FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

ADDITIVE MANUFACTURING OF MEDICAL DEVICES

PUBLIC WORKSHOP

Thursday, October 9, 2014

FDA White Oak Campus

10903 New Hampshire Avenue

Bldg. 31, Room 1503

Silver Spring, Maryland 20993

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Capital Reporting Company

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P R O C E E D I N G S

OPENING REMARKS

DR. DI PRIMA: Just covering a few housekeeping notes before we get started with today's program. You saw a lot of FDA people up interacting with everyone yesterday and I want to thank them for all the hard work they've done. And a lot of people you haven't seen They are the workshop staff as well as - our center's liaison with them and they've done a lot of work on the logistics. And they've also done a great job of telling us what works and what doesn't work in terms of workshops. So if you would give them a quick round of applause; that would be wonderful.

[Applause.]

So from yesterday we had a few comments from the webcast. When giving comments from the audience, please approach a microphone otherwise the webcasting attendees can't hear you. And if everyone would please be a little bit more vigilant with stating your name and affiliation every time you speak. Again that would really help the webcast people.

So a few other notes. We have room 1406 which is over by the restrooms available for luggage. So if you have some suitcases you'd like to drop off and not have in here, that is available.

We are going to spend the morning doing some recaps of what was discussed in the break-out sessions with everyone here.

Now we have invited and have participants from many different industries who have many different perspectives on this. We'd like to get as many of your views as possible and we -- along with hearing what you are doing, we also are really interested in sort of an ideal

world what you would like to have done.

And along with that there are many different sort of device areas represented here covering Class 1 to Class 3 devices. It is very important to understand that FDA looks at all the devices for their risks. And we have existing device guidances for many specific devices. So we are going to look at a 3D printed device that is Class 1 very differently from one that is a Class 3. So I know there is a little bit of a concern about you know for implantable devices having the same level of concern for something that is Class 1.

So you need to understand that we are looking at some general technical considerations but again a Class 1 device is going to be looked at much differently from a Class 3.

So with that I would like to introduce our opening speaker. We have Dr. Bill Maisel. He is a Deputy Center Director and Chief Scientist here at the FDA and currently Acting Director of Office of Device and Valuation.

[Applause.]

DR. MAISEL: Good morning. You know it is really great to be here talking about Additive manufacturing 3D printing because it is really emblematic of the types of challenges we are facing as a device center but also as an industry. We have these amazing technologies, these disruptive changes and it really forces us to step back and think about the current models we have of scientific evaluation and engineering evaluation and regulation and think about how can we do this right. How can we strike the right balance and take the right approach.

A couple of years ago, we being CDRH modified our vision statement. And the first line of our vision is that patients in the U.S. have access to high quality, safe and effective medical devices of public health importance first in the world. And the first in the world part is

somewhat aspirational but it really forces us and forces the community I think to think about how can we bring these really great technologies to the bedside as quickly as possible particularly for those areas where it has a meaningful potential impact on clinical outcomes and really to help patients and advance public health. And so we have been focused on certain strategies in certain areas in accomplishing that and getting good technologies to patients more quickly.

One of them is to think about the regulatory science aspects, the tool standards and approaches we can use to assess the safety, effectiveness, quality, and performance of products. And in many respects being here today is our reach out to help us figure out the best approaches for doing that. And reaching out and collaborating and understanding the needs of the community and the health care providers and the patients is also another thing we've really made a conscious effort to do. And I think just having this workshop is emblematic of that.

We've also established more formal areas and approaches to doing that. For example we have what we call our network of experts which are agreements with professional societies and organizations that allow our review staff to reach out more easily and more quickly to get input on what is going on in the community, to get other viewpoints and vantage points of some of the technologies and scientific issues that are going on.

We're very public about that so if you go to our Website there is a network of experts Website. It lists more than 30 organizations that we currently have agreements with. If you are with an organization that you think would be a good candidate for the network of experts, there is information about how to contact us. Currently our staff has access to literally tens of thousands of experts around the country now that they can reach out to get input.

So we are really trying to not regulate in a silo, not decide on our own what the

science and engineering is but really to understand the landscape. And I think this meeting is emblematic of that.

The other thing we've done is we've really tried to focus on balancing benefits and risks. And I think the opening comments that Matthew made are really emblematic of that that there is not a one size fits all approach. And we really need to think about what is the technology that's coming forward, who is it going to be used for, how is it going to help patients. And so certainly for a product that is really going to help patients who have no good alternative therapies we are going to think about very differently than a me to product that isn't going to really make a meaningful difference.

And so striking that right balance of benefits and risks in our approach to evaluating the products is certainly something we are focused on. And we've issued guidance in this area and talked explicitly about the factors we consider in assessing benefits and risks. That is also available on our website.

The final guidance that is up there applies to PMA and De Novo devices, not to 510ks. But we've also issued a draft guidance on how benefits and risks apply to 510k devices. And some of those factors include things I've mentioned: what are the available alternatives for treatment; how sick are the patients; what alternatives are available to them.

But we also talk about things such as patient perspectives. How do patients view the risks that they are willing to accept? How do they view the benefits? Because again we really want to incorporate in our decision making the views of the community.

One of the interesting things I think about 3D printing is the aspect of personalized medicine. FDA is certainly interested in it. It is a phrase that we hear a lot; and most of the time it is talked about in the context of drugs or genetics identifying a certain

genetic profile of a patient, maybe tailoring a therapy to the patient. But in many respect 3D printing is the quintessential personalized medicine or has the opportunity to be that where we can start thinking about anatomic differences in patients and tailoring a device that is perfectly constructed to treat an individual patient. So it really is the future and the vision that we share I think in trying to get the right therapy to patients tailored for their exact needs.

There are many other challenges obviously with additive manufacturing and it is great to have people here to talk about them today. So I think at the 50,000 foot view this workshop is really emblematic of the challenges we have.

The other aspect it relates to is digital medicine which as many of you know is a place that is rapidly evolving. We've issued FDASIA Health IT Report which was mandated by Congress in coordination with the Office of the National Coordinator and the FCC that Congress asked us to develop a strategy, a framework for digital health that promoted innovation, protected patients, and avoided regulatory duplication.

Well in many respects there is this overlap between 3D printing when you might have software that can be transmitted out to a hospital that could then print a device. And so I know while we have standard manufacturing and additive manufacturing the game is changing. And the delivery of health care is changing. And the environment of health care is changing. Things that used to be in a manufacturing facility can be out in a health care facility or might be in a patient's home.

And so all of these are the disruptive change that we're undergoing and this technology is right at the crossroads of many of these moving parts. And so we're very happy to have you here.

We really welcome the input and we look forward to another productive day.

So thanks for being here.

[Applause.]

DR. DI PRIMA: Thank you Dr. Maisel.

So Christina Savisarr and the Materials panelists if you would come forward we will get started with the breakout session recaps.

MATERIALS BREAKOUT SESSION OVERVIEW

DR. SAVISAAR: Good morning. We had a lot of good discussion in the Materials Breakout Session yesterday. And I did want to point out that recordings of the breakout sessions will be released if you'd like to go back for more details; because this morning I'll just be summarizing some of the high light points and then leaving some time to open it up to the audience for questions and comments.

So we heard from several people about materials they've been using successfully to build additive manufactured devices. And we also heard about lessons learned from failed candidate materials.

We talked about properties that may make a material printable including things like viscosity, crystallinity, thermal properties and elasticity. However, these things I think there was general consensus on the fact that the properties that are most important do depend on the processes you are using and the equipment and the requirements that are inherent to the intended use of the device that you are trying to produce.

So another comment that was made in this session is that extensive knowledge of the material is necessary in order to use it appropriately in additive manufacturing processes. At the present time this isn't necessarily push button technology.

So the challenges that we face with materials can differ based on the type of

material. Natural materials used in conjunction with cell printing technology have more variability. Some in the audience noted that polymers can be more complex than metals. And for all materials material sourcing can be a challenge. Good suppliers are critical.

And though additive manufacturing is growing supplying materials for these types of processes especially for medical use where choice of materials is further limited are not a major market for the materials producers. So quality control is important with materials. And careful selection of the materials used and the material suppliers is important.

Another comment from the breakout session was that there is definitely a role for standardization because whatever material you are using it's very important to insure consistency of the properties. And some standards exist and have been successfully relied upon for metals.

Generally there was consensus that at this stage extensive validation is necessary and that small changes in the material or process require revalidation. And, therefore, a number of industry members echo the sentiment that materials should not be tweaked once you have developed a reliable validated process for your material of choice. Don't change it.

Perhaps because of the validation burden there is not a plethora of information publically available but if there are more data in the future one thing that was mentioned is that it would be ideal if eventually computational modeling could be used to reduce some of the validation burden. It was also mentioned that there are only so many compatible materials. And that at this point using well known materials does speed development.

And there was also a remark that although these processes are not brand new we are still at a learning stage especially with material selection.

Finally in response to FDA's questions about post processing challenges there were discussions of a number of specific issues such as residual stresses and anisotropy effects. And it was acknowledged that there can be many more post processing considerations for additive manufacturing than for traditional processes and that these need to be thought about in advance of the design stage. But that their consideration is not necessarily insurmountable challenges.

So with that I will open the floor to questions and comments from the audience.

UNIDENTIFIED PERSON: -- custom made -- the Agency shouldn't commit -- of vital importance to all of us. I think that there is some concern that in the discussions of yesterday there may have been more questions raised than light shed. And I think for some of us even some confusion.

The question isn't -- of course it is axiomatic that the regulatory and legal environments will always lag technological development. That is a given. We all accept that. The question is can the regulatory environment advance rapidly enough so as not to put a chilling effect on innovation and development. And that is I think a concern of many in the room here and I am hoping something that the
Agency can address.

Thanks.

