REMEMBERING ALLAN S. HOFFMAN 1932–2023

BIOMATERIALS FORUM

OFFICIAL NEWSLETTER OF THE SOCIETY FOR BIOMATERIALS

FOURTH QUARTER 2023 • VOLUME 45, ISSUE 4

ALSO INSIDE

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BIOMATERIALS FORUM

The official news magazine of the **SOCIETY FOR BIOMATERIALS** • Volume 44, Issue 2

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BioInterfaces	TBD
Biomaterials & Medical Products Commercialization	Subramanian Gunasekaran • guna@encoll.com
Biomaterials Education	Jeremy Mercuri • jmercur@g.clemson.edu
Biomaterial-Tissue Interaction	Patrick L. McGee • patrickmcgee.dds@outlook.com
Cardiovascular Biomaterials	Astha Khanna • akhanna@gravertech.com
Dental/Craniofacial Biomaterials	TBD
Drug Delivery	Eun Ji Chung • eunchung@usc.edu
Engineering Cells & Their Microenvironments	Silviya Zustiak • silviya.zustiak@slu.edu
Immune Engineering	Yaoying Wu • yw195@duke.edu
Nanomaterials	Mahboubeh Nabavinia • NABAVINIAM20@ecu.edu
Ophthalmic Biomaterials	Frances Lasowski • lasowsfj@mcmaster.ca
Orthopaedic Biomaterials	Roche C. de Guzman • roche.c.deguzman@hosftra.edu
Surface Characterization & Modifications	TBD
Tissue Engineering	Jessica M. Gluck • jmgluck@ncsu.edu

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ON THE COVER

Dr. Allan S. Hoffman, 10th president of the Society For Biomaterials, passed away December 15, 2023 at age 91.

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From the Editor

By Roger Narayan, MD, PhD, Biomaterials Forum Executive Editor

I would like to welcome you to the fourth quarter issue of *Biomaterials Forum*. The feature of this issue is a remembrance of Allan S. Hoffman, a pioneer of our field. The issue also contains a letter from our president, William R. Wagner, on the role of biomaterials scientists in the evaluation of risk associated with polyfluoroalkyl substances (PFAS). In Industry News, Subramanian Gunasekaran shares information on the commercialization of medical devices in the United States, including the roles of the U.S. Food and Drug Administration, the Centers for Medicare and Medicaid Services, the American Medical Association (AMA), and hospital purchasing departments. His report also suggests a potential role for the Society For Biomaterials in advocating for new medical device technologies.

Carl Simon describes the Food and Drug Administration draft guidance on a potency test approach for biologics, including tissue-engineered devices and cell therapies. In addition, he highlights a new report from the National Institutes of Health on novel alternative methods, including computational modeling, cell-free assays and cell-tissue-organoid culture models, for understanding the physiological response to therapies. Moreover, the government news section includes information on the National Academies of Science, Engineering and Medicine on the use of digital twins as virtual mechanisms to obtain predictive information on cancer treatment; this mechanism may be useful for informing treatment for many types of biomedical challenges.

I want to thank the Society For Biomaterials members, staff and volunteer leaders who supported the preparation of this issue. As always, please do not hesitate to contact me at roger_narayan@ncsu.edu if you are interested in sharing news and other information for inclusion in an upcoming issue of *Biomaterials Forum*.

From the President

By William R. Wagner, PhD, SFB President

The one weird trick that tells you when your pacemaker will fail (your doctor will hate it!)

How's that for a click bait title? To be honest, I was leaning towards:

"The top five things the government and big business don't want you to know about your medical device (....and you won't believe #5!)"

but it was a bit long. Oh and be sure to read to the end and follow if you want me to be able to continue to put out nonsensical content that plays to your health fears and concerns.

Quackery has been around as long as medicine. Prior to the scientific method, distinguishing where one ended and the other began was not easy (see "Theodoric of York" of the old Saturday Night Live skit). Today's social media has provided the means for everyone to potentially reach a large audience with their message, and it is not surprising that sensationalism has come to dominate over nuance and rigor. Of course, this phenomenon reaches beyond scientific issues and affects so much of our political landscape today, but the point of this article is the impact on our world of biomaterials and medical devices. Specifically, how can we best engage in this new landscape and what are our responsibilities as scientifically trained experts to the broader societal debate?

