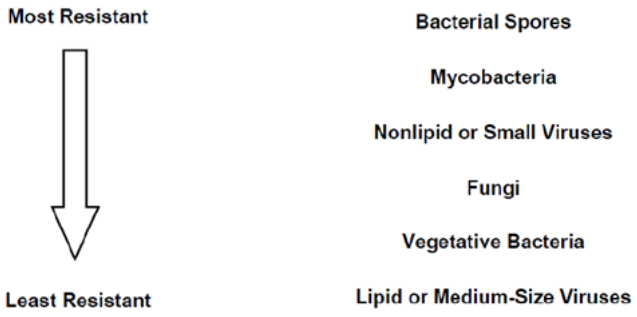

***Figure 1. Descending Order of Resistance of Microorganisms to Germicidal Chemicals (from FDA's* Enforcement Policy for Sterilizers, Disinfectant Devices, and Air Purifiers During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency – Guidance for Industry and Food and Drug Administration Staff)**

Modified from Favero, M.S. and Bond, W.W., Chemical Disinfection of Medical and Surgical Materials. In: Disinfection, Sterilization, and Preservation, 5th Ed Phila: Lippincott Williams & Wilkins 2001: 881-917.

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low-level disinfection rather than a high-level disinfection or sterilization. Low-level disinfection requires a 6-log reduction of a number of vegetative bacterial species rather than spores or Mycobacteria and is easier to obtain with less-harsh chemicals. It seems that this approach could be applicable because the clinical microorganisms of concern are not spores and there is not a high level of concern with Mycobacteria in many places of the US. The representatives felt this might be a reasonable approach if the mask is to be returned to the same user. This seemed to be a reasonable approach to obviate the potential for a user who has Mycobacteria to pass it on to a different user.

Soils on the masks: Regarding the requirement of either removing any soils on the masks or showing that they do not interfere with the disinfection process, a discussion was had regarding having the reprocessing staff perform a visual inspection and to simply not reprocess masks that are soiled. The representatives felt this was a reasonable approach.

Approved EUAs: As of early June 2020 the FDA had shown great responsiveness in reviewing and approving a high number of EUA applications. For example, 15 EUAs were granted for decontamination and sterilization processes or equipment; 94 EUAs were granted for test kit manufacturers and laboratories; 35 EUAs were granted for molecular-based laboratory-developed tests; and 23 EUAs for ventilators and other medical devices.

Reprocessing Modalities

There are a number of reprocessing modalities (both sterilization and disinfection/decontamination) that either are common in the industry or that are being assessed, specifically with masks and other personal protective equipment (PPE) such as gowns, in mind. Sterilization methods that have been considered are vaporized hydrogen peroxide (VHP), ethylene oxide (EO), radiation, and moist heat (steam). These methods are well characterized in the sterilization industry and are regularly used on health care products. Thus they become primary potential modalities for reprocessing of PPE.

Several of the EUAs issued by FDA use VHP to reprocess masks. The data seem quite convincing that N95 masks can be reprocessed with VHP with little impact on the filtration efficiency and physical requirements of the masks. The question is how many times the masks can be reprocessed before seeing a negative impact on filtration efficiency, materials and fit. This will vary depending on the VHP system.

EO has been used for many years to sterilize masks used by health care workers but has not been previously addressed sufficiently for re-sterilization. Radiation has also been used historically for sterilization of PPE, but again the issue of re-sterilization has not been fully addressed. Moist heat is a viable option for materials that can withstand the high temperatures of 121°C and higher (e.g. polypropylene), but it often eliminates many types of PPE because of the inability of one of the components to withstand the high temperature. N95 masks often obtain most of their filtration efficacy due to the material itself, but obtain the additional efficacy to reach 95% by an electrostatic charge on the material. That static charge is removed with high levels of moisture, which makes moist heat a difficult choice for these types of PPE.

Reprocessing modalities other than sterilization include methods that sometimes are used for sterilization, but in the context of masks and other PPE are reduced in their intensity to obtain a necessary level of inactivation of some microorganisms while leaving the PPE still fully functional after processing. Modalities such as dry heat and ultraviolet light (UV) fit in this category. For example a typical dry heat sterilization process might require temperatures up to 160°C. However data have been accumulated to show that temperatures of 80 or 90°C are sufficient to inactivate a coronavirus load on PPE.