DR. SAVISAAR: That is a tough question. I mean I think our role as a regulatory agency is to promote public health. And innovation is a part of that. And forums like this where we are trying to get a better understanding of the science so we can make informed regulatory decisions. I mean in balancing risk and benefit when there is more unknown sometimes more information is necessary. And that is why we try to make an active effort to

learn more.

UNIDENTIFIED PERSON: I appreciate that. The question I guess for many of us is who will do the basic research around the unknown issues. Is it left to industry and we are in this kind of terra incognita or will the agency pick up the mantle and lead the charge. Also there are silos of excellence and knowledge which are not to be shared with the rest of the industry because they are proprietary.

So, most of us are left out in the cold in terms of those silos of knowledge that do exist.

DR. SAVISAAR: I think even outside of FDA like standardization processes and other forums do try to bring to light knowledge gained by different groups. I would say that FDA does do research. We do have some projects ongoing in this area. But we have various roles to balance.

DR. PATWARDHAN: Good morning everybody. This is Dinesh Patwardhan. I am with the Office of Science and Engineering Labs within OSEL. And I want to address that in a sort of multi point answer. The simplest way to say it is all of the above. So we are a regulation agency, FDA, CDRH. We look at ourselves as the central glue rather than doing all the research we do what is regulatory most impactful. That is the first point.

We try to work with national institutes NSF and IH all of the above NIST and we try to encourage any progress that can be made whether it is academic funding or research to work towards a common goal. That is the second part.

And then this third part is obviously industry plays a very important role. Standardization plays a very important role. We think of these forums as a very important tool for achieving what you just mentioned when we try to bring all of these players together we

hope that next steps can be talked through and some effective progress can be made.

Thank you.

MR. MORRIS: Good morning. I'm Ed Morris. I'm the Director of the America Makes National Additive Manufacturing Innovation Institute established by the Federal government for the specific purpose of advancing additive manufacturing to boost the U.S. economy in all manufacturing sectors.

It was quite intriguing to me from my background in aerospace and defense to hear the presentations on the various topics yesterday and the tremendous amount of overlap; huge amount of overlap on all the other industry sectors.

We are in the process of doing public private partnerships, investing in advancing the technology in multiple business sectors including medical. One of our projects we are investing in with the public and private funding is with University of Pittsburg in bioregional magnesium for medical applications for bone replacement, et cetera.

We are in the process of maintaining roadmaps for additive manufacturing on multiple business sectors. We are taking on the task of doing some road mapping for medical with our members. We have quite a few members in the medical community, health care, et cetera. And we are looking forward to partnering with FDA in that process.

And part of our activities include working with the federal government, our program major is Dr. Jennifer Fielding out of Air Force Research Lab and she has just formed a Go Additive community of practice with just the federal government partners and FDA has already joined that. So there is huge opportunity for collaboration leveraging what we are doing in multiple industry sectors and minimize the duplication of effort, investment and so forth to benefit the taxpayer and advance this technology for the United States.

So if any of you have questions, feel free to reach out to me, Ed Morris, America Makes.

MR. BULLEMER: Maybe I can add a little bit because I believe that industry plays a vital role in that game. The industry, machine manufacturer, the one who is sourcing the powder, qualifying the powder, of course research can do that. But if you remember my triangle that I presented several times yesterday the machine itself is just part a good quality. And you have innovation on every side. You have very interesting materials like magnesium which is definitely interesting. And you also have the innovation rapidly going on on the machine side.

So you have to cooperate with the industry. The industry itself is not able to do all the development because they are just a couple of companies on the market. They can't do everything. So you need good research centers to do that. I think that is the combination out of that that will answer your question hopefully.

MR. KUMAR: Mukesh Kumar with Biomet. I heard the term research and silo and silo of knowledge. Please remember we also started learning this. And the best place to start is literature. Additive Manufacturing and compliments of that have been around since late 80's and early 90's. I strongly urge the community to look at literature. There is a lot of information. And look at the patent literature which is now in the open space. But there is a lot of science in there.

Thank you.

MR. BOLAND. I'm from academia and I also heard the word silos and it seems maybe also from some of the comments yesterday that some may be newcomers and so are a little bit afraid of duplicating work or the learning curve may be very, very steep. But we in

academia can play and maybe you can ask industry we should be playing a larger role in offering maybe degrees or courses in additive manufacturing, maybe writing handbooks about the various materials and so on. And so I think there is a role to play for academics as well. And it is just up to this community really to let us know what the pleasure is of this community.

We are at your service.

DR. SAVISAAR: No additional comments or questions from the audience especially people who didn't get an opportunity to attend the materials breakout session?

MS. STEPHENSON: Katherine Stephenson from Stanford University. Just for those who may not be in the technical field there has been a lot of kind of generalized questions like go to the literature, go to this Website. If anyone lists specific references, professional references they can go to to create a good overview of the technology at this point for those who are new to the field Websites, specific journals, professional associations, they could be good foundations they could go to to get up to speed on the technology.

MR. SLOTWINSKI: Certainly those Websites and papers are out there. I couldn't quote them from memory but perhaps we can take as an action as part of the proceedings to collect some of those and make them available.

MR. KARPAS: Hi, Les Karpas, Metamason. This is more of a food for thought comment than it is a question. But for those of us in Class 1 and Class 2 devices as we approach our 510ks there is an inherent tension between how the process is currently written encouraging design freezes, encouraging very relatively strict parameterization of what your product is going to be, and a desire to make a product that can be fit in size per patient with the opportunity for a physician and patient input. And so a re-examining of how the regulation is currently written to allow for the customization that is inherent in the process to maximize its

benefits to the end users is something that maybe we should have a separate time to talk about.

MR. JOSHI: Sameer Joshi, Gendex Medical System. To answer the question that was raised about specific literature there is a company run by a guy called Terry Wohlers (ph) who publishes something called the Wohlers Report every year. If you want to get a good overview of the whole additive manufacturing technology that is one good resource I would recommend reviewing. It comes out every year and covers the whole gamut of all additive manufacturing technologies, the current state of the art, where we came from and all of those things.

LT. COBURN: James Coburn, FDA. I would like to also address the literature comment in that I guess John's mention of a work item for the group to compile such a list. We do have an address additivemanufacturing@FDA.HHS.gov it was on the screen a little while ago. It is also on the Website for the agenda. If you do want to put some literature or references that are available to people you can send them to that email address and I believe we can post those references with the agenda on that Website. From there it can go wherever you want it but if you would like to send additivemanufacturing@FDA.HHS.gov, put workshop in the title that way it will get filtered to the right spot.

MR. BONINI: Just an additional comment about sources of information -- Julius Bonini, Lucideon MMP, I spoke yesterday. The best place we are seeing these day is at conferences and unfortunately again aerospace is leading the way as you saw from Greg yesterday. For example next week is the MS&T conference in Pittsburg; there are three whole days of technical papers on ALM. There is a TMS meeting next year, the big meeting in Orlando. There is going to be three days full. And then the Titanium meeting at the end of the

year next year October in San Diego is probably going to have a whole session just on ALM just for titanium. So those are great places to see what the aerospace community is doing with at least the metal point of the conversation. So that is a great place to go.

DR. HOLLISTER: Scott Hollister. I'm from the University of Michigan. I wanted to follow up on James' comment. I think that is a great idea to send references into this Website. But it would be also nice if we could organize them like things that have been bend here into materials and machine validation and things like that so we can see how things are organized as well as pre-clinical use of these devices and clinical use. I think that would be very useful.

MS. REITMAN: I am Maureen Reitman from Exponent. I'm also active in the Society of Plastics Engineers and as a follow-up next year the big meeting for us in Orlando is in March, it is a combined national plastics expo and annual technical conference. There will be a session for plastics in additive manufacturing, it is a full day session focused on new technology and how that can work from a plastics prospective.

MS. ZHOU: Good morning everyone. My name is Simin Zhou. I'm from UL. What we are doing and we've actually spent a lot of effort on this is consolidating all the different materials, putting it online, putting in video format that is easy for learning. So we will start putting all of that out on our site, UL.com/3Dprinting; so all that information becomes available to folks.

It is I think a big learning curve at this point and I think the approach we're taking hopefully that is going to be helpful to everyone is to build it in a foundational level and then building up to a more advanced level to get the information in a more I think digestible way.

MS. MATSUMOTO: Hi, I'm Jane Matsumoto from the Mayo Clinic in Rochester. And we were looking for a course that was just really devoted to medical modeling because

we've started doing that pretty heavily in the last year. We got our own dedicated lab. We couldn't find one and so we've established one and it is going to be this winter, February 7 and 8 in Scottsdale. It is really going to be focused on medical modeling in the medical industries. So we have our surgeons, our researchers, and our education people talk about how we use it in clinical practice. So if anybody is interested and it is SIMI accredited.

MS. McDANIEL: Hi, I'm Lauralyn McDaniel with SME. I've heard about all these resources and I just had to stand up and talk about SME has been in additive manufacturing since 1990. The RAPID Conference has been around since 1990 and next year there will be two and a half days of nothing but medical information. We also have a Website SME.org/3D which takes all the sources we've found in additive manufacturing and 3D imaging and puts them in one place including SME's database of technical papers which you can search by terms and whatever you need.

DR. SAVISAAR: Since the audience seems to have a pause in comments I was going to ask the panelists if in my summary from yesterday there were anything that I skipped over that you would like to highlight for the whole group?

MR. BULLEMER: I presented yesterday just have your controls in place so look for the right partner resource. Do it according to quality management standards which are in place. And don't be afraid. It is not much different than sourcing any other material and you have to have the standard controls. There is nothing magic about it.

DR. SAVISAAR: If there are no more questions and comments then we might conclude this session early and move on to the summary of the next breakout session.

Thank you.

[Applause.]

DESIGN, PRINTING, AND POST PRINTING VALIDATION BREAKOUT SESSION OVERVIEW

DR. ANDERSON: Hello. I am Joel Anderson. The next breakout session was Design, Printing, and Post Printing Validation. And if I could could I get the panelist to come up from yesterday for that please.