You have probably provided counsel to friends and family faced with a decision on a medical implant. Certainly, during the pandemic you likely engaged in discussions where you sought to interpret the best evidence available and provide guidance. While it might not have been fully appreciated, you were able to distinguish the anecdotal from the statistically rigorous, and maybe even dug through the FDA filings and scientific reports on the vaccines. From your training, you likely have a good appreciation of risk/benefit analysis and can differentiate between scientific publications in terms of their rigor. The latter skill has grown in importance with the explosion of predatory journals, that to a lay audience appear equivalent with similarly named periodicals.

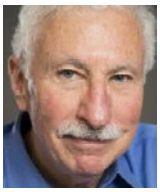
At this more personal level, I know that we serve to counter the non-sensical and seek to educate as we explain the scientific rationale behind our position. But what about on a larger scale? The FDA and standards organizations serve critical roles in ensuring quality, safety, and efficacy. The FDA approval pathway explicitly confronts the issue of risk/benefit in a rigorous and open way. With limited data sets, and known risks to the patient, is there benefit that offsets that risk for a defined group of patients? We know that approval means safety and efficacy in a defined context, and not without recognized risks. Unfortunately, the nuance of risk/benefit and a discussion in that context is rarely found when attention and clicks are the goal.

On the global stage, an issue has arisen that is a great example of where our understanding of biomaterials, medical devices and patient safety are desperately needed in guiding highly impactful legislation. If you have not heard about the growing concern regarding "forever chemicals," I am not able to provide a full background here, but some quick googling will bring you up to speed. More specifically the molecules in question are per- and polyfluoroalkyl substances (PFAS), a group of 9000+ chemicals used in hundreds of types of products. Due to the incredibly broad definition, the term captures highly disparate materials, from commonly prescribed pharmaceuticals to fire-fighting foam and fluoropolymers like PTFE. A subset of this group, generally of lower molecular weight and with specific functional groups, are of significant concern, and have been linked with cancer risk and other pathologies. Some of these molecules also have been found in drinking water, soil and in exposed populations and the food chain. There is compelling evidence with some of these molecules for protective legislation, clean-up efforts and more investigations into toxicity mechanisms. Legislation is moving forward in Europe and the US towards PFAS restrictions, but in many cases without considering the costs of casting too broad of a net.

The issue here, where biomaterials experts are needed to engage, is providing perspective on the risk/benefit for biomaterials that may become ensnared in legislation that is too broad. For instance, PTFE-containing implants have been implanted in millions of patients, in many cases for decades, in a range of devices with little to no evidence of material-related morbidity. Fluoropolymers are broadly used in the medical device industry to allow minimally invasive procedures, prevent biofouling, and allow precision processing. All of these PFAS containing medical devices that are in clinical use have met the rigorous safety standards required for FDA approval.

As legislation is being written and public awareness grows, it is critical that we convey nuance and how the risk/benefit varies dramatically across this group of molecules. Importantly, I believe most will agree that a position cognizant of PFAS benefit to medical devices is not inconsistent with the strict regulation and cleanup of high-risk chemicals. Rather it seeks to preserve access to low-risk materials that are critical to dozens of life-saving medical devices. Furthermore, it is our field that best can address the ease or likelihood of identifying or synthesizing alternative materials where current PFAS materials are used medically.

Well, thank you for reading to the end. If you want some more click-bait, wander through the myriad PFAS articles on the web and you will find dozens of stories where it is assumed that any PFAS molecule is a cancer-causing molecule because one PFAS molecule is. For instance, one post entitled "Study identifies cancer-causing chemicals in popular contact lenses." (The study in question "measured organic fluorine.") Unfortunately, this content serves to scare patients and takes focus away from a very real environmental and safety concern. Your voice and expertise can help society make better informed decisions in this and other critical areas.