Preliminary data gathered at Nelson Laboratories indicated that a 70% IPA spray on masks was effective against vegetative microorganisms and reduced the bacterial filtration efficacy to about 85 to 90% as opposed to the typical target value of 95%. The assumption is that the liquid spray on the masks was reducing the electrostatic charge previously mentioned. Additional preliminary data showed that radiation sterilization at 25 kGy at dry ice temperatures reduced the bacterial filtration efficacy to about 90%. This was fairly promising data because 25 kGy is likely more than what is really needed to reprocess masks. The significant disadvantage is that radiation facilities are expensive and thus are only offered as a contract service and cannot be done on site at the hospital.

The WHO spent a significant amount of time and effort with a large group of experts to try to validate processes that would be easily usable in third world countries. They also limited their scope to inactivation of coronavirus rather than being concerned with vegetative bacteria, Mycobacteria, and spores. Those data will be published in the near future. Initially they desired to gather data on UV light, methylene blue plus light, dry heat at lower temperatures, as mentioned above, and VHP. The testing using UV light was removed from the list of modalities, but the other testing is

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near completion. The process using methylene blue plus light was not well known by many in the industry but there is a large amount of literature regarding its effectiveness, so it will be interesting to see the data that are generated.

Testing of Masks

Testing to verify the performance of masks also significantly increased as a result of COVID-19. Many questions arose from companies who had previously not manufactured masks but who were desirous to get involved during the shortage. Surgical face masks and N95 respirators each have performance requirements which reflect their use. Surgical face masks are used to protect the surgical environment from droplets originating from staff and to protect the staff from large splashes or sprays. Testing for these products according to ASTM F2100 (US standard) and EN14683 (European standard) includes bacterial filtration efficiency (BFE) of 95 or 98% for approval. This test employs a polydispersed aerosol with droplet sizes ranging from 0.6 - 9 microns and controls the mean particle size to 3.0 ± 0.3 microns. Testing uses a flow rate of 28.3 liters per minute (LPM). There is no fit test required, as these masks are not made to protect the wearer from small aerosols.

Particulate filtration efficiency testing according to ASTM F2299 is performed using latex spheres in a variety of sizes. ASTM F2100 indicates that a size of 0.1 microns should be employed. This testing is meant to help determine whether these masks are protective against very small particles. Testing takes place at a flow rate of 28.3 LPM, using a non-neutralized particle.

N95 respirators also require particulate filtration efficiency (PFE) testing. This testing uses a monodispersed aerosol of neutralized sodium chloride (NaCl) at a size of 0.26 microns and a flow rate of 85 LPM following US FDA 42 CFR Part 84. Included in the requirements for this type of mask is a fit test to ensure the mask seals to the user's face to protect from small droplets in the air.

Due to differences in the BFE and PFE test methods it is difficult to compare surgical face masks and N95 respirators without additional testing. In a 2016 study (see S. Rengasamy, et al), surgical face masks and N95 respirators were subjected to testing according to both the ASTM/EN standards and 42 CFR Part 84 protocol. While the mean results for the BFE and latex PFE testing were comparable for all products (ranging from 98.12 - 99.99%), the results from PFE testing using NaCl were telling. The N95 respirators performed as expected, with all reported results >95% filtration efficiency. The different surgical masks tested showed mean filtration efficiencies for NaCl PFE testing of 54, 72, and 88%, indicating that in spite of their ability to filter out the droplets used in the BFE and small, charged particles in the latex PFE tests, they do not perform as well as N95 respirators when tested according to this harsher, NaCl PFE test method.

The plethora of masks being developed and sold by manufacturers new to the mask industry only have surgical mask and respirator criteria to consider. The intent of the fabric masks is usually not to meet the N95 criteria, but to be somewhere close. Data from one unpublished study demonstrated that a multilayer fabric material could obtain BFE results in the 80% range. Since this is close to the BFE performance requirement of surgical masks, it seemed a reasonable approach for the typical users who are not health care workers. One of the main efforts of these alternative masks is to minimize the use of surgical and N95 masks by the general populace to allow these to be available to health care workers who, in many instances, are directly interacting with patients known to have COVID-19.

At its foundation, the approach for reuse of masks involves three critical aspects. The first is to ensure the efficacy of the reprocessing methods, followed by ensuring the functionality of the reprocessed masks. Lastly is to ensure the safety of the user, both with respect to the microbiological inactivation as well as the biocompatibility of the material and any possible residuals from the reprocessing activities.

