UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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VIRTUAL PUBLIC WORKSHOP - 3D PRINTING IN HOSPITALS: VETERANS HEALTH ADMINISTRATION'S EXPERIENCES IN POINT OF CARE 3D PRINTING OF DEVICES AND IMPLEMENTING A QUALITY MANAGEMENT SYSTEM

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M E E T I N G

(12:00 p.m.)

DR. DI PRIMA: Good morning, afternoon or evening, wherever you may be. Welcome to the second day of the FDA/VHA workshop on point-of-care 3D printing.

Some quick housekeeping notes. First, this workshop is being recorded and yesterday's recording is already live using yesterday's webcast link. Two, there is a docket for this workshop, and feedback and comments can be posted to it. And three, questions for the discussion sessions can be submitted via the "ask a question" bubble on the bottom right of the webcast interface.

With that, it is my pleasure to introduce Dr. Ed Margerrison, Director of the Office of Science and Engineering Laboratories within the Center for Devices and Radiological Health at the FDA, to give today's opening remarks.

DR. MARGERRISON: Thank you, Matthew, and thank you to everybody who is attending this afternoon.

I think Day 2 is going to be extremely interesting and getting at the heart of a lot of the questions that we've been debating internally at FDA over the last few years. I think Day 1 was a great success and I think attendance was well over 200 attendees, and I know there was a lot of interaction and a lot of discussion and I think that really bodes well for the rest of the workshop today.

FDA's intention in this space has always been to try and ensure that we are retaining as much flexibility as we possibly can and together, as a community, going forward with point-of-care 3D printing in the most responsible way that we can. I think for us to do that, workshops like today and yesterday are absolutely essential because this is very much a team sport to get to the right place. We're going to need all stakeholders including government, of course; hospitals and clinical settings; standards organizations; and possibly

most importantly, our industry partners, to come together and really work out a framework that is going to be least burdensome and most productive for the people who really matter, which is the patients.

Clearly, the implications are quite a change in the supply chain and going back to my previous life in industry, the implants that we saw were pretty weighty and chunky. It would be much nicer for us if we could just sell a bit of software, that would've reduced the shipping charges enormously. So of course, there's going to be changes in this.

I think that facing up to big change is something that's particularly in additive manufacturing that we now have a good history of with this community. If we think back 2 years to those early days of the pandemic, it was incredible to me how people really pulled together, even very, very large governmental organizations, and really started acting more like a startup company. Everybody knew some of the things that were really important and urgent to get done, and everybody rolled up their sleeves and got things going. Without that sort of mentality, I don't think we would have forged such fantastic alliances and things like the NIH print exchange probably would never have come about. Thank goodness we all managed to do that in time because I know it had a really, really big effect.

A few people I'd like to thank before I hand it back to Matthew and we'll get on with the important parts of the afternoon. A big thank you to the VHA. They are very much a fantastic partner for us. We hope that partnership is strengthened further by things like this afternoon. It's an extremely important partnership, not just that we can share resources, share thoughts, and really move the area forward, but understanding their experience in this area and how they've been really meeting that point to get 3D printing has been enormously useful and I think there could be a lot of interesting questions and debates this afternoon on those.

One of the areas that we find particularly interesting, and I think the VHA has again

pioneered a lot of this, how do you cross-train engineers in clinical stuff? We're suddenly dealing with very, very different skill sets that have traditionally not been in certain workplaces. Manufacturing engineers have typically not been in the clinical setting, clinical staff typically haven't been in the manufacturing setting, and all the associated expertise and skills that are required for making a good quality product for patients. That's one of the challenges, I think, for this afternoon. I hope we have very, very good ongoing, very open, very creative discussions so that we can start putting answers to some of the questions that we posed in the white paper recently published.

Finally, big thanks to Kirstie Snodderly from the ASTM International Additive Manufacturing Center of Excellence, who has the unenviable task of organizing all of the stakeholder questions. I have no doubt she's going to do a fantastic job of that because she used to work in OSEL with Matthew, so that's fantastic training.

So with that, Matthew, I shall hand it back to you and wish everyone good luck and great enjoyment for the rest of the afternoon.

DR. DI PRIMA: Thank you so much, Ed.

It is my pleasure to announce the first session today, which is going to be focused on VHA's experience in implementing a quality management system within their hospitals, and our first speaker is going to be Joe Beedle, he's the chief financial officer of the VHA Puget Sound Health Care System.

MR. BEEDLE: Good morning, all. My name is Joe Beedle, I am the CFO at the VA Puget Sound and I apologize, my screen has switched over, I'm not used to using Zoom, so don't mind the background. What I was asked to share today was really my experience with how things have worked with the VA Puget Sound and how it related back with quality, a quality management system. I'm sharing my -- I'm trying to get my slides up here. If you could confirm that you're just seeing the slides, please.

UNIDENTIFIED SPEAKER: We need you to switch to presenter mode. There you go.

MR. BEEDLE: Okay, thank you. We use Teams, which is, given all of its faults, still a little different than Zoom.

So what you can see -- let's start here, just making sure. So I'm the CFO at VA Puget Sound. So VA Puget Sound is a 1A medical facility, which means we have an intensive amount of services, research, we have 5,000 employees, we're over a billion dollars in our total budget as we move forward, and so it's a great environment to start any type of a project. And really with 3D printing, what I was able to see and grow with on -- sorry, I forgot about the disclaimer slide. So if we take a quick second here. Not too much information necessary for disclaimer as we go, but please read for a quick second.

(Pause.)

MR. BEEDLE: Okay. And I'm proud to be presenting for Veterans Health Administration and following up after all of the wonderful speakers from the first day of the workshop. I was able to listen in to some of those virtually when I was stepping away from work yesterday and then following up and I'd like to thank the FDA for the opportunity and being able to allow us to see it so quickly.

So what I was asked to bring is my perspective from the financial side of the house. My experience really has been watching 3D printing maturing at our medical center and in combination with generating a quality management system, not just ours but nationwide, and really trying to tie that back to how do we generate financial value as well as high-quality medical care and really expanding the opportunities that we have to provide that care to our veterans.

And so the goals, as you can see here, is really explaining where did this start and these are all from my perspective, which will be different than what Dr. Ripley's are and any of the other engineers, and where this started for me was with the orphan needs, seeing it

on the research side, and then leading up into the pandemic when things kind of exploded and really, my maturation of learning about what a 3D-printing network can look like and then the next was determining how a quality management system and point-of-care 3D manufacturing can relate to finance and create value which, when it comes down to it, past the points of research and expanding what we think about and what we're capable of, most of these decisions are going to have some sort of financial component to them in the end.

And the three areas I'd like to talk about on that is the potential for cost savings, cost avoidance, and any kind of value-add outside of those two above. As a government entity, revenue is not always something that we are capable of bringing in, but there is the potential for it, especially given the fact that with 3D printing, really there is no limit to what can be created and what can be delivered.

And then I'll round it out with where is the Office of Advanced Manufacturing and VHA headed, or at least where we see it as of today, and a lot of that is just about the increased scope of what we can provide and scaling it to the largest medical system within the United States.

So for me, where did this begin? And it began with a lot of fun for me, really getting to see what the 3D-printing groups were able to do and kind of the starting up of the technology and seeing it from a practical sense. So the examples I have really are from the center of the limb loss and mobility and, as you can see on the side of the slide, it's the insoles in shoes that we are able to provide for our diabetic patients than those, and the fact that we able to provide those insoles faster, with more variety and more comfort for our patients, really a quality of life improvement as well as being able to bring in more, just again, quality of life improvement for the staff and our veterans. Also, personalized orthotics. Besides that, with the prosthetic aids, we were able to provide assistive devices. So again, back to the quality of life, this is creating something so that if an amputee wanted

to do something that they weren't able to previously, like the Hamburger Helper, that was for someone who didn't have the use of hands and they were able to enjoy -- they said one of the things they wanted to do was just be able to hold a hamburger, and with the engineering side of things, we were able to move -- bring a bunch of engineers together, they were able to create a device very interesting to see and showed up very well in the news. And then the latest, of course, thing like that was the Geo Stent that had come out. These are all very patient specific and does not really have a lot of finance to it other than the upfront costs and then people being able to kind of use their imagination to assist with patients.

What did that lead into? My next interaction with 3D printing was really seeing what happened when PPE was necessary for the pandemic support, you know, the flagship for that being with the nasal swabs. This was not something that we had seen beforehand, we saw the destruction of our supply chain and there was a need for something just as simple as a nasal swab so that we could perform the necessary tests.

In addition to that, the team got together and basically set up a command center in some of the empty space we had once we weren't able to bring patients in, and they created everything from PAPR hoods that didn't use preexisting medical-grade equipment, shields, masks, you name it, whatever was needed, the group was able to go and create it. And that largely is due to the flexibility that 3D printing provides, as well as the experience that we had working with FDA and getting approval, like NIOSH approval for the PAPR hoods as well to push-out. Really, there is no limit to what the 3D printing can provide, especially when coupled with that quality management system of saying what we put out is safe, it's usable, it's duplicable wherever it's at, and we're able to show that to any regulatory bodies that are coming forward or potential customers, as well.

The other thing that kind of my maturation with what was going on in the program

was I was able to see -- and then this is just across the United States -- how widespread our 3D-printing sites were already and if you notice, this really does point us in the direction of showing that VA, exclusively on this, we already have a network for distribution and we also have a population that has demands. So now we'll lead into the really financial type of things and what we can show for the value-adds.

And a quick view of how VHA is able to use 3D printing. So mileage will vary as we go through these, as we go through the next slides. But in the Veterans Health Administration, we are a capitated system, so every one of our patients has a reimbursement that comes back in and it's set, almost regardless of what the cost is, except for the high outliers, we have something for very expensive patients as they come through. But your general patient, if you're trying to improve their quality of life, if you're trying to work with them, what our goal is, to be able to provide the care to the most individuals possible and to have the most effect is really based on efficiency and effectiveness, because we're capitated. As soon as we -- if we exceed those numbers per person, on the average cost of care, we're losing, we're taking away from something else.

And so the next three slides we're looking at for the cost savings, cost avoidance, and the value-add is really explaining why, when we look at these, that it makes sense for us and at least in our environment. It's about lowering that average cost of care, it's about increasing the ability to see patients, various patients, and how we can get that to work within our revenue model, which also is very lengthy in time from the point that care is provided until we actually see the reimbursements based on that new care. It can take 2 years before it actually hits our revenue model and that's just because, as a government entity, when we're looking at these we have to request funding from Congress and the way it works for ours is we present saying here's the workload we provided and then it shows up. Basically, it sets the budget for 2 years into the future.

So cost savings. I picked an easy one for discussion on the cost savings and really, the most mature area that we have in production and with dental 3D printing on those, you know, the things that we can look at is implants, apparently top dentures, bottom dentures, and night guards. But when we're looking at these, each one of these items was brought forward and because of our quality management system, because of how we pipeline ideas when they come through, before any of these were put into place, we were going back through and saying what devices will it take to create these, whether it's an implant, whether it's the denture wear, whether it's the night guard, what is our demand, which again, VHA is very data rich and so it's quite easy for us to go back in and say here are the instances of care that we have and here's the potential population.

And if I went back up and showed you where everything was within the system, we would be able to show not only is it worthwhile in Seattle because of the population that we have at our 1A facility in a metropolitan area, but we can pick every other site within the United States and say these are financially viable areas to bring in something like dental 3D printing, even if it's only implants, even if it's only something like a night guard at that point, because with that quality management system we have and the work that we put on in the front end, we're able to say what our demand is that we can have within the medical facilities themselves, what we're buying out in the community, and then make a diagram out when we break even, when we make money based on any of those items from a pure cost savings, i.e., an implant costs $1 for us to make, if we buy out in the community, it will cost us $2.

So that straight cost savings is something that we recoup immediately, which is very important on the finance side and especially within VHA because that's immediate, it doesn't take 2 years for it to catch up. And there are many other cost-saving enterprises that we're working on right now and that we're actually implementing, but this is just the

most mature example.

Cost avoidance. So this gets a little -- it becomes calculus instead of just addition and subtraction when we're looking at these. But with the cost avoidance, because of the variability and flexibility of what 3D printing can provide, what we found is, is that when we look into areas like the cutting guides, this is something -- so if it's for the jaw, if the doctor is going to have to go in and remove a bit of bone as it's coming through, in our current environment to procure a cutting guide that works for our patient and is patient specific, the lead time on it is so extreme, at least for the VHA on those, that it makes sense for us to say could we do this, could we do a cutting guide within the VA or within VHA? And if we did, what are the benefits for it?

Well, the easiest one is it's no longer freehand with the cutting guide. And again, these are all pending, all of these items are pending approval as we come through. Anything new that we bring forward, of course, it goes through that quality management system and it's made sure that we can actually use it. Similar to the Geo Stent, had to make sure, compassionate use, that it was being brought forward.

But in the sense of the cutting guide, the cost avoidance, and under the cutting guides we're able to say that there is a potential market for it because of the cost to have to buy the cutting guide out in the market, if you even can, and it also improves significantly what the surgeon is able to do going in, they're only cutting out the right amount of bone, they're able to see it previous or prior to, they're able to make a surgical cut on that and not have some of the freehand errors that can occur.

So what's that doing? And then similar with the anatomical modeling, before a surgeon is going in, they can touch a 3D image of an anatomical model, they can get it to scale, they can have the colors show what they're looking for, they can show it to the patient because it's there, all of those things can and we're -- I know that we're working on

the cases studies and the rest, but the potential for all of these items, you know, new methods of providing treatment that allow an orphan disease treatment, it's allowing us to decrease surgical complexity on some of these items. It's allowing for, or at least potentially, because the complexity is going down, because people have extra practice on those, on a physical object, it potentially reduces surgical time which also tends to decrease the recovery time. Everything is specific to the patient.

Coming into health care, I was not aware beforehand of the variability. Once I thought a doctor would go in and cut something and you'd be better about that not realizing what the variability is per human being as you're going through just because of size, weight, whatever it might be, and with those anatomical models it allows a better sense of what the surgeon and what the doctors are going to see. And as I focused on beforehand, if we can decrease the average cost of care for every one of these instances, because of that capitated rate, it provides another financial incentive for us as we move forward.

Value added. So this is the catchall, this is everything else that can potentially come forward. And so every bit of these has some value to it and it's really our job to identify the potential areas of where we can have value-adds and then also to try, if you can, to put some sort of numeric value to it, which adds to that value proposition.

Now, in the medical world and especially within the VA, due to the average cost of care, unlike in the private sector or if you're designing a device, a specific device, you have to go out and put together all of the documentation that's saying what's the return on investment, what's the costs, what's your barrier to entry, what do you have to create for it, and really, inside a medical center these value-adds become much easier and the value becomes much greater. That's because for every device that we're creating, if we do our jobs right, it's going to make it so that that device doesn't need to pass some of the barriers

that you get in the private sector or if you are creating the device, because you already have a market for it, you're already showing the value with a single item as opposed to you have to have a market of thousands at that point, you have an immediate return if you've done your planning properly.

And so the next item I want to talk about is, is that as we've seen because of the pandemic and just in the day-to-day life within a medical center, we need to find ways of decreasing our reliance on vulnerable supply chains and making sure that we don't end up in the circumstances that we're in for or as best we can, mitigate whether that's through 3D printing, whether that's through contracts with our vendors, it's just one of the values that we can. You know, powder can be turned into anything, resin can be turned into anything at that point, it's not specific. One item of supply becomes one item at the end. You have a variability.

So orphan disease treatment increases the incentives to improve our return on investment. What does that mean? Once you have a 3D-printing device, once you have the engineers, once you have that quality management system, you're able to pick up those one-offs that really, again, in the private sector and if you're in a hospital, you wouldn't really be able to pick up that orphan disease, that orphan instance, and realistically be able to provide that care and not have the cost explode.

The next I have, there's increased patient awareness and informed consent. If you're saying that you're going to go in and take out a tumor for someone, how many laypeople, myself included on that, understand what's really happening, whereas with the 3D printing and the anatomical modeling, you can get more, you can increase awareness and it's easier to get that informed consent because they can see and touch what's going on.

The next and very interesting one for us is the potential reimbursement via CPT codes. Right now, for anatomic modeling, there is no CPT code that says that you can go

through, except for they do have some that are for research purposes and what that's leading towards is on the anatomical modeling for the diagnostic imaging CPT codes, they're being added to that, billing for the patient, and it's allowing medical centers to really see what the cost is and eventually get those brought in so that the CPT codes can be billed through Medicare, Medicaid, insurance, as well.

So 3D printing, because it's very friendly for blue-sky thinking, there is the increased potential for intellectual property at that point. There is going to be some surgeon somewhere or an engineer somewhere that's going to develop a product, it will have value and it has the potential for that intellectual property and revenues into the future.

Again, kind of combining the others, new business opportunities for health care. We all know that if we can bring patients into our individual hospitals it creates a market, and it increases the value of what we already have in our fixed assets and our fixed spaces. And that's where that potential increased patient demand and market share comes from.

And then the final additive at that point, you're allowing people to be part of the development process for health care. So increased creativity and buy-in from staff.

Where are we headed? So from my experience of coming in and seeing kind of the unique and the orphan items that are coming through 3D printing and some of the small-scale practical applications all the way up through the pandemic, where we were able to show, due to our experience, our need and the weaknesses within our system, what we were able to do given the 3D-printing potential, given the quality management system we were able to put into place which allows a few other things which I'll show in just one second. It's really where do we see ourselves into the future.

And that specifically goes back to that quality management system and 3D printing at this point. What it allows us to do is scale and review each item. Once we have a product in one area that has gone through, because of 3D printing, as long as it's on the

same machine, we can train those individuals at different sites. So Seattle has created something, it's in a digital world. We send that over to Charleston or vice versa or to any of the other sites. We are able to create an item and ensure that it will be safe to either put in to work with a patient or provide what is necessary for the surgeons as they go.

Because of the flexibility, as mentioned, and that existing quality management system that pipelines through to make sure that it is safe and that it is backed by both the VHA and, like with the nasal swabs, FDA at that point, we were able to have -- in the grand scheme of things, it's light and quick to go from an idea that someone has, again back with those orphan instances and the rest, to actual clinical use.

Training becomes more transferrable, it's quite easy once you have the system in place. You're sending also that digital booklet that says step one, do this, and then about 30 pages worth of "and don't do all of these other things." It also provides a safe environment for idea development and increases the variability in the care that can be provided.

And out of everything that I've discussed so far, this is probably the most applicable and important slide to show about this, because it's that combination of not just that you can build something with a 3D printer but that you have guarantees over what the quality is and when it gets into our patient, that it's really providing the higher level of clinical care and we have assurances to them.

Future state. Every VA medical center will have access and every patient will benefit. It's not that there will be 3D printing in each one of the sites, but as you saw from the map, we have nodes in almost every state and in most major cities at this point, which means again that if you have a team in Seattle that's working on something they can then send over the digital documentation and have it printed someplace else. So you're building out that idea of a hub and a spoke model, which can be transferrable about that, and it

allows the most important resource in any of this, which is the people power, it's the brain power, it's the experiences that we've got to be able to be used in every location without travel necessarily, without any of those. So we're empowering our staff, those are the anticipated benefits as we mature in advanced manufacturing within the VA. You know, advocating as Dr. Ripley had mentioned on the first day, it's the *n* of one, we're able to bring personalized devices in, increasing patient satisfaction, again just from those items where it works for a single veteran, but also so that we can have patient education and consent. And then again, as I mentioned, cost savings, cost avoidance, as well as the remainder of the value-adds.

So a future that we see ourselves in, current and future, we're showing any number of items that we're 3D printing and different methods, not just through 3D printing, we're into the future, we're talking about biofabrication, mixed reality type of care, and then future -- you know, it's that robotics, it's AI, 5G, it's metal printing, all of those items, and that's just an idea of what we can into the future because of the flexibility and because of the quality management that we put in place.

Okay, thank you very much. I'll check the chat for questions.

DR. DI PRIMA: Actually, we'll be sending questions for the panel at the end. So thank you so much for that discussion of the financial aspects of this.

I'm very excited to introduce our next speaker, Greg Voss, who's an engineer and will present an engineering perspective of a quality management system.

Greg, the floor is yours.

MR. VOSS: Just a second, I'm getting the video on.

(Pause.)

MR. VOSS: There we go, sorry about that. All right. Thank you, Matthew, thank you for giving me the opportunity to talk today about our high-level lessons learned as a

healthcare facility taking on the responsibilities of a medical device manufacturer, otherwise known as what we learned implementing Scenario 3.

As Matthew said, I'm Greg Voss, I'm an engineer working on standing up the quality system at VHA. Prior to working at VHA, I worked in Class II and Class III medical device manufacturing and hopefully can offer a view that touches both the device manufacturing and healthcare delivery worlds. This talk is geared more towards people in the healthcare setting, not medical device manufacturing professionals. Next slide, please.

These are the standard disclosures, no financial disclosure, the work is the product of the Office of Advanced Manufacturing and there are no product endorsements. Next slide, please.

So topics today. So we're going to start our story today by talking briefly about how devices get to end users currently, and how the different rules and supply chain led to differences in quality system implementation at healthcare facilities and medical device companies. After looking at high-level models of the different quality systems, we will go one level deeper into the medical device model and its sub-system. Finally, potential skills, knowledge, and ability that a healthcare facility may be able to leverage to accelerate the implementation of a manufacturing quality system and what gaps may remain. We'll wrap up by looking at some considerations around organizational structure and reemphasizing some of the lessons that we learned. Next slide, please.

So we start with how devices make it to the healthcare facility end users. The simplest model is a medical device company manufactures a device and sells it to a healthcare facility. A more complicated model is that the clinician is presented with a problem, doesn't have an existing technology to solve this problem, who's in contact with the medical device company, the medical device company goes away for a while, it's been a couple years, they think about the problem, they develop a solution, they test it to ensure

safety and effectiveness, then they come back and sell it to the healthcare facility.

Transactions are at an arm's length, but I think of interest it's not particularly how products flow within healthcare facilities, but rather the information exchange between the entities and how that information flow manifests through the different quality system models. Next slide, please.

So this first quality system model that we'll look at is the medical device quality system. The graphic on the right is a common model of a medical device quality system, ISO 13485. The standard was first introduced in 1986 and it's widely adopted in the medical device industry.

The circle at the center of the model is a company bracketed at each side by commercial and regulatory customers. In the medical device company model, the core processes for information flow start with the collection requirements for customers, on the left-hand side of the model, which lead into product realization processes located at the bottom of the central circle. Think development and build products, resulting in goods and services that can be delivered to customers. The model is completed with feedback from customers, on the right-hand side of the model, that lead back to new products or improvements to existing products.

Other elements in the quality system consist of continuous improvement cycle, measurement and analysis, review by management, resulting in adjustments to resource allocation which lead back into the product realization processes.

In this model, healthcare facilities provide information flow to medical device companies. This information flows in the form of (a) customer requirements for new products or feedback on faults in existing products. In this model, the medical device companies provide devices that have been vetted prior to use, including control and suppliers, materials and processes, thinking about human factors in the design cycle,

thinking about how devices may fail, applying safety standards for better industry standards.

Things that are not explicitly following the model but should be thought about when moving manufacturing to a healthcare facility are this, customers are thought about in this model in aggregate, i.e. device companies are removed from individual patients and to a large extent, individual clinicians. Most of the time they do not know who will be using the device or whom the device is used on. Since patients and clinicians are considered in aggregate, the product realization process must consider a range of clinicians, patients, and situations that a device may be used in. So medical device companies are typically not thinking about a use case of one or developing a device for an individual clinician.

Additionally, this model is not particularly well adapted for dealing with emergent problems. The lack of emergent problems is that medical device companies have extended periods of time to consider a multitude of conditions that may be encountered, and through the application of risk management during the development cycle ensure the safety and effectiveness of the device for a wide variety of use cases.

The last thing to note about this model is that it's more standards and procedures based rather than best practices or competency based. ISO, IEC, AAMI, NIST, ANSI, ASGM, ASM, for example. Next slide, please.