All right. For those who I didn't get a chance to introduce myself to yesterday, I am Joel Anderson, a Medical Device Reviewer in Dental Devices at FDA. And so for this panel I had joining me Mr. Jon Cobb from Stratus, Martine Sanburgen form Materialize, Ernesto from Renovis and Axel Krieger from the Children's National Hospital. So I'll give a brief summary of what was discussed in this breakout session yesterday.

But before doing that I want to thank the scribes who did a great job of writing feverishly and hopefully capturing all the information that I will give a brief summary of. But it was most appreciated.

And then for this breakout session yesterday we covered six main questions. So I'll hopefully briefly go through that. And then open it up to general audience for the continuing Q&A.

So the first question dealt with how this process validation for general 3D printing need to be adapted taking into account the nature of the medical devices such as implantable or non-implantable, load bearing, not load bearing or patient match versus stock sizes. What we found was discussed is that we don't see as vastly different from traditional manufacturing means. The types of controls are very similar aside from monitoring the builds and this also you have to take into account the materials. You will need to account for segmentation design, printing, post-printing have all steps to be covered.

For covering process validation you have it open to variabilities so some topics of

discussion included a need to work with the OEM to understand the equipment, the processes and the challenges of that specific system. The need to obtain the initial data set so that it is accurate and critical for creating the virtual 3D models. And that can vary across tissue type from soft tissue to bone tissue and other things of that nature.

And as a whole the system can be variable so it is very important to have critically trained doctors, professionals that play crucial role also in that process validation.

For the second question we addressed how the software and 3D printing differ or is the same from the software used in other manufacturing processes. And then are there new considerations necessary for validating the interoperability and capability of the software program taking into account different versions with file types, printers, and other accessories to produce safe and effective medical devices.

What was discussed was that the complexity of the software in the chain of the system including the file types, printer and other items it will depend on if its stock sizes or patient match you use. With patient match you potentially increase the complexity. You want to make sure that the whole product cycles are compatible and operable leaving no gaps in the process including the automation steps.

The software or CAD portion is to be taken in conjunction with the hardware and CAM output portion so that the machines meets the precision requirements and that the software matches with the hardware material, therefore, providing a closed loop system if you will. And the main file types discussed for this questions were STL and AMF file types being the main ones.

Next we discussed what process parameters should be considered for establishing process validation and subsequently monitored for 3D printing of medical devices.

And how are these parameters and the process evaluation to be evaluated to be predictive of medical devices and conform to the established specifications.

We discussed that there is a need to develop process validation, the sampling plan that demonstrates the controls looking at the build, testing the parameters of the build chamber such as the heat and other factors and inspecting the incoming material.

And along with patient match you'd include considerations for validating the geometry, weight, size and others that will be necessary for the various materials.

Once you've developed your parameters including dimensional stability and how stable materials you want to continuously monitor those parameters and this does not tend to be different than what you do for traditional manufacturing and it is recommended to lock those parameters in as revalidation can be timely and add additional cost. And it is important that as with this technology maturing is that you have validation to where you want to minimize variability.

Lastly other process parameters to consider that were discussed included geometry, printer type and precision, mechanical strength, powder, energy source, and shrinkage with all those playing a large role that need to be established in your process validation.

The fourth question dealt with what non-destructive testing methods are available for medical device validation and verification. And then what quantitative validation metrics can these imaging provide.

There are many types of non-destructive modalities that were discussed. They included optical inspection scanning, looking at the internal structure to see cracks or surface pitting, a CMM system for taking measurements, x-ray was discussed for porosity, gas

impregnation to measure the amount released afterwards for evaluating surface porosity, CT imaging was discussed for evaluating density which can also be related to the modulus, and then FEA analysis can also be used. And all of these are important to validate the different components and to compare to your design files.

The fifth question asked was how do you approach reproducibility: one, across printers and two, at different locations of the printer bed within the same run for the 3D printing of medical devices.

What was discussed was this does not tend to be different than traditional manufacturing. You perform validation specific to that product and the machine and if you have multiple machines you would need to provide a rationale for why you would use different machines for the same product and recommended to validate each machine; and then taking in consideration the testing in the worst case to cover the entire spectrum of variables for your validation.

And lastly we had a question of how do you determine worst case design scenario with a continuum of designs rather than a finite set of designs. Do you have to test each parameter to determine worst case and does modeling play a role.

And the points of discussion from that were there are potentially many different parameters and permutations especially for the patient match type device so you will need to consider what is the most essential. And it is recommended to validate a certain range that determines the boundaries of the parameters, thereby determining the worst case to give consideration to and accounting for the extreme potential conditions within those parameter ranges.

So that concludes the summary.

And as the last session we will continue with opening it up to general Q&A. So if you have any questions from the audience, please come up to the microphone and we will open it up. State your name and affiliation.

MS. KANEGSBERG: Barbara Kanegsberg, BFK Solutions. I'm not sure which session these comments should be addressed to but I'll start here anyway. There are a number of issues with validation and not all the test are necessarily non-destructive. In terms of validation we have to consider cleaning validation and that's a very separate series of tests; the validation and the monitoring particularly if we consider life cycle. So that has to be considered and I wasn't in the cleaning session so I don't know if it got considered there but I'll bring it up anyway.

Another issue is what we tend to call materials compatibility and that is in setting up the initial process we have to be certain that the post-printing materials that are used -- fluids that are used either for cleaning or in terms of lubricants that they don't produce undesirable surface modification. That becomes more important in additive because most of the product is the surface. So if you have a large solid device, yes, it is important but the thinner the device the more surface it is the more important materials compatibility becomes.

In general in terms of validation Dr. Maisel mentioned that we are moving to hospitals so I guess that is a related comment. There is a different way of approaching validation and cleaning in hospitals than in manufacturing facilities. So as we get into customized medicine I think we have to think about the design and handling of 3-D printed devices in the hospital setting.

I know that some of you folks from FDA have been around at ASTM meetings and we have treated cleaning and manufacturing for reusables in the hospital quite differently

than we have in manufacturing facilities. So I guess that means a reconsideration and more committees and more standards perhaps.

Thanks.

MR. RIOS: I completely agree with your statements. I mean I think that additive manufacturing has a lot in table for technology but there is also the other segment which is cleaning, validations. And again what I consider clean validations it's specific to additive manufacturing but then it starts taking on its own which is pretty traditional with cytotoxicity, biocompatibility, stro (ph) validation, and all those validations which you will do in any case whether you use a different technology just because you are using these parts and because these are implantable devices.

So, yes, there are considerations that are specific to additive manufacturing but then it kind of morphs into what traditional manufacturing will be. Maybe there are some specifics like powder residues, those things need to be looked after. But in cleaning validation it's also to make sure that you are removing all the manufacturing residues if you are post-processing those parts. But it gets to the point where it kind of like gets back into traditional manufacturing.

MS. KANEGSBERG: Yeah, Barbara again. I think it's really important because at a hospital certainly everybody understands that you basically have certain procedures before surgery. But in a trauma situation in an emergency situation the processes have to be really rock solid, steady, simple, quick. Yeah. Thank you.

DR. HOLLISTER: Scott Hollister, University of Michigan. I think Barbara raises some interesting questions that we've been thinking about. And I think Materialize is going to have a conference in a few weeks talking about 3D printing centers at hospitals and I guess my

question is how does the FDA view that? Are these centers going to have to be registered as legal device manufacturers? And is there any formal policy on that right now on customized 3D printing centers at hospitals?

DR. ANDERSON: I cannot comment at this time. We're -- that is still going to be on a case by case basis and under development. So that would be a separate conversation that as Dr. Maisel was saying it is emerging technology something we are working toward. But that would be a separate conversation.

MR. KRIEGER: Just a few comments. We have a printer at our hospital so we use it primarily for making models for procedural planning. So those models are not in the OR and so not implanted so it is a lot easier and we work, of course, with our IRB for doing validation of our processes.

If we make devices that come in patient contact, you know we printed some models for placing sensors on babies, and then we include in our processes all the cleaning steps and validate the final products. So this is part of our process.

LT. COBURN: James Coburn, FDA. I had a few questions I guess because I wasn't in this session. I was in the other room. I wondered Joel mentioned about monitoring your processes when you are printing. Did real time monitoring parameters come up as far as you can monitor how much power goes to the beam and you can monitor the internal temperature of your chamber? But maybe monitoring at the point of melt to see if you are getting the right amount of melting, you were getting the right temperature gradient if any of that -- did that come up during your validation discussion.

DR. ANDERSON: We didn't have a specific discussion of real time versus others. So if anybody would care to comment at this time, feel free.

MR. RIOS: Well it is very system specific depending on what equipment you have. But systems I am familiar with they do have a continuous feedback and the machine adjusts itself within the parameters to stay within those parameters that you have specified. So there is a window of operation that you work with your OEM and that is where the machine works so it is continuously producing feedback and adjusting to get those parameters that are critical.

So if something external happened like power surge or something happened to the machine, the machine has the capability to stop the build and that is probably the best thing to happen at that point just completely stop the build and not produce a part that is questionable. But the machine has systems to provide feedback and it is a closed loop and it controls itself within parameters.

MR. ZANDERBERG: I think there are still some variability from manufacturer to manufacturer which parameters exactly can be monitored or that you can track. So I don't know maybe there is room there for standardization as well. Something that we've seen with different machines that we have that there is definitely a variance there.

DR. DEAN: David Dean, Ohio State University. I think our general theme is design and we're talking about design that has been mentioned design of load bearing versus non-load bearing or soft tissues versus hard tissue but the load bearing is going since we are talking about patient specific and each person may have a specific defect of a specific geometry and so on load bearing will be different for that person depending in the load they are bearing. And getting further out into the design life cycle of what we are making for them so the material properties what is going to happen some things are maybe load bearing but only traumatically so that person has -- we don't want them to ever fall down the stairs but what

happens in that case where over ten, twenty, thirty years what are the types of loads that their -- so again life cycle considerations might be important to add to design of patient specific implants.