Table 1 (next page) provides a comparison of the primary standards referenced for masks in the US, from ASTM F2100, and in Europe, from EN 14683. Although there are some similarities, specifically with one of the more critical tests, BFE, there are significant differences in which types of tests are to be performed. Although these requirements are usually referred to for single-use masks, they are still applicable for assessing reprocessed masks.

Biocompatibility of Reprocessed Masks

The last of the general topics to address is biocompatibility. Although biocompatibility has certainly been addressed for the masks that were commercially available prior to COVID-19, there were little data regarding biocompatibility on masks that have been reprocessed or masks that were used for a longer period of time than previously anticipated. Biocompatibility is often assessed for these types of products using the three main tests of cytotoxicity, sensitization, and irritation. However, in light of the COVID-19 pandemic many regulatory

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U.S.A.: ASTM F2100-19 STANDARD SPECIFICATION FOR PERFORMANCE OF MATERIALS USED IN MEDICAL FACE MASKS
EUROPE: EN 14683:2019 MEDICAL FACE MASKS – REQUIREMENTS AND TEST METHODS

		ASTM F2100-19			EN 14683:2019 Barrier Levels		
		Level 1	Level 2	Level 3	Type I	Type II	Type IIR
Barrier Testing	BFE % ASTM F2101, EN 14683	≥95	≥98		≥95	≥98	
	PFE % ASTM F2299	≥95	≥98		Not required		
	Synthetic Blood ASTM F1862, ISO22609	Pass at 80 mmHg	Pass at 120 mmHg	Pass at 160 mmHg	Not required		Pass at ≥ 16.0 kPa (>120 mmHg)
Physical Testing	Differential Pressure EN 14683	<5.0 mmH_2O/cm^2	<6.0 mmH_2O/cm^2		<40 Pa/cm^2		<60 Pa/cm^2
Safety Testing	Flammability 16 CFR Part 1610	Class 1 (≥ 3.5 seconds)			See European Medical Directive (2007/47/EC, MDD 93/42/EEC)		
	Microbial Cleanliness ISO 11737-1	Not required			≤30 cfu/g		
	Biocompatibility ISO 10993	510 K Guidance recommends testing to ISO 10993			Complete an evaluation according to ISO 10993		
Sampling ANSI/ASQC Z1.4 ISO 2859-1		• AQL 4% for BFE, PFE, Delta P • 32 masks for Synthetic Blood (Pass = ≥29 passing, Fail = ≤28 passing) • 14 masks for Flammability			• Minimum of 5 masks up to an AQL of 4% for BFE, Delta P and Microbial Cleanliness • 32 masks for Synthetic Blood (Pass = ≥29 passing, Fail = ≤28 passing)		

***Table 1: Comparison between US (ASTM F2100-19) and European (EN 14683) requirements (from Nelson Laboratories at* https://www.nelsonlabs.com/wp-content/uploads/2020/03/Face-Mask-Testing-Requirements.pdf)**

agencies are accepting more of a risk-based approach rather than requiring that all tests be performed. This is because some biocompatibility tests are quite lengthy and could significantly delay the ability of a good reprocessing method to be used, or a new product to come to market. Use of a risk-based approach is not new to biocompatibility or to the health care industry; it is common to use risk analyses as a means of intelligently reducing the amount of testing that occurs and to make better-informed decisions using risk rather than a check-box approach.

In the context of mask testing, regulatory agencies have been amenable to the approach of performing a cytotoxicity test first, which can be performed in a matter of days, followed by a review of the mask materials that will have contact with the face and identifying any materials that are known to be sensitizers or irritants. A review of any potential residues from the sterilization or decontamination method should also be undertaken. Based on these materials and processing agents, a toxicological risk assessment can be performed to understand whether additional testing must be performed or not. It must be understood however that if a manufacturer intends to continue selling masks after the pandemic, it will be expected that they conduct the irritation and sensitization testing to fully meet the requirements from the primary ISO standard for biocompatibility, ISO 10993-1. It should also be noted that any additional residue testing mandated by the ISO 10993 series should also be conducted (e.g., ISO 10993-7 for ethylene oxide).

Conclusion

As a scientist reviews publications in the literature related to the reprocessing of masks it is obvious that the data can be difficult to interpret and compare. Since there have not been established processes or procedures for validation of mask reuse, questions often arise such as whether the correct tests were performed or whether all of the critical variables were considered. Thus it is incumbent on the industry to obtain as much of the full picture as possible prior to making decisions based on published data. Generally it is wise to not make decisions based on one publication alone, but to find several publications on the same topic to

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obtain a more complete picture. Even when multiple publications are obtained, it is often found that they either do not corroborate well or there is still a piece of the puzzle that is missing. This increases the need in the industry for standardized approaches for validation of PPE reprocessing. Since it is likely that the coronavirus issue is going to continue to be something to be dealt with, it is a good call to the industry to work together to provide standardized approaches to reprocess PPE so that in times of pandemic there are readily available options to assist the health care industry in continuing to protect their employees.