Let's contrast the medical device company model with the healthcare facility quality system model. The graphic on the left in this slide is from the American Society for Quality, which developed this as a model healthcare quality management system. The core of this model really meets expected results, exceptional quality, safety, and patient outcomes.

The middle circle details the four key components for information flow in the patient's delivery -- care delivery, sorry -- which is identification assessment, development of a treatment plan by all primary and ancillary services, delivery of care, and then

transition of care to the next level or discharge.

Things to think about. We have more granularity in patients and clinicians. We don't have individual patient and clinician interactions, interactions to be emergent, they can be chaotic. The pacing of the cycle is very different in the healthcare facility model, which -- and the device development cycle is measured in years in the medical device company model. Since medical practice can be chaotic, device manufacturing design should not. The last thing to note is that you don't see medical devices in it. Next slide, please.

That leads us to our first lesson: definitions matter. Do not introduce a medical device quality system as a quality system to your organization. All organizations have quality systems. The quality system should be tailored to the desired output of the organization. The healthcare quality system is not a medical device company quality system. Rather, introduce it as good manufacturing practices.

Manufacturing is something that healthcare facilities generally do not do. The bulk of the requirements in the quality system regulation are in place at manufacturers of devices, medical or otherwise, because they are necessary to run a manufacturing organization, not for regulatory consideration. Reshaping the existing understanding of quality, I believe, is more difficult than introducing a new concept, good manufacturing practices. Next slide, please.

We're going to go one level down into the medical device quality system, we're going to look at the seven major sub-systems identified in the FDA's GMP regulation. These sub-systems are

- Corrective and preventative action
- Equipment and facility controls
- Product and process controls
- Design controls

- Materials controls
- Records, documents, and change controls, and
- Management

Note the lack of the term "quality" in any of the seven sub-systems. This is in keeping with the current thinking on quality systems, which is through the adoption of practices pioneered by Deming, Juran, and others, of improving all organizational processes through the people that use them and away from the separate quality function and inspect the quality in the product. Next slide, please.

So the first system that we want to look at is CAPA, corrective action and preventative action. So what currently exists in a healthcare facility? There are a couple of analogous systems that are already in place. The first is reporting on adverse events, near misses, and errors. The second is medical device reporting, which healthcare facilities and medical devices companies work hand in hand in providing information into a database, the MAUDE database, that can be accessed by anybody.

Potential gaps. The first one is program scope. How do you handle broken devices that did not lead to adverse events or medical device reports? They may or may not be reported back to a manufacturer. These device failures could be a useful information feedback loop if integrated into internal device development.

The second one is resources may exist in disjointed areas. For example, complaints may currently go to patient handling, patient safety, or infection control. There should be a central clearinghouse established for device failures that feed back into your manufacturing operations.

The third is engineering resources for complaint investigation, i.e., practice failure analysis is not the same as device failure mode analysis.

The last two things are you need to think about are two tiers of correction and

corrective action. How do you fix the current problem, its correction, including items that may not have been delivered yet, versus how are you going to keep the problem from being great (ph.), which would be the corrective action.

Finally, the process needs to be formalized with the following goals in mind. We want to be able to look back and determine if corrective actions are effective or trending, are you systematically looking over, overlooking an area or an error? Next slide, please.

The next sub-system is equipment and facility controls. What currently exists is that there are systems for tracking medical devices inside healthcare facilities. Our system resides in biomedical engineering. They are very capable of executing preventative maintenance on durable medical equipment per manufacturers' instructions. We also have systems in place for control of measurement and test equipment and for facility controls. It resides in a different engineering group at our facility.

Potential gaps. You are going to need to develop the capability to generate maintenance programs for manufacturing equipment when instructions are not available from the manufacturer. Your facility controls may or may not be available in non-patient care areas. You're going to need to be able to develop control limits of operating environments for when that operating environment may not be established by an equipment manufacturer, and these processes need to be formalized. Next slide, please.

Production and process controls. So some hospital departments have experience operating under formal process controls, for example, sterile processing, they operate under AAMI ST79 for pharmacies. SPS operates a lot like a device company; in fact, they're processing devices and they're operated according to standard operating procedures. They, however, execute to manufacturers' instructions and cannot develop their own sterilization processes.

Pharmacies. Labeling control at pharmacies is very similar to a labeling control that

is exhibited at medical device companies.

Potential gaps. The first and largest, this is the training to be able to move from being a recipe follower to a recipe creator. So rather than being able to execute a standard operating procedure or a work instruction, you need to be able to learn how to create those work instructions and SOPs. You'll need to expand those capabilities for 3D printing for medical devices. Your processes need to be documented and changes controlled. Process validation has come up a number of times over the last day and a half. Arrianna Willis will be covering her approach to product production and process controls, including validation, in her talk, so I will not address it here. Next slide.

Design controls. Design controls and device design is where the largest knowledge gap likely exists and you could fill up a number of talks. What currently exists at healthcare facilities, their source of customer requirements. They also have extensive design validation capability. So a healthcare facility's strengths reside at the two ends of the product development process, gathering requirements and ensure many of the products meet customer needs.

However, there's a lot of thinking that goes on between those two endpoints. A few of those gaps are listed on the right side of the slide, including design verification, does your product meet a specification. Using a caliper to verify the change is still within established specifications and orders of magnitude easier than rewriting a simulation study or potentially an animal study to validate the design meets customer needs. Note that you cannot perform design verification without generating design endpoints for specifications to test to.

Another one is a formal risk analysis process. We thought about how does your device work under a variety of circumstances and with a variety of operators. If it fails, how does it fail? What is the harm of the failure? Did you take action in a new development

process to mitigate the harm in the event of failure?

Or human factors. What happens when the maker of the device has not been used for the device? Of if you've designed with the endpoint from only one clinician and spread that device across a variety of clinicians for clinical specialties, or a design based on the clinician and they retire. If all individuals thought alike, we feel that human factors would not exist and we know that human factor considerations are critical to device design.

The last point I want to touch on is generating design inputs. What do you do when your customer requirements are incomplete, conflicting, or vague? The process of generating design inputs is intended to resolve these conflicts, there's a higher order of capability that you, as a healthcare facility, would need to develop, and your engineers.

Keep in mind that customer requirements are not the only input in generating design inputs. You need to consider mitigations that come out of risk analysis, human factors, relevancy, standards, and regulatory requirements in generating your design inputs.

Generating design inputs is a very difficult task, you could complicate it. According to some guidance documents, you could expect the development of the design inputs to take up to one-third of your total project line.

Finally, development activities need to be planned and this planning needs to be documented. Each member of the development team needs to understand their role in the project and how they want to interface with others on the team, as well as the goal that they're operating towards. Next slide, please.

Materials controls. What currently exists today? Systems are or should be in place at healthcare facilities to track material stock levels, when and how those materials are pulled out of stock and whom they're used on. If you are capable of tracking devices in a healthcare facility, you have the capability to implement medical device material controls. This capability just needs to be extended to raw materials in production of devices.

Other gaps. Receiving inspection. Receiving inspection is a service that is baked into the supply chain at medical device companies. Functions at healthcare facilities will need the strength when they do not have medical device companies providing the service. So healthcare facilities likely don't perform destructive testing as part of their test and sampling and to release sterilized devices, for example.

Or supplier controls. This is another service that medical device companies, in fact, are still performing for healthcare facilities. If a healthcare facility is going to go reach into the supply chain from a medical device manufacturer, commercial raw material and equipment suppliers, the healthcare facility will need to develop the capability to control these inputs to their production processes. When you think about medical device production, a good analogy is devices do not appear in the operating room by accident. The raw material used for those devices should not arrive at your manufacturing workstations by accident. All those processes need to be designed. Next slide.

Records and change control. Healthcare facilities already are keeping -- they have recordkeeping systems for activities that make sense for their activities. The first is medical records, these are analogous to medical device history records, a record of all the materials and processing of those materials during the production of devices and are kept at medical device companies.

As a carryover, the other thing that's common is material controls as logistics or records and materials transactions already being generated and tracked. You're going to need to expand those information systems out for handling records related to your medical device and quality system outputs. These include things like the device master record, which is -- I think of it as the recipe for making devices; your design history file documenting your thought processes about creating the device recipe for the next engineer working on the product so they understand what you were thinking about and that may not be present

in the specification. Or device history records, raw materials went in, what processes were used, who built, who inspected, who labeled for devices shipped. You need to build awareness that processes are documented and cannot be changed without proper review and approval. Really think about it as if you were not doing things correctly, if you cannot demonstrate to others the objective evidence that you did things correctly. Next slide, please.

This brings us to our second lesson, which was knowledge of manufacturing matters. You likely will have pockets of knowledge that's applicable to implementing a quality system. You need to do your own assessment of that existing knowledge base and you may need outside expertise. At VHA, we address this by locating internal resources with the medical device industry experience. We brought in a consultant with a wide spectrum of medical device industry knowledge and experience. We added some quality assurance people with a manufacturing background, not medical device specific, but a good manufacturing background. Next slide, please.

This brings us to the last GMP quality sub-system: management. What currently exists? Obviously every healthcare facility has a management structure.

While the skill sets may be present, they are not organized in a way that's effective for control of operations, at least we didn't find that to be true. They're siloed across the healthcare facility, they're not under a common structure. A couple of detail points from the regulation is that you're going to need to establish formal reviews of the quality system and you will need to establish the individual responsible for ensuring that the quality system requirements are effectively established and maintained, and the reporting on the performance of that quality system to executive management. So let's look at a couple of management structures and resource location. Next slide, please.

When we looked at the seven GMP sub-systems, we identified areas that might have

relevant skills, knowledge, and ability and existing processes that you may be able to leverage. On the right we have a high-level organizational chart from a healthcare facility at the VHA. In this case, it's the Puget Sound Health Care System organization chart. I highlighted in red rectangles on the chart areas that you may be able to leverage. I also highlighted in green the location of that critical knowledge that is a relative strength of the healthcare facility versus a medical device manufacturer. We found that the functions you want to harness in our scenario resided at the local executive management areas and the expertise are located in small pockets. As a management team, you will need to do some work, both to connect those red rectangles together and making appropriate interfaces to the clinical staff. Next slide.

Let's contrast that with a medical device manufacturing organization. The first thing to note is that all functions are inside of the quality system up through the executive management level, single point of authority at the top. The other thing to notice is that you will have engineers, engineers, engineers everywhere instead of product development and production and purchasing. Like commissioned specialties, you will need to develop engineering specialties within your organization. Next slide.

So how do we handle this management problem? So we handled it by setting up our factories with all disciplines having direct reporting lines inside of the manufacturing structure. You may find that a different structure works for you, which you'll need to address a different function to interface to create a cohesive manufacturing operation.

Additionally, your manufacturing organization will need the ability to make unilateral decisions. Obviously, they'll have to report and justify their decisions to hospital executives, but much like reporting to a board of directors, your manufacturing organization will need to have the responsibility and the authority to perform work affecting quality and the independence to perform tasks affecting quality. One thing to think about at some point in

time, your engineers will tell your clinicians that we cannot do a certain activity. You need to figure out how you're going to react to that situation. Next slide, please.

This leads us to our third lesson, which is structure matters. As such, you need to establish -- structure matters is a fundamental responsibility of management. You're going to need to establish and maintain an adequate organization structure to ensure that devices are designed and produced in accordance with the requirements and GMP. Medical device product production, regardless of the manner or location of production, is not a solitary activity.

Suitable resources need to be assigned to all aspects of manufacturing. I've listed a number of them here, controlling materials, processing controls, addressing complaints, designing devices, documentation. These are resources in the organizational structure so that everyone is aware of their duties and the duties of those around them. Next slide, please.

So a recap on our lessons learned. The first one is that we would suggest that you introduce a quality system as good manufacturing practices. Again, it gives you a chance to introduce it from a fresh perspective.

You're going to find that you have operational pockets that are similar to medical device manufacturers.

You're likely going to need to reach outside your organization to acquire additional knowledge and you'll have to address your organizational structure. Next slide.

Thank you. Back to you, Matthew.

DR. DI PRIMA: And thank you, Greg, so much for getting into such detail on the quality management system. I think highlighting the difference between the healthcare setup and the medical device company was really useful.

And continuing that same sort of discussion, I'm very excited to introduce Arrianna

Willis, who is the Director of Operations of Advanced Manufacturing at the VA Puget Sound Health Care Office. System, sorry.

MS. WILLIS: Thank you so much for that introduction, Matthew. As you said, my name is Arrianna Willis, I'm the Director of Operations at the VA Puget Sound Health Care System and I'm really excited to be talking to you all today about our experience with operationalizing a quality management system within a healthcare facility. Next slide, please.

As you guys have seen before, here are the standard VA disclaimers, so I'll give everybody a second to read over those.

(Pause.)

MS. WILLIS: Next slide, please.

So I'm sure I don't have to convince anybody here that across the nation, people are using 3D printing technology for a wide variety of applications, especially in health care. For example, our team at the VA Puget Sound has almost 10 years of combined team experience using 3D printers within a healthcare facility for a variety of applications.

However, there's a big difference between using 3D-printing technology to make tools that support work in and around a hospital, to make prosthetics and assistive technology devices, and then using it to produce regulated medical devices. Most healthcare workers, engineers, technicians, clinicians, are not formally trained on FDA regulations and most likely don't have understanding -- I'm sorry, don't have experience in traditional manufacturing.

Based on the experience we've had within the VA, I believe that understanding what it really means to implement and operationalize a quality management system is one of the biggest hurdles for healthcare facilities getting into medical device manufacturing. We're all capable of reading the regulations and quality management procedures, but I think

there's a big transition from understanding what the written word is and putting it into action in day-to-day operations and truly understanding how does this apply to me. So today I'll be sharing some of the major lessons we've learned on the manufacturing side of the house at the VA Puget Sound as we put our QMS into operation.

At a glance, the broad topics we'll discuss today include process controls, so what does this mean and how does this apply to me; equipment validation, how do I know that my process is behaving as it should; and acceptance activities, how do I verify the quality of my product. Next slide, please.

Lesson Number 1 is becoming a medical device manufacturer is not just purchasing and installing the equipment needed for manufacturing a device. Next slide, please.

So I think in several conversations I've heard over the last year, it sounds like this idea of just needing to purchase the equipment may be the common understanding from the hospital leadership perspective of what it takes to start making medical devices in your healthcare facility. While purchasing the equipment and getting it installed in your facility is certainly a big step in the process, because I know we all deal with purchasing and facilities and logistics hurdles, but there's much more involved when it comes to bringing the systems under your quality management system.

In the previous talk, my colleague, Greg Voss, addressed the need for a quality management system as a point-of-care medical device manufacturer. Specifically, the federal regulation, 21 C.F.R. 820, states that "Each manufacturer shall develop, conduct, control and monitor production processes to ensure that a device conforms to its specifications." As we, as the VA team, started to build out our manufacturing processes for medical devices and following these regulations, the questions that immediately came to our mind were what does this mean and how does this apply to me.

For starters, implementing process controls basically means that you have a clearly

defined process that your manufacturing team can follow and is traceable from the start of your process all the way through your finished device. Your goal as a manufacturer is to be able to clearly point to all of the parts in the process that went into manufacturing your device and show that you adhered to procedures you established and validated for manufacturing.

So how does this apply to me as a manufacturer? I think one key word here is documentation. The amount of documentation that is needed can vary by process, but I think one big area of implementing the QMS where we underestimated the amount of work that needs to be done is the documentation. It's definitely up to your quality management system in conjunction with the regulation to lay the framework for what documentation aspects, the documentation aspect of your process looks like for your facility.

But just as an example, process controls for a given 3D-printing manufacturing process might include maintenance procedures or work instructions that outline your daily, weekly, monthly and annual maintenance activities completed on each piece of equipment; operational procedures that specify details such as how to prepare the parts for printing, how to operate the printer and assign correct settings or print parameters; how to post-process specific types of parts and the settings associated for each type of post-processing equipment.

And for each procedure that gets completed, there's often an associated form that gets billed out to tie in that traceability aspect for the actual manufactured part. All maintenance procedures need to be documented and signed off by the person completing the procedures, and then you also have your forms and travelers for recording each billed run, the printer, the settings that were used, and how and when post-processing was completed.

So just to give you an example, as we worked through setting up our SLS

manufacturing process and integrating it with our quality management system, our team generated 15 different work instructions for maintenance and operations of the equipment, and then 15 different forms for logging the different maintenance procedures and operations. This is not to say that this is a magic number for these process control documents, but just a reference for the amount of documentation that we deem sufficient for our quality management system. Next slide, please.

Now obviously, all that documentation isn't going to write itself, which leads me to my next point, it takes a significant amount of resources to generate and maintain these controls.

As Greg mentioned, becoming a medical device manufacturer means changing from being the recipe follower to being the recipe creator. I know for our team at the VA Puget Sound and our sister sites in Charleston and Richmond, we all have small teams with team members wearing multiple hats, so from an organizational perspective, one individual may be doing the duties of a process engineer, a product engineer, and a machine technician all in one. So the amount of work involved with generating these documents may fall on the shoulders of one to two individuals who are also doing multiple other tasks. And I have a feeling that this is the same in many other healthcare facilities as you are starting to implement your 3D-printing service lines.

In addition, once the documents are generated and established within your quality management system, the operators of the equipment are required to be trained on the process and then to adhere to those written procedures and documentation and record the completion of all those procedures on those designated forms that you created.

Healthcare facilities often have designated engineering staff to maintain medical device equipment. For example, the VA has a team of biomedical engineers that maintains all of the hospital's medical equipment. However, maintaining our 3D printers and your

ancillary post-processing or manufacturing equipment is probably on the order of a full-time job depending on your current volume. So we found that we needed to bring in additional team members to run and maintain the manufacturing equipment fully independent of any existing hospital staff. As you can see on this slide here, our lead powder bed technician, Michael Cook, is pictured and he came to us as an outside person with industry experience in manufacturing and equipment maintenance and has been a great complement to our team. Next slide, please.

Lastly, I think many of us who have worked with 3D printing in past experiences can attest to always wanting to change up the process, to try new things, test new settings, etc., to really hone in on that best print. However, once you're operating within a controlled process, you can't do that without justification and documentation. Any time you want to change a process, it may require testing and/or additional validation to show your changes don't adversely affect your product, changes to any affected documentation, which must be formally reviewed and released within your QMS. There's also additional training for staff to ensure that they are trained to those changes in the procedures.

And I think the biggest thing here is time. Changes to a process are not likely going to be implemented overnight. It all takes time and resources to implement those changes, I think, as most healthcare facilities are aware, and changes in other realms of the hospital. We have set up our organization so that a request for a change can be initiated at any level within the organization. However, from a management perspective, there's always a tradeoff to keep in mind of how much time and resources it will take to implement your change versus what the effect of that change may be. Next slide, please.

Which brings me to Lesson Number 2: Just because you can 3D print a device doesn't mean that you have a proven process. Next slide, please.

Process validation goes hand in hand with process controls and that it takes the

controls you have established for your process and test them to ensure that you are repeatedly producing the desired product. In our experience, and as was mentioned in a previous talk from yesterday, printer OEMs have variable experience with process validation with some manufacturers having a complete set of process validations that they're willing and able to share, and say the IQ/OQ/PQ format. Others have maybe only an IQ and some maybe don't have any existing documentation to share. Regardless of OEM documentation exists, process validation is a requirement for manufacturing cleared medical devices.

It also requires a great deal of resources that I think many healthcare facilities may not be well equipped to handle or be prepared for. I know this is one thing that was a big lesson for us.

For starters, process validation can take time. For one example, at the VA Puget Sound, our first process validation was a situation where we had existing IQ/OQ/PQ protocols from the OEM, that they were willing and able to share, which is, I think, probably one of the best-case scenarios. But it still took us about 8 months to complete the validation work start to finish. So you can imagine that if the OEM hadn't had existing protocols that they were sharing with us, there would've been additional upfront work to establish the variables tested, develop the validation strategy, and write the protocol.

Additionally, because process validation is testing and proving the repeatability of your process, they often require multiple builds that test different print variables such as build volume, printer settings, print geometry, etc., which means that the validation work may require a lot of material usage, and the costs associated with validation work may not have been part of the facility's budget in bringing this equipment on house.

For example, the Seattle VA is going to be starting a process validation in the next 2 months and we're estimating that it's going to cost over $15,000 in printer material alone to

complete the validation, and that's assuming that all builds run well and according to plan without any failures.

Lastly, process validation requires staffing resources in several different capacities that all healthcare facilities may not be able to accommodate. Engineering and quality resources are critical for developing the validation strategy and running protocols. Engineering and/or machine technicians are responsible for execution of the protocol and then also potentially, inspection of your printed parts. And the final report writing will require engineering resources, as well.

Similar to my point about process controls, some facilities may have staff in engineering or technician roles already, but not in the same capacity as what's needed for process validation. These individuals would need to be trained to the QMS and would likely require a significant amount of time from these resources, which makes a strong argument for dedicated staff to support these efforts. Our team has grown to support these needs in Seattle and currently has three full-time engineers and three full-time technicians to support these activities. Next slide, please.

Lesson Number 3: Just because you can 3D print a device doesn't mean that's a quality product. Next slide, please.

All right, so now that we've established our process controls and we validated our process to ensure that we get repeatable results, we're now ready to start printing and manufacturing, right? Almost. Now I've got to make sure that I can maintain continuous quality of my product throughout or through acceptance activities and inspection.

And I think that one of the biggest lessons we learned about acceptance activities is that they are implemented throughout your process to ensure the quality of your product. You don't just inspect the finished product and call it good. Acceptance activities actually starts with receiving your raw material from your supplier. Once again, your materials that

you use to make your devices should be controlled as the other parts of your process are controlled as well, which means writing specifications for your purchasing and then also completing inspection and acceptance activities when the material is received from your vendor and prior to it actually making it onto the manufacturing floor.

Having to maintain strict controls around the received product and designated inspections for raw materials has been the challenge for our facility because the hospital uses a system where the purchasing, shipping, receiving, and inventory control staff are centralized for the entire hospital. These individuals don't have the capacity to be fully dedicated to following our specific controls for receiving inspection of these materials and supplies. So we've actually had to staff our own personnel for the purchasing and inventory control activities to ensure that we're able to maintain compliance with our own receiving inspection and procedures.

In addition, in a dedicated manufacturing facility there's often space designated for shipping and receiving and quarantine; however, being located within a hospital, space is often limited. Our hospital has a dedicated warehouse for all incoming and outgoing shipments, but this space is often chaotic and often full with other hospital equipment and deliveries and including the hospital warehouse staff who are doing their tasks on a day-to-day.

Within our 3D-printing footprint in the hospital, we have found it challenging to identify and maintain designated space for these acceptance activities, especially as we continue to grow and increase our capabilities and with that it comes with an increasing amount of supplies and materials that need to be maintained and housed somewhere. Next slide, please.

So once your raw materials have been approved, you can move on to manufacturing your product. Your device is then informally inspected throughout the production process

to ensure that no anomalies have appeared during the printing or post-processing steps of your process, and then it moves to quality control or final inspection where you need to verify the quality of your finished product. Before you can inspect your finished product, you really need to establish what criteria you're inspecting to. For medical devices, this may mean both a typical manufacturing inspection, which could look like dimensional or mechanical testing, and clinically relevant inspection.

Defining these inspection criteria can be a challenge, especially with patient-matched or patient-specific medical devices because of the variability in product output. Some features may be present in all devices in a product line, while maybe other product lines have changing features because of the variability needed for product output.

Compared to traditional manufacturing, it's definitely not as simple as just creating a drawing for a device and giving it to the quality control technician to inspect. There's some additional upfront knowledge and training that needs to be established so that quality control staff are able to properly inspect each device.

Tacking onto the staffing resource challenges that I've already addressed in my previous lesson, healthcare facilities may not have trained quality control personnel as an existing resource. At the VA Puget Sound, we've been able to pull talent from other departments within the hospital to fill this role. We found that utilizing staff from more tightly controlled or regulated departments such as sterile processing services works well because they're familiar with working in a highly regulated, highly controlled environment. However, becoming a quality control technician does still require upfront training and some engineering staff support to get them up to speed.