Remembering Allan S. Hoffman

By Buddy D. Ratner

I first met Allan Hoffman in 1970 when I was a graduate student in polymer chemistry at the Polytechnic Institute of Brooklyn. Brooklyn Poly was, at that time, a world leader in polymer science and polymer engineering. There was an invited seminar by a Professor Allan Hoffman of M.I.T. The biomaterials-focused topic looked interesting to me – most of the Brooklyn Poly professors were immersed in fundamental polymer science, and not biological applications. At the seminar, Professor Hoffman, in his lucid and engaging style, articulated a philosophy integrating synthetic polymers, engineering and biology. His concepts were expressed clearly and persuasively.

The audience asked many questions. I did not get the opportunity to ask a question of Professor Hoffman. And then the seminar was over, and Allan Hoffman was being escorted down the hall by the "old guys," Brooklyn Poly senior professors. I ran after that group and asked if I could get a few minutes to talk to Professor Hoffman. I can still remember one of the senior profs, a rather gruff, old-style professor born in eastern Europe, glaring back at me. I don't remember the exact words he used but the meaning was clear – "get lost punk." I was mildly devastated by that interaction. But, undeterred, in 1971 when I was seeking a post-doc position, I put a 6-cent stamp on an envelope, typed a letter on a manual typewriter and wrote to Allan Hoffman. The letter first went to M.I.T. and they forwarded it to the University of Washington in Seattle, Allan's new home. Allan's response (typed on a typewriter and mailed with a stamp) took a month to get back to me. In the letter, he suggested a long-distance phone call, an expensive proposition in those days which, thankfully was paid for from his end. I remember his friendliness and warmth from that first phone call. He offered me a postdoctoral position in Seattle.

I arrived in Seattle on May 1, 1972, in a dented, blue, 40 horsepower Renault 10, after a 6,000-mile meandering journey through the heartland of America. Driving into Seattle, my first stop was the University of Washington campus and Allan Hoffman's office. There was Allan, sitting at his desk and looking at me with a surprised expression on his face. At that time, I was a bit of hippie, with long hair and a beard -- perhaps Allan wondered what he had hired. In any event, he greeted me warmly and set me to work in his University of Washington laboratories.

Within my first few days in the lab, I met Tom Horbett, another postdoc. It would have been hard to imagine at that moment in 1972 that, 50 years later, I would still be close with those two individuals. Allan pointed me to a laboratory and a desk. He communicated to me a creative approach to science and engineering that launched me on my career. And then, 50 years flew by. Pat Stayton, Dave Castner, Suzie Pun and many others joined us over this period. This intellectually rich span of time led to more than 100 publications that I co-authored with Allan, and, of course, the textbook, *Biomaterials Science: An Introduction to Materials in Medicine*, that we co-edited along with Jack Lemons and Fred Schoen. I think of the hundreds of individuals that have gone through the Hoffman lab and other labs that he nucleated at the University of Washington. A good fraction of the

Remembering Allan S. Hoffman (Continued)

world biomaterials and drug delivery community can be traced back to Allan Hoffman's leadership and vision. Importantly, Allan Hoffman's special charisma directly touched every one of these people.

Personal recollections of Allan Hoffman are numerous and vivid. In 1974, I remember Allan patiently coaching me on presentation style in a hotel room in Jerusalem before my first international talk. I remember Allan 'bloodying' my draft manuscripts with his incisive red pen, teaching me the art of written communication. Over the years, there must have been a hundred brainstorming sessions, in lab groups, government forums and companies, where Allan impactfully contributed with creativity and vision – he consistently "lit up the room."

I remember Allan showing me Paris, France on my first visit to the City of Light – on that visit in 1974 Allan introduced me to John Brash, another 50-year friendship. Allan's passion for Paris infected me and many years later, after many visits, I met my wife there. Allan also toured me around Istanbul, Kyoto, Capri, New Orleans and who knows how many other cities. In fact, New Orleans has a special story. We were there for a Society For Biomaterials (SFB) meeting in 1977. The first evening after the sessions ended, Allan took me to Felix's Oyster bar. I swallowed my first raw oyster then, learned to love oysters and now I start every visit to New Orleans with a trip to Felix's (and a memory of Allan). I am not sure I swallowed every line Allan's fed me over the years, but the oysters were a hit.