LT. COBURN: James Coburn again, FDA. I have another question. So you mentioned in your discussion about the interoperability of the different component software versions, the different machines, different pilot types, can you speak to, again this is because I wasn't there, so I might -- you might have already talked about this. Can you talk about the amount of revalidation that you do or don't do when you change say software version or if you migrate to different software in your experience or in anybody else's experience in the audience.

MR. COBB: Just so I understand the question. You are talking about the software that we would use to control our own system? Are you talking about software that comes into the system? I think it is a different answer.

LT. COBURN: Right. And I think I would ideally ask all of it from tip to tail there. If it is the imaging software all down to the machine, the tooling code, you know, that is actually doing your path which is the most sensitive. And what kinds of revalidation do you do on any of those steps if you have experience or if anybody has experience doing that in any of those steps I'd be interested in hearing.

MR. COBB: Again from a manufacturing standpoint I can probably answer the question better from the software that we update. In that particular case when there is a software upgrade that is made available to in our particular case any customer that's on a service contract that software is typically sent out or uploaded and yes, then the whole product needs to be then recalibrated if you will. So, as I think I mentioned before we really look at a

closed loop system that we have. And that closed loop system that we have in our particular case would look at the material, the material delivery portion of it, and then the basically the X, Y, Z controls that would go on there.

So the short answer to the question is yes, all that would be revalidated with a software that we would update with.

MR. RIOS: I'd like to address that. But when you have multiple cell or something we have had discussion that you have to convert from one file type to another, to another, I mean sometimes two or three times just to get to the final version that you need for your specific equipment.

I think that you at the beginning when you are using your conversion you have one type of software. That is not as critical when it comes to getting to the final software. What I mean is the first software let's say that you have a CAD system; right, 3D modeling system. That can be updated. I mean that is definitely updated every year. That comes and it is updated every single year. So those systems can be changed.

What in my opinion cannot change is the software within the machine. Once you come up with that program, once you put it into your machine and you have your themes or your settings, your parameters, those cannot change. Now you can keep adding to that machine. You can keep coming up with new programs. You can be using different 3D modeling systems as long as you get to that system and you freeze that software, that program then you can continue using that.

Now in our experience we do not make software updates on the equipment just because there are so many setting within the equipment we do not want to rely on our supplier that they made all the right changes or the specific changes do not alter what we have already

validated. So once we have validated the equipment we stay, we lock it.

Now we are going to be like these for I don't know how long because we have so many builds and we keep adding project that we are in the stage. But I mean as long as it is working for us it is fine. Maybe when we go to a newer version we'll go to a new software, a new validation and then we will catch up. But at this time we see the first software, the initial software, that is something that can we change it. But once you get to the equipment software that cannot change.

LT. COBURN: Just so I'm clear when you say equipment software are you including -- I have two things that you might be including either just the firmware on the machine or also the slicing and paths software that usually comes with one of the machines.

MR. RIOS: The slicing software is of two -- gets you to the final build, the build project. But that is slicing in all the prior 3D modelings I think those can change as long as you have the same setting which is the layer thickness, something like that, something critical like has to be the same for the prior. But the most critical in my opinion will be the machine settings; that software within the machine that cannot change.

MR. ZANDBERGEN: Not just looking at the machine control software as such but also everything that takes place prior to that when you are working with patient specific devices. At Materialize we use a lot of different types of software that most of them are developed in-house, they usually go through validation or they all go through validation cycles before they are being released commercially. Next to that we also look at implementing those in our processes and also validating them for specific use in our processes.

MR. HOROWITZ: Eric Horowitz, FDA. So kind of piggybacking on James' question; are those revalidation considerations that you were just speaking to in any way

different from the considerations that you would have with other automated processes? Are there things that are specifically concerns for 3D printing?

MR. RIOS: I think 3D printing that the software within those machines, I mean it depends on each machine, but the software it is quite complicated. This is not a type of software where it is just quick encoding of probably a CNC machine. So in my opinion it is the software that you really do not want to be tweaking, altering, I mean you try to avoid that as much. I mean you definitely need to avoid that. You need to lock your software and stay with it. I think in that respect additive manufacturing is more -- is different because the software is definitely more involved than in traditional manufacturing or what you would have with a different machine.

MR. CHRISTENSEN: Andy Christensen, 3D Systems. I think several comments kind of on this general topic. I think the software -- I think I would differ a little bit. I think it is much like any other process that is driven by software and you need to watch it and when things are locked down you need to lock them down and not change despite what happens with in even things like operating systems and small updates.

And I think there are probably many good stories in the past of things that have gone wrong based on small tweaks that seemed unrelated.

So I feel like there are two aspects. I think one is a manufacturing tool you know additive manufacturing and Ernesto I think your approach going in it as a manufacturing tool is a little different than a personalized surgery system where the softwares we discussed yesterday is kind of a part of that device, so the device includes the software and the outputs of it.

And I think there in our experience, same thing, we've got several softwares that

led to the final product. And I think once you lock them down none of those really can change without serious consideration looking at revalidation obviously but then looking at potential resubmission because of the fact that those devices are an integral part of the clear device. So just my comments there.

MR. HIGGINS: Sean Higgins, BOSS Instruments. I don't see it to be such a huge difference from subtractive manufacturing as far as you are not, with the exception of the one awesome printer that was printing skin directly on a human, the machine, the printer is producing parts. You are concerned about the validity and the end part that the machine is producing. So I mean there is a lot of complexity compared to subtractive. I mean if you look at the code that is actually producing the part it is not tens of thousands of lines of code and if you kind of change that engine it is going to change that. But you are really concerned about what is coming off the machine and that is what you need to really look at and verify that that is what you are looking for.

So I mean you are not making cubes. No one is making cubes. But if you were in the business of making cubes and you wanted to do it on a 3D printer you would have a standardized test part that you would need to rerun to re-verify. If you change something, you change the parameters in the machine, you change software, you upgraded something you'd want to re-verify that you are producing the same cube. If that cube was load bearing you'd probably have some characteristics from your original validation, the original part. You need to rerun it and retest it. I mean whatever the part is you are producing you need to have some standardized test piece that you can reproduce just like a subtractive machine if you change the code to produce a part on a subtractive machine you are still going to measure the part and you are still going to qualify the parts that come off the machine, not necessarily diving in the

machine itself because that is really complex. But I think if you verify the end.

And the sterilizations they are kind of the same thing for that matter. You're still fighting the same organisms. So if you produce it on a 3D printer and it can't pass sterilization validation through the same exact techniques because it is still the same critters you are trying to kill, yeah, central sterilization so you develop the products and you take it to the hospital and if you can't produce a valid cleaning procedure for 3D printed object then you can't use 3D printed object or you've designed it wrong or you need to go back. But you still need to pass the same validation for a 3D printed object as you do in traditionally manufactured product. So it is not that much of a different animal if you just look at it that way.

MS. STEPHENSON: Kate Stephenson, Stanford University. To go back a little bit on this go back to producing in hospitals versus producing in manufacturing site, software updates is a big concern there just because I dealt with highly technical software in a highly regulated software environment. Most hospitals have a lot of privacy concerns. They have a lot of major technology protocols they have to follow including regular updates of operating systems. I have a couple of very technical equipment get crashed because of some well meaning IT guys.

So just to make sure that we are looking at if you do bring a printer into the hospital to realize that those software revisions, those updates may be subject to outside forces and protocols rather than just direct manufacturing. You are also going to deal with privacy and standardizations at hospitals that you would not inside of a manufacturing facility.

MR. KUMAR: Mukesh Kumar with Biomet. Speaking of validations and software the first question to ask is what has changed in the software. Second question to ask is do I want to inherit this change or is the previous version good enough for me, right. Then you

make the decision okay if this change is so critical that I have to adopt this change how and where is it effecting in the process. Based on that you make a decision whether you have to do a revalidation or not.

So speaking to Ernesto's point in my opinion the most critical part in all this are at two stages: a) if you are working with say segmentation and imaging and you go from say for the sake of argument MRI to CT or whatever if you have changed the modality completely of course you need to do a validation. But if it is the same technology and you are making a change in the user interface where you have to press a button over here probably you don't need to do a validation.

But more importantly in my opinion at least where the machines are involved the actual where it lays down the beam parameters or the energy parameters if you make a change over there you will have to do validations.

LT. COBURN: Thanks very much for those points about the places where the software validation is required. And actually I'd like to bring an analogy in. I do a lot of work with the computational modeling area and we are looking at with the ASME committee on verification of validation these question. And one of the big things that everybody agrees on is installation validation in obviously computational modeling the software is -- we are not talking about format, we are not talking about computational modeling as a medical device, we are just talking about computational modeling here. But the installation of the software is the thing. There is no other product. And so there have been instances where something will change and I think one of the ones I was told is that the company changed the constant, one of their elastic constants in the built in modules and so somebody reran -- their simulations got completely different results, had no idea because it was such a small change to the software

maker that they didn't realize because it was like four decimals down, they didn't realize how big that change would come up to the end user.

So I really appreciate the comment about having that standard test cube, the same thing holds with computational modeling where you have a standard problem, you solve that problem and if it comes out any different you know that something has changed. So I appreciate that comment.

MR. BERNAL: Andres Bernal with Bioniko Consulting. I have a question regarding validation or certification for the safety of proprietary 4 0 polymers, maybe a question for John is how if you want to certify the safety or at least the toxicity or non-toxicity of cured 4 0 polymer there are few actual articles or literature out there since it is so new and since it is proprietary. So are these companies like Stratasys and 3D Printing thinking about this supporting the manufacturers, the users of the technology by doing some test of the polymerized photopolymers somehow to share this information?

And finally based on a comment in an earlier session this multi material blending of materials complicates things even further because somebody pointed out that you can validate material a and material b but then the blend might not be validated.