Because of our relationships with other departments in the hospital and our existing engineering resources on our team, pulling from other departments has been a viable pathway for us. However, other healthcare facilities may need to hire on their team

additional team members with previous industry quality experience to support this aspect of the production process and quality management system.

Lastly, most inspection and acceptance activities require additional equipment on top of your manufacturing equipment. Just like manufacturing equipment, all inspection equipment needs to be controlled and calibrated. I know for us at the VA, calibrated measurement and inspection equipment wasn't common within our facility. As we established our inspection procedures, we needed to procure additional equipment that could be used to execute on these procedures.

In addition, I think most hospitals probably aren't set up to maintain this equipment along with their other medical device equipment. Again, as an example at the VA, we've kind of had to set up our own system within our quality management system for logging this equipment and tracking it and preparing it for calibration, and I think it's safe to say we're still working out the kinks of this system. Next slide, please.

So as you can see, there's a slight -- there's a significant difference between using 3D printing to support operations around the hospital and manufacturing medical devices. In addition, healthcare facilities are really well equipped to provide quality care to their patients. However, when looking at bringing medical device manufacturing into a hospital, there are still some clear gaps between the existing hospital infrastructure and what's required for a quality management system. Operationalizing a QMS within the VA hospital system has really helped us identify what those gaps are and taught us several lessons about what it really takes to become a registered medical device manufacturer.

To summarize, our lessons learned include the following:

Lesson Number 1: Becoming a medical device manufacturer is not just purchasing and installing equipment needed to complete the manufacturing. It's your job as the medical device manufacturer to establish those process controls, ensure adequate staffing

and resources are provided to maintain those controls, and also to ensure that your device meets its required specifications.

Lesson Number 2: Just because you can 3D print a device doesn't mean that you've got a proven product. As a medical device manufacturer, it's your job to test and prove the repeatability of your manufacturing process, which can take a lot of time, money, and human resources.

And then Lesson Number 3: Just because you can 3D print a device doesn't mean that it's a quality product. The quality of your product is defined throughout your manufacturing process, from receiving inspection all the way through to your final product inspection. It's your job as a medical device manufacturer to establish your acceptance activities throughout your process and provide adequate resources for maintaining compliance with those procedures. Next slide, please.

Thank you so much for your time and attention today. I hope that sharing our lessons learned has provided an interesting learning experience for you all.

DR. DI PRIMA: Thank you so much, Arrianna.

And it's my pleasure to once again introduce Laura Gilmour, who is the principle consultant for additive manufacturing and regulatory strategy at the VA or VHA, I should say, and she's going to be the moderator for this discussion.

And again, for the audience, please keep submitting questions through the webcast button on the lower right side, thank you.

MS. GILMOUR: Thank you, Matthew, and thank you to all of our speakers. It's incredible just how much information you all just shared with the audience and I strongly encourage folks in the audience to review these talks again, there's just so much information that is available just in this recording this morning.

So I'm going to start with a couple of broad questions and then we'll get into some of

the details that the audience has asked. As Greg mentioned, the intention of a quality system in business is not to check boxes, right, that's a common misconception. It actually does describe how you do business and the philosophy of doing business. So how do you feel that this mindset and understanding can be helpful in a healthcare facility as you're setting up something like what you have described so far today? Any one of you can take it first.

MR. VOSS: I think that's a super helpful framework to use. Yeah, obviously, there's a lot of thought that goes into creating this quality system and what you want to do is have it guide the thinking so that way, people won't have to -- whereas users of a drug think you start at the beginning, am I going to inspect this, how am I going to inspect it. So you thought through that one time, so things you do many times, think about once.

MS. GILMOUR: That's great. Joe, Arri, anything to add to that, so far?

MR. BEEDLE: Just to echo, we are in -- in the VHA, we're used to checking boxes, we're used to having a list, we're used to going through it, and the fundamental shift that we've got to change is really to say -- and again, as the presenters have done this morning about it, we are moving from something where we're very used to, you know, we purchase something and we use it and then we move on from those and with more of a device manufacturing mindset, it's going to be something where we have to take into account that which are not normal. I'll get more into detail when we go to the specific questions because it directly addresses that. Thank you.

MS. WILLIS: I think I'll just add onto that, as well, is that I think what we're trying to do in implementing our QMS is in not checking those boxes, just trying to set up our procedures, as Greg said, really thinking through them so that we're following them in a way that makes sense for everybody who's doing the work involved and in setting up your own quality management system, you have that flexibility to generate your procedures so

that you're doing them in a way that's smart for your team, that you're not just checking those boxes and saying okay, I did this, but I understand why I did this and this works for me and my process. So I think that's another point there.

MS. GILMOUR: Great. Thanks, Arri.

This is a more broad question as well, so -- but you can get specific within the answer. What inputs went into the development of the VA QMS, such as ISO 9001, medical device QMS requirements, 21 C.F.R. 820, pharma requirements, or healthcare facility standards? Can you share a little more on the specifics around that?

MR. VOSS: I'll start with that one. That's an excellent question. We structured our system for both 21 C.F.R. 820 and ISO 13485, i.e., our structure is fused pretty closely to the 13485 framework. Where 13485 and 820 deviated from each other, we went to the 820 route. So things like, if I remember, there's some continuous improvement activities in 13485, customer-focused activities that I don't think are in 820. But those were the two primary sources.

MS. GILMOUR: Okay. Anything else, Joe, Arri, to add or --

MR. BEEDLE: Just quick, there was a question that was about costs that were going in, is this a good place to talk about that because they're interrelated, or do you want just keep those separate?

MS. GILMOUR: I'll ask it in just a second, Joe, yeah.

MR. BEEDLE: Thank you.

MS. GILMOUR: Okay. Greg, you mentioned the 820 versus ISO 13485. As we know, the FDA is moving -- transitioning to move away from 820 and more into the international regulations. Is that impacting the process that you've done so far and how do you expect that to change things, if at all?

MR. VOSS: It hasn't impacted us yet. We are monitoring 13485, so we are looking at

13485 and we're kind of monitoring FDA communication and we'll adjust as necessary. But it has had no imminent impact.

MS. GILMOUR: Okay, great. Okay, Joe, so your cost question. How do you factor the cost of implementing the quality system when making a financial decision whether to print or purchase a product?

MR. BEEDLE: And for us, that's that fundamental shift, again, we're moving from what we're used to doing, which is where you buy a thing and then you move forward with it and it's the cost, it's only the cost, and the example we like to give for this is learning from our own lack of knowledge in some of the areas, which is when we first started establishing costs, what we said is oh, well, the material costs for this thing are $4, so this product costs us $4 every time we produce it, that's what we're going to bill folks, not recognizing -- and that's just because, as an entity for VHA, we're more interested in providing care for patients and not necessarily setting up an entire accounting structure.

And so that's really what we had to do, we had to set up a new tracking system for costs, we had to identify what was going to be a direct cost to that product coming through and how to apply those things that were more of an overhead and overarching. And so we'll have some questions a little later on about those specialists and how do you have -- at a single site, how do you know something with it. Really, it takes a specialist for those and through the use of contracts, through the use of the broader VHA network, what we've done is we've been able to secure some folks full time and other times what we've done is we've identified that it's going to be X number of hours for that.

And so we generated -- if you have a new device, we have kind of a pricing model to say we think it's going to cost X number of dollars to develop that and then after the development of that item, it's going to cost something on a per-item basis. And so that's really how we're identifying those costs and really, it goes to that make/buy decision that

we've got. There is a benefit for being in the VA, which is no matter what we do, if this is going to be additive to the patient we can make those value decisions and really be able to bring something in that we might not, in the private sector about it, use the normal pathways. But as we said before, a blue sky type of we really want to get people in the environment where they can do that. If they can develop an idea, we now have that process and the tools in the broader VHA area to really start to examine those and determine whether or not it's something we can move forward with, not just on a single instance, but then being able to bring it out to the rest and actually apply those costs.

MS. GILMOUR: So following on with that, you mentioned about leveraging existing experts or employees within the VA. Are the VAs with established GMP manufacturing standards using existing VA platforms like Maximo or other equipment PM management programs or was it necessary to use something separate?

MR. BEEDLE: A combination of both on those and it really is because we can view anything on those. Anytime we can use Maximo for those with the existing systems, we use those. But what we found is, is that we're an awful lot of snowflakes while we're going through and making these purchases since everyone is unique as it's going.

And to Mr. Voss's point on it, really what we're trying to figure out is, as much as everything is unique about it, we can pull out those factors where we can have an overriding thought process and say yes, it's not specifically this, but here's what we have and that gets us 90% of the way through that so we're not recreating the wheel for every device, which becomes incredibly expensive as we go, and leveraging the people that we've got from more national programs or within the 3D-printing group at all of the sites, because we have an incredibly broad pool of experts in various areas.

MR. VOSS: And we've made provisions inside of the quality management system for the use of existing systems, i.e. Maximo or EE numbers, and we're trying to make sure that

in addition to having our unique identifying number inside a paper-based system so we can capture things that aren't typically put into Maximo, such as non-capital stuff; calipers, for example.

MS. GILMOUR: Um-hum. So a little bit different flavor but kind of the same thing, using existing full-time employees, for example, a lot of these 3D-printing organizations that are in a healthcare facility are relying on a smaller number of full-time employees as compared to a medical device manufacturer. How do you recommend smaller organizations right-size their quality system? Since quality systems are generally built for larger organizations, do you have recommendations on that?

MR. VOSS: Yeah, so I think the first thing is that you obviously get to take into account the training level and the competencies of the employees inside of the system. I think that's one thing that I didn't talk about in my talk but I think is worth mentioning, is that the competencies of the people in the healthcare facility are at or higher than the average competency that you would see at a medical device manufacturer, certainly on the manufacturing floor.

So you can take that into account in your writing of procedures. You should also make sure that you are thinking about your organizational structure and if somebody has to wear multiple hats, clearly define that and make sure that those hats aren't arranged in such a way that somebody who's doing something critical to quality doesn't have the independence they need to do their work.

MS. WILLIS: And I think --

MR. BEEDLE: As Arrianna -- oh, go ahead.

MS. WILLIS: Yeah. Just to add on to that, I think we've utilized cross-training where we can and had multiple people train to multiple roles, as Greg said, but tried to minimize or maybe triage their responsibilities, but then also say, on the manufacturing side, we

don't want somebody who's manufacturing a product necessarily inspecting their products. So we've tried to kind of -- we have technicians who are cross-trained on both the manufacturing and the quality control, quality inspection side of things, but then set up their specialties in a way so that we're covered on both ends of the system.

MR. BEEDLE: Yeah, and I'd like to -- Arrianna, during your presentation you had made the comments to not everyone can and just -- well, not everyone should just because you can in some instances and one of the lessons learned for us on that, too, is we couldn't be everything as we were maturing, as we were bringing in other devices and saying well, could we do this. What we were quickly finding is, is that "oh, well, once something is printed or designed now it has to go to sterile processing." "Oh, well, we'll take care of that ourselves." There is no way we would've become a huge entity and there was no way that we could have existed at that point.

So a lot of it was leveraging what we had within the medical facility, as well, so if we needed an industrial hygienist, there is one that's in the facility that can come over and at the very least point us in the right direction or a better direction than where we might have gone for things like SPS transportation within the facility over two and SPS. So really reexamining what you have as your resources locally and then the pathways that you did.

We leveraged, incredibly, we had no used contracts in the particular way before with our academic affiliates and we were able to reach out to them to bring in folks even for like single type of use items, that we were able to bring them in and say you're the specialist as we're going, but recognizing the reason why we did that was not because that was a one-time use only, it was that once we had that in place it allowed a larger production of what we were trying to accomplish, but we didn't have that one subset that should be necessary to move the device forward or the process forward. Thank you.

MS. GILMOUR: So you mentioned sterilization and sterile processing, Joe. The next

question is do items that require sterilization, such as reusable surgical instruments, have cleaning and sterilization processes approved by a third party? Is the validated process then shared with other VA MC manufacturing the same device and using the same materials? So how are you approaching sterilization, I think, is the root of the question.

MR. VOSS: So I think I wouldn't characterize it as approved by a third party but certainly, so far sterilization validations, they are done by a third party, a lab who -- a third-party lab who has an ISO certificate that covers them for that activity as a research lab for both cleaning and sterilization. And then the other part of the question was once validated, do we --

MS. GILMOUR: Pair it with other --

MR. VOSS: Pair it out. Yes, if the manufacturing processes are similar enough, we will have our justification to allow us to use that cleaning and sterilization validation or leverage that activity.

MR. BEEDLE: And we use that sharing model across the U.S. as we create something. The idea behind it is, is that there isn't going to be a Charleston book, a Seattle book, whatever it is, that it really becomes VHA wide and that would be the same for processes as well as the products themselves as we go forward.

MS. GILMOUR: This, I think, fits nicely into what you were just saying, Joe. The question is will VACO establish a program office to act in the role of oversight to what facilities are manufacturing and also ensuring those facilities and GMP standards are being met?

MR. BEEDLE: So the Office of Advanced Manufacturing was funded through an executive decision memo for this year and what we're developing and what we're pushing for is a sustainability model that will allow the OAM group to provide those kind of services and again, it's not for the one device that's being done in Peoria at that point in time and

saying that this is for a single use, necessarily. If they don't need us, it's not going to be an issue on those. But really, we're setting up the guardrails. As things start to expand out, as we're starting to see similar devices coming on board, what we're doing is we're saying to the Office of Advanced Manufacturing that we will be able to provide those services and say yes, you can move forward with this within these parameters and by the way, here's your playbook for how you're going to -- using SPS as an example, here's what you need to hand to your SPS group, here's what you need to make sure that your engineers know that if you create this device you're going to have this kind of off-gas and you're going to have these type of things.

And it's really that shared services model of saying every VA, if they try to do it themselves, it would collapse under the weight of itself on those. But with OAM, it's kind of overarching and largely, through pain and suffering and blood, sweat and tears, to make sure we kind of pave the pathway on it, is follow this, it will get you much farther along the path than if you're trying to do it yourself and then yes, that there are those shared services like the quality management group. So like Greg's time, like Arrianna's time, you can always pick up the phone and call us for those.

MS. GILMOUR: So Arri, this question is for you. Have you registered your facility as a medical device manufacturer and listed any devices? And then following that, have you been subject to an inspection either by the FDA or a certified body and what was your experience there?

MS. WILLIS: Okay. So yes, we are registered with the FDA as a medical device manufacturer. Our first listed product has been listed and it's in distribution in the Erie -- I forget what VISN it is -- Erie region, thermal-fused cover is what it's named, called. So, yes. And yes, we have a medical device and we also have a 510(k) submission in for -- I think Beth mentioned it yesterday -- another product that's making its way through and hopefully

to be a fully registered device before the end of the year. And as far as the audit is concerned, we have not had any sort of formal inspection from an external body, but we have been conducting our own internal audits and that's part of our quality management system, as well, to conduct those on a regularly scheduled basis to make sure that we're covering all of our bases and are maintaining compliance with our procedures at our site and then at the Charleston and Richmond sites, as well.

MS. GILMOUR: Great. Thanks, Arri.

So here's a question probably for all of you. What potential considerations are there for conflict of interest in reporting of in-house failures in manufacturing if the manufacturer is no longer a third party, but the healthcare facility itself? So essentially, how is transparency guaranteed if everything's occurring in one facility within basically -- you know, could be one group, right? So how would you approach that?

MR. BEEDLE: And I'll give my thoughts on it for that portion. That same type of internal and that transparency, we are all medical facilities as we go forward. So even if a third party isn't necessarily coming in to review anything, we do have those internal build watchdogs, whether like, again, for OSHA, there are rules and regulations, it's not that OSHA comes in every time, it's that we have internal -- our safety officers are coming through, they're reviewing it.

We even had a few instances when we were starting to ramp up, where we were calling in safety and saying please come through and inspect, and our industrial hygienist and making sure that -- you know, are the fume hoods proper or coming through, do we need fume hoods as we're coming through. So kind of using that as an example, a healthcare entity itself is well designed to have internal controls in place to make sure that there is zero harm, you know, the whole HRO mentality as we're coming forward. And if we apply that, it does raise the ability for us to catch those and with the conflict of interest on

those, that reporting of failures, we are better designed than -- well, better designed than some industries to be able to have that internal monitoring going, as well as the idea of saying OAM, you're going to have visitors, you're going to have people come through, there are discussions and not that everything needs a checklist as it goes through, but there will be checklists to make sure that we're monitoring that with multiple parties seeing it as well as the quality control. Thank you.

MS. GILMOUR: Greg, Arri, anything to add?

MR. VOSS: That is a super interesting question. It's one that I've thought about a fair bit because you can realize that once it's all under one roof, how do you control that? And part of that is in that organizational structure you're bringing that manufacturing location and bringing it up to executive level so that they are not under that same -- get as much separation as we can inside of the OAM structure. We also have a group that is overarching, so they'll be outside of the facility and also having independence for the people on the regulatory and quality side, so they are not directly responsible for production, but their responsibility lies in doing complaint handling and making sure that those types of issues are transparent to the outside.

MS. GILMOUR: Okay.

DR. DI PRIMA: I'd like to thank this group for such a great discussion and I see we have a lot more unanswered questions coming in. We will do our best to get responses out for those. But with that, we have a 5-minute break and then we'll reconvene with some external non-point of care views of quality management systems. So we'll see everyone in 5 minutes.

(Off the record at 1:41 p.m.)

(On the record at 1:46 p.m.)

DR. DI PRIMA: And welcome back. I would like to introduce our first speaker for the

non-point of care quality management system experience and it is my pleasure to introduce Patricia Fleenor, Director of Global Healthcare from 3D Systems.

MS. FLEENOR: Thank you very much, Matthew, and thank you very much for the opportunity to join this very interesting workshop. As Matthew mentioned, I work for 3D Systems and I am located in Denver, Colorado, where we have our healthcare additive manufacturing business. And today I would like to talk to you about implementing a risk-based quality management system.

So for those of you that are point-of-care manufacturing, I'm starting from the very beginning by trying to implement a QMS to support your new business, my guess is to start with the basics, so reviewing the standards and regulations, so 21 C.F.R. 820, ISO 13485, ISO 9001, 14971, etc. And it can get very overwhelming very quickly. There are a lot of requirements that need to be fulfilled and a lot of chapters to go through. My advice is to start with risk. Next slide, please. Next slide, please.

As you start thinking about risk, really from the very beginning of the process you're thinking about what product you're going to make; potentially, the materials, is it biocompatible; the printer, has it been used before, is it already validated; potentially, the manufacturing facility you're going to be using, is it near a highway and are there any vibration issues you need to consider in your 3D-printing experience. All of these decisions are things you should start documenting as early as possible.

At the end of the day, as you start building your QMS, you want to start building a really good risk management file and document that contains information about what can go wrong, what is the likelihood of it going wrong, what are the consequences, and how can you prevent it. The most important thing, again, is to start documenting this information early in the process. I see many companies that decide to wait until maybe a year or a year and a half after they start talking about, again, what are we going to manufacture, how are

we going to make it, and all of these decisions that take place in the meeting rooms gets lost. They wait until they have released documentation and released forms to say okay, now I need to start documenting my risk, at that point potentially being too late and losing a lot of the information that was already discussed and potentially, again, capture within notebooks or things that are not well identified at the moment. Next slide.

So there are many different ways to start documenting your risk. Different tools that you can use, like a preliminary hazard analysis, also known as a PHS, also a failure mode and effects analysis, many companies choose to bring these type of FMEA into different sections. You can have a design FMEA for your design-specific failures, a process FMEA for your manufacturing failures, use or application FMEA for those failures that happen in the field by the users, software FMEA and many others. You also have a fault tree analysis, etc.

Again, there are many tools and what I've also seen is many companies or businesses, really, when they're starting out, they get very confused by how to use these tools, what is the terminology, where do pins fit, and they spend hours in a meeting room talking about is this a failure, is this a cause, an effect, maybe a hazard, a hazardous situation. Again, it can get pretty overwhelming quickly.

My advice is don't get too caught up on the terminology early on. Make sure that all those discussions and all those risks that are being identified are documented somewhere. Later on in the product life cycle, you can then go back, review the information and make sure that it is captured correctly, and as long as it is consistent, that is the main point of documenting this information. Next slide, please.

So I wanted to just give you a quick example of one of these tools. The first one that can potentially be used is a hazard analysis. I mentioned sometimes it's also called preliminary hazard analysis depending on what kind of columns you include in this type of tool. It is very helpful because this tool forces you to think outside of failures. For most of

us in the medical device industry, we know that with medical devices there's always going to be risk whether or not your device was designed correctly, manufactured correctly, and used correctly. By default, putting something in somebody's body could potentially lead to some harms that we want to assess. Hence, the hazard analysis. Hazard, by definition, is the source of harm. Hazardous situation is the exposure of that harm. And my advice is to start with those main columns and document the source.

Again, for those of you in a medical facility, I'm guessing early on in your process you're looking at potentially literature and reading articles about products that have been developed similar to the one you're planning to do, different manufacturing processes, and through some of that literature search, you find already some risks that other manufacturers identified. Likewise, when you're meeting in an R&D type of setting and you're talking about the testing that was completed early on, you find some failures.

So those are some of the sources that you can start capturing in this type of document, again, the source being maybe a published paper; a design FMEA type of early assessment; potentially, just an early meeting; competitive device evaluation; and many others.

One more time, don't get too caught up in the terminology, simply document what you're finding, where it's coming from, and then later on, when you have the time and you have the right team in a meeting, you can then continue filling out the rest of the table. Things like the cost, the effects or harm, what are the existing conditions, so like in some cases early on in your development process you make choices to prevent some risks, you can capture those in here. The severity level, the occurrence of it and is it going to happen, the risk region. Most companies choose a risk base or a risk matrix that has like a red, yellow, green type of zone and you can define very easily how risky that particular line item is. You also have to identify your risk control measures, make sure that they are

implemented and that they're effective. And so on. So again, early on just focus on the first three tables and that should get you in a pretty good shape to start creating your risk documentation. Next slide.

All right, outside of product and process risk, which is mainly what I was talking about, the standards also talk about risk-based thinking, and many companies get very confused by this term, right, is this tied to product risk in 14921, is it something different, and what I've seen is really regulators are trying to get us to think about how we make decisions in our business on a day-to-day basis.

So risk-based thinking can really be applied early as you start drafting your QMS procedures to establish a proactive culture of prevention and improvement. It allows you to start planning and take actions to address QMS risks based on the impact and how big it is to your quality management system.

So again, when you think outside of product and process, this can be risks like the training system. In some cases you may identify the work instruction that has to be executed very well for your product to have good quality. In that case, you may want your operator to go through hands-on training for several months before we allow that person to perform his or her duties.

Likewise, if you have a paper-based quality management system, paper-based normally requires a hand signature and for situations like the pandemic, for example, it is very difficult to maintain a QMS with employees being remote.

These are the kind of risks that normally get documented and discussed in our management review meetings. For those of you not familiar with the process, management reviews are those meetings with the key stakeholders within the business or the company to assess how we're doing with our data and trends. Most of the inputs are things like complaints, CAPAs, field actions, corrective and preventive actions, and many others, and

basically what we do is take a look at that data and determine how we're going to assess and how we're going to take action for each of the issues potentially identified. Again, the regulator basically wants to see that you are taking a risk-based approach to your QMS. I might tackle my training deficiency first, while I'm tackling potentially the safety issue in the field. Document it and explain why you made that decision. Next slide.

So the idea here again, my main thought is if you start your risk documentation early on, you can build enough on that through all your product life cycle. You start with a very basic foundation of the risks identified not only for product in process, but also from your QMS. And at the end of your product life cycle, before you move into production and large volume production, hopefully you will have very good and detailed risk management files and those will be according to 14921 with a risk management plan, a risk analysis, a risk report, and potentially a procedure that dictates how, as a company or as a business, you're going to be making risk-based decisions within your QMS on a daily basis.