Allan Hoffman taught me about, writing, lecturing, grantsmanship, leadership, eating, drinking and savoring the rich life that our biomaterials community creates. Importantly, Allan Hoffman also taught me, by example, lessons in the importance of friendship, mentorship and humanity. I do my best to carry the torch forward and communicate those worthy Hoffman lessons to future generations. Allan: you are so, so missed… your humanity, *joie de vivre* and technical contributions keep your memory alive.

Industry News

RECAPITULATING THE COMMERCIALIZATION PROCESS OF MEDICAL DEVICES FROM THE INDUSTRIAL PERSPECTIVE

By Subramanian Gunasekaran, PhD

With 40 years of experience in the Society For Biomaterials (SFB), coupled with expertise as a biomaterial device developer and active involvement in the commercialization process of developed medical devices, the author aims to share insights about our industry with the younger generation.

MARKET CLEARANCE OF A MEDICAL DEVICE BY FDA

Embarking on the journey of commercializing a medical device involves navigating through various intricate processes, with the first critical step being clearance through the U.S. Food and Drug Administration (FDA). This federal agency plays a pivotal role in approving and ensuring the safety and efficacy of medical devices.

CMS COMMERCIAL VALUATION

Following FDA clearance, the product's commercialization journey continues with the submission of detailed information to the Centers for Medicare and Medicaid Services (CMS). This submission includes comprehensive data on the product's description, indications, and clinical performance. CMS, in turn, assigns a commercial value and a Healthcare Common Procedure Coding System (HCPCS) Code to the product, setting the stage for reimbursement procedures.

CONCEPTS OF MEDICAL BILLING & CODING

The process of medical billing and coding is a nuanced yet indispensable aspect that manufacturers must master. Understanding how coding and billing are executed by healthcare providers is crucial. Notably, medical coding software companies like Codify, AAPC and Supercoder.com, may exhibit biases favoring major pharmaceutical products. Smaller companies often find their clinically superior products facing challenges in receiving fair reimbursement due to such biases.

ROLE OF BILLING AGENTS

Billing agents play a pivotal role in facilitating the proper submission of CMS-1500 forms by healthcare providers. Their responsibilities include ensuring accurate coding, submitting necessary documentation, and navigating the intricacies of reimbursement from insurance companies.

INFLUENCE OF THE AMERICAN MEDICAL ASSOCIATION (AMA)

The Relative Value Update Committee (RUC), consisting of 32 Clinicians affiliated with the American Medical Association (AMA), performs the triannual commercial valuation of medical devices. However, a notable gap exists as the RUC lacks representation from the field of biomaterial science, potentially impacting the accurate valuation of advanced medical devices.

PROVIDER PAYMENTS AND INSURANCE

Providers, upon utilizing a medical device, receive payments from various payors, including government insurance agencies like CMS & its MACs (Medicare Administrative Contractors) and private payors such as PPOs (Preferred Provider Organizations) or HMOs (Health Maintenance Organizations). The reimbursement process involves meticulous coordination and adherence to specific billing procedures.

ISSUES WITH HOSPITAL DISTRIBUTION

Selling a medical device through hospitals involves engaging with complex supply chain management systems operated by the hospital's Purchasing and Materials Management departments. Most hospitals will have their own confidential Group Purchase Organizations (GPOs) through which the manufacturer should strike a purchase deal after convincing their Value Analysis Committee (VAC). There is no systematic approach to organizing and monitoring this committee of every hospital system to value an advanced medical device. Mostly, it is orchestrated by nurse practitioners and purchasing managers who may not be qualified people to assess the value of advanced products, especially those biological products meant for tissue regenerative applications.