Bibliography

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ASTM F2100-19, Standard Specification for Performance of Materials Used in Medical Face Masks

ASTM F2299 / F2299M-03(2017), Standard Test Method for Determining the Initial Efficiency of Materials Used in Medical Face Masks to Penetration by Particulates Using Latex Spheres

EN 14683:2019, Medical face masks - Requirements and test methods

ISO 10993-1, Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

US FDA 42 CFR Part 84, Respiratory Protective Devices

Decontaminating N95 Respirators in Response to the National Shortage

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materials science, and chemistry, while their operational expertise is in project management, quality systems, and the regulatory process. This allowed NovaSterilis' team to focus on its technology while iFyber identified what data would be required for the FDA filing. iFyber seamlessly integrated with the NovaSterilis team to provide expertise from concept through submission.

Central to the project's success was iFyber's trusted network. For example, ZeptoMetrix Corporation (Buffalo, NY) not only performed the viral inactivation studies within a week of securing the SARS-CoV-2 virus, but in that same period they brought NovaSterilis' equipment in-house, trained on the process, and then executed the inactivation protocol in their BSL3 facility. At the time, ZeptoMetrix was one of the few labs in the U.S. with access to SARS-CoV-2. Similarly, other partners including Imperia Engineering Partners, Cornell University, Cayuga Health, and Nelson Labs contributed test articles, equipment, and facilities to complete the work for the EUA submission within the targeted time frame.

Figure 2: N95 respirators packaged for decontamination

As data collection began, iFyber engaged the FDA connections NovaSterilis had established as a recipient of the FDA Innovation Challenge Grant focused on industrial alternatives to ethylene oxide sterilization. iFyber's interactions during the submission process solidified NovaSterilis' reputation as a science-centric, data-driven sponsor. The open and regular communication with the lead reviewer resulted in an incredibly positive experience. We never wondered where we stood with the process. Would we have liked the process to have gone faster? Of course. But we appreciate and respect the FDA reviewers working tirelessly out of a shared concern for healthcare workers, which is what this project was about from the start. The foundation of NovaSterilis' relationship and technology understanding within the Agency is much stronger today.

Using the "strike team" approach allowed us to pursue a market opportunity that would have otherwise been lost. We were able to go from idea to EUA submission in 28 days with great capital efficiency. Through this experience, we built an ecosystem that includes end users, testing facilities, materials and packaging suppliers, and regulatory agencies, all of which are critical to future development partnerships. Our experience can be used as both the map and vehicle for companies of all sizes looking to get to market efficiently. If you would like more insight, contact us at **tre1@novasterilis.com.**

Ethylene Oxide (EO) Sterilization Alternatives for Medical Device Applications

Dr. Mallika Kamarajugadda, sr. principal scientist, Medtronic Corporate Science and Technology

Disinfection and sterilization are essential for ensuring that medical and surgical instruments do not transmit infectious pathogens to patients. While disinfection refers to the process of eliminating or reducing the number of microorganisms to levels that no longer pose a threat to human health, sterilization refers to any process of destroying or eliminating all forms of microbial life, including bacterial spores. It is used in many different industries including different fields of healthcare [1,2,6]. The classification, developed by Dr. Earle Spaulding in 1968, categorizes objects based on their intended use and patient contact, and forms a basis for regulations on planning methods for sterilization. Sterilization is required for all "critical" medical devices and instruments; i.e., those that are used in direct contact with bloodstream or normally sterile body tissues. For "semi-critical" devices, those that are in contact with mucous tissues or non-intact skin, sterilization is recommended [7]. Table 1 shows the specific classifications.

Sterilization efficiency is defined as the ability to remove or destroy all forms of microbial life. Since absolute sterility cannot be verified, for all practical purposes, the statistical definition of sterility known as 'Sterility Assurance Level' (SAL) is used. SAL is defined as "the probability of finding a single viable microorganism occurring in or on a product after sterilization."