But having this information early is really going to allow you to create a QMS that can be scalable, meaning you are not treating every failure or every process, every document, the same. You are looking at it based on risk and taking action accordingly. This can take place for every process within the QMS: design controls, verification and validation, corrective and preventive actions, complaints, field actions, change control, nonconformances, etc.

Some examples are, for example, in the CAPA system you may break down your CAPAs by risk, maybe three categories. For those CAPAs that are very high risk, you may require additional review and approvals, regulatory, a medical doctor and so forth and so on. Potentially, you can also require very strict timelines for closure for those CAPAs that are very high risk. Again, you want to focus your resources and your efforts into those issues that are the highest impact to the customer or to the business and then treat the

other ones maybe with less priority. So for those CAPAs that are low risk, they can be open a little longer, maybe they can be completed by a quality engineer with manufacturing support, close it and move on. So again, you can scale your CAPA process that way.

Similar with complaint handling. You can have different tiers for complaints. Potentially, in your PoC facility, you have instruments and you have implants. Maybe you decide as a company that for instruments you will document those complaints, you look at the DHR, you make sure that is not really a trend, and then you close them and you're done.

For those complaints, on the other hand, tied to implants -- therefore higher risk, potentially -- you want to make sure that you get that product back, that you do a hands-on product evaluation -- hopefully, by one of your engineers -- but you potentially also do additional testing to ensure that you can recreate that failure so they can really understand what went wrong and get to real root cause.

So again, the level of investigation and effort that you have to bring to complaints can be based on the risk that you assessed and documented very early on in your process.

Another example is field actions. For field actions, you may decide, based on risk, that you may just want to send a letter to your customer letting them know "hey, something went wrong, it is up to you to decide if you want to continue using it or not," or if it's a high risk you say "hey, it's a recall and I need all of the product to come back to my facility so that I can ensure that it has been basically removed from the field and is no longer available for use."

Another example of using risk for the QMS is change control. When you're trying to make a change to potentially one of your components, one of the first things you may want to do is determine is this component critical to quality, what is the risk associated with it. Based on that, if it's low risk -- again, last review and approval -- you can complete the change and be comfortable that nothing major will be impacted in your product safety. Or

if it is a CTQ and it requires additional evaluation based on risk, you may decide to do revalidation of whatever the initial documentation was. You may want to get regulatory involved to make sure that we don't need to add an additional addendum to the 510(k) or something like that. Again, for change control, risk can be very critical. And also ensure that you are always updating your risk management files, if needed, if anything's changing.

Moving forward to, let's say supplier quality, that's another great system where risk-based decisions can be used. You can have your tiers of suppliers, you can have your higher-risk suppliers making sure they have on-site audits more often, you require more documentation from them. Potentially, any product that's coming from those high-risk suppliers, from any company inspection perspective, you may have a lower AQL to make sure that you're inspecting more parts and you can, with a hundred percent certainty or not a hundred percent, but with high confidence ensure that your product is good coming into the building.

Again, these are just some of the examples how you can use the risk, identified early, to create a QMS that can be scalable and can be risk based.

At the end of the day, when you have all these files well established, really, all you're asking is the same questions over and over again through your post-production activities. Normally, those are: Is the severity higher than what we expected? Is the frequency higher than we expected? Is the residual risk different? So that's usually that green, yellow, or red zone that I mentioned earlier, in some cases that changes and that should really trigger additional work on your end to determine what needs to be addressed to eliminating additional risks. Or lastly: Is there a new failure mode identified or a new hazard?

Again, once you have this risk management documentation well established, it is very useful and critical and required to go back always to review those documents and ensure that for every process that you're completing within the QMS, you are performing as

you expected when you established the device. And there's again a lot of benefits to have a risk-based QMS. There are shorter product development life-cycle timelines, faster regulatory clearance. As I mentioned, it's normally what regulators expect to see. Reduction of the overall cost of compliance, higher confidence in product quality, higher customer satisfaction and many others. Next slide.

That's what I just covered. And next slide.

Yeah, thank you very much. I hope you found this information helpful.

DR. DI PRIMA: Thanks so much and please definitely stick around for the panel discussion at the end.

Our next speaker is Alain Fortuney, Director of Scan2Health and 3D Printing at Point of Care Engineering with Johnson & Johnson.

MR. FORTUNEY: Thank you. Thank you very much. And thank you for the opportunity and also for the great presentation and this great workshop.

So my role in Johnson & Johnson, I'm part of the 3D printing innovation and customer solution team, and I evaluate and execute the technical strategies and developing capabilities for personalized products and solution.

First off, I'll disclose a disclaimer. The views and opinions expressed in this presentation and during the panel discussion that's going to follow in the next few minutes are mine and do not necessarily reflect the views and policy of any of the Johnson & Johnson family of companies.

My presentation today is going to be centered around the Johnson & Johnson quality management system, and what I'm going to try to do is provide you a broad overview of a QMS of a large medical device manufacturer. We operate globally and distribute our products all around the world. So I intend to provide this overview and try to zoom in and zoom out on different aspects covering, of course, 3D printing and manufacturing. Next

slide.

So you've seen this before in some of the slides or some material out there, a quality management system is essentially a collection of processes and the focus is meeting customer needs while meeting, of course, regulatory and technical requirements. As I mentioned before, Johnson & Johnson distributes its products globally. We develop them, we develop these products and manufacture these products according to most stringent and conservative regulatory and technical requirements. And the reason for that is that as we distribute the products around the world, we don't want to create different products according to different specification for different countries. We want to have one end-to-end process for all of these products.

So our QMS provides essentially the mechanism for directing, controlling, and coordinating all these different activities to achieve and sustain a high-quality product. And essentially, our QMS is applied on everything we do that has an impact on the product or services that we provide.

So if we think we about this model, it's a hierarchical model and it's guided by a core set of principles and policies, you can see these on the top of the triangle here, and these are shaped by external factors such as these regulatory government requirements. They're shaped by industry trends or strategic imperatives that J&J wants to achieve.

And as we hone down on these policies, we get clarity around procedures on what to do, how to do it, and who needs to do it and when it needs to be done, and we get the really good step-by-step action-driven work instruction and standard operating procedures. And then we have a whole set of forms and quality records that essentially create the body of evidence that provide us the assurance to demonstrate our quality and compliance.

Now, the QMS, of course, impacts everyone across the organization in Johnson & Johnson. It affects our facility and makes sure the products are researched, are developed,

are produced, tested, labeled, and stored, and these can be different or located in different sites, sometimes even in different countries. So it affects every single process, the way we develop, qualify the process, qualify the equipment and manufacture, and essentially touches every single individual across the organization that is trained and qualified to follow these procedures.

Now, as I mentioned before, the QMS is dependent on these requirements coming from regulators from not only the FDA, the U.S., in the U.S., but also Europe, Japan, China, and many other countries, but it's also dependent on the national/international standards that develop and release quality and technical standards such as the ASTM or ISO, for example, that are relevant to our business. Next slide.

Some of these regulatory agencies have, over the years, issued specific requirements for 3D printing and back in 2017, the FDA itself issued a guidance specific to this technology, and our own engineers and quality professionals have worked and are active members to many of these standard organizations.

Here, we call out the F42 from ASTM or TC 261, for example. All of these create a body of requirements that we embed in our procedure. There are also other standards that aren't necessarily related to 3D printing but have an impact on this technology.

So on the next slide here you see that -- next slide -- you see that we have incorporated -- I'm sorry, the previous one. I think I missed the -- yes. Perfect. I'm sorry, go to the next slide. Yeah. Perfect, thank you.

So as mentioned early, the QMS provides us the mechanism for directing, controlling, and coordinating our activities and we rely on the ISO 13485 that was mentioned in the previous presentation. So what I'm going to do now is provide you some of these highlights, some of these elements; not all of them because we've seen, in the previous presentation from Patricia, Greg, and Arrianna, that they covered some of these

elements.

Design control, we start out with the customer requirements, understand the product functional requirements of the CTQs and the material properties, we do all that body of work to create the evidence around design control.

On the document control, Arrianna Willis, again, has done a great job in describing this element. And the QMS, again, is not a static collection of documents, it is constantly evolving, there are always changes because we increase our knowledge on our process, we get feedback from our customers, we improve the product and services, etc., so there's a constant change and we work through a change management process to manage these documents themselves.

Purchasing control is important, the raw materials coming from different suppliers such as parts subassembly, we have a section of the quality management system that handles how to manage the suppliers.

Identification and traceability, also very important to link together the raw material to the part on some of the personalized products. For example, they are done at point of care, we link the product itself to the name of the patient or the surgeon that has ordered the product or prescribed the product.

I'm not going to cover the production and process control. And also the acceptance activities were discussed extensively before, but the testing is done from the moment the raw material or the components are received in house all the way to a final product release with final inspection. And in between these two very important steps there could be many, many different testings and acceptance testing, depending on the complexity of the production system, the design system, and of the supply chain.

We covered already in the previous presentation the nonconforming products and the corrective and preventive action.

And one important element is the labeling and packaging. We consider the labeling and the packaging as the product itself. We ship the product across the world, so the container and the way we protect the product is important and so this is something that, for example, should be considered at the 3D printing at point of care if the product also needs to be shipped to other locations.

We discussed about the records, as well. We have different types of records and different types of collections of records, I heard before from Arrianna, about the device master record or the device history file. These are important documentations to prove out that we have traceability of the raw material, the manufacturing instruction, revision number that we use, the machine setting, so on and so forth.

An important element for us is also related to the servicing. Some of our devices are placed in hospitals and/or in the surgical theater and we need to provide instruction on how these products are serviced, how they should be installed by the customer, how they are maintained, what's the maintenance interval, calibration, what's the type of technical support that is needed. And I'm thinking about this one here because there's this concept of medical device production system that is going to reside at the hospital facility and this is an important element.

And of course, statistical techniques, we have many procedures related to what statistical technique to use depending on the type of activity, whether we are in a development space or in a production or validation space.

And the final one is the management review activities, and Patricia just mentioned the importance of this, and we use a process, for example, through the product development that is a formal stage gauge process that dictates also the different steps of the process and the presence of independent reviewers during that process.

So these are general elements that are part of the QMS, they're not necessarily

related to 3D printing, but are elements that should be, that are considered in our own QMS. Next slide, please.

So when the FDA issued in 2017 the guidance, we took that guidance and incorporated it into our own J&J 3D printing procedure and we incorporated it into the procedure, not only the FDA requirements but also the ones that were coming out from ISO and ASTM. Next slide.

So what I'm going to do now in the next few minutes is hit on some of the elements that are important for the QMS and 3D printing, first off with the validation side. So we essentially do validation on every manufacturing process and 3D printing is not different, but the difference is that we add additional efforts for monitoring and verification, and the reason for that is that the 3D-printing technology is newer and there's not a lot of body of evidence or experience around this process, so we complement the traditional approach with additional efforts in this space.

One thing that was not mentioned on the device design in the early presentation is the concept of the design envelope. So when we design a product that is 3D printed, we develop a design envelope so that we come up with a minimum and maximum design space and we validate that entire space.

Software workflow is very important, it's not only a manufacturing technology but it's also a constant conversion of different file formats, especially in the personalized patient specific ones. We have the presence of technicians or biomedical engineers that are interacting with the software so we consider the risk that could be added by the presence of individuals interacting with the process.

The post-processing activities for 3D printing, extremely important. We need to ensure that the device performance and material properties are maintained and we need to understand whether there are detrimental effects on the final device from this post-

processing and that gets incorporated, of course, in the validation in these acceptance procedures.

On device testing, for example, we think a way of leveraging testing using, for example, coupons, so design of the coupon, the coupon should be representative on not only the design but also the different features on the product.

Device cleaning and sterilization, also very important. The 3D printing requires the existence of a support structure that needs to be removed. Cleaning and sterilization challenge may be added just because of this technology.

On the biocompatibility standpoint, we currently rely and we comply with ISO 10933 and we ensure that the material is not affected by the 3D printing process or vice versa.

And additional consideration relevant to the labeling. And again, I mentioned before, a patient identifier on the label or on the product itself or, for example, specifying the anatomical location of the product, whether it's a left or a right product for the right part or left part of an anatomical part. Next slide, please.

We already covered the ISO, the risk management aspect related to ISO 14971 and the reliance on different types of FMEAs. So next slide, please.

Patient specific risk consideration, a heavy reliance again on a digital workflow besides the manufacturing aspect, this concept of digital manufacturing is very important, we rely on FDA-approved software as a medical device product, for example. We know the existence of open source type of software to do, for example, segmentation work and that would not pass any type of validation exercise within Johnson & Johnson. And of course, the efforts to maintain the patient data and ensure data integrity. Next slide.

This part is related to the way we measure quality, it was hinted, addressed already before in some of the previous presentations and we rely on physical coupons, chemical coupons, we track the build logs of our manufacturing process and we review the data for

anomalies. We use blue light scanners, for example, to ensure that the device was built as intended. Next slide.

And again, on the regulatory aspect, we are part of a regulated industry, of course, and our products are FDA approved in the U.S. and they go through an approval process in every country in which they are distributed. And so the product approval pathway is one aspect of this, but there are also responsibilities with respect to what happens to the process, to the product, or to the processes after the products are launched. So there are audit and inspection requirements and also, we have dedicated resources that essentially play an important part just on this specific aspect.

And with that, I hope I provided you a broad overview of what Johnson & Johnson does. And with that, I'll pass it back to you, Matthew. Thank you.

DR. DI PRIMA: Thank you so much. A quality management system is very in depth and complex, and I'm sure we're going to get lots of questions about them during the discussion.

I'm very excited to introduce our next speaker, FDA's very own Phil Pontikos, who is a national medical device expert investigator, and he can share all of his range of experiences doing inspections that people were asking earlier.

So Phil, take it away.

MR. PONTIKOS: Can you hear me okay, Matthew?

DR. DI PRIMA: Loud and clear.

MR. PONTIKOS: Fantastic, thank you. I want to welcome everyone and I'm looking forward to being able to take a few moments and discuss FDA medical device inspections. I work within the Office of Regulatory Affairs for the Food and Drug Administration and what that basically means is we're the field force in FDA. We're the ones that actually come on site at the manufacturing sites or the design centers and we conduct device inspections for

all medical devices, which would include 3D and additive manufactured products that are intended for medical use, and we're ensuring that those devices are meeting the quality system objectives and in essence are safe and effective for public health purposes.

I'm going to give you a brief overview of the types of FDA inspections we do and the compliance programs that we actually use that govern these types of inspections. Then I'm going to wrap up with a discussion of the additive manufactured products and how we would address some specific issues during the inspection, so more targeted towards the inspection view point of 3D-printed products.

Our inspections are founded based on an inspection technique that we have that's known as the quality system inspection technique. The acronym for that is QSIT. It really helps us ensure that the systems and the methods and the procedures that are established are in place and are effective for these products. So it includes, really, an assessment of postmarket data, as well, including recalls or corrections and removals; any adverse event reports, known as medical device reports; and complaints that may have been received on products. So during our inspections not only are we conducting the quality system inspection, but we may also be doing follow-up on pertinent recalls, those pertinent adverse events and any complaints that we know of.

So the quality system inspection technique, it's based on covering four major sub-systems that are within the quality system. Those sub-systems are management controls, corrective and preventive action, design, and production and process controls.

We use one of two compliance programs that we have which really govern what we're going to be doing. The first one, for all our comprehensive inspections, would be our compliance program at 7382.845, Inspection of Medical Device Manufacturers.

We also have another compliance program that we use for premarket and postmarket approval inspections. Now, those would be devices that are submitted to the

FDA and approved under a premarket application, or a PMA. In those particular cases, we would do a premarket inspection and a postmarket inspection, as well, and that is done under CP 7383.001.

The postmarket -- I'm sorry, let me talk first about the 7382.845, which is the comprehensive inspections. Within that group, we actually have three different levels of inspections that we can conduct. We've dubbed them Level 1, Level 2, and Level 3.

Level 1, also coined and known as the abbreviated inspection, is when we cover the corrective and preventive action sub-system plus one additional sub-system which could be either design or production and process controls. We typically will alter those in between inspections if we do back-to-back abbreviated but at minimum, we'll cover CAPA plus at least design or production.

For a Level 2 inspection, known as a comprehensive inspection, we're going to cover all four major sub-systems. That's going to include management, CAPA, the corrective and preventive action sub-system, design, and production and process controls.

Our Level 3 inspection is known as a compliance follow-up inspection. These are more directed in nature and we typically will come on site when there's a directed reason to be there. So for example, it may be a follow-up to previous FDA inspectional findings during a previous inspection where we may have had some significant issues that arose. So that's a compliance follow-up example. Another one may be that we're coming out to review and discuss numerous recalls that have occurred in a short period of time. During a Level 3 inspection, we do tend to follow the QSIT approach but in fact, because it's directed, we may be very focused on certain elements and not necessarily follow the approach in its entirety.

On the 7383.001, the premarket and postmarket inspection for PMAs, the premarket will occur before the Agency grants approval of the PMA. It tends to be one of the last

steps in the process of PMA. We're notified by the Center for Devices that the firm is ready for inspection and then those inspections are scheduled and conducted. After FDA grants PMA approval, typically within an 8- to 12-month period after approval, we will also conduct a postmarket inspection of the PMA device to determine how it's doing after approval as we're gaining more experience with commercialization of the product.

During our inspections, we classify them when we're done. Basically, we have three classifications. We have what's called a no action indicated classification. This would be indicated when there's no Form 483 issue. The 483 or list of objectionable -- list of observations, I'm sorry, is issued during an inspection when the investigator on site finds areas of the quality system that, in their judgment, are deviations from the quality system requirements under 820.

So if there are no findings issued, most typically that would be classified as NAI or no action indicated. What that basically means is there were no findings and you're going to be put onto a routine inspection cycle. I'll discuss what that means in a moment.

If it's VAI, that's known as voluntary action indicated. During those inspections, most typically a Form 483 would've been issued for some findings, but the findings that were issued may not warrant or rise to the level of significance that we need to do something beyond looking for voluntary action and then setting you up for an inspection cycle. So no further action is typically happening at that point but, again, there were still findings.

OAI, which is official action indicated, would be indicative of a firm that had significant findings on the 483, most typically, one or more major deficiencies in the sub-systems and/or inadequate corrections to previous findings. When a company is labeled as OAI, we send those reports to our compliance branch for a determination of whether we need to take additional regulatory considerations for the company. And those are the things you may have heard out there in the media, we can issue things called untitled

letters or warning letters and if it's egregious enough and it happens repeatedly enough there are other remedies under the Act that we can take which could include civil money penalties, seizures, and injunctions.

But most typically, most firms fall under the NAI and VAI category, a large percentage, I would say greater than 90% of the companies fall under that category. So that's a little bit about the differences. On an NAI cycle, we typically inspect every 2 to 3 years. So under NAI and VAI, you might fall under that category unless we have a reason to accelerate it for some reason. On an OAI situation, we may do follow-ups on a more accelerated scale.

So let me talk a little bit about additive manufactured devices and how this all relates to the quality system. So we all know that these have a broad medical application and just some examples would be implants and surgical guides, and dental with complex and intricate and patient-specific geometries.

So when we're looking at management controls, what are we doing, from an FDA inspection perspective? So we're first off trying to see that the company has met its quality system objectives that it has in place. Those objectives would include objectives not only for what top management wants to say about how the quality system is going to be effective and implemented for the devices that are manufactured.

We're also looking at resource allocation from top management, as well. That is pertinent because without adequate resources, whether it be financial or personnel, just to name two examples, it is very challenging for a company to be able to appropriately meet all the requirements and continue to make safe, effective products. So the idea of allocating those resources where necessary is integral with that process.

We look at quality auditing of the management system. These quality audits may be in the form of internal or external audits or a combination thereof, but those quality audits

are integral for the manufacturer to understand and be aware of what types of issue may be occurring, and that can be fed in through the management controls through management review meetings so that decisions can be made on issues that are occurring, to try to self-correct, if you will, issues that are happening before an auditor or regulator like myself may find those findings. And that is done through the management review process.

A couple of key points I want to bring up here, though, is number one, for quality audits and for management reviews, the FDA inspectors or investigators do not look at the deliberations of those audits or the management reviews. Those are something that you, as a company, can have and we don't request them nor do we look at them. What we do look at, though, are the inputs into those audits or reviews and we look at the outputs that come out, whether they're corrective actions or preventive-type actions.

But the actual deliberation of what occurs we do not look at nor will we request it and that's by policy. And that's a good thing, I think, because it gives the company an opportunity to deliberate openly about the issues that have arisen and to be able to exchange that information without reprise from the FDA.

So when we move into design, we have certain requirements and design controls. The basic list is you have design inputs and design outputs, verification and validation, risk analysis, design review, design changes, and design transfers.

So what are we looking at here from an additive manufacturing perspective? If I were to select a design of a 3D-printed product, one of the key areas I would focus on initially would be the quality of the patient specific data that's been received. We've all heard this term "garbage in equals to garbage out," I know that sounds a little bit harsh, but basically if the raw data or the quality of the patient data is not sufficient, then it creates challenges in the design process, so it's critical that that is controlled and is meaningful and

it can be used by the manufacturer. We look at the types of data and imaging that are conducted, as well, to make sure it's suitable for the design space that has been put in place by the manufacturer, focusing mainly on accuracy and resolution for those particular issues. Another focus we'll have is obviously on the post-processing steps and how that affects the design, as well.

All of this is predicated on risk analysis. So one of the activities that will happen early on when we're reviewing design is that our investigators will ask for the risk analysis that's conducted during design. Whether you did a preliminary hazard analysis or maybe an FMEA, failure modes and effects analysis, or some other type of analysis, we're going to ask for those because that's going to help us understand how risk mitigation and risk controls were put in place from a design perspective and we can also understand which areas are considered the risky areas of the design. We want to be very patient centric, we want to be very risk centric, as well. So that's definitely one area that we focus heavily on during design.

We're also going to look at the base model that's used, we want to make sure that that falls within the design space, as well. We're going to look at algorithms that are used for patient matching and any software that requires either validation or if it happens to be off-the-shelf software that's validated for its intended use.

We're going to look at the design limits and the specifications and then ultimately, we're going to select design verification and design validation activities that we're going to follow throughout the process to verify that the appropriate design verification and design validation activities were conducted.

If a company is using some standards that are out there, luckily FDA recognizes standards as consensus standards and one example would be ISO 14971, for example, for risk management. And so if those standards are used, we ensure that those standards were

applied appropriately.

You can envision during design, depending on the complexity of the device, there could be numerous areas we target here for inspection. It could be the actual 3D modeling, but if it's a sterile product, we're also going to be very interested in how it's sterilized. If it goes through complex cleaning processes, we want to understand, from a design perspective, is this product cleanable and sterilize-able without adversely affecting the design. So there's numerous things that we look at here. Ultimately, it really comes down to looking at the raw data and the verification and validation activity is being conducted appropriately.

For CAPA, for corrective and preventive action, we're going to be looking at the evaluation of quality data sources that the company uses for monitoring its quality data. That will be in the form of compliance or nonconformances, it could be returns, it could be supplier data, it could be servicing, installation, or acceptance data. What we're looking for is that the CAPA system integrates those quality data sources and somehow evaluates them through some type of data analysis to determine whether there's the necessity to take a corrective or preventive action based on adverse trends that may be there.

We will be drilling down into any investigations that were conducted regarding these matters, looking at verification or validation as necessary for those issues. We're going to follow through to the implementation of the corrective or preventive action, and ultimately to verify whether it's effective and we'll be verifying the effectiveness of the action, as well.

When we go to production, there's a number of controls that would be relevant to 3D printing that we would look at and it would be first off, the print parameters. We would want to make sure that coming out of design that there's been an appropriate transfer from the design controls over to production into what's known as the device master record which would house the print parameters ultimately down to the device history record, which is

the actual product or batches that are being manufactured.