ANTICIPATED ROLE OF SFB

With all due respect to the AMA and their evaluation process for a medical device along with our respect to the hospital purchasing system, we Biomaterial Scientists should take precedence to influence the system to assess the biological efficacy and safety evaluation of a medical device especially that involves tissue repair and regenerative application. Recently even the rulings of CMS related to one of the LCDs (Local Coverage Determinations)

Industry News (Continued)

were overthrown by a special interest group. Similarly, our Biomaterials group should have a stronger hold and power to express our knowledge towards updating the current flaws in recognition of a biomaterial-based device. This is the reason the author of this article underscores the need to establish a Consortium comprising Clinical Associations and Basic Scientific Societies, such as our SFB, to aid the FDA in assessing Safety & Efficacy, and assist the Centers for Medicare & Medicaid Services (CMS) in delivering a more equitable Commercial Valuation for Tissue Regenerative Medical Devices. Otherwise, the public might miss the opportunity to choose an appropriate biomaterial device for their medical applications.

CONCLUSION

The path to medical device commercialization is loaded with complexities, confusing the providing doctors and nurse practitioners specifically from the reimbursement procedural points of view. Navigating these challenges requires a deep understanding of the regulatory landscape, billing intricacies, and the influence of key stakeholders in the healthcare ecosystem. SFB should be in a position to advocate the manufacturers of advanced medical devices and the relevant government regulators to strategically approach each step to ensure fair recognition and reimbursement of any innovative technology product.

CALLING ALL BOOKWORMS!

If you'd like to contribute a review of your recent favorite read to the ***Biomaterials Forum***, send it for consideration to the Editor at ***Roger_narayan@ncsu.edu***. If it's approved, it will be published in a future Forum Book Review column!

Government News

By Carl G. Simon, Jr., PhD

FDA ISSUES NEW DRAFT GUIDANCE FOR POTENCY TESTING

FDA defines a biologic as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, applicable to the prevention, treatment, cure of disease or condition of human beings."[1,2] In order to market biologics in the USA, FDA requires that the manufacturer develop a potency test for product characterization. The goal of potency testing is to assure that manufactured lots of released product have the specific ability to achieve the product's intended mechanism of action (MOA). An ideal potency test might be described as a cell-based assay that measures a dynamic product attribute that is related to the product's intended MOA. Developing effective potency tests has been a major challenge for cell therapies and tissue engineered medical products.[3] In response, FDA published a new draft guidance entitled "Potency Assurance for Cellular and Gene Therapy Products."[4] The draft guidance provides recommendations for developing a science- and risk-based strategy to help assure the potency of a human cell or gene therapy.

NATIONAL ACADEMIES PUBLISHES REPORT ON DIGITAL TWINS

The National Academies of Science, Engineering and Medicine (NASEM) organized a series of workshops to gather information for a report on digital twins in multiple domains: biomedical, climate and engineering.[5] "A digital twin is a set of virtual information constructs that mimics the structure, context, and behavior of a natural, engineered, or social system (or system-of-systems), is dynamically updated with data from its physical twin, has a predictive capability, and informs decisions that realize value. The bidirectional interaction between the virtual and the physical is central to the digital twin."[5] The report focuses on four areas: 1) definitions of and use cases for digital twins; 2) foundational mathematical, statistical, and computational gaps for digital twins; 3) best practices for digital twin development and use; and 4) opportunities to advance the use and practice of digital twins. Examples that are discussed included digital twins of a cancer patient; an earth atmospheric, oceanic and terrestrial system; and a manufacturing process.

NIH PUBLISHES REPORT ON NOVEL ALTERNATIVE METHODS (NAMS)

NIH convened a Working Group of experts across disciplines and sectors to prioritize development of NAMs in a report.[6] NAMs were classified in three categories: computational modeling and predictive technologies (in silico), cell-free methods and assays (in chemico), and cell-tissue-organoid culture models (in vitro). The WG found that NAMs are already contributing to basic research in many biomedical fields, but future goals should focus on improving NAMs so that they more fully recapitulate human physiology. "More needs to be done to unite and interconnect the underlying disciplines, technologies, data, and areas of expertise." "For NAMs, the real opportunity to integrate AI, computational modeling, and 3-D organoids, human genomics, and more, into an increasingly sophisticated model provides a powerful opportunity to maximize the public's investment in biomedical research."[6]

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Contact: Carl Simon, carl.simon@nist.gov

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