A SAL of 10^{-3} is used for products not intended to contact breached skin or comprised tissue, and for topical products that contact intact skin or mucous membranes. A SAL of 10-6 is generally accepted for all critical items, frequently used for the terminal sterilization of medical devices (probability of 1 in 1,000,000 of finding a nonsterile unit) [2,6,7]. Since most of the microorganisms, especially bacterial spores, are extremely resistant to environmental stress requirements, SAL sterilization requires sterilant exposure under validated conditions that are entirely different from typical device use conditions. Sterilization is not just about eradicating microorganisms, but it also involves making sure that the device performance is not affected across the life cycles. It impacts manufacturing and distribution of devices across the entire supply chain. Thus, material compatibility is one of the most important characteristics that needs to be considered for selection of the appropriate sterilization technique.

Sterilization methods can be divided broadly into two categories based on the nature of the sterilant and its reaction with microorganisms: physical processes (e.g. ionization radiation, dry heat, steam) and chemical processes (e.g. Ethylene Oxide, Hydrogen peroxide and "EO", glutaraldehyde). These processes target and deactivate the structure or function of the organic macromolecules in the microorganisms leading to their death or inactivating their ability to replicate. The chemical processes can further be classified based on the nature of the chemical sterilant [4]. Figure 1 shows broad categorization of different sterilization modalities.

Application	Level of risk	Spaulding classification	Recommendation
In close contact with a break in the skin or mucous membrane	High	Critical	Sterilization
For introduction into sterile body areas			
In contact with intact mucous membranes	Intermediate	Semicritical	High-level disinfection or sterilization
Prior to use in immunocompromised patients			
In contact with healthy skin	Low	Non-critical	Low-level disinfection

Table 1: Classification of medical devices according to Spaulding [7].

Each of the sterilization modalities has pros and cons. Material compatibility analysis with the process parameters is mandatory before selecting the most suitable technique for a specific device. Steam sterilization or autoclaving is a relatively simple, rapid, and low-

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cost process used for sterilizing metals and heat resistant polymers. However, the elevated humidity and temperature can lead to hydrolysis, softening, or degradation in some polymers and corrosion of metals. Also, devices has some significant disadvantages related to its toxicity, suspected carcinogenicity, and its residuals in the environment and the device. Long aeration times are required during post-sterilization cycles, and this can via the mechanisms of chain scission and cross-linking [4,5,8]. Table 2 summarizes the important parameters for consideration before selecting the sterilization technology.