We would be focusing also on material selection and quality. It's very pertinent here that the material quality and vendor selections and material selections are appropriate based on your own incoming and your own specifications that you have in place. This would also include looking at the controls on the suppliers, as well, making sure that the appropriate controls are in place, including receiving the appropriate information from the suppliers and any in-process or incoming inspections that you may conduct on those materials.

We would definitely be focusing on cleaning and finishing steps, as well. We believe those are very critical to the process, as well. And again, we would be following that process through.

We would also be trying to determine whether the entire manufacturing process has an accurate description of all of the post-processing steps and any identification of detrimental effects and mitigation steps that may need to be conducted during manufacturing. We'll be focusing on monitoring and how the process is monitored and whether that monitoring is effective. We'll be looking at training of the employees and the individuals actually performing the tasks at hand. That may actually also include if you're using vendors, as well. We'll be looking at nonconformance evaluations, as well.

From a process validation perspective, we'll be looking at documentation of processing steps, the acceptance criteria, any protocols that are used, the demonstration of consistency, and the control of critical process steps and parameters. And for acceptance testing, we'd be looking at established criteria from a risk-based perspective and that they're all documented.

And lastly, on purchasing controls, we would be selecting pertinent vendors based on risk for how you control and evaluate those suppliers and how you document that, as

well. And then we would also ensure that any design transfers that were conducted and needed to go to the suppliers were done effectively, and that the specifications were transferred appropriately, as well.

So with that, I conclude just a brief discussion about FDA inspections and how it applies to 3D printed products. Thank you, Matthew.

DR. DI PRIMA: Well, thank you so much, Phil.

And it's my pleasure to introduce Kim Torluemke, who is a regulatory affairs consultant with KT Regulatory Consulting, and I'd like the rest of our speakers from the session to bring their cameras on.

And Kim, take this discussion session away.

MS. TORLUEMKE: Thanks, Matthew. That was a great group of speakers. I can tell by the detail and depth of your individual presentations that we could all talk about this topic of quality management systems and regulatory compliance for days. Me, included. So we're going to take some questions from our audience. I'll help direct them, but if I don't call on somebody and you have something to add to the conversation, please speak up.

First, I want to start with what each of you think is the greatest risk with 3D printing and I'm going to limit it to anatomic models or cutting guides and how does a QMS system mitigate it. Jump right in. I'm not sure Phil's the right person to answer this question but Phil, if you've seen something, please speak up, otherwise I'm --

MR. PONTIKOS: Yeah.

MS. TORLUEMKE: -- going to call on Patricia to take the answer.

MR. PONTIKOS: I'm going to take a stab at this.

MS. TORLUEMKE: Okay. Go, Phil.

MR. PONTIKOS: I mean, I'll do the best I can here, so I think the anatomical model -- although I mean they're both accurate, but I could tell you that I have experience with one

particular manufacturer where the anatomical model had to be redone twice. Because the first model was not done appropriately, there were some issues with the image quality that had come in, they actually had to reimage the patient, and then -- but that was an interesting scenario because it was an emergency situation at the time and so they took what they could under those circumstances and did the best they could. But that's what I -- you know, that's what I'll say I think is the most significant.

MS. TORLUEMKE: What piece of the process do you think is the most risky, Patricia?

MS. FLEENOR: Yeah, so I think similar to what Phil had mentioned is the input coming into our system and really, the quality of the data. One thing we found is that sometimes the CT scan gets taken months ahead, right, and sometimes it's a tumor or something like that, it may change rather quickly, and by the time we print the device we're already not matching but, you know, anatomical released structure as it is today, so it's one of the biggest things we look into.

MS. TORLUEMKE: Anything else to add? Otherwise, I'll move on.

MR. FORTUNEY: Yeah, on the other hand, on the anatomical model, for example, if these are taken inside the operating theater and these are anatomical models of a particular shape that are difficult to sterilize, that could be a concern. If there are, for example, nicks and burs that are on the product itself that can pinch on the glove for the surgeon.

Again, if they are taking this device inside the operating room or, for example, going back to the image, if there's not a true correlation between the image and the dimension of the product that could be -- you know, provide an inaccurate model, essentially. So I think that these are all things that can be controlled but, again, in order to put the control in place you need to understand what is the risk and where the risk is coming from, so it's going back to what Patricia was saying before, take a risk management approach and try to

understand where these risks are and how to mitigate them.

MS. TORLUEMKE: Yeah, I think sterilization and image quality is definitely very, very specifically related to anatomic models and maybe challenges and risks that the audience didn't necessarily think of. Perfect.

What certification bodies do the panelists' companies use to assess and certify compliance of their respective QMSs? This is going to not be for Phil, but I'll talk about J&J's and 3D Systems' QMSs. Who are the certification bodies and what standards, I think you both talked about 13485, but if there are others, please mention.

MR. FORTUNEY: So of course, yes, 13485 is one of them and we operate globally, so different -- we don't look only at international bodies, but also sometimes local requirements, local permits, and of course, FDA approval if the product is sold in the U.S., but FDA approval is not necessarily required for other countries, but it helps, right? But on top of that usually you also need an approval for a Chinese market or a Japanese market, so the number of certification and bodies that are certifying J&J are quite numerous.

MS. FLEENOR: Yeah, for 3D Systems we have VSI, who comes inside. And most recently we had our Medical Device Single Audit Program audit, so MDSAP certifies different countries certifying to 13485. We also do 9001, we have some aerospace, so AS9100, as well. So a lot of different certifications that have to be taken into consideration.

MS. TORLUEMKE: And then a follow-up question. If there were a third party to certify hospital QMSs, do you think it would differ from the certification bodies used by medical device manufacturers or should it be the same? If it's different, who do you see stepping into that role? So you can throw your opinion out, too.

MR. PONTIKOS: Well, I don't know if I'm the right person for that one. I don't have a direct answer for that, I wish I did. But my gut feeling is I think we are the right people, meaning the FDA, but I would be guessing if I say anything different.

MS. TORLUEMKE: Does anyone have an opinion that are willing to be on the spot and share today?

MS. FLEENOR: I would imagine it has to be very similar, right? The basics of the QMS are the same no matter where you are and you're still trying to achieve this end goal, so I don't see why it would be any different, personally.

MR. FORTUNEY: Yeah, same personal opinion. You know, I cannot see a difference between different regulatory bodies or different providers, so yeah, I second that.

MS. TORLUEMKE: If your respective firms develop and market an MDPS, which is that device, that system, that turnkey solution for an intended use paired with a 3D printer, I don't know that that acronym has come up much today, but if your companies were to market that, what level of quality control or QMS would you expect your customers, the people you're selling that MDPS to, to have it in place and maintain, and how would that be controlled? And again, this is going to be more to industry and not so much to FDA, so either the other of you two can speak first.

MS. FLEENOR: Yeah, I mean, I imagine that they have to have some of the basic same processes in place, right, training of their individuals that are managing and printing the devices. We have to have some inspection in place, I imagine that they want to make sure whatever's coming out of the printer is indeed what they expected. So, you know, quite a bit of procedure should be in place at their facilities to ensure everything's being done correctly.

MS. TORLUEMKE: And who would control that, the person that -- or the company that's providing the MDPS or would it again be a sort of third body or a third -- is there an opportunity for a third party to certify a facility to operate an MDPS or -- I'm imagining both of your companies have put quite a bit of thought into this, what can you share with us?

MR. FORTUNEY: So we are not developing any such system. However, I would think

that there would be a lot of thought about what are the risks that we're bringing into the hospital system that would operate a medical device production system and the tendency would be to de-risk it as much as possible, also considering who owns the liability for that product. So that is the key question and if the liability resides with the medical device production system manufacturer, then I'm sure there has to be in place all the mitigation to eliminate any risk that can be created at the point of care.

MS. TORLUEMKE: Great comments, yeah. Just to level-set on kind of size of quality systems, can you guys give us a number of people that are involved in your quality regulatory programs? I know this is going to be a really hard question, especially for a global company as you both are affiliated with, but just to kind of give the audience a size and scope of what this includes.

MS. FLEENOR: Sure, I can start. I will say between probably 15 and 30 people, a combination of engineers and technicians. I think at the moment we have about 20 engineers on site and a few more inspectors that are in the quality organization.

MS. TORLUEMKE: Can you throw a number at J&J?

MR. FORTUNEY: No, J&J side, I'm sorry. I'm not part of the quality organization, I cannot throw that number in, but I would expect it to be in the hundreds. The medical device business in Johnson & Johnson is structured around different franchises, we have an orthopedic franchise, DePuy Synthes; we have cardiovascular; electrophysiology, etc., etc. Each one of them has their own quality system, they all feed in to the same J&J policy, so it becomes really complex because of the number of products we distribute and I think that we have 400,000 different SKUs between medical device and pharmaceutical products and consumer products. So each one of them has a quality system and again, I imagine the core structure is enormous.

MS. TORLUEMKE: Yeah, I would guess thousands.

MR. PONTIKOS: Yeah. So Kim, I can give you an estimate from FDA's perspective, at least.

(Cross-talk.)

MS. TORLUEMKE: Oh, great. Great.

MR. PONTIKOS: So in the field, in the Office of Regulatory Affairs, I'm not speaking for the Center for Devices, but we have roughly about a hundred and twenty to a hundred and thirty FDA investigators dedicated to medical device inspections. Now, that's all medical devices. And then we also have our compliance officers and then obviously, our management in ORA. And the Center for Devices has their own dedicated staff of those individuals, but from the FDA perspective about a hundred and twenty to a hundred and thirty FDA investigators. All of us are trained, so in fact, we have training going on this week, actually, I had to break out of it to do this. And we do cross-train our individuals, our investigators, in various technologies including 3D printing, so that would be our answer.

MS. TORLUEMKE: So you mentioned that a 3D printed device or maybe a 3D printed device that needs a PMA pre- and postmarket inspection, the people joining are wondering if you could give an example of a product that's been 3D printed --

MR. PONTIKOS: Yeah.

MS. TORLUEMKE: -- that requires a PMA.

MR. PONTIKOS: I don't have an example. Matthew might be a better person --

MS. TORLUEMKE: Yeah.

MR. PONTIKOS: -- to answer that one because I'm not on the premarket side --

(Cross-talk.)

MS. TORLUEMKE: Right, right, right.

MR. PONTIKOS: But if there is one, that is the process if it goes under PMA. But --

MS. TORLUEMKE: And can you give a definition of what kind of products, maybe just

an idea of what kind of products you see under PMA?

MR. PONTIKOS: What type of products? Well, first of all, they're usually very novel products, very high risk and one where there is not a classification for that specific product. So over the years, I could tell you products that were under PMA or currently are, but I mean, at one point in time a pacemaker was under a PMA, for example. So the best way to describe it is there is not a predicate device for it to match up against that we can claim or it's just not there, so that would be a PMA, now. Then you have the opportunity to file what's known as a 510(k), premarket clearance, and those have various avenues, as well, including a de novo process that kind of bridges that gap between a 510(k) and PMA. But I'm the wrong person, I'm not a premarket person.

MS. TORLUEMKE: That's great, yeah. Thank you.

MR. PONTIKOS: But I stated that in case there was one, don't be surprised that we would be doing a premarket inspection before you commercialize it and before you get approval.

MS. TORLUEMKE: Is there a fee associated with FDA inspections and if so, what is it? I think I know how quick you're going to be able to answer that, so I'm going to move on to the Part B of that question. If 483 form findings exist, are there fines associated with the findings?

MR. PONTIKOS: Okay. The first answer is our inspections are free if you consider the taxpayers' dollars as free, so a company does not have to pay for our inspections. Now, Patricia mentioned the Medical Device Single Audit Program, okay, and the FDA participates in that program, there are five regulators that are in that program, there's Japan, we have Australia, we have Canada, ourselves, and then ANVISA out of Brazil. Under the MDSAP single audit program, that audit can suffice all five regulators. So basically, that audit you would be paying for because you have to go through an accredited organization who's been

accredited to perform those. So under the MDSAP model, you would be paying for it. Under the FDA model, you get to see us for free, so that's an answer to Part A.

MS. TORLUEMKE: Free, free.

MR. PONTIKOS: Free. "Free" in quotes. I'm sorry, repeat B again, please.

MS. TORLUEMKE: If there are findings found in those inspections on a 483, are there fees associated with those?

MR. PONTIKOS: Okay, I think -- let me -- there are no fees, but if you're thinking like a fine, let's say, or some type of penalty, a financial penalty, we do have a provision in the Food, Drug, and Cosmetic Act for a civil money penalty. It is limited in nature in terms of what we can assess that penalty for. We very rarely have done it, but we have done it. For example, for not filing medical device reports, if it's egregious and it's been ongoing, we have the potential to levy a civil money penalty.

Most typically, though, our mode of action, when we go into something above a warning letter, would be more of a seizure or an injunction. A seizure would be seizing product that would be violative in nature or adulterated or misbranded and significant, by the way, too. We don't execute seizures all that often.

And then when we have a systemic quality system issue with a company, again, usually have quite a number of opportunities to get into compliance, but if you happen to be one of those firms that is having some challenges there, we could ask for an injunction of a company through the federal court system and under an injunction, basically we would try to stop you from or prohibit you from violating the Act anymore. So we would work with the company under the provisions of the injunction to try to bring the firm into a state of compliance. So there's no penalty, like you're not going to be charged $10,000 a 483 observation, that doesn't exist.

MS. TORLUEMKE: From each of your perspectives, what aspect of implementing a

QMS at a hospital would be most difficult?

MR. PONTIKOS: I'm going to start it off, if that's okay. I mean, I think I've seen this in my experience, not directly with 3D printed stuff, but I've seen it with re-processers, people that re-process medical devices, and they use the equipment and one of the first things is really the training of the employees and keeping them contemporaneous with the process itself. I keep thinking of endoscope re-processing as my classic example here, but implementing the QMS, you've got to have the employees that are properly trained and understand the impact of what they're doing in the process. In a hospital system, people come in and out quite a bit, there's a lot of turnover, there's sometimes even 24/7 shifts that occur. So I would say the employee, you know, the person or the employees are one of the areas I think would be a challenge for them to keep contemporaneous.

MS. TORLUEMKE: Anybody else?

MR. FORTUNEY: I'll add my two cents in here. And Patricia, you mentioned this one here before, it's all about starting and the sooner an entity will start with that journey because it is a journey, the better it is. There are a lot of decisions that are made early on that might get lost, and so building the infrastructure to get a seed QMS, a light form of a QMS that then can evolve into something bigger as the hospital scales up its operation.

MS. FLEENOR: Yeah, and to follow up on that, because there's a lot of people being responsibly trained, I think having that really critical structure of who's responsible for what in top management and different roles can become potentially pretty blurry in a hospital setting, I imagine.

MS. TORLUEMKE: Great. Are there any additional procedures or considerations you have for incorporating any third party, whether they're registered -- no, they are registered and listed contract manufacturers, to your overall manufacturing where you might have less oversight as compared to an in-house manufacturer? I might have to read that again

because I struggled a little bit.

MS. FLEENOR: I think supply management, right, is all about how well you control your suppliers and to ensure that you're keeping track of are the validations in place, change control, are they informing us of any changes coming through the pipeline and stuff like that.

MS. TORLUEMKE: Are there any procedures or additional considerations you have for incorporating third-party listed contract manufacturers? Yeah, do you want to dive a little bit more into what supplier management means? Do you hold them to an ISO standard or do you hold them to an internal framework, what does that look like in supplier management?

MS. FLEENOR: Sure, yeah, absolutely. So we definitely start with a quality agreement, right, so we need to define what they're doing for us and how we're going to treat that relationship, who's responsible for what pieces of the QMS, request a ton of certificates depending on what they're doing for us to make sure that they are capable and they're performing as expected.

I mentioned, I think, in my presentation audits, on-site audits. So those are pretty big for us to ensure that we can put ISO on the production process and make sure that it's working well. So yeah, it goes back to, again, the risk-based approach and how much you do for those suppliers based on what they're actually making and how risky those products are.

MS. TORLUEMKE: Perfect. Anything else to add?

MR. PONTIKOS: I could probably add a couple things from the FDA perspective on this. We see quite a number of issues in how companies control suppliers. In fact, if you would look at our recall database, recalls associated with supplier issues are in that 10% range and that's plus or minus a few percent here and there year to year. So it is

significant, it's something that we actually spend quite a bit of time on during our inspections.

So here are some thoughts on that. So number one, remember that that manufacturing that you're contracting out, for example, because it says contract manufacturing, it's not just the supplier part but you got to make sure that they have a quality system in place, number one.

Number two, any processes that require verification and validation, you need to ensure that they're doing it. And in fact, not only ensure it, but you need to have a way of monitoring over some periodicity, if you will, that they keep it in a validated state, which would be basically meaning that you understand what type of changes they may be making to their processes and how that impacts it and possibly even being part of that process may not be a bad idea, as well, not only being notified of it, but maybe you can also have input into it in case there are changes. What you expect them to provide to you as evidence that they comply with what you told them to do needs to also be in place.

And then ultimately, I think some type of verifications of what they do, meaning a sampling of records that will demonstrate that over an X amount period of time that indeed they've been doing what they said they'd be doing. Those are just some classic examples I can bring up

MS. TORLUEMKE: Great points. How do you manage labeling models or guides, this is going to be very specific, how do you manage labeling models or guides in your organizations? How would you recommend hospitals label and trace their devices?

MR. FORTUNEY: I mentioned this one here previously and we don't distinguish between models or guides or implants, pretty much every product must be packaged and must be labeled so there's the same level of controls that are risk based for any of those. And we heard a couple of examples of personalized products that we add to the label of a

personalized product, for example, either the patient name or a patient identifier or the surgeon that requested and prescribed the product, something to link that product with that patient in the case of patient specific products and again, there has to be the traceability labeled to the package, package to the product, and the product to the DMR that I mentioned before which is like essentially everything that has happened through the production and design of that product for that patient.

So it's a really holistic approach, the label is the end product in this case but like you can trace it back, you have to trace it back all the way to the raw material and there's a lot of information that goes into that label. You know, we talk about the expiration dates before of the medical images. Well, that expiration date also is valid, as well, for that anatomical model, for example, that if it's patient specific, if it is representative of a medical image that was taken on a certain date and is not good forever.

MS. TORLUEMKE: Great points. Anything else to add on how hospitals should track, how they should label and trace their devices? I think I hear you saying it should be similar, traceability is essential. But if I'm misconstruing that, use your own words, please.

MS. FLEENOR: I would agree. I mean, I think labeling has its own requirements that we have to follow no matter what it is and I don't imagine that being any different at a hospital.

MS. TORLUEMKE: Great. Two more questions. Are there any guidelines or advised practices on optimization of coordinate orientation of image and model?

MR. FORTUNEY: I'll try to take that one and that is not really QMS dependent, that really goes down to the technology studies used to make that product, the material, and a lot of effort has to go into characterizing the material and the process to understand what those optimal parameters are and even what is the worst-case scenario, right, because you want to make sure that you understand the process and be able to set up controlled

parameters around it.

So this is part of the development effort that happens in a standard and traditional medical device manufacturer, we spend a lot of time making sure that the processes are under control. And maybe one thing that links back to the point that was made up by Phil before, you want to catch these risks as early as possible in the process and if they get caught later in the process at finished goods or during an audit, the expense on remediating that failure or that problem goes up exponentially. So as part of the risk, the risk management process is to understand where the risk occurred and how to catch it as fast as possible as early as possible.

MS. TORLUEMKE: Great answer. One more question here. The potential update to harmonization to ISO 13485, and we're talking about the adoption of the GMP to harmonize with 13485. Do you, Phil, expect management review meetings to still be outside of the inspection of scope, inspection scope? Industry can weigh in on whether it should or should not be, but --

MR. PONTIKOS: So just recently it's been released to the *Federal Register*, you know, our attempt to have -- to rewrite the 820s to include ISO 13485. I think this is a matter still being discussed --

MS. TORLUEMKE: And it should be posted to the docket.

MR. PONTIKOS: Yeah, yeah, yeah, yeah. So there's not a -- I mean, there's not a definitive answer here I can provide you at this time.

MS. TORLUEMKE: Um-hum.

MR. PONTIKOS: Throughout my career, I have not looked at audits and I've been doing this for 28 years. I've been able to do my job effectively doing that and I will say if you participate in the MDSAP program, they do look at the audits.

MS. TORLUEMKE: They do look at the audits, that's right.

MR. PONTIKOS: Absolutely. Right now. Now, mind you, we receive those audit reports, meaning the regulators receive them, and the regulators can do what they want in that program with the information that's provided, but again, right now at this point in time I think this is still on the table. I don't know what to expect, per se, but I've been able to effectively do my job without them, I can say that. And I know the other auditing bodies do look at them, so I mean, I think we may be the exception to the rule in the world.

MS. TORLUEMKE: Absolutely.

MR. PONTIKOS: Yeah.

MS. TORLUEMKE: Okay, that concludes our Q&A section. Thanks again to our speakers and for your open responses to the questions. And I will pass it back over to Matthew.

DR. DI PRIMA: Yeah. Well, thank you so much, Kim, and that was a wonderful session.

A little bit of housekeeping, we're going to give everyone a 10-minute break and shorten the final Q&A by 5 minutes, and there is going to be a transcript of the sessions, so I know Phil had a lot to say, all of that will be on the record for everyone. And again, as was mentioned, if you have any comments, please submit them to the docket. So we'll see everyone in about 10 minutes.

(Off the record at 3:17 p.m.)

(On the record at 3:25 p.m.)

CDR COBURN: Welcome back, everybody, to our final session to our workshop. This session will follow on nicely from our previous one by discussing the gaps and needs or opportunities and needs in point-of-care quality management systems. We have four speakers, so we will get right into it with Brian Strzelecki, who is Director of Quality and New Products in the Office of Advanced Manufacturing at VA Puget Sound Health Care

System in Washington, who's been at the forefront of 3D printing at point of care for a few years now.

Brian.

MR. STRZELECKI: Thank you for the introduction. I'm pleased to kick off our final session over the 2-day workshop that we have here. As James said, I'm Brian Strzelecki with the Veterans Health Administration, under the Office of Advanced Manufacturing. I'll be kind of closing up the presentations that you've heard from my colleagues over the past couple of days. You've heard a lot of countless applications as they explained the advantages of applying 3D printing at point of care, the advantages this technology has for really improving patient care through advanced personalized medicine and advancing those techniques there, and a wide range of applications from assistive technology devices for improved patient quality of life to a variety of dental applications, prosthetic sockets and accessories, as well as surgical devices such as pre-surgical models and cutting guides, as well.

And my presentation here today is from a VHA perspective and pursuing these applications from a point-of-care and healthcare perspective, looking at them after applying the quality system regulations and through the lens of the scenarios laid out in the discussion paper that the FDA released a couple weeks ago. So next slide, please.

Before we get started, I do have to share my standard governmental disclaimers that you've seen before. Any reference to products here is not an endorsement from the government, these are my own with my work from the VHA Office of Advanced Manufacturing, they do not reflect those of the government and I don't have any financial disclosures. Next slide, please.

So before we kick off, we kind of need to have a starting point of what is a quality system, what are the quality system regulations. In the last session, we had a lot of great

insight of what this means from industry's perspective and not a lot of that is going to deviate in the conversation here today, we're going to take the same framework and kind of the perspective from the FDA of the quality system as outlined here, is the regulation is not a prescribed list of steps detailing how a manufacturer must produce a particular device, but provides a framework on particular controls that may need to be put in place for manufacturers of a finished medical device or distributors of such. These quality system regulations are outlined in Title 21 of the Code of Federal Regulations Section 820. We'll be referencing that here a lot today. And you can find these online in detail. Next slide, please.

But I'm presenting them here, kind of an overview, because there are multiple subparts to the quality system regulations that we'll break down in discussion and really, everybody should be aware of if you're considering or already partaking in point-of-care manufacturing and really exploring medical device manufacturing from within a healthcare facility or within industry.