MR. COBB: If you first of all we'll go back to a statement. What we offer, what we validate or inspect it would be materials that we've manufactured through our system. So if somebody is using a different material on our system I would say we can't validate that. And having said that if you look at where we are today we have two materials in our portfolio, PC ISO and ABSI that carry an ISO 10993 class c certification and then we have some materials that can be 134c autoclaves. Now that information that pertains to that is available on our Website.

We buy the materials from known suppliers and they make the claims. Then of

course what we do then would be test the material to make sure it conforms to that. But again it would be only on the material that we would supply ourselves.

DR. ANDERSON: Any other questions from the audience or comments?

MR. KUMAR: Mukesh Kumar with Biomet. I've heard this a lot about blending of material with additive manufacturing. Let's not forget that science does not change. Technology is changing. So if you are doing some kind of blending and if you were to do it in a for the sake of argument an extruder and if you can get it blended for whatever parameters you are imagining over there, the same kind of technology applies to 3D printing.

So just to give something in prospective, if you were trying to do a polymerization and 3D printing at the same time using UV light and for the sake of argument if your intensity of UV light is not enough whether you did that on a beaker on a bench top and you did that on a 3D printer the same problems will happen. So whatever you would do as leaching of your initiator in a bench top beaker test you could do the same thing with a bench top beaker test and determine if you had the right parameters for your blend.

So to think that there would be a necessity of a new set of protocols so that only additive manufactured parts could be determined for safety and effectiveness as opposed to what you could do with other traditional manufacturing methods I think that is stretching it too far. It is the same science. The technology of doing it is different but all the things you could do for testing at one place you could do at the other place as well.

DR. ANDERSON: Any other comments from the audience?

I'll ask the panelists if they have any other comments I left out of my summary or want to add on?

Hearing none, I will thank the panelists and conclude the session to have the

next one come up. So thank you everybody.

[Applause.]

PRINTING CHARACTERISTICS AND PARAMETERS BREAKOUT SESSION OVERVIEW

DR. KELLY: Good morning. I'm Jennifer Kelly and I led the Printing Characterizations and Parameters Breakout Session. I'd invite my panelists to come up and join me.

So we had Gerald T. Grant from Walter Reed National Military Medical Center; Severine Valdant Zygmont from Oxford Performance Materials; Scott Hollister from the University of Michigan; and Andy Christensen from 3D Systems.

Our first question addressed what are the critical parameters in the additive manufacturing space for a successful printing process and what needs to be considered.

I think the first item is the device function and what is its intended use. And then you want to look at what material you need for that function. And then what process can work with that material.

And then you look at all the other supportive equipment. It depends on a combination of material process and equipment. Your material may need to be biocompatible. You may need to look at processing the raw material and processes that may change the chemistry of your material and if the equipment can really support its intended use.

Other critical factors may include the layer thickness, the laser beam power, temperature, surface roughness. One critical parameter for one type of material may not be applicable for another type of material. And really process specific so whether it is metals, whether its polymers.

Reproducibility and repeatability is important and you want to have your process

to be consistent. You want to be able to test worst case scenarios, define your ranges of properties and you may need to run specific tests for a specific device.

If your material can meet a standard or there is a standard out there for your specific device it probably would be good to look towards those standards. The process may be very well understood and you may not need to raise additional questions but in this space until more work is understood I think the process is important.

Anything that I left out from my panel?

Our second question looked at what parameters can you track to insure a successful build. And I think it starts with the design and raw material. You want to look at the builder ports and temperature, power of beam, validating the process, human elements, strength and hearing time are good parameters to look at. But it may be specific to your process whether you have a scaffold or porous structure, particle size, how old the powder is, laser power, again heating temperature and post-process verification like sampling and non-destructive evaluation like mechanical testing.

So you can track a lot of parameters, validate, run statistical analysis, inspect often, build up your data base to build up your confidence for successful build to insure process control.

For metals a major issue may be defect detection such as localized unmelted areas. But again looking towards your builder ports is important to insure a successful build.

Our third question looked at our specific considerations for determining if a print job should be rejected. So I think one distinction was made rejecting a print job is not necessarily the same as rejecting a part after post-processing.

You want to reject a print job if it doesn't meet your design. And accuracy

depends on really how you set everything up. Poor calibration of your instruments can lead to fatigue issues and general failures.

And best practices included printer maintenance, cleanliness, synergization of your processes, and inspecting your instruments often that should lead to higher tolerances.

You may have a localized problem that wouldn't affect your entire build process but those may not be detected upon visual inspection so again you want to go back to your builder ports and monitoring your process control. Mechanical failure of testing, test coupons is important and if you are changing your printer system too often that may lead -- or affect your rejection rate.

Reworking: a question was raised whether a print job can be reworked. The debate seemed to look at what your failure rate is and that it is hard to rework a print job and that it is not the same thing for a traditionally manufactured part.

Recycling of a material is material dependent. It may not be cost effective and recycling powder may be fine for some polymers, some re-melting of titanium can be okay but again it is process dependent.

Printing too close to your control limits may affect your rejection rate and really looking at what is needed, what type of products are needed and what you can actually build may affect your rejection rates.

I think I covered what we discussed. I'll open it up to my panelists and the audience for any additional thoughts, questions, if anyone wants to discuss more detail parameters in the print space.

DR. DI PRIMA: Matthew DiPrima, FDA. So mechanical testing of couponed or some sort of destructive testing of like a dummy print device is always an option but I think

some of what we were going for with these questions was is there some way we could reduce the testing burden by looking at sort of the print process. Is it possible to lock in your printing parameters such that you know with enough confidence that you don't have to do a like coupon test with every run? And could you do it every five runs if your process looks good. Once you validate it could you just say okay everything coming off the printer is okay. Or is the technology at the point where we are always going to need coupons.

So I think that is sort of where some of the questions were going and having not sat in on that session, I am sorry if I missed any discussion but was wondering if the panelists in the room could sort of speak to the ability to sort of control the print job well enough to maybe reduce required testing or to sort of understand where that line is.

Thank you.

MS. ZYGMONT: I think from our experience it can evolve over time. For us it is like one other point that was made was like you build a data base and you build confidence. So the more data the less verification you are going to do because that data is going to go towards your validation and you are going to gain confidence. After that it becomes kind of a risk assessment type of decision because one of the things where this type of batch process put a few coupons in is really not a big deal, is small, but the time to test and verify. So at that point you make the decision do you want to still verify -- what is the risk versus the reward of continuing kind of the mechanical testing of some of the test coupon.

In our experience you reduce the amount of test coupons as we build the data base and validate the process and kind of lock up our meters. But the ultimate decision comes to what do you really gain from getting rid of the test, what do you gain for keeping them as well.

So that is kind of our experience.

DR. HOLLISTER: I would like to weigh in. I think what you can do with setting the process parameters is I look at it sort of mathematically as sort of the necessary and sufficient conditions. It is definitely necessary to get a good build but I don't think it is sufficient to tell you because obviously the thing you are going to do with 3D printing is you're going to vary the structures you're going to make, you're going to make different devices and you can do that so readily that you can say yeah, in general these are the parameters that give us a good build, you can have coupons and you can test those. But if we are getting into things like scaffold and you are producing very complex pore structures and complex architectures a fundamental question is as you shrink that resolution and get down to the resolution the machine your probability of defects goes up. Just to be honest the modulus of a very thin straw is that the same as a coupon; maybe or maybe not because you tend to have scale factor effects.

So I think it is in my mind at least for the foreseeable future it is going to be a mixture of both. It is going to be mixture of validating and locking in parameters that in general can give you good builds for standardized specimens. But if you are building specimens that vary significantly from that with different designs then I think you are always going to have to go back and verify and probably you can do non-destructive testing. I think micro CT is a great way to do that as well as mixed computational modeling; micro CT as well as destructive mechanical testing.

MR. CHRISTENSEN: I would answer it similarly. I think it is a combination of things and if you look at additive manufacturing as a manufacturing technique and just another manufacturing technique and not something anything different than casting or forging or machining, many of these processes which can be controlled. I think you can learn a lot

through doing a detailed validation but there are a lot of times when you don't pick up you need to monitor the process or you want to monitor the process to see variables and over time you develop confidence as Severine said in the process and in the capability of the process and you kind of over time can determine sampling and reducing sampling from maybe a start at every build and then you reduce sampling based on what you see. But potentially you still keep coupons, you still make coupons. We've kind of seen many different strategies for that.

I think you could look at -- you are talking about strength I think primarily but you could also look at it from a dimensional stability standpoint as well. When you look at sampling and quality control for things like we make a lot of patient matched kind of parts, plastic parts and looking at certain geometries and getting confidence in how close you are hitting the dimensional tolerances as well. So the same kinds of things exist and you get to some kind of a sampling plan in the end that probably isn't 100%, that you reduce that based on confidence.

DR. DEAN: David Dean, Ohio State. So the question about coupons is really interesting depending on why you're preparing the coupons. So Dr. Hollister mentioned you might want a coupon to look at the design aspect, you are changing the porosity or you are changing something that might affect the specific part that you are making and you are allowed to do that. So that is one reason that is something that is going to be variable in the process.

Another way you might use coupons though is to check if the material is still good. Has it been changing over time? And so you make a coupon to see if I can still use this stuff.

And then another one -- another aspect of making coupons is is the device still good, so is the laser power going down? Is it time to replace the laser or calibrating the device?

So there are so many different reasons to make coupons. And I think the question might be what does the users who are at that site what decisions are they making as opposed to what are they told to make coupons and test and see if it is to validate so you can keep going that day.

DR. KELLY: Thank you. Any other questions from the audience?

LT. COBURN: James again, FDA. I asked this question in the other session and I'll ask it here because it is a larger group. The question is what is the one or two most -- one or two things that reduced your rejection rate the most in the devices that you print if you can mention any of that. I would just say call it out and I'll repeat it for the mic or the transcriptionist, the two we got that I remember from yesterday were really controlling the quality of your consumable, your material and making sure that is within a very tight spec that reduces rejection rate. And then the second was additional maintenance. So somebody said that they increased their maintenance like one extra maintenance cycle I think they said per some timeframe and that reduced their rejection rate by quite a lot.