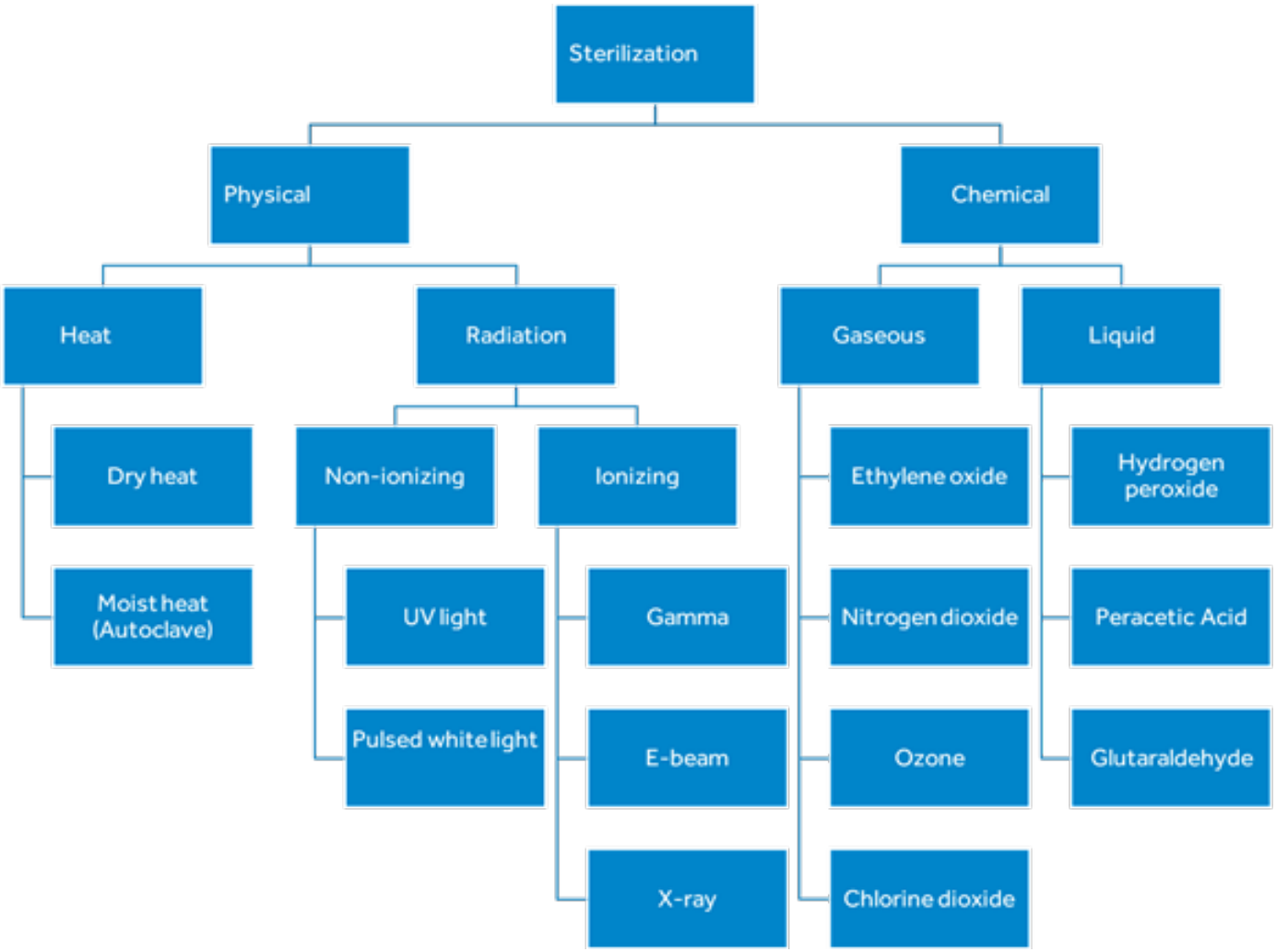

Figure 1: Broad categorization of sterilization modalities [4].

with active power sources such as pacemakers, Implantable Cardio Defibrillators and neurostimulators cannot be autoclaved. Ethylene oxide (EO) is a commonly used sterilization technique for processing medical devices today due to its low processing temperature and broad material compatibility. However, EO affect costs. Gamma irradiation is another sterilization technique that is used when materials are sensitive to high temperatures of autoclaving, but compatible with ionizing radiation. Most metal-based medical devices can be sterilized using this technique. However, it can alter physical and chemical properties of some polymers

The Global Universal Device identification database lists more than 20 million medical devices out of which 40% are provided as sterile to users and patients. Literature data shows that about 50% of those devices are sterilized with EO and 45% with radiation (gamma, X-ray, E-beam). The market share for industrial steam sterilization as it relates to medical

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products is <5% [3,8]. Comparison of the three common sterilization modalities is shown in Table 3.

Characteristic	EO	Gamma	E-beam	Steam
Process Description	High humidity, low temperature, gaseous system	Radioisotope generated gamma rays	Accelerated electrons	Moist heat
Material compatibility	Most materials unaffected by temperatures <135° F	Plastics need to be evaluated Avoid acetals, teflon, propylene	Plastics need to be evaluated	Heat resistant materials
Cycle time with shipping	3-14 days	3-7 days	2-5 days	2-4 days
Sterilzation time	16-72 hours	5-6 hours	1-2 minutes	1-3 hours
Post sterile hold	0-12 days (aeration) Biological Indicators or Parametric release	Dosimetic release	Dosimetric release	Parametric release

Table 2: Comparison of some characteristics of traditional sterilization methods.

The medical device industry has seen significant changes in the last 30 years with the introduction of new complex devices, novel technologies with combination devices, and an evolving regulatory environment. Until recently, the most common sterilization processes remained the same with radiation and ethylene oxide being the primary terminal sterilization technologies. Figure 2 shows the time line of the evolution of sterilization technologies.

Over the past decade, the development of the art of sterilization seems to have accelerated with the introduction of several emerging processes [3,8]. Ever since EO was moved to the list of known carcinogens in the late 1990s, there has been increased scrutiny over its usage as a sterilant. Alternative methods for sterilization have emerged and these efforts have recently gained momentum with new regulations being considered in both the US and Europe. Of significance, the closure of 7 EO facilities between February 2019 and January 2020 has added additional incentives to shift the market away from EO as the primary form of sterilization. All the alternative sterilization technologies involve low-temperature gas, gas plasma and vapor phase sterilants. While EO is an alkylation agent, hydrogen peroxide, nitrogen dioxide, ozone, peracetic acid and chlorine dioxide are oxidizing agents[ref]. When evaluating a change in sterilization method, a careful analysis of the material compatibility and device functionality with the process parameters and the chemical sterilants of each of these techniques is necessary.