The different subparts of that regulation is outlined here and you can see that it spans anything from initial design and development controls to records to purchasing controls, how you approach statistical techniques and etc.

So we at the VHA have -- as you heard earlier from my colleague Greg Voss, we stood up our own quality system, have been working on implementing that over the last couple years and pursuing the listing and clearance of our own medical devices as VHA, as the registered manufacturer in the eyes of the FDA. So I'll be sharing some of our experiences of going through that, in the lens of the scenarios in the discussion paper that we're all familiar with. Next slide, please.

This discussion paper was published a couple weeks ago and like I said, and like Matthew Di Prima spoke on yesterday, this is a continuation of the conversation around 3D

printing applications in this space. From a point-of-care perspective, what are the nuances when considering this technology from within the hospital walls? We're deeming this term "point-of-care manufacturing." Are there considerations, are there gaps, are there holes in the current quality system regulations that we need to consider or address after seeing this wide adoption of the 3D printing technology as a fabrication or even a production method and being used by healthcare facilities across the nation, VHA being one of them. Next slide, please.

So within this -- I hope everybody's read this. If you have not, please go seek out this discussion paper. It lays out these scenarios, these three theoretical scenarios, in detail and present a bunch of questions out for the community for consideration here. I provided a copy of these scenarios as outlined in the discussion paper here and will be breaking this down a little bit during the presentation today, each scenario and kind of the observations that we've had from a VHA perspective and applying the quality system to them and kind of exploring how these different scenarios may work in practice and implementing it from a point-of-care manufacturer's point of view. Next slide, please.

So to kick us off, we're going to start with Scenario 1, the most obvious place to start. This Scenario 1, as outlined in the discussion paper, this is the concept of this medical device production system, the MDPS. The idea of this medical device production system is the product, it's created and developed by the traditional manufacturer who holds registration as a manufacturer with FDA, and that product is released or cleared for sale where a healthcare facility can purchase that whole system and use that to produce products for patient care. Next slide, please.

So the discussion paper lays out this scenario in theory, saying the manufacturer of that MDPS would ultimately be responsible and held to all the quality system regulations that go along with being a medical device manufacturer, and the healthcare facility in this

scenario would just be a user of that product, and the product outputs from that system would kind of be an extenuation of that original MDPS system and all the same quality system regulations apply. And I think for starters, that makes sense, but in practicality, if we roll that out, kind of what are the implications there, what are the nuances that may -- we might need to still work out if this -- we want to roll this out in larger adoption? So next slide, please.

The VHA has been exploring this, this scenario, in some sense with products that are already on the market, that kind of get at this scenario where it's a combination of software and often a 3D printing system with supporting equipment for post-processing, etc., that's sold together or paired together under the same clearance or rapid clearance for use for producing models such as pre-surgical models or other devices at the point of care.

Now, from a user perspective, those at the healthcare facility, when using these types of systems, I think we heard some challenges from my colleague, Nikki Beitenman, yesterday on actually applying this and using these in practicality, but kind of bringing this back to the quality system regulations, some of the gaps that we observed with this potential scenario are outlined here and it kind of all comes back to, for starters, the validation approaches. What considerations need to be taken into consideration when looking at the validation approach for this type of product, the MDPS itself as a system, as a whole? There's a lot of variables that go into or could -- challenging features that could go into those validation activities, both from a process control aspect and a process validation consideration, as well as design validation, too.

Now, as it's currently laid out, it's under the responsibility of the original equipment manufacturer, the registered manufacturer of these systems, to make sure that their validation approach covers all these different scenarios, even though the user may be introducing additional risks when using those systems at the point of care or at the

healthcare facility themselves. How are they supposed to capture that? Is it supposed to be a more broad validation approach or do we need some kind of feedback from the users, as well?

This kind of extends out into the design validation and considerations to the risks that are involved with biocompatibility, cleaning and sterilization of some products. How do you come up with a validation approach, a designed validation approach, knowing that those risks don't just incorporate the device itself, but it's a combination of device plus the process used to make the device? And if that process is not controlled by the original equipment manufacturer but is actually being used at the healthcare facility and kind of controlled at the healthcare facility, are there issues with rolling that out in terms of making a robust enough validation plan to clear these types of devices in the future?

So something for consideration regarding these two potential gaps is do we need to broaden the expectations on what the original equipment manufacturer needs to cover here with their validation approach for these types of products in the future? Do we need to leverage other controls to make sure this is covered when these systems are rolled out for use at the healthcare facility? Do we need to lean more on service plans? Do we need to require more descriptive labeling in terms of instructions of use that the healthcare facilities can follow so that there's no risk of easily diverting off of that validated process and using these systems off label?

Alternatively, we can take the other approach or at least discuss the other approach here, is do we need to shift some of that responsibility to the users of these systems? Is that a potential path forward, too? Is there some kind of data that these users need to provide back to the original registered manufacturer of these systems to make sure that validation process still holds up when it's being used in the field?

Some additional quality system regulations that we've also observed that may be

more challenging in practice than in theory also relate to traceability and records, as well as responding to issues that come up when you have nonconforming product or there is open CAPAs that need to be addressed that the root cause analysis or the root cause of the initial issue spawned from the user of the system itself. So in regards to appropriately addressing nonconforming product or closing out CAPA events, if that's the responsibility of an original equipment manufacturer and the cause of that spawned from the user, which is kind of out of their control, how are the expectations laid out where they're supposed to address those scenarios? Is this something we need to add to the current regulations or maybe adapt the current regulations to capture, as well?

Records is kind of in the same breath, how do we keep that traceability? I think it's pretty clear that records need to be kept to show what was manufactured, by whom, and when the manufacturing took place and with what processes, and that makes sense for the manufacturing of the MDPS equipment and software.

But when you're talking about the outputs of those systems, how do we keep those device history records when the user is the one producing the end product and that's being used on the patient themselves? Does there need to be some kind of input from the user to have a complete DHR? Do we need to have some other mechanisms to feed that into the device history records for these types of products in the future to make sure that traceability is still there? So next slide, please.

To continue a little bit on this scenario, I'm going a little bit beyond the quality system regulations themselves, there are other considerations for medical device manufacturers that apply to all medical devices, most explicitly the labeling requirements and the reporting requirements here.

Now, when there's an output of these MDPS systems that interact with the patients themselves, what additional label requirements need to be put in place? So like I said

before, we still have that traceability if there's ever a complaint or an issue in the field with those product outputs. Do we need to have the traceability of the users that use those systems or do we just need the original manufacturer of the MDPS themselves?

The same with device reporting. There is existing device reporting mechanisms and pathways now, but do we need further specification during that reporting process to pinpoint exactly what system was used, but also what user is using that system where the output product spawned the initial complaint from the field? So just some additional holes or potential gaps that we have observed from the VHA perspective regarding this first scenario. Next slide, please.

Now, the second scenario is this idea of co-location, this co-location of a traditional manufacturer, as they're calling it in the discussion paper, with the healthcare facility themselves and breaking down who's responsible for what in Scenario 2. Next slide, please.

This scenario is a little more intuitive to wrap your head around, but I like to think of it of like taking a manufacturer and just setting it inside a hospital and thinking about that manufacturer inside the hospital producing product that's delivered for patient care. And it's pretty clear that it's that manufacturing group within a hospital that's potentially or at least laid out in the discussion paper, ultimately responsible for adhering to the quality system regulations and the other requirements from the regulatory bodies. Now, does it work that easily in practice? I guess, what would be the complications here, potential gaps for this scenario, as well? Next slide, please.

Now, I think the application of the quality system requirements are pretty straightforward. The biggest gaps with this scenario that we've observed from the healthcare facility perspective is kind of what are the limits that we're applying to the definition of this co-location. Does it just apply to a room within a hospital or a building on a hospital facility campus or does it also extend into not just shared space or equipment,

but personnel? Does this scenario extend out to just a shared design group that sits at a hospital and the manufacturing's off site at another location across the country, for example?

And then what about in the scenarios where resources are shared, where the healthcare facility wants to partake in this scenario, have a traditional manufacturer co-located on their space for a particular product, but also pursue their own printing activities and other devices? Can you share personal resources, can you share equipment resources across those different applications that may be transferred across these scenarios, as well? There are other complications within that, other gaps that we need to consider in those types of scenarios with larger healthcare institutions that may want to partake in multiple scenarios at a single time.

And the biggest perspective or feedback on this scenario from a healthcare facility side of things is the square footage in a hospital is extremely valuable, we're competing with rooms that could be used for direct patient care, and I think the argument that we're going to give up some that space for a traditional manufacturer to come in and do manufacturing, traditional manufacturing for a particular product line and that space also could be shared, I think it would be problematic in terms of seeing adoption of this type of scenario in the future. And I think really the questions that you answer here is, is can we pursue a scenario like this and have shared resources, too, and really define what that co-location definition means? So we'll move on to the next slide, please.

And finally, the third scenario. This lays out the circumstance where the healthcare facility themselves is a registered manufacturer with FDA. This is something, as I said earlier, that the VHA is very heavily invested with. We've already rolled out our own quality system and are registered with FDA as a manufacturer, a traditional manufacturer, and have a listed product and have full intentions of getting more products listed on the

manufacturing registration. From that, I think we've seen some challenges and gaps in this scenario, too. Next slide, please.

So kind of in that middle section, this scenario plays out most directly in theory where the hospital has that manufacturing registration, they make product under the existing quality system regulations, products delivered for patient care, that's pretty straightforward. And it's our opinion that all of the existing quality system regulations should apply to the hospital just like it does with industry.

However, in the discussion paper there's this conversation around a kind of subset of manufacturing of very low-risk devices and the applications that may fall in that bucket where a physician is directly working with a technical team at a hospital to produce these products that we classify very low risk, wherever that line may be, where that falls in the future, and those products are used to help further patient care. What are the implications for that? Are these viewed the same as a traditional -- for a Class II medical device that needs 510(k) clearance or do we need to break these out in their own bucket? Next slide, please.

So from a VHA perspective when considering this scenario, the biggest gaps that we still see existing in this is in regards to really defining the different classifications or the terms used, and the first one being having a clear understanding of where device manufacturing begins and the practice or scope of medicine ends.

And there seems to be a lot of back-and-forth on where this line exists in the current state and I think this is an important part of really having the healthcare facilities understand the upfront investment that may be required for some of the things they want to accomplish using 3D printing at the point of care and what things they can already do by just leveraging their current expertise, clinical expertise, and staying within the practice of medicine.

Kind of in the same breath is how are we going to define this very low-risk device classification and how are we going to differentiate that from other devices that already have classified risk Classes I, II, and III?

From a VHA perspective, we think we can really leverage, especially at the point of care, the clinical expertise to keep particular applications within this very low-risk device classification and have some kind of a subset of the quality system regulations or quality system lite for these type of device classifications and really keep it flexible to keep supplying the patient needs at a rapid pace as those needs keep ever changing. But there will also be applications where that's just not going to be able to fall in and it's always going to fall back in higher-risk devices and more traditional pathways, just like we're seeing that's available for the industry.

Lastly, the point we want to bring up for this scenario is for the larger healthcare facilities such as the VHA and others that span multiple facilities or even across state lines, what are the implications for those facilities or those systems that want to get involved with multiple levels of risk of devices, very low risk all the way through Class III or partake in multiple of these scenarios? Are there other considerations from a quality system requirement perspective that needs to be added or emphasized in those types of systems that want to partake in a variety of applications such as these and not just be surgical anatomical models alone? Next slide, please.

And kind of outside of the quality system regulations for this scenario, we think one of the bigger needs is still building that community consensus around this space, like I said before, coming to a consensus on what those definitions are regarding the very low-risk type of devices regarding where medical device manufacturing really begins at the point of care, but also really continuing the great work that we're already seeing being done from the technical consensus standards side of things where we're seeing many organizations

already attacking this and creating new technical standards that kind of address the gaps or the holes that additive manufacturing may present as a newer technology, newer production technology in the future. There are a lot of great examples of groups such as ASTM that established the F42 committee and a subcommittee underneath that that focuses on new standards that need to be developed for this space and what needs to be focused on in the future in terms of technical standards.

We've also seen the collaboration between America Makes and ANSI to produce that standardization roadmap for additive manufacturing that was published a couple years ago and a lot of continued work going into that publication, which is a great start, and we encourage a continuation of that and having those groups speak even more with healthcare facilities that are getting involved with point-of-care manufacturing, and the medical device industry as a whole, to keep identifying gaps in the technical standards space and which ones need to be filled and approved upon in the future.

We've already seen some outputs from this, such as the ASTM 52900 standard, which kind of captures really just standardizing the general principles of additive manufacturing and the terminology around that, as well as ASTM F3335, which is really specific to medical devices using additive manufacturing and the complications of residual powder of devices that use powder bed fusion as a manufacturing method.

And lastly, on top of the technical standards, there's still a need for consensus around professional education and training. So there's once again a lot of good groups tackling this from many angles. SME, ASME, and ASTM all have certifications or professional pathways available to them or available out to the public, which people can pursue and get on their own in trying to tackle the technical nuances of additive manufacturing. But how do we extend that even further and meet the needs for point-of-care manufacturing? RSNA, the 3D Printing SIG there, has tackled this from a clinical

perspective and trying to train the next generation of radiologists and get them understanding what 3D printing is and how to appropriately apply it. But how do we continue that work and really grow that and leverage that for community adoption as a whole? And on that point, I kind of want to throw the question out there, is there something we can learn from other industries, something like a technical degree or a certification such as a professional engineering certification, similar to the civil engineering industry, where they leverage that? It's a formal test curriculum, it's a formal apprenticeship for a certain number of years and then it's another test to be a professional engineer in that industry. Can this application take this similar approach and apply this to point-of-care manufacturing?

So on that, the overview of our perceived gaps are as follows: it's really finding clarification and delineation of the responsibilities for that first scenario with medical device production systems, getting a clear definition of where the practice of medicine ends and medical device manufacturing begins, as well as defining the very low-risk classifications, coming to a community consensus on that, as well as clarification on timing, are there going to be additional regulations added and enforce point of care for manufacturing and what are those and when. And then continuing the adoption and creation of technical standards, specifically for point-of-care manufacturing and medical device applications, as well. And finally, the biggest lift is continuing the education of those involved from the healthcare facilities and participating in point-of-care manufacturing to understand the regulations in place and making sure they apply those appropriately. So next slide, please.

And final slide.

So on that, I'd like to thank you all for joining me today and if you have any questions, please make sure you add those in the chat. I will be attending the panel at the

end of this session and will hopefully address those questions at that time. Thank you.

CDR COBURN: Thank you very much, Brian, that was a great overview of your thoughts and the VA's thoughts on the discussion paper.

Our next speaker is Amy Alexander, Unit Head of Biomechanical Development and Applied Computational Engineering for Mayo Clinic's Division of Engineering. She's worked in Mayo's 3D printing program for many years and I would say is groundbreaking as the first female unit head for the Division of Engineering.

So please, Amy, take it away.

MS. ALEXANDER: Thanks, James. Doctor -- I mean, Commander Coburn. Thank you very much to the FDA and to the VHA for this introduction and for the invitation to speak, it's really an honor and I'm excited to be here.

I want to start by saying I am in no way an expert in regulatory affairs. My career has been at the hospital side and I have experience in registration and listing of a device, a Class I device, and that's what I'm going to speak about today.

One tiny correction, I'm the first female unit head in the mechanical units in Mayo Clinic. There were female unit heads in our machine shop and in project management, so I don't want to discredit those women who came before me. We all stand on the shoulders of others. But thank you for the shout-out.

Okay, so I'm hopeful that you can see my slides. I'll give you a brief background on my education, I have a bachelor of science in biomedical engineering and master of science in engineering management, both from the Milwaukee School of Engineering. I've been at Mayo 10 years this year, actually, and before that I worked for a medical device manufacturing company that did FMI equipment and processing software. So I'm really happy to be in this field. Being here at this time is monumental, I think. All of us can recognize that it's a big gray area that we're in and we're coming together and this

particular meeting is an example of the ways that we have all committed to hearing different perspectives and listening to the voices of the others who we may not consider in our own little bubbles. So I'm excited to give a little bit of an overview of my experience, within the year of 2020 and a little bit into 2021, of designing and developing a mid-turbinate COVID-19 testing swab that was mass manufactured at Mayo Clinic between those 2 years, resulting in the fabrication of nearly 500,000 swabs that were entered into Mayo Clinic's inventory for patient and employee testing. So next slide, please.

Okay, I know we're all fatigued with hearing about the pandemic, but this really was my way of showing the experience that I have and the experiences I had while doing a registration and listing with the FDA. It was an incredible learning experience, but it was all brought about because very early on in the pandemic, as everyone knows, we all recognized that there was going to be an interruption to the delivery of testing swabs. Notably, in Northern Italy there is a company that was kind of wiped out right at the beginning of the pandemic and was not able to fulfill orders and then later on, some of the orders were confiscated for governmental use. And so as a company, Mayo Clinic had to figure out what are we going to do to address this. And so obviously, the problem was that we're running out of swabs, there's a deficiency kind of all around the globe and we figured out what to do. Next slide, please.

So April 2nd, about 2, 3 weeks into the pandemic, there was a lot of activity happening on the forefront of 3D printing nasopharyngeal swabs and a national IRB was formed by Dr. Summer Decker, Dr. Jonathan Ford, and Dr. Todd Goldstein from Northwell Health, along with their partners, Formlabs, to utilize the surgical guide resin to 3D print their design of a nasopharyngeal swab.

It's extremely exciting work because it brought to mind the capabilities that additive has where you are located right where you are. And because of all of the transportation

and delivery and pickups that we were all facing at the beginning of the pandemic, this opened a lot of people's eyes to what could be done using 3D printing to start helping people. And for most of us, that was already on our minds prior to the pandemic but the pandemic brought the opportunity for others, people in leadership, people at the executive tables, to say "Wow, we are unable to get these from a manufacturer, what if we took tools that we have, materials and consumables that we already have, as well as talented individuals who are already training and using this equipment to fabricate things that could help?"

And so I think I want -- I mean, I do want to credit, absolutely, this effort that was done by our colleagues in 3D printing in medicine to push this forward and I know I only named three, but it really was a massive effort and they are credited to opening the eyes of leadership, the people who are able to make the decisions for hospital-based or smaller-based companies to start producing their own product as needed.

So we started the discussions on April 2nd and the only reason it came to us is because Mayo Clinic has an arm called Mayo Medical Laboratories and it's kind of its own entity, its own venture, and it does testing for all sorts of sites across the Midwest and beyond, and the clinical biochemistry department was also aware of the lack of swabs and so they came to our group, the anatomic modeling unit in the Department of Radiology at the time, and said, "Do you think we can do this?"

And, you know, we had heard about what our colleagues were doing and we had had long conversations with them over the phone, talking about how is this even feasible, and then that's when we made the decision to join the national IRB study and start making the nasopharyngeal swabs that were designed by this group.

So it was a very exciting time, it was a very stressful time, but the fact that our institution very quickly could pivot and understand the risk of not being able to test our

employees and our patients and having to close down entire procedural suites or surgical corps because of that, that's what allowed us to have the green light to go forward to keep exploring whether this was an option. Next slide, please.

So we joined the national IRB for 3D-printed nasopharyngeal swabs, very quickly were able to print a batch on our own, another kind of historic, exciting event, again communicating very closely with those at USF and Northwell Health and working with Formlabs to optimize our processes using the exact same protocols and quality management techniques that the IRB set forth. This gave us the confidence that we needed to even consider doing this as our own entity and it was really important to prove, not only to ourselves, but to all of those people involved in making larger financial and risk-based decisions that we might be able to actually do this and provide some swabs and address this great need.

At that time also, we were thinking about the entire workflow and the pathway that a swab -- we'd need to take the life of a swab, a day in the life of a swab, so it gets 3D printed and then what? It's post-processed, it is checked for quality control and verified and then it needs to be validated that this swab is going to work in the intended way that it is supposed to be working as a regular nasopharyngeal swab.

But in between there, you need to be packaging it and sterilizing it and having traceability, what batch of resin did this swab come from, what date was printed it on, who did the post-processing of this swab, all of the different metadata that go along with 3D printing an item needed to be contained and documented and controlled, and that was something that we did not take lightly and it took us a number of months to fill in all those blanks and we certainly didn't do it alone, we did it in conjunction with so many different groups and I'll get into that a little bit later.

But we started talking with the surgical corps because we already worked with them

in sterilizing our patient-matched guides, patient-matched anatomic surgical guides for cutting and drilling, and so we had context there with -- over the years, we developed these processes with them and they have a line in their SensiTrack surgical sterilization documentation program for guides and we knew we would need to create a line for swabs, that's what we were going to be doing, and that's just one tiny piece of that puzzle, but we had to start those conversations and see if these people would even be willing to help us develop a system.

So at that time we just started bringing in anyone and everyone that could help and everyone was very eager and kind of had the adrenaline at the beginning of the pandemic and they really wanted to help, so it was an incredibly collaborative team. Again, we're still printing nasopharyngeal swabs at this time. So next slide, please.

So about -- let's see, we printed our first nasopharyngeal swabs on the 6th and April 27th we got an e-mail from biochemistry at Mayo Medical Labs and they said, you know, we've been doing a lot of research, we've been doing a lot of lit reviews, and we found that mid-turbinate swabs, you know, they're a type of a swab that has been proven to work successfully for influenza testing and we're wondering if you'd be willing to explore 3D printing a mid-turbinate swab instead of a nasopharyngeal swab and we were like maybe, we don't know, we can certainly try. We're unsure about the differences here, we need your guidance and advice on what physical attributes the swab needs to have and how to make that into a three-dimensional part, a mesh that could be printed and then determine how to mass produce it.

We are learning so much in this process, it is just constant intellectual fatigue a little bit from learning so much about what was happening with this swab. And so we started doing our own research, we worked very closely with the biomechanical -- sorry, biochemical group at Mayo Medical Labs and we created a prototype. Prototype 01 was

fine, but we iterated through four different prototypes. It's a fairly simple design, so it doesn't have a lot of different features that can be changed and given the feedback from the biochemists, you know, this is what they need. We ended up selecting Prototype Number 04 and they were excited about this mid-turbinate swab idea mostly because it only has to go in about 2 inches instead of the nasopharyngeal which goes in about 6 inches into the nostril cavity and we were just kind of gung ho, we were up for anything, if this is what they needed and this was what was going to help Mayo patients and Mayo employees get the testing that they needed, we were down for that and we only had the confidence for that because of the work already done in the field as a result of the supply chain interruptions for swabs. So this certainly didn't come from someone's idea on our team, it was external input and external requests that were coming to us and we just tried to make it happen.

So in the upper right corner there you see a swab that is commercially available and that is a similar type of swab that our biochemists wanted us to produce. It does not have the exact same features, nothing about it is reused, I suppose, but it's a similar type of Class I device that we were told to try to replicate, asked to replicate. All right, next slide, please.

So at that point, after we had designed the swab and we figured out how many can we actually fit on a build platform. How can we reduce the risk of failure of print? Can we reduce the size of the files to increase the workflow speed of transferring the build to the printer, etc., etc.?

We worked out so many different kinks around just basic feasibility and proof of concept and then finally felt like we had something, we had done enough trials and done enough -- we had failed enough to succeed. That's always kind of been my message, is that I like the idea that no one should be afraid of failure, you're obviously not going to get

everything right the first time you ever do it and if you do, then it's probably not that difficult to do. This was definitely a very difficult thing to do and we expected to fail and gave ourselves that grace. At the same time, we wanted to fail early and work out the kinks far in the beginning of the process and pooling all of our team members in the beginning of the process in order to work out those kinks and find a solution that was going to work all the way through loading the printer, removing the platform, soaking the swabs, curing the swabs, removing the swabs individually from the platform, and then doing verification on the swab plates, which we call cakes because they all do kind of look like a bunch of candles on a cake. And then figuring out how are we going to get these swabs to the people who need to package them in the peel pouches? Where are the labels going to come from for the swabs? Where are the indicators going to come from that need to be included in the packaging? You know, we had to work with all of our internal teams to figure that out, we certainly didn't have all the answers ourselves.