So are there any single most influential thing that reduced your rejection rate from the audience besides those two? Anyone? Come on. Somebody.

Optimizing the design for the process. That makes sense; that goes back to your point Dr. Hollister of when you get down to your limit you're treading on thin ice sometimes.

Learning from the OEM the vendor because they know their machines and getting the history. So the same control and maintenance.

Any others?

So when you are printing your own stuff hairspray helps.

[Laughter.]

Extra hold.

Anything else? Because all different process obviously have very different mechanisms.

Technician training. Ah, I think that was actually the one I missed from yesterday was making sure your technicians are very well trained and have a great idea of exactly what they are doing and if you change the process then you retrain so that they aren't missing something.

There you go. Follow GMP and you've got everything.

So feedback loop. And you've asked a couple of questions about hospitals. And that is a big thing in hospitals where nurses and floor staff will change the process and procedure from the stated procedures because they find it is more efficient. But they never tell anybody who made the established procedure that it is more efficient to do it a different way so feeding back from the people that are actually doing the technician work; very important.

Great. Thanks very much.

DR. KELLY: Anything else from the audience to address?

DR. DEAN: David Dean, Ohio State. I just want to come back to an issue that was raised early in the discussion of yesterday's session. And that is the issue of cleanliness of the devices and a lot of discussion about making the same thing on different machines but how about making different things on the same machine, changing the materials and the materials may have different effects on the machines over a long run. We've found that with photo cross linking of polymers sometimes they aerosolize and they might gum up things and be in the environment. And then you put something else in there and some of what was in there before gets into what you are doing now.

So cleanliness not only of the part and thinking about what creeps into the part from post-processing and how you are working with it and the cleanliness of the machine.

DR. KELLY: I think that is an excellent point and from what I heard yesterday and other conversations even if you have the same type of printer they may behave a little differently; to really understand your printer is important. Would the panelists agree, disagree?

DR. HOLLISTER: Yes, I would definitely agree and I agree with Dave's point that it becomes an issue if you are going to -- like we right now are only using one material in our machine but if we are going to start switching materials that is going to be an issue. But, of course, on the flip side that is what you want to do to expand your applications is try to that was the whole material section when you use it with a broader range of materials and then I think having some sort of standardized cleaning protocol and looking at how the different materials affect the machine is obviously a great idea.

MS. ZYGMONT: I think this is pretty much like any other manufacturing process or any other piece of equipment if you change the material you clean it. And you make sure it is cleaned right and you kind of validate the cleaning if there is no residue and what it does. And then the second thing if you change the material because you are changing the process is that you have to validate that as well. And I think this is pretty much the same. It may be a little bit more as you discussed before when you start 3D printing there may be a little more aspect of the process you might have to go deeper in. But -- the same thing you change something you have to look at what the effect of the change and do you need to revalidate yes or no. But the same way you would do with any other manufacturing processes. I think that will be enough today.

MR. CHRISTENSEN: I think if you look at the machines as machine tools you'll

find more variability between a machine, say you start with a Model 100 and you are using it and you are producing your part. And you decide that for whatever reason the 100 isn't available or you've got to buy the 200 you are going to find more variability and need to validate and test and evaluate that change more so there versus buying another 100 or another two 100s. You may see some variability as you would with any machine. But you'd see less variability than you would from moving to different platforms which you see over time. And a lot of the manufacturers keep improving their process so if you buy a tool today and you lock it down it doesn't mean that when you need another one in three years they're still going to be selling that same tool. So you are kind of forced to look at those questions and study and determine how much revalidation needs to be done.

DR. KELLY: Thank you.

DR. KANEGSBERG: Ed Kanegsberg, BFK Solutions. When we start to talk about changing materials or multiple materials, changing from one product to another that is starting to sound very similar to what happens in the pharmaceutical world, a different side of the FDA, but still some of the same issues in terms of making sure that if you are changing from one product to another you've done the ground work to make sure that there is not going to be any cross contamination.

DR. KELLY: Thank you.

DR. DI PRIMA: Matthew DiPrima, FDA. I have another question for the panelist and the room. Is the difficulty in sort of swapping the materials out of a printer so prohibitive that you sort of only use one material per printer?

DR. HOLLISTER: No I don't think it is prohibitive. And part of the thing just speaking personally on our own process of doing the laser sintering it is just -- you sort of have

to tailor the material to the machine parameters. In some sense you have to have certain particle sizes and a certain melting temperature and flowability and things like that and then expanding that to another material is a significant amount of work especially for our under-funded academic laboratories. But I think that it is not prohibitive but it takes a long time to do that. You are looking at probably a six month to a year process for these sort of going with the new biomaterial into an industrial style printer.

MR. CHRISTENSEN: I think it depends on the process a lot. I mean there are many different processes and some of them are really hard to change, decently hard to change out materials and so you kind of want to lock them down and just have them produce one material. But you have to think about dissimilar materials and then batches of the same material kind of in the same way where batch control becomes a key part of this whole process and knowing the raw material that goes into the final part.

And I think for that same reason you've got to have really good procedures for kind of cleaning and relating to contamination in a different -- cross contamination of different batches of the same material as well.

DR. KELLY: Anything else from the audience?

MR. PETRAK: Martin Petrak from the Orthopedic Innovation Center just on that topic of batch changing. As we are getting into the potential DMLS area my understanding is that if you are sticking with that titanium powder moving to a cobalt chrome powder in that same machine we are going to have significant problems with the potential allergies when it comes to nickel allergies in total knee replacements and total hip replacements. So I think that if it is impossible to actually clean a batch out from when you have tiny little particles you are going to completely remove that one batch or whatever if you are talking with titanium to

move into another batch of cobalt chrome so I think nickel allergies are probably your number one concern when it comes to hip or knee replacements.

MR. CHRISTENSEN: My comment would be that it isn't practical to probably do that but is it possible? I think it is possible. I think cleaning machines and cleaning -- I think all of that is possible. Is it pain? Sure. And I don't do that for that same reason. But could you do it? Could you decide to switch? You wouldn't -- I don't think you'd want to be in a process where you were switching every day or every week to radically different materials. I think it would create a lot of work surrounding that, less time to actually make parts.

DR. HOLLISTER: I just want to raise off the topic a sort of different question relating to printing parameters and properties. Are there a set of properties that people feel are important to characterize a part whether it is -- we've talked a lot about static properties, stiffness, strength, but what about fatigue or durability properties. How are printing parameters related to that? And if we talk about resorbable materials how do printing parameters relate to changes in resorption?

I think it is a conundrum because I obviously understand companies have proprietary parameters so they are not going to share and things like that but maybe there is a broader between the public agencies and the academic institutions. Maybe there is research that could be done to put some of these parameters out into the public space. And I think that would benefit the field as a whole both the private and the public sector.

DR. KELLY: Thank you for that point. And my question is would say printing a bioresorable part be different than some other batch process? Would the material behave differently? Is there still the need for that to be researched more heavily you would think within additive manufacturing?

DR. HOLLISTER: I think there is need to do research because we just don't really know the answer to that question right now. I mean from our experience we look at the molecular weight of let's say the raw material we get and we look at the molecular weight of the post-process material. We don't see any significant degradation of the molecular weight due to the sintering itself. But does it affect the long term in vivo resorption characteristics or the in vivo fatigue characteristics? I think those are important questions that we face and we don't really know the answers to those.

DR. KELLY: Any thoughts from the audience?

MR. KUMAR: I have some experience with processing of resorbable polymers not with additive manufacturing but in general. Just to give you an idea what the Lactide Glycolide polymers that we have worked with; if you were to say ETO sterilize it and do a resorption of that as opposed to gamma sterilization and resorption for that electron beam, completely different resorption profiles you will get. So you are absolutely right. I mean if you break the molecular weight and you change, you start with a different material you will have free radicals in there, you will have completely different resorption profiles.

However, with our many batches that we have made on resorbable polymers many -- same kind of sterilization methods say EtO we don't see much of a radiation and drops in profile. So if the same kind of physics applies over here I would not expect that it will change too much.

So you are absolutely right if you are looking at molecular weight I think that is right because that is what we have been doing.

I think you had asked a question, I'll go back to your question. Variability between machines and machines. So to Andy's point you are absolutely right. I mean if you

completely change a machine yes, you will have differences. But the question then becomes is it the same difference that you see with a subtractive manufacturing like a mil machine. So yes there will be some variations but statistically if you're within the output that you are expecting; it is fine then.

DR. KELLY: Thank you.

I had a question speaking to the resorbable polymers. Is there a challenge for homogenicity during printing or I can imagine being able to tailor between layers different compounds may lend itself to be more advantageous and you would be able to facilitate that with 3-D printing. Can anyone in the panel speak to that?

DR. HOLLISTER: Speaking about resorption one of the things we know is that is not necessarily a byproduct of the process but of the design and the flexibility that 3D printing gives you is obviously going to create different wall thicknesses. We know what hydrolytic degradation of polyesters for example that dramatically effects the way they resorb because of the sort of acid catalysis of the process; if it is really thick and the acid can't diffuse out of the matrix that tends to accelerate the degradation. I think those are concerns to look at. It is a very interesting question about introducing more or heterogeneous components into the system as you build. We haven't done that.

But and maybe Thomas Boland can speak to this more with more of the ink jet processes you can introduce cells and growth factors and things like that. I don't know. Thomas is here if you would like to comment or anybody else who has experience with that process.