Metals and metallic alloys are generally not adversely affected by low temperature sterilization processes.

	Ethylene Oxide (EO)	Radiation	Steam
Approximate percentage of sterile medical devices sterilized with the modality	~50%	~45%	< 5%
Sterilant source	EO gas	Gamma radiation (cobalt-60), X-ray radiation, electron beam radiation	Pressurized steam
Critical process parameters	Gas concentration, temperature, humidity, exposure time	Radiation dose	Steam quality, pressure, temperature, exposure time
Generalized examples of medical devices sterilized with this modality	Single use devices, reusable device, surgical kits, electronic devices, heat sensitive devices, devices with hard-to-reach crevices	Some single use devices, heat-sensitive devices, radiation resistant plastic devices	Heat/moisture-resistant devices, some metal devices

Table 3: Common Industrial sterilization modalities [1,3,8].

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However, polymers can be affected by the same mechanisms that affect the microorganisms and different sterilization processes may result in hydrolysis, oxidation, and chain scission reactions that can alter their physical and chemical properties. Figure 3 shows the compatibility of different material categories against specific sterilization methods.

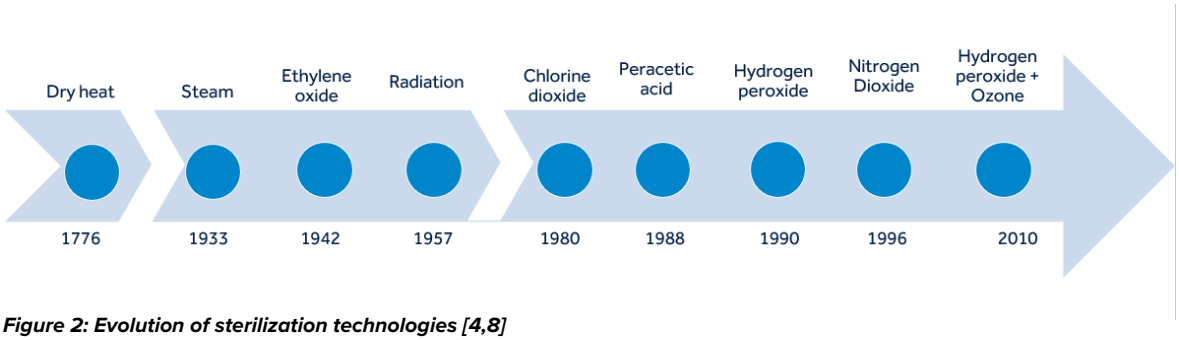

Figure 2: Evolution of sterilization technologies [4,8]

While traditional sterilization processes have remained essentially unchanged, some of the technologies discussed offer additional benefits and should be considered as potential alternatives to EO has become the most popular sterilization technique however recent scrutiny has revealed its potential toxicity. EO. The important mechanisms of microbial kill are well understood for all the different sterilization processes. This information should provide fundamental insights into the interactions of the sterilization modality with different materials. The available guidance on the material compatibility along with the mechanisms of different sterilization modalities offers an exciting opportunity for scientists to gain fundamental insights and develop new materials and process technologies to overcome some of the current challenges.