So if you go to the next slide, I have a list of all of the groups that we worked with. So Laboratory Medicine and Pathology, that's the group that initially came to us with Clinical Microbiology and Biochemistry saying, "We really need this, can you make it happen?"

The Institutional Review Board was included from very early on, as well. Of course, I mentioned we had joined the IRB, that was a national IRB for a nasopharyngeal swab, but this is a different swab and so we went back to the IRB and explained what we were trying to do and they allowed us to conduct a study of 308, I think, patients and that was to validate that the swab was doing what we want it to do with the PCR testing.

The Department of Radiology, that was a huge commitment by the Department of Radiology and I'll go into that a little bit deeper in slides below, but the leadership in that department, including Dr. Jonathan Morris, were instrumental in presenting the

information to even a C-suite level member of Mayo Clinic and communicating in layman's terms that this is what we want to do, here's how we want to do it, and here's why we think it's going to be safe. And that was really incredible.

Healthcare Technology Management, they came in and did -- they were the people who created the swabs. So as engineering, the engineers, myself and my co-engineer at the time, Hunter Vickens, we worked to develop the swab and figure out how to mass manufacture it, but Healthcare Technology Management is the group of technicians that were going to load the printers, remove the cakes from the printers, post-process and prepare the swabs for transportation down to the central services for sterilization.

The Regulatory and Compliance office was incredible help to us. We also reached out to them very early on to understand what is needed for tracking batches of material that are being used to manufacture the swabs.

Surgical and Central Services were instrumental in helping us understand how peel pouches work and what indicators need to go on the peel pouches, and helping us figure out how the labeling should be so that each swab can be scanned in as it's being sterilized and scanned out when it's being sent to inventory.

Supply Chain Management helped us figure out once it was sterilized, you had 500 peel-pouch swabs in a box, where does that box go? Who picks it up, where does it sit in inventory, how does it get scanned and when it gets to inventory, who's managing how many swabs we have in inventory and who's allocating them out to the various sites that need them?

And finally, Hospital Project Services was important because we had a 7,000 square-foot 3D-printing area, again, led by medical director Dr. Morris, but we did not have room for an additional 20 desktop Formlabs 3Ds, and so we needed a conference room to be converted into lab space. And so they were able to do that for us and we had just

incredible power strips and network strips coming down from the ceiling across a giant island and we had printers on all walls and down the middle island and they were just incredible at helping us figure out flow rates, air turnover rates that we needed for that many printers, the power that we needed to power not just the printers, but the wash stations and the cure stations, as well. I mean, just this list right here of all the people involved is so meaningful because you may not find that in every hospital system and that does make Mayo a bit unique in this space where we have access to these groups where if you put this all together, it's one pie but we each only have our small slice and we come together and can make something happen. All right, next slide.

So just a brief timeline. It doesn't seem too long, I guess, of a time from inception of the idea, which was early April, to the beginning of manufacturing, which was November. It's quite short, from what I understand, to bring a Class I device to "market." But we did what we needed to do, we did our IRB study with our 308 subjects. Our clinical microbiologists had to come up with a new LDT serology assay with a human genome marker and that had to be tested and validated. And we finished the study in August. We built and created the facility from the STS swab production facility in October and registered and listed with the FDA and began production in November of 2020. We ran production November through April of 2021 and, like I said, produced nearly 500,000 swabs in that time. Next slide, please.

So I did touch on the collaboration required to make this happen, but I'm going to go a little bit deeper into the individuals who were at the front of it, at the top of everything. Go to the next slide for me.

So I want to call out Dr. Paul Jannetto. He's really the one who came to us with this idea and this excitement and this eagerness and this adrenaline, like I said, "we really need this, can you guys make it happen," and we continued to communicate with him throughout

the process of the development of the production, the sterilization, the packaging, and the swab's usage in clinical care.

Dr. Bobbi Pritt was also instrumental as a clinical microbiologist helping with the validation of the new assay.

And Dr. Joseph Yao was instrumental in providing feedback on the geometries of the swab, telling us what he really needed. And, you know, I would be sending him screenshots at 8:00 p.m. and he'd get back to me at 8:15 with his red lines and his drawings all over my pictures.

And that's how we made it happen. These three are just an incredible resource to the clinic and an incredible resource for this project. Next slide, please.

I also want to commend Dr. Matt Callstrom, the department chair of radiology, who was not afraid to listen to us when we came to him and said, you know, microbiology really needs this, we want to do it for them, how can we make that happen, and he could've shut the door and said we're not exploring this, this is not what we do, we do one-off patient-matched guides and models, but he didn't. He said okay, tell me more, keep talking.

And the person who was talking was Dr. Jay Morris and he was just a phenomenal leader per usual in drumming up the excitement needed, not just excitement, but confidence in those leaders to make this happen because again, that long list of partners that we have throughout the clinic, we have their input and we have their knowledge and background and expertise and their certifications and their board records and all of those things, but he can tell the story and make things happen. And when people did try to shut a door here and there, he would say, "Well, I understand that that's typically what would be done, but we're not in a typical situation anymore, this is kind of all hands on deck, we need to be doing what we can to help," and he really just made it happen.

Administrative partners were incredibly important, Ron Menaker and Linda Nesberg,

as administrator of radiology and operations manager of the anatomic model unit, couldn't have been more supportive. Again, these are people that are very near the top that could have said no, we're just not going to put the effort into this, we're not going to put resources into this, and instead they said "let's try it, let's give it a try, let's see if we can do it." A lot of us expected things to fail, we didn't know, we didn't expect our swabs to be so successful in their IRB testing or through the assay development, but things were very smooth because again, I think we were able to get such incredibly talented and skilled and intelligent and knowledgeable people on this team and that's what made it go by so smoothly. Next slide, please.

So just a brief recap. You know, the Department of Radiology and Engineering, we did the 3D printing application, we figured out the design, the mass manufacturing system. Healthcare Technology Management really took it and ran with it and made it happen. We ended up hiring 2.0 FTEs, so that's two full-time employees who did remain and stayed on after swab production as full-time employees at Mayo Clinic, so that's a win in and of itself, you're creating jobs in this process. Speaking of that, we created seven and a half jobs in general services, the people who were in charge of putting the swabs in the sterilization pouches and getting them sterilized and boxing them up. Just an incredible collaboration. And next slide, please.

So why we're all here, we're talking about quality control, we're talking about the different elements of control that should be taken into consideration and documented, not only performed, but documented. And this was definitely a big learning experience for all of us in point-of-care manufacturing because for the most part, we operate under the practice of medicine, which does not have a stringent need to comply with a strict quality management system. It's absolutely beneficial and worthwhile and necessary to a degree, depending on the end use of the product and the risk level that the product brings with it.

But we did have our manufacturing compliance office present with us and they were kind enough to perform an internal audit, as well, of all of the documentation of what we did and how we did it and provide us feedback. So if we go to the next slide, please.

Let's see. Okay, so it was important for me to not get too worried with my description of how our process went for the audit and what findings were there. I did want to put this up there because, in layman's terms, I think these elements are useful, the different controls that are necessary and the categories of controls that are necessary in order to comply with 21 C.F.R. 820.

Oh, James, we have to go. All right. Sorry, I'm over. But long story short, we did find gaps in electronic signatures, the type of documentation that needs to be done, and we're very much encouraged to have used paper to begin with and then explore electronic signatures later on. On the whole of it, there wasn't anything that was glaringly missing except for, because of our inexperience, we didn't do the documentation as thoroughly, I guess, with electronic signatures as we could have.

So with that, I want to go to the next slide and just thank you all and sorry, I went over.

CDR COBURN: That's all right. Thank you very much, Amy, that was a great journey through how you got from nothing to a product out the door and I think it's great for everybody to hear about that.

Our next speaker -- well, I should say, because we are a little over now, we can -- if we can make everybody try and keep to time and we might make the discussion a little bit shorter, but I think we'll still be okay.

Our next speaker is one of the pillars of the medical 3D-printing community, Lauralyn McDaniel, who currently directs strategy engagement at Metrix Connect from ASME, and she has many other experiences throughout her career in medical 3D printing, so we are

looking forward to hearing what you have to say, Lauralyn.

MS. McDANIEL: Well, thank you, James. I thought I would share with everyone kind of a snapshot of the community to understand what the gaps are, what the needs are, that sort of thing. So I'd like to share with you the results of a survey that was conducted second quarter of 2021. Next slide, please.

So we did survey everyone in the medical community, including device manufacturers, point-of-care manufacturers, dental, and those in the biofabrication area. What you're seeing here are responses from just those who were point-of-care manufacturers. It involved both hospitals as well as university engineering groups connected to hospitals.

So hopefully none of this is a surprise to anyone that the anatomical models, prosthetic and assistive devices were the top responses. And you can see surgical planning, I think there was a miscommunication of that because I think that might be a little higher, and what processes are they using in these areas. Next slide, please.

So again, probably a little surprise to everyone, the top is material extrusion or also called FTM, those are the machines with the big wheels of filament; that photopolymerization, those are your DLP and CLIP and stereolithography systems followed by powder bed fusion, which my thought is most of those are coming from the hospitals connected to a university engineering department. So let's look at some of the challenges that they're facing. Next slide.

So this is a list and it's long, plenty of challenges. This is where we asked them to just mark all the challenges that they were facing and you'll see up top the lack of standards specific to 3D printing. Second to that was understanding regulatory compliance. Now, I have been doing surveys like this for a few years and I can say, for the point-of-care people, that moved up dramatically in the last couple of years with all the discussion, so lots of

questions going on there.

So if we look a little further down, there are things like understanding process validation and verification, available training programs, available workforce, repeatability of processes, all important to everyone working at the point of care. Now, we then asked them to identify only the top challenge. Next slide, please.

And the standards stayed at the top but, reflecting that we are talking to point of care, reimbursement jumped up to the second and then you can again see similar ranges of what was going on. So with all of this, the encouraging news is that growth is still expected. Next slide, please.

So as you can see here, this actually was the first year I've done a report and asked a question like this, if anyone expected a decrease in the use of 3D printing in the medical field. But as you can see, it's a pretty strong growth they're expecting, more than 20% expected -- you know, about a quarter expected more than 20% growth. It's a very active area. So as we look at that, we also wanted to understand where growth is expected. Next slide, please.

So probably not surprising to everyone here, patient-matched devices, whether that's at a medical device manufacturer or within the hospital; more development as we saw with AAMI and the development of the swabs, it's an exciting opportunity for physicians and engineers to work together. Also expecting growth in biofabrication. Next slide, please.

So let's take a look. I'm going to really focus on standards and Brian mentioned some of this, but some of the reasons I think standards help and why we saw it as a top challenge was that it definitely supports quality systems. These are consensus standards, they are experience based. The idea is people who have made the mistakes already are sharing what they know and they're agreeing on it coming to a consensus on this is kind of

the way you should do it.

So one of the activities that's exciting, and Brian mentioned before, is the additive manufacturing standardization collaborative or as I like to call it, the ASME, this was definitely a big effort. There were a lot of medical device manufacturers involved in identifying existing and needed standards. Some of the gaps included data processing, design of lattices, cleanliness, because even if it's sterile but it has loose powder or loose resin, not a good thing. Personnel training, material data. This is all a very exciting part. I'm very interested in actually getting involved with a group of point-of-care people to review what's there and identify their gaps, their needs, and what the priorities are so that SDOs will get involved and step up to the plate to do those.

So just an example of some of the SDOs involved in this project: DICOM, ASTM/ISO, ASME, SAE, which might be surprising to some of you here. So some of the things, standards coming up -- next slide, please.

Some of those that have already been published. Now, Shane's swallowing and so he's probably going to cover more on the ASTM/ISO, but I did want to point out this one, which is technically not a standard, it's a technical report, but for this audience it's so spot on. It is ISO/ASTM TR 52916, but you can see by 2022 it was just published. It is talking about optimized medical image data. This project was begun by Dr. Moon, who is an orthopedic surgeon based in Korea.

So what might be surprising is SAE, which is usually aerospace and automotive, absolutely has some published standards for those of you using the material extrusion systems. So it's the fused filament materials, they have two standards that have already been published, one on materials, one on process specifications, and there are nine additional work items in process. Next slide, please.

So I couldn't do this without mentioning some of the things available through ASME.

One of them is Y14, so anyone who's been involved in dimensioning and tolerancing will be very familiar with Y14. Twenty seventeen there was an addition to that with a product definition for additive manufacturing, lots of great information in there. And then VV 40 or as we call it, V&V 40, verification and validation. This was a terrific project that was published in 2018, we had people from the FDA involved, and there are several different areas. The goal is it's a standard to validate/verify through software. So beyond everything you're doing, beyond using 510(k) cleared software, there are additional ways that you can validate your entire digital process in doing what you expect it to do. Some of the subsections include clinical data as a comparator, as well as patient-specific models, surgical planning, clinical decision making, using software as a medical device. Next slide, please.

So within ASME, we're looking at more. There's a working group on additive manufacturing for nonmetallic materials, which we know is the most common type of material used at the point of care, different areas. If you are interested in getting involved in this and having the point-of-care voice heard in the standards development, I'm going to encourage you to get involved with ASME or any of the standards development organizations working in the area. Next slide, please.

So I wanted to talk about the same idea as standards but some guides, some best practices that are also available. In my mind, they go towards the same goal, to help you learn from others to do the best process.

One of the great resources available is the journal, the open journal for *3D Printing in Medicine*. In fact, they have published guidelines for medical 3D printing and appropriateness for clinical scenarios. This was a project of the next group, the RSNA 3D Printing Special Interest Group. Brian mentioned them. They have within the last few months kicked off a quality assurance subcommittee, so looking forward to see what they have coming up.

And of course, I have to mention the Medical Advisors. One of the things that they have published is particularly for those who are new to the idea of what V&V is, is a review of existing standards and regulations and kind of the approach to what you need to know to develop your own process. All of these are available free to download on the website here. And next slide, please.

And that is all I have. So thank you so much for joining me and I look forward to hearing from you if there are any needs we might be able to help you with. And I think Shane is up next, but maybe I went so quickly he's not quite ready.

DR. DI PRIMA: Lauralyn, thank you so much for saving us a bit of time there and it's my pleasure to introduce Shane Collins, who -- I will apologize since we seem to have lost James -- but he is a consultant currently with ASTM's AM Center of Excellence.

MR. COLLINS: Thanks, Matthew. Happy St. Patty's Day, everyone. Let's go ahead and get started and I'll see if I can't bring us a little bit back on track.

Shane Collins, I am with Wohlers Associates, powered by ASTM, that's through a recent acquisition that we had for Wohlers Associates recently. And this is a really important topic for us to cover with respect to training and point-of-care additive manufacturing and as we heard, Phil mentioned earlier, he believes that this is probably the number one challenge.

And if we go to the next slide, I'm going to be talking about the training needs in additive, current training approaches and gaps for PoC, QMS approach utilizing standards and certification and ASTM training and certification opportunities.

And why this is such an important topic is, is because we've heard so many different business models, from doing complete production of thousands, if not tens of thousands of nasal swabs to mass customization of dental components, porcelain fused to metal substructure and restorations, as well as patient-matched low production. All those

business models could potentially exist in the same healthcare facility, which would necessarily require different types and different approaches to the training for the organization. Next slide.

This is the most important slide probably I have in my deck and it's because it shows that additive manufacturing is not a simply 3D printing process as many people have unfortunately the misconception. And particularly, when we talk about the patient-matched devices, we start out at the very left with an imager who pulls down some 3D representation of patient anatomy and that's usually in the DICOM format, that has to be converted to something that can be useful later on in terms of an engineering product.

So then we have the next step of the chain is design for additive manufacturing and why that's important is because the DICOM file, even if it's converted to a 3MF or an STL file format, is not necessarily what gets sent to the 3D printing process. So we would normally take, for example, a cutting guide or some other engineered product and that would be a solid-works CAD program, possibly, and it would have to be mated to the imaging STL file or the 3MF.

So now we have two different file formats, if you will, two different training requirements and oftentimes those are going to be the same person in a small organization. So the training requirements, although they're significantly different, you can usually keep it within a small group and make it work.

But then once we have the CAD file, that's also not what gets sent to the printer. The printer usually likes to have a solid model like an STL file, but we don't send that, either, we actually send a slice file or a solid model. And so why I'm going through this detail is because the configuration control is so important of all those different file formats and the translation from one file format to the other that nothing gets lost.

And it's not uncommon for the patient information to change over time, as we heard

earlier, because that is only a snapshot in time and the engineering may take place on an original patient dataset and the actual device would be made with a more updated dataset later on. And although they may have a lot of things in common, making sure that you have the right configuration control so that you're printing the right part with the right file is super important. And all of those steps are going to take a significant amount of training and reinforcement of the training to make sure it's done correctly.

Then we get to the feedstock part of it, whether it's filament or if it's powder or if it's liquid, whatever that is, it's going to take a requirement where we need to make sure that we have a material, we blow down to the supplier the requirements for the feedstock and have a material specification and then when the material comes in, it needs to be sampled and a quality control to make sure that it's going to meet all the requirements, that it in fact was what was ordered is what came in, and you might be surprised how many times you get surprises in that aspect.

So now we've gone through about a 5-minute discussion before we even get to the 3D printing process where we are taking feedstock and consolidating it into some type of a shape for a medical device and as we heard before, we need the IQ/OQ/PQ and the training required behind ensuring that the people operating the equipment have done a good FMEA and understand what all the inputs are so that the output is satisfactory.

And then we have -- after printing, there is typically a support removal or at least, at a minimum, there's a sterilization process and we have to make sure that the sterilization process matches what was done previously in terms of biocompatibility. If it's a nylon part, there's a step oftentimes of a bead blast to remove the powder on the surface. Are we contaminating the material with the bead-blasting process? Are we using the right beads? Is this in a controlled environment?

And then we have to have the packaging, labeling, and then inspection. So

inspection is really important, especially as we talk about these organic shapes that don't conform to a simple engineering or a fit check where it's easy to determine that they have met the geometric tolerances. So all of this requires a variety of different types of personnel training and that training needs to be concurrent, as we heard Phil talk about, and it needs to be recurring, as well. Next slide.

I didn't hear much in the last couple of days about continuous improvement when it comes to a QMS and really, that's what we're trying to drive. Of course, we have to know how to handle a nonconforming material or a nonconforming part. And then we have the corrective action and then we have the preventive action, the cars and the parts. But what we're trying to do with the QMS is drive continuous improvement through the whole cycle and that takes a level of training, I think, that we can overlook.

And so what we're doing with the QMS is we're trying to build this quality of culture, a culture of quality, and that is so that anyone in an organization can issue a nonconformance and this is going to be something we'll have to come to terms with. If you have a QMS within a hospital organization, is the janitor capable of issuing a nonconformance to a 3D-printed part? Well, if you have a 13485 environment in the industry, certainly anyone within the organization can write a nonconformance and it has to be looked at. So those are training aspects we'll have to really look at so that the product realization happens in a continuous manner.

And then of course, from a quality perspective, compliance with the internal QMS and related standards so that we have objective evidence that the training has occurred and we're accurately following all of the work instructions that I heard earlier, just for the additive process is 15 or 20 work instructions. And as you include the post-processing and even the pre-processing in that previous slide, that could grow to be quite a few work instructions that have to be maintained and they have to be updated whenever there's a

change. Next, please.

And this is kind of the fear, especially when you have a smaller organization where you have folks wearing many, many different hats. So I'm using the machine manufacturer as a model here. This would be the MDPS in the number two scenario that was given earlier. And so this is not uncommon where you have initially the system or the processes brought in and you have an initial employee training that occurs. And then that employee is empowered, and rightly so, to train Employee Number 2 and then Employee Number 2 trains Employee Number 3 and in the meantime, Employee Number 1 has moved on to greener pastures.

And so what we have here is a loss of custody of the training process in that we have -- we've developed this tribal knowledge rather than making sure that we're meeting strict work instruction requirements. And so the more -- the way it needs to really be implemented is that every time there is a machine manufacturing or an MDPS training, that we have the original information and that there is a certification and providing objective evidence that the training was effective. And that's kind of the way the next stage is. Next slide.

So the training approach within ASTM, we have four basic sectors or four quadrants that is technology specific, so whether it's metal or polymer based and within the polymer-based, you would have the liquid feedstock-type machines, whether it's stereolithography type or material jetting, and then you would have the powder-based or the material extrusion or powder bed fusion. And on Lauralyn's slide before, the powder bed fusion could also be metal or plastic. In this case, we would separate metal completely because that has some significantly different requirements for training, particularly on the safety side.

But then it needs to be multiple discipline where we have many people wearing

different hats and we have to make sure that, from data acquisition all the way through the process and to the post-processing, that the training is covered and the folks have many different types of training and they're not pigeon-holed into a single discipline.

And then, of course, it needs to be sector specific, whether it's anatomic models, cutting and drilling guides, surgical instruments, prosthetics, implants, and even now the nasal swab production, each one of those has a little bit specific training requirement. And then the competency, it needs to be based on the level.

And I could really see how, in aerospace, we have right now in ballot a part classification work item that hopefully will become approved here in the next couple of months, and it's based off of the consequence of failure in aerospace as to part classification and that's an A, B, C, or D. And I could see how the point-of-care AM would benefit greatly from a consensus standard based off of that approach, as well, so that you could identify the requirements as well as the training requirements and the material requirements off of that. Next slide, please.

All right, so this is the current landscape of training within additive manufacturing. There's continuing education courses, higher education by universities, there are some competency training programs, and the training of technology is rapidly evolving. Next slide.

There are some gaps and opportunities. Of course, we're covering end-to-end processes, this multidisciplinary approach. We need to have training programs tailored for industry specific needs. And for AM at the point of care, in addition to the above, the staff often requires training on medical imaging, image segmentation, device design, really handling nonconformances and how to achieve that culture of quality I talked about earlier. Next, please.

And this is sort of a graphical format of that, where we have the AM workflow, we

have all these different needs from the different roles of the employees that are working within the AM sector until we get all the way to the QA/QC. So as I mentioned before, we have all these organic shapes, we have lattice structures, how do you measure that? How do you make sure that you met all the requirements? These are very varied, there's a lot of variety in the requirements for the training and you have to make sure it's effective. Next, please.

This is a graphical representation of how standards could be applied to a QMS. On the left-hand side we have material specifications along with process specs. Then we have next in line would be the design for additive manufacturing specifications and then we have the machine-centric specifications, how they conduct a factory acceptance test, a site acceptance test for the equipment before it arrives, and then how we handle the post-processing, and then the required training along the bottom row for each one of those sections. Next, please.

Here's a list of some of the ASTM/ISO specifications. In addition to these, we also heard Brian talk a lot about the 820 QMS and then earlier, the F3335 for removing powder was mentioned. So there are a lot of ASTM and ISO specifications. I would like to add that we have a monthly meeting or a regular meeting when we can, when we can meet monthly, between the ASTM F04, the ASTM F42 and TC 261 and TC 150 technical committees from ISO and we talk about where are the gaps and where do we need to put our efforts so that we can meet all those standards requirements. Next slide, please.

So certified AM professionals, this is an important slide. We have the 52942 ISO/ASTM standard that is -- that's for aerospace, it does have some overlap because it is for critical applications. We have the qualification by theoretical testing and we have a range of qualification and validity of qualification testing. Operator certification program applies to any contract that needs to demonstrate a quality operation. Next, please.

ASTM's workforce developed an approach. This week, at Auburn University, we have a role-based training program going on. In 2 weeks we have another training before the F42 meeting. And in 3 weeks we have another 2-day training on setting up an additive manufacturing facility before the AMUG event. ASTM is highly involved in different types of training for additive manufacturing at different levels and we believe that re-skilling, up-skilling and cross-skilling is key to keeping the training relevant. Next.

I think this is the last slide, AM educational workforce development initiatives at ASTM. In addition to those on-site trainings that I talked about, we have a webinar series. We also have personnel certificate courses where folks can get certified at the training from, say for example, an equipment manufacturer was effective. We have e-learnings online. And I hope that everyone can come to our ICAM event in November and see probably more than 800 talks being given on additive manufacturing. Next.