DR. DEAN: David Dean, Ohio State. In addition to the molecular weight aspect of this the tightness of the molecular weight is going to be rated in the materials. So the

polydispersity of that you've got long chains with short chains those long chains are going to strengthen things up. But if you've only got short chains and you've got a very tight polydispersity then you are looking at how tightly can you make the mesh, how many cross lengths can you get? What is the density of cross lengths as you are building? And you can try to affect that by as you were saying the layer thickness. So the layer thickness and then maybe if you don't step the whole layer so you have inter curing between the layers or what we call stitching, over curing beyond the layers so that increasing the mesh that way. Or you can take the part afterwards and post cure it and blast it with light after you've got your shape fixed and try to make that cross linking mesh even tighter through those processes. So there are ways to affect things either molecularly or cross linking density.

DR. KELLY: Thank you.

DR. BOLAND: I'll give a couple of comments. So in ink jet printing the way the drops are formed and the range and the way the cohesion of the printed material works is this is very porous, these structures are very very porous. And so we in our research we used this to our advantage because we want the vas to actually to grow into these pores, so we can actually design where the pores go.

But in terms of hydrolysis of the materials for example I think one ought to look into porosity because I think a lot of these surface degrading polymers if you have a higher surface area that is going to be faster degradation so I wouldn't be surprised when you see the overall absorption profiles changing with the kind of process that you are using. I'm not sure what the sintering, what sort of ink jet would expect there'd be a difference.

DR. KELLY: Thank you. Any other thoughts or questions from the audience?

MR. GRIFFITHS: Steve Griffiths from Materialise. I am with the software thread

and manufacturing side of the house and a lot of the things that were talked about this morning I think can -- there is an event that goes on every year. It is the Additive Manufacturing User Group meeting. This year it is going to be in Jacksonville, Florida. And a lot of things that we talked about like file optimization or specific parameters for certain machine setups are addressed at this event. I'd recommend anybody in the audience to go there.

For example for file optimization we have a workshop that is included with the event that will provide for file optimization.

Thank you.

DR. KELLY: Thank you.

Anyone else?

Any final thoughts from our panelists?

I want to thank our panelists again and we'll have a ten minute break and we will come back for the next breakout session. 15 minute break. Sorry.

[Applause.]

BREAK

PHYSICAL AND MECHANICAL ASSESSMENT OF FINAL DEVICE BREAKOUT SESSION OVERVIEW

DR. LEE: Okay. I think we have a quorum now so we can get started.

So basically as moderator I took some notes and got some additional help and I am here to summarize at least the highlights of what we discussed at yesterday's session.

I thought maybe I'd just flip through the questions that we posed for the panel and the audience especially for those who may not have been in our session and been in the other track.

So the questions, we had very broad questions. And I know this posed some

challenges to the panel as well so I appreciate their efforts in addressing them.

The first question was how do you determine through testing that what you have printed is what you intended to print?

Second question how do you determine the worst case build for a patient matched device? I will say a lot of our discussion was more of a general nature so I think it is applicable to all devices. And some points that we pointed out was the orientation on print characteristics as well as the accounting for the printing and isotropy in their material model for finite element analysis.

And the third question was how does post-processing alter the mechanics? Is there a consistency concern in the final mechanical properties of metals, polymers and ceramics? And I'll just leave the online docket up there for people to provide comments.

So just looking through -- rather than commenting on each question I'm going to just go over all the issues. I think these are somewhat interrelated issues as well as being interrelated within the questions as well as the other sessions. I'll just point out what we discussed.

Regarding testing I think broadly there were two issues that were kind of interlaced in there. Testing of the final product versus testing as a part of verifying and validating your process. I think we didn't really separate the two. But recognizing that for medical devices obviously the final intended use, the clinical use is what is driving it.

And I think we kind of hit a little bit on this issue is that the existing standards that is probably applicable to the existing devices; I think there probably is going to be some need to either evaluate for yourselves whether those standards are still applicable to your specific device. I think that is a recommendation that we have with all devices not just with

additive manufacturing.

So because of that we kind of emphasized just the manufacturing aspects so we got into the validation and that aspect of the process, understanding the process aspect more. So a point that was made it is very important to identify or define precisely early on what the design requirements are. Before you do validation and testing consider what testing make sure you put into design parameters things that you can actually test. That kind of helps you define early on what you can test and how you are going to go through the validation process.

Again these comments were more focused toward medical devices in general. But I think we did poke at some examples of patient matched devices or very small lots of medical devices which can cause some challenges.

With respect to testing it was somewhat difficult to be very proscriptive because I think it really depends on what you are manufacturing and also you'll see with some of the questions we were trying to get at different classes of materials and things like that. But as the discussion evolved it became very -- in order to be very specific we had to have specific examples. So that was a challenge.

I think a point was made that possibly with respect to physical aspects you could use potentially some simple methods, I think you pointed out possibly something as simple as mass might be important to track. But at the same time we also understood that for complex structures and things like that obviously you need more sensitive and advanced techniques which might be somewhat expensive and time consuming. And I think the example of the CT was brought up to assess the structure, density and things like that of complex structures.

I believe and this is pretty obvious to this audience that for the physical obviously one of the key criteria you are tracking is all the dimensional aspects and that all

those aspects of your printing processes is within the tolerances that you've set from your validation processes. And it is important to keep in mind I believe we had a couple of clinicians spoke up yes on the anatomical clinical needs of the final printed devices are actually very important obviously so you need to kind of keep that in mind and as you are doing all these testing you need to keep in touch with that.

So beyond like dimensions and feel obviously we need to better understand things like stiffness and I believe thickness was mentioned as well as potentially measuring different parameters.

And I will mention this over and over again but I believe it was highlighted and these are in the context of the metals and the additive manufacturing of the metals. So one of the properties that we kind of kept repeating was the surface roughness that exists and obviously exists in other process as well that potentially there is anisotropy and things like that that are introduced during the additive manufacturing process. And surface roughness as it applies to mechanical properties obviously is an important issue.

As we were talking more about the anisotropy and the build orientation I think we ran across more metal focused examples. So in the cases brought up for obviously materials like titanium and its alloys where there is a strong grain and growth directionality that is present and that will be the direction of the build. However with some metals obviously you have existing heat treatments and various thermal treatments that's being used to kind of remove some of that anisotropy that is introduced. However once you switch to things like polymers that doesn't really go so well. Obviously it is more material dependent consideration. But yes there are anisotropy introduced and there are existing processes that can be used to remove that, understanding that is material dependent issue.

And I think this is an important point that Steve brought up that I wanted to mention that there are some limitations in the current amount of understanding at least I think the example was of polymers that a lot of the knowledge base that exists are maybe from like injection molding or some specific techniques like that. Some of that might be informative but I think it is up to you to kind of determine. That might be a good starting point. It may or may not be applicable to your additively manufactured products. I think part of the repeating theme is that you need to gain experience with the material and obviously with the process. And you have starting points but right now at the state of the technology there is going to be gaps in knowledge and you are going to have to build on that.

And we did try to kind of span the different material, three broad material classes. I believe Greg was the one that clarified that. Yes ceramics do exist but at least the bulk of the experience has been with metals and polymers. So I think the discussion kind of skewed to that more.

And specifically metals in terms of surface post-processing I think again we touched on the surface roughness as the parameter and also the finishing that reduces the surface roughness and things like that being critical.

We somewhat finished up with some broad broad strokes. We had the time so we had the panel give take away messages. And I think it certainly does affect mechanical properties so I think it's worth mentioning. So the experience aspect just kept popping up more and more because we have a lot of new entrants to the field of additive manufacturing.

I was looking for numbers and I forget which one of you provided it but I think we were thinking that it takes two, three years to understand actually your process and the product that you are making so you kind of need to be involved in this technology for the long

haul. I'm sure that many in the audience already have that kind of experience. But I think maybe it is a message that is more useful for the new entrants to this hot field of additive manufacturing.

Again this may not necessarily be specifically mechanically related but I think there was a point made about a human --.

[Phone.]

So the last issue was the human capital. I think because it is a new manufacturing technology you might not necessarily have the people. So I think we got into some staffing issues or human capital issues as well as vendors and things like that. You have a lot of new people coming in so if you are the sponsor of a medical device using this technology I think you need to really be on top of all the existing qualification methods that you have established. But be aware that there might be less experienced people jumping into the field and it is up to you to establish control over that as you make your medical device.

I think those are the highlight issues that I had. So I think we could probably open up the discussion to the panel for additional feedback. And I am going to try to solicit at least the people with the red cords on your name tags who were not in our session to selectively come up to the mic and possibly ask questions or comments on the questions.

So I don't see anybody coming up. Well, don't be shy. We do provide this docket for a reason so you can comment.

I think we do understand that there might be some proprietary aspects to this. I think we were trying to delve into some of these questions and we recognize that some of that information might be proprietary; you might not want to share.

Perhaps -- are there anybody in the room that are making more patient specific,

like patient matched devices. I think that is one thing we didn't really discuss that much. Maybe hands or would you like to tell us maybe some of the challenges you might have had as you go through the process. I know some of the standard things don't work so well in that area.

MR. BINKLEY: My name is Peter Binkley. I am with E-NABLE. And we make prosthetics for people missing fingers or in some cases wrists. So we work on hands and in some cases forearms. And of course there are a lot of different limb differences we have to account for. And as well a lot of different body types we need to account for. We try to work that into the design with hard materials like mostly 3D printed materials and then soft materials we'll use I think things like leather and Velcro.

Sometimes we will run into issues if we make something that for example goes around the arm but it is in a hard material then you could be better off making a device that the hard part rests on the top of the arm. And the soft material would wrap around as an example. We do a certain amount of customization in 3D modeling software before the print. We also design quite a bit of forgiveness in the models that we publish so that they'll work pretty well on a variety of printers. You might need to sit down with a nail file for a couple of minutes if you are over extruding or something like that and when there are failures it is upper limbs so it is not exactly catastrophic. You can reprint the part; you can design a little bit stronger. But we've got them pretty strong by now I'd say.

DR. LEE: So for your application is there a huge range of sizes that you're trying to do with this. I kind of wonder how you tackle that issue?

MR. BINKLEY: Sure. Well we are making devices for as young as two year olds so we've got the little kids up to any adult you can throw at us.