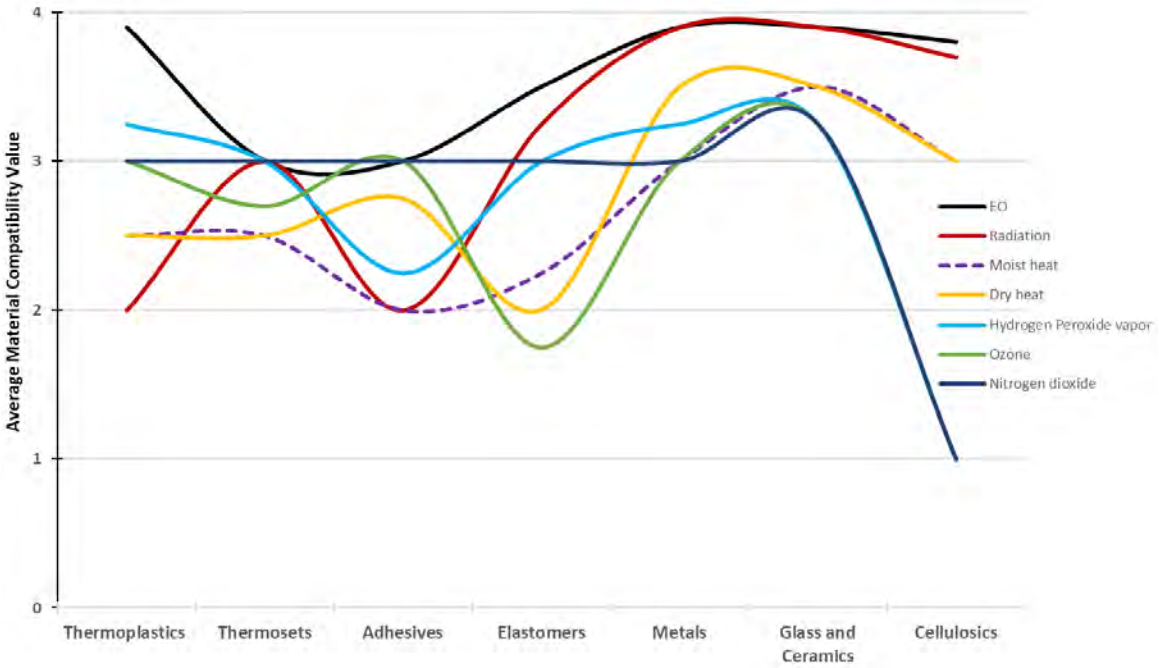

Figure 3: Material compatibility chart (Graph produced using data from AAMI TIR17:2008. Data points indicate the average compatibility for all materials in that category.)

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My first SIBF workshop and symposium experience transformed my understanding and aspirations for industry collaborations and truly highlighted the power of bringing together technical experts with a passion for transparent communication and intense problem solving. SIBF is a passionate collection of fantastic engineers, experts, scientists and deep thinkers dedicated to changing the biomedical field. I am constantly learning, laughing and growing my network of friends and colleagues through my participation with SIBF.
— ***Angela DiCiccio, Verily Life Sciences***

Hello friends! I am a Principal Scientist at Medtronic Corporate in the Microscopy and Surface Analysis Group specializing in surface and interface analysis of materials. I attended my first BioInterface Symposium in 2011 and immediately enjoyed the smaller, more intimate setting that encouraged interaction between attendees, presenters, and exhibitors. Since then, I became an active member and held various leadership roles including chairing technical sessions and board positions (Treasurer, President). The industry focused topics are directly relevant to my career and offers a fun and exciting way to stay informed of new technologies and current challenges in the medical device industry.

SIBF offers many opportunities for eager and energetic individuals. Please contact me or Ingrid for more information. We look forward to hearing from you! — ***Bill Theilacker, Medtronic Corporate***

I was invited by a colleague to attend my very first Bio Interface a few years ago. I discovered that it had a lot to offer for personal growth, learning and was beneficial for the business, relationships as well. Surfaces in Biomaterials Foundation members and attendees represent a good balance of academic, industry research excellence with consistent participation from regulatory experts. The annual Bio Interface Conference covers current industry topics of interest such as advances in wearables, 3D printing and drug delivery devices among several others. Due to its intimate set up and great agenda setting Conference provides excellent networking opportunities. Participating in various committees and the Foundation board helps develop leadership and team building skills.
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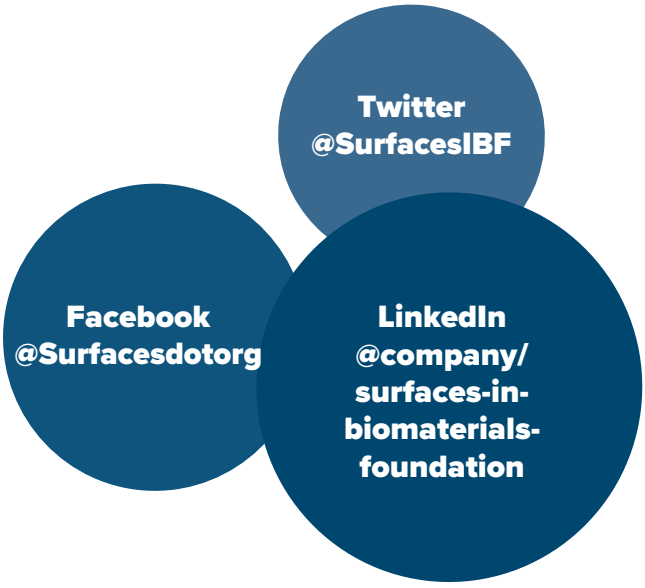

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