I think that's it. Thank you for your attention.

CDR COBURN: Thank you very much, Shane.

We're running a little bit late, so we'll cap the discussion. So like I said, it will be capped at 5:20 to end on time, but I think we'll be able to get through a lot in that time. Our moderator for today's panel is Andy Christensen. He's been a part of medical 3D printing since the beginning of medical 3D printing and has been involved from many different sides, bringing another valuable perspective to the discussion. He's adjunct faculty for the University of Cincinnati and chair of the Radiological Society of North America's special interest group on 3D printing.

Andy, welcome.

MR. CHRISTENSEN: Thank you, James. Thank you, everyone, that was a great set of discussion topics. I wanted to say first, I'm really impressed with this workshop in general and thanks to the FDA and the VHA for putting on something that's got so much great

content and many different stakeholders' views, so thank you.

Well, it's great, we've got obviously a diverse group here in terms of topics that kind of break us up mostly into the clinical point-of-care world and applying this at a hospital environment, and then standards and training and education, which all tie together, obviously. I thought I'd start, you know, there was a bit of -- kind of on the quality management system side, talk about the large institutions like Mayo Clinic and the VA implementing these technologies and implementing GMPs and quality management systems. Talk to what your thoughts are -- and I guess I'll direct this at Brian and Amy -- for the smaller organizations that may have just a few people and maybe how do you scale some of these things and can you scale some of these things?

MS. ALEXANDER: I can go first. I'm not sure that there's a level of appropriateness for very small institutions or very small centers to build a robust 3D printing lab in house. There's a lot of debate about when you should outsource and when you should in-source 3D printing specifically, and I don't know the answer to that because I live in my bubble of Mayo Clinic where, as you saw, I do have access to all sorts of these internal resources, but should I have moved to a different place where I didn't have access to that, I don't know that it would even be on the table. It's not meant to be discouraging, it's just a fact that there are so many different levels of input and knowledge that one would need to build up a lab or even a venture that could do this in the hospital walls.

So I guess if you needed to scale something, you always have to start with something that you can do a lot of and do well and then move on to different applications, so look at your greatest need, address that first, see how that goes and then see if there's another great need there. But it does come down to being able to convince leadership of effectiveness and the fact that you're improving patient care and then indirectly saving costs in the end.

MR. STRZELECKI: I would add to that. I think it really comes back to your cost-benefit analysis and kind of understanding the lift before you even jump in head first. I think we heard a lot from some previous sessions earlier today on the challenges we saw even from large organizations and trying to stand up our own quality system, and if you're a smaller healthcare facility trying to follow the same suit or the same path, my recommendation would be just get as much understanding of what that entails before you get started, really get a solid understanding of what that cost is going to be, both in terms of time, additional personnel you need to bring in, the expertise you need to bring in, and compare that to the goals you're trying to accomplish. What applications are you trying to print? Do the market analysis. Are there companies out there that provide services that make implementing that much faster and much easier and see what better fits your scenario.

So it's hard to give a blanketed response for that, but I'd really start there, is what are your goals with 3D printing and then what can you provide in terms of commitment and making those goals happen, because there are a bunch of solutions out there whether it's building something up internally or finding an existing service.

MR. CHRISTENSEN: Yeah, I guess maybe building on that question, this concept of co-location is interesting to me and how it could tie together. You know, there's the "all or nothing" scenario of medical devices provided by industry and sold to hospitals or hospitals making all of their own medical devices themselves, but maybe some in-between scenarios. It makes me wonder if the economics of that might help for some of the markets, too, right? If you have to decide to invest in something fully inside, could you leverage an industry partner that might be able to again leverage that to other hospitals? I don't know, have you thought about those types of scenarios?

MR. STRZELECKI: That's definitely a potential starting point and I think we've seen a

couple examples of people playing around in that space, both from the industry side and from the healthcare facility side. We haven't, from a VHA perspective, dove into that scenario as deeply as some of the others yet, but that may be depending on your goals, again, may be good for a starting point and saying I can give this investment in terms of space on my hospital campus but not willing to commit to hiring all this additional staff and buying this capital equipment. Let's start with the Scenario 2 type approach and see where that leads us and if we want to bring that in-house later, we can make that decision after we get some experience on our build. So I think that's definitely a potential option.

MR. COLLINS: And Andy, we're starting to see, in general, in all of additive manufacturing, a distributed manufacturing model where we're starting to decentralize manufacturing in general and manufacturing at the point of care is just an extension of that, it's sort of the way things are moving.

So we've talked a lot about patient-matched work, but I wouldn't be surprised to see a lot more going in the direction of the nasal swab or at least a lot more higher production-type application seeing the light of day. As we are essentially cutting out the distribution network, there could be some economic savings there that would be realized.

MR. CHRISTENSEN: Yeah, I think we all kind of recognize the flexibility of additive manufacturing and I think that's why, during the pandemic, you saw one printer that could make a hundred different things, and the reason for the VA's great work with the NIH and the FDA and others surrounding the 3D Print Exchange trying to share some of that information, too.

Yeah, I do wonder, I guess maybe not to switch gears but to talk a little bit about training. You know, Shane, in your talk you talked in that one image that really walked through the whole product life cycle or the production life cycle. You talked to training. I'm curious, I guess from all of your standpoints, about standards and which of those areas

standards may be written for and how training -- I guess how training and standards kind of play together. But obviously, the full workflow for the personalized products going from the imaging through production to use in surgery, talk to me about what are the areas that you think are the lowest-hanging fruit for future standards.

Lauralyn, you can take that one.

(Laughter.)

MS. McDANIEL: Well, I can say, because it's such an issue, there is an ASTM/ISO joint group working on personnel requirements for additive manufacturing. I will say that it is primarily driven by different areas, but definitely will provide a foundation combined with some of the competency models that have been built previously specific to working at the point of care. So that is an area where ASME does some certification, it's not necessarily an area they're looking at right now, but there are some resources going out there.

So some of the other kind of low-hanging fruit, I would like to see the technical report that's already been published and get those people who actually are doing it, so a broader group of point-of-care people can review it and take some of the "coulds" to your "shoulds" or your "shalls" to turn it into a standard for optimizing your medical imaging to be used in 3D printing. I think that seems like a very easy thing to do.

MR. COLLINS: It seems that folks are looking at the 820 QMS methodology of a quality system rather than 13485 for some valid reasons and I think that using that, you get away from the audit aspect oftentimes. And having been responsible for different aspects of QMS in the past, I always looked forward to the audit because that was the opportunity to catch up on all the paperwork that was missing or that we didn't quite have under control, but that's a good way to put it. And so I think that, in general, we can't get away from that, somehow getting a routine checkup to make sure that we're not something falling through the cracks, and I think that could be some low-hanging fruit that we could

work on in the short term.

MR. CHRISTENSEN: Yeah. I mean, that part to me is really interesting, I guess, is there's further harmonization between the FDA's quality management system and the regulations surrounding it and ISO 13485, it seems like the difference being that you could voluntarily -- you know, at this point maybe there wouldn't be a reason for a hospital to need to be complying with the FDA's system and list, say, today and say that they're doing things under the practice of medicine, as Amy, I think you pointed out a lot of this stuff happens today.

But I wonder if external oversight and this third-party review is useful. I mean, in my own experience it kind of keeps you honest, it's somebody in your facility at least once a year that's kind of kicking your tires and somebody that isn't necessarily going to penalize you apart from the fact that they could take away your cert.

But I guess a question for Brian and for Amy: Was 13485 thought about? Did you think about certifying to 13485 fully in your process of building up your quality systems?

MS. ALEXANDER: We are actively considering the different standards that we want to comply with. Not necessarily because we're being told you must or you shall, but because we want to get to a level of excellence and the only way to do that is to follow what's set forth in, for example, 13485.

I heard through the grapevine that 13485 and 21 C.F.R. 820 are coming closer and closer together. I don't know what that really looks like down the road but, for example, we have a microfabrication laboratory in our Division of Engineering and it's possible, you know, in 5 years' time that we fully look at 13485 certification because we're manufacturing deep brain stimulation electrodes, things like that. That's a different category of what we're doing here because it's microfabrication and not standard additive, but similar. And so those are all concerns, not concerns, but considerations that are bringing up more and

more questions than there are answers at this point. So yeah, I guess we focused on the FDA compliance for quality when we were doing swabs because we really had little time to consider anything else at that point and we knew that we needed to register and list with the FDA, so it was a logical choice.

MR. CHRISTENSEN: Yeah, taking a question from the audience related to that, the question is: The production of nasal swabs Mayo Clinic produced obviously during COVID times, what did you learn or wish you had known before COVID to implement GMPs that you later needed? Like what were some of the big "aha" moments there?

MS. ALEXANDER: Yeah, definitely there were more than one. One of the biggest was just the idea of stronger purchasing controls and understanding exactly where your feedstock is coming for the resin that we were using for manufacture. That shouldn't be overlooked. Right now you can buy on Amazon filaments from probably a thousand different companies. But if you were going to use those for medical device fabrication, you do need to have some understanding of where they're being initially sourced and fabricated and whether any of the components that go into that filament, for example, are being changed and there are certain things called batch record agreements you can enter in with supplier companies and things like that. So purchasing controls was one of them.

Training controls was another. We did a lot of on-site, hands-on, verbal training and kind of checked the box but did not formally write down "this person was trained by this person on this date and here's what they learned and here's when they were recertified," and so that's a big one that was a gap for us.

MR. CHRISTENSEN: Okay.

MS. ALEXANDER: Anything else? Your gaps?

MR. CHRISTENSEN: Yeah. I don't know, Brian, anything there, kind of thinking about gaps and maybe the biggest gaps to close? Obviously, we heard a lot today from your team

across the country and it's an impressive group and you've got a lot of talent. I'm sure there's some areas that have been more painful than others.

MR. STRZELECKI: Yeah, I think the biggest overlooked aspect was the items or the controls that impact the other business units, the arms. Amy spoke to this a little bit, is the purchasing controls. When we really started out, I think the group was unaware of if our quality controls extend out into who a supplier is, how we're dictating what we're purchasing from them, and then also after we see that, what's the mechanism for looking at what was received and confirming that we got what we ordered.

And that goes into document control, too, is this whole other, almost a standalone role of we need to have consistent methods for controlling how we control documents and revision control, and that's just something brand new when we were strictly focused on the clinical application and bringing in the technical expertise to figure out how to run these machines efficiently and reliably. So I think those were the two biggest ones that we learned very quickly that's going to slow us down if we don't have an answer to, from the beginning.

MR. CHRISTENSEN: Okay. That's good. I was thinking about, let's see, where to go next. Maybe very, very low risk, this category of very low-risk devices that the FDA has kind of floated as, I think, a little bit of an exception that they would potentially consider for things that could be made by, we'll say, a qualified lab at the point of care. Leaving aside anatomic models, which have been talked about a little bit in and out of that category, what other examples are used in your institutions that could fit in this very low-risk category?

MR. STRZELECKI: I can kick that off. We're seeing a lot of application examples, what we call assistive technology. So within our rehab department there are a lot of needs or requests just for little augmentations or little adapter pieces for patients that request just to improve their daily care of quality, just to help them brush their teeth in the morning

or put on their pants and stuff like that. So we're seeing a lot of right applications for that, for 3D printing, because it's a one-off device unique to that one user but still falls in -- in our eyes -- a very, very low-risk category because a failure of a device such like that would be very little harm or any risk to the patient.

And then we're also seeing, in the prosthetics realm -- orthotics and prosthetics -- a huge demand coming from the field of 3D-printing applications there for the very same reasons, patient specificity and one-off devices there and being agile and adaptive with your design techniques on that.

MR. CHRISTENSEN: Yeah.

MR. COLLINS: Yeah, I would agree that the prosthetics is a very low-risk area that could be expanded greatly, as well as the Y-adapters on the ventilators that allow multiple patients to get the same ventilator, I think that also falls into that similar-type category.

MR. CHRISTENSEN: I think you may find a person or two that would disagree. It kind of depends on a lot of things. I mean, the COVID time, I think, was a really interesting, I don't know, kind of test, you know, kind of a test of our system and like what can you do, what should you do. Everybody, lots of people did all kinds of things, so then you kind of debrief after and say what was -- you know, what worked, what didn't work. And I know some of us, you know, we've all been at meetings where that's been done.

I think it's interesting to think going forward is potentially a way -- like, if I look at the whole of the talks today, you know, if I'm a really small lab, it looks kind of overwhelming to think about implementing a system to the level that we've heard about. And not that it's impossible, but it looks a bit overwhelming. So thinking about these things that could be outside of that, outside of the need for having such a robust quality system, Amy, are there other things you would add to that?

MS. ALEXANDER: I was going to mention that I'm working now within the actual

Division of Engineering, which has opened my eyes to a lot of different ways that additive can be used to help in basic equipment maintenance. We get requests for a broken component redesign for a coat cart, or something has torn or broken and they're asking for a replica of that and it may not have patient contact at all, it may just be involved in a lab system. Maybe it's a test tube holder that's a specific size because our glass blower made these weird-shaped test tubes and they need a holder for that. A lot of those things can be additively manufactured and would not require a level of stringent quality systems as a traditional medical device.

MR. CHRISTENSEN: Yeah, interesting. I want to go back, so there's a question from the audience about product liability and I wanted to kind of tie back into Alain's earlier comment about this medical device production system and the liability of -- who has the liability for the final device, if made by a healthcare facility using an industry supplied MDPS system.

The question, just to tie it all in here, was how should the product liability in the case of the healthcare facility as a manufacturer, distributor, and user of the product be distinguished from the liability of the hospital as a user? Let me see if I can understand this. How should this -- or is it already realized? I think the difference is to do it with somebody, the healthcare facility buying it versus the healthcare facility making it, and then if they make it using a tool that industry provided, how would you see that being broken up from a liability standpoint? There's a lot in there.

MR. STRZELECKI: I think a lot of that goes back to figuring out the nuances of the different scenarios laid out in the discussion paper and determining where that line is, who's the registered manufacturer? Is that going to be a shared registration? Is it going to go to the healthcare facility or is it going to what we're calling the traditional manufacturer? And I think that determination really points to the majority of the liability right out of the

gate. And there's going to be obviously some applications that don't fall nicely in those buckets or aren't medical devices at all and if those fail, who's liable for those types of applications? But I think initially, it comes down to who do we expect to adhere to those quality system requirements as the registered device manufacturer, and where that line falls kind of points to the liability concern.

MR. COLLINS: And who has the deeper pockets, probably. And so I would think that having a robust QMS and having all your ducks in a row would be of utmost importance from a liability standpoint.

MR. CHRISTENSEN: And to me -- go ahead, Amy.

MS. ALEXANDER: Well, I was just -- it's an interesting thing to ponder. It's tough to think of a world where the person who's manufacturing a device that comes from an MDPS is going to just say "no, I have no liability for this, talk to that company over there, we bought it from them." But there are so many steps that are taken in the fabrication of the device where errors can happen. I don't think that's feasible. I don't know for sure, but I don't know that you can just point to somebody else and walk away if you're the person manufacturing the device.

MR. CHRISTENSEN: Yeah, I could kind of see all sides, I mean, it points to training, the robustness of that MDPS, how locked down is that system. You think of things like the computer system in your car, which usually doesn't glitch, I mean, they seem quite robust; when things should work, they mostly work. But here we've obviously gotten very, kind of -- what I'll say, open systems that allow for a lot of flexibility, which is great. And in the future we may need more, what I'll say, locked-down kind of systems that actually have really specific indications and specific outputs.

Here's another question from the audience. For these types of AM items, it seems that there is a high amount of savings from manufacturing on site. Is that savings fully

offset by QMS requirements or is the QMS something the point-of-care facility should have anyway? So I think it's a really interesting question just about a baseline QMS/GMP system versus something that might come along with an MDPS or otherwise.

MR. STRZELECKI: I'll take a crack at that one, and I think we heard a little bit about it, I think, in the first session today on rebranding the quality system regulations and approaching it and thinking about it as just good manufacturing practices. And I think if you think about it that way, if any institution, whether it be a business or a hospital, is performing any type of fabrication or manufacturing activities, you want to -- it's just good practice to follow good manufacturing practices and have quality controls. Whether it's a line strictly to 21 C.F.R. 820 or not, you still want, at the end of the day, to produce a high-quality product that fulfills your customer needs and you know is safe.

And if you sum all that up, that's essentially what your quality system is, is ensuring that the systematic framework to ensure that's going to take place and all the nuances to make that happen. So it's just a matter of how deep you need to go into that with the existing regulations and adhere to the existing standards or regulations that are out there in that space, for what applications you're trying to apply that to.

MR. CHRISTENSEN: Let me interrupt.

MR. COLLINS: And that's why --

MR. CHRISTENSEN: Let me interrupt there.

(Cross-talk.)

MR. COLLINS: Yeah, that's what continuous improvement is all about, a robust QMS should drive down your costs instead of being a cost plus.

MR. CHRISTENSEN: Yeah. I think many of us that have been through it have seen that and kind of see what it looks like on the other side, and I think when you're faced with it in front of you, it looks a little differently and it looks like a cost center, but in the end it's

going to save you money.

We have only 1 minute to go, so I'll ask a question and I guess just get a quick couple of words from each of you as we wrap up this panel. Thinking ahead to the future, we all see this area growing and if we look to maybe 10 years ahead, what do you see and what do you see being the driving applications that are pushing more toward this distributed manufacturing done in a hospital environment?

Shane, why don't we start with you?

MR. COLLINS: Well, I know we talked a lot about QMS and standards. The last thing we would want to do is stifle the good work that's been going on in places like the VA and Mayo and other places. We want this type of work because it is a better outcome for our patients and they live a better life because of it. So certainly, whatever we do needs to promote that in the long run and that's how I'll end my session.

MR. CHRISTENSEN: Okay. Brian, just a couple of words.

MR. STRZELECKI: Improving personalized medicine, so it's those one-off devices that is unique to the patient, itself, and I think that can span anything from instruments to implants themselves.

MR. CHRISTENSEN: Okay. Lauralyn, what are your thoughts?

MS. McDANIEL: Precision medicine, precision devices. I also expect to see the tissue fabrication community watch what's going on right now with the point-of-care 3D printing.

MR. CHRISTENSEN: Yeah, good point. And a last word from Amy Alexander.

MS. ALEXANDER: I'm really hoping to see all of us come together in agreement on appropriateness criteria throughout additive manufacturing in medicine. It's such a massively broad field, but I think it's important that we start thinking about why -- not start, we have been, but continue thinking about why you use additive in a certain situation where you could use traditional manufacturing just the same. And I'd also like to see us

doing more comparisons between the two and looking at the standards that apply to traditional manufacturing and comparing them to our additive world.

MR. CHRISTENSEN: All right, with that, we will turn it back over. James, thank you.

CDR COBURN: Thank you very much, Andy, and thank you very much, everyone on the panel, for a great discussion. So many good questions and answers and discussion that will move the field forward.

One item that came up in discussion about ISO 13485 being harmonized with 820, to the degree that it can be, FDA has published a proposed rule to adopt ISO 13485 requirements as the future 21 C.F.R. 820 and the docket for public comments to that is still open until May 23rd, so you may comment on that in the public docket.

Now, for our closing speaker, I will introduce -- it's my pleasure to introduce Dr. Jacqueline O'Shaughnessy, who is FDA's Acting Chief Scientist. She recently became chief scientist after joining the Office of the Chief Scientist in 2017. Previously, she has worked throughout FDA's Center for Drug Evaluation and Research and many of the areas of pharmaceutical regulation, policy, and quality practices and is a supporter of advanced manufacturing, so I'm happy to have her as our closing speaker.

Dr. O'Shaughnessy.

DR. O'SHAUGHNESSY: Thank you, James, I appreciate your introduction. And good afternoon, everyone.

I think we can all agree that this has been an extremely productive and informative 2 days of discussion and shared experience on 3D printing. I'm glad that we can support the important role of this relatively new technology in our efforts to meet the challenges of COVID. I want to say that I'm truly pleased to be here today. This workshop is precisely the kind of effort that the Office of the Chief Scientist works to encourage, facilitate, and support internal and external scientific engagement and collaboration that advances FDA's

regulatory mission. Working with the centers, we've tried to meet emerging and future trends in science and technology in a number of ways. We've worked to strengthen extramural collaborations with our stakeholders, industry, academia, and federal partners, as Dr. Margerrison mentioned earlier today, and to create a more supportive culture of scientific excellence and innovation.

The cross-agency advanced manufacturing technologies working group that is managed out of the Office of the Chief Scientist is just one example of this. The working group provides input on strategic planning and reporting for advanced manufacturing technology topics affecting patient safety and regulatory science. It also serves as a focal point for advanced manufacturing, public-private partnership interactions such as the National Institute for Innovation in Manufacturing Biopharmaceuticals, America Makes, and BioFabUSA. These working group activities and others are supporting FDA's research and facilitating the regulation of innovative and emerging medical applications.

From its earliest uses, 3D printing in medicine has occurred in close collaboration with clinicians. The COVID-19 public health emergency particularly revealed weaknesses and gaps, and it also identified new opportunities for meeting those challenges and modernizing aspects of patient care. This workshop is a key example, and the workshop continues our fruitful intergovernmental agency collaboration that began during the COVID-19 crisis in early March of 2020. With the memorandum of understanding among FDA, VHA, and NIH, we've been able to use 3D printing to respond to COVID-19.

As we've heard today, technological advances and changing conditions have accelerated the desire of clinical sites to adopt 3D printing to increase clinical capabilities and improve patient outcomes. As always, the FDA wants to ensure that patients receive high-quality care with access to the best technologies with reasonable assurance of safety and effectiveness. The number of attendees and types of interactions we have seen during

this workshop demonstrate clearly that this community is dedicated to these goals and holds those values as paramount.

You've heard from our speakers that the FDA is no stranger to 3D printing. FDA has collaborated with clinical and industry stakeholders on 3D printing for almost a decade. In 2013, CDRH launched its first forays into 3D printing and in 2015, the Office of the Chief Scientist sponsored the FDA's 3D printing core facility. CDER approved the first 3D printed pharmaceutical in 2016 and in 2017, CDRH released guidance on technical considerations of additively manufactured medical devices.

Since that time, the FDA medical product centers and offices have devoted resources to understanding this technology and how it can be used and adopted. CDRH has made great strides for 3D printing by engaging externally, holding webinars, writing standards, performing research, publishing discussion papers and guidance documents and discussing topics like this regularly with stakeholders. FDA has been both leading the way, as well as listening to feedback and new developments as technology in these spaces have changed.

As Acting Chief Scientist, I'm proud to continue to support the regulatory science research, scientific working groups, and other inter-center collaborations on this significant cross-cutting topic. Nothing happens in a vacuum and the careful thought and feedback that you are dedicating to this topic will help set the stage for other patient specific and clinical site manufacturing activities that are already under way. This is why it is so important that we continually engage in these discussions and maintain the open and collegial atmosphere that you have fostered in this 3D printing community.

Thank you all for your attendance at this workshop and for the productive discussions that have taken place over the past 2 days.

CDR COBURN: Thank you very much, Dr. O'Shaughnessy, and I echo those thanks to everybody who has attended. Please remember that the recordings from this will be on

that same website link, you can even get the recording from yesterday right now. The slides should be available on the website. And please comment on the docket, both for the ISO 13485 and also, if you still have comments you want to give for the discussion paper, please go and do that, as well. Thank you again and have a great day.

(Whereupon, at 5:29 p.m., the meeting was adjourned.)

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C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC WORKSHOP - 3D PRINTING IN HOSPITALS: VETERANS HEALTH ADMINISTRATION'S EXPERIENCES IN POINT OF CARE 3D PRINTING OF DEVICES AND IMPLEMENTING A QUALITY MANAGEMENT SYSTEM

March 17, 2022

Via Microsoft Teams Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

TOM BOWMAN

Official Reporter