DR. LEE: So how do you approach your testing and trying to --

MR. BINKLEY: We fit devices to individuals and we get feedback. My son was born without fingers on his left hand and he is kind of our device crusher. That is kind of his title. And he will put devices through a lot of stress, lifting heavy objects; he did some work for FEMA. They were building houses -- rebuilding houses and things like that and so he was doing some fairly heavy lifting with his device. And he'd tell me that something would crack or break and I'd bulk it up and send him a new one which is quite practical with 3D printing because you are using such a small amount of material each time with additive manufacturing that breaking things and even like breaking as part of the testing process is really quite practical.

DR. LEE: Okay. Thank you for that example.

So maybe we can move on to somebody else. Anybody else in the customizable device space?

So none of you are designing. Okay. Thank you. And please, we have plenty of time.

MS. STEPHENSON: Katherine Stephenson, Stanford University. I can speak from my experience working in the Gait Motion Lab at Lucile Packard Hospital where we were doing fitting individual customization of surgical procedures and devices on a range of patients. And one overall observation I can make is a lot of times the testing for devices devised per on a patient basis is a lot of times as expensive and as technically complicated as the actual design of the devices themselves.

I ran a ten camera motion capture system to try and document human walking motions and deviations and pathologies. And being able to find even repeatable markers on a body to be able to track deviations in motion or performance or function is highly variable and generally involves some highly trained personnel; physical therapists, anatomical specialists. So

realize in making sure that this is not -- is an automated process at this point either. Motion capture is definitely an area where we are attempting to automate it. Yet the fact that our lab still had to retain a fully qualified bioengineer to be able to run the system is definitely something that should be taken into account.

Again I am making the point about the variation in human bodies. Being able to put a marker system on a two year old, I also had to put a marker system on a six foot seven 350 pound man. And one thing we talk about is politely, not so politely, jiggle effect and what it does to measurement systems when what you are trying to measure moves around in ways that the bones do not.

A lot of thought needs to be put into that; something to remember.

DR. LEE: Thank you.

MR. KARPAS: Les Karpas, Metamason. We're developing customer C-PAP masks for sleep apnea patients. Our process is to 3D scan the patients face using a fuel 3 or structure IO scanner. And then that gets dropped into a run time where we apply smart geometry to the facial features. One of the things that we are finding is that people's faces are incredibly different. People have very different size nostrils, different size noses, people's eyes are different, spaces apart. And though the smart geometry does a fairly decent job of auto detecting this and adopting the parametric definitions as such we would like to enable either the patient or physician to be able to control elements of the features of that product. But we are very nervous about how far we can take that customization and still stay within the scope of the 510k that we are trying to move through right now because there is not a lot of precedent for that.

And then one of the other concerns that we are sort of dealing with is in a

perfect universe we would be able to have an interface that would allow a physician or patient to say I've already got this piece of hardware or this coupling and for us it is a simple module within the software, within the smart geometry to be able to couple the one machine or another machine but from the FDA perspective that would be a whole separate 510k because we are connecting to a different C-PAP machine in this case because those couplings are different. But for the smart geometry it's totally simple.

And so there are lots of opportunities to do things in a more effective and more efficient way and enable control of patient and provider. But we are terrified of pushing the scope and the limits and bounds that the FDA is comfortable with. And so any kind of guidelines within this space right now would be phenomenally helpful to us and I am sure a lot of other people in the room too.

DR. LEE: Okay. And thank you for that feedback. But obviously we are not going to address it at this forum.

[Laughter.]

But certainly I do want to give him an opportunity to --

MR. KARPAS: It is not going to get figured out now of course.

DR. LEE: Yes, go ahead please.

LT. COBURN: Well I agree we won't address the specific feedback, please don't be terrified of us.

[Laughter.]

Because much in the same way we are having this workshop we are trying to learn the best practices and the concerns of the industry and the academic players in this realm so that we can make the best decisions moving forward. And we can only do that with

feedback from you guys. And if you do have regulatory questions on a specific product or a specific process we have a pre-submission process which you can give us a submission and it is called pre-submission and that is in the regulatory context you have a confidential meeting with us and you can discuss those things outside of a 510k and it is free.

MR. KARPAS: I shouldn't say this out loud but every regulatory consultant ... SOL, I know two device ... very far south after submitting

LT. COBURN: While I can't speak to the regulatory consultant world. It seems the comment was that regulatory consultants advise against pre-submissions. I don't know why that is. In my experience and the experience of people that I have interacted with the industry it has been very positive.

Most of the branches that I know of actually welcome pre-submissions as a way to give us some advanced notice about what you are thinking about and then it can also help us work with you to decide how best to move forward in a way that is both regulatorily feasible and feasible for the sponsor.

DR. LEE: Okay.

DR. HOLLISTER: Scott Hollister, University of Michigan. I can comment a little bit. We've done patient specific implants with resorbable devices and tracheal splints. So we basically get digital models of patients from CT scans and we have software parameters that we input those and we automatically generate the designs.

I think some of the big things going forward for patient specific implants are understanding I think as Kate mentioned loading and patient specific environments that they place on the implants. We are trying to look into modeling because there is no other way to look at the deformation of the airway within the splint. We can get inhalation exhalation

pressures from the literature but knowing that for individual patients is difficult. Knowing tissue properties for individual patients is very difficult. I think those things are what we have to consider. I think we are going to have to try to incorporate more modeling because it is the only way you can really look at parameter variations on a patient specific level. And I think that is probably a good area for research.

MR. MATHERS: This isn't necessarily mass customizable the project we worked on. My name is Derek Mathers. I am from Worrell Design up in Minneapolis. And we were developing a dual flow catheter. Initially we had five concepts or whatever and then sat down with the client, he basically selected that they wanted to use four different iterations of the same design; two by two, two purposes for each catheter for two different sizes of patients. And so that came into a problem after we had done formative and agreed on okay these are the four different designs we are going to move ahead with for each of these dual flow catheters. But once we got through formative and agreed on the verification we approached validation and said how can we move forward with the production of a product and so what we did is we actually 3D printed. This is the first time we did it and now we've really gone hard with 3D IM. Printing injection molds, moving them into our injection molding press and manufacturing those production level parts 100 each so we could do all the summative testing, bench testing, animal testing, in about three or four days as opposed to waiting for the tools and all those sorts of things and saved our clients a bunch of money.

But the interesting part is using 3D printing for another manufacturing process and integrating it with it I think is something that is definitely going to -- because it is not going to necessarily displace the existing manufacturing technology we have but by tethering it with these existing technologies we are going to have some incredible applications over these next

couple of years as the -- because it is poly jet part we are using but as we can use metal quickly as we can use all these other different sorts of photopolymers I think that is going to be an interesting space for the FDA to kind of have its thumb on and at least be aware of because their production of a part and we can sterilize them after the fact.

Thank you.

DR. LEE: Thanks. Any other --

DR. DI PRIMA: Matthew DiPrima, FDA. It is not going to be a patient matched question. So in the literature of looking at the effective orientation and sort of the layering I see a lot on either static testing or there is some I'd say relatively simple sort of fatigue testing. With the industry panelists and people here is there investigations into more complex loading, multi axial fatigue really trying to get into I'd say more extensive testing of the effect of the layering process in orientation.

Thank you.

MR. WAUTHLE: Yeah, since I think it is mainly experience with metal additive manufacturing and I think yes since it is a relative new technology we've still got a lot to learn and still a lot of things to investigate and a lot of parameters that we have to investigate. But I think if you look at the number of new publications on metal additive manufacturing that is raising a lot. Recently there was a new additive manufacturing journal established also in cooperation with America Make. So it illustrates the fact that there are still a lot of things to investigate. And still a lot of interesting topics to do research about.

But in general and I would like to add to the nice summary that Mark made about yesterday's discussion. I think on this topic we're talking about right now I think there is like to my opinion two main take away messages. And they are like first question is how do you

insure that what you want to print is actually what you printed. I believe that additive manufacturing is a manufacturing method to manufacture medical devices. And it is as the same with casting or forging or traditional C&C machining there is no such thing as a zero failure manufacturing method. You have got with casting you can have defects with milling; you can have defects because of your tool that wears down. So that is not the question and I believe that you should treat additive manufacturing the same way as you do it with conventional techniques. So you have got like standards if you talk about titanium 64, ELI you've got F136 standards. If you fulfill that standard that is already a certain guarantee that you fulfill certain requirements. Of course you can do functional testing of all devices but that is not possible in practice. I believe that for any manufacturing technique of medical devices you've got statistical quality control systems in which you can monitor certain influencing parameters that kind of indicates the quality of your product. Are you 100% sure of that quality? No. But it is one system to insure a certain level of quality or a certain confidence level of quality.

But at the same time I also believe that the other questions more specific and technical questions like what is the worst build orientation or the micro structure that is related to it, what is the consistency. I think those questions kind of illustrate what Mark and Greg yesterday summarized real nicely is that it is not easy to achieve that and it's a complicated matter and is all based on experience.

So everybody can buy metal additive manufacturing machine. Can they print medical devices? To my opinion, they cannot. It is more or less the work of experts and based on a lot of experience of people that know what is happening during the processing, know what are the influencing factors and know what is the microstructure after the manufacturing, know

what heat treatment to apply to it in order to obtain or fulfill the mechanical requirements.

And that is the key -- two key things so you've got standards and quality control systems that can be used for additive manufacturing like they are used for conventional machining methods. And additive manufacturing to my opinion is also a combination of the large experience of the early adaptors.

DR. HOLLISTER: We actually have or are hoping to get published soon some fatigue data on 3D printed bioresorbable spine cages, cervical spine cages that we ran under ASTM F2077 that we did with our colleagues at UCLA. And what I'm hoping to do is we will -- because we are not a proprietary, we are academic so we'll publish our printing parameters as well as our fatigue results.

My take away from that is probably the fatigue properties when we ran them up to five million cycles depend less on sort of the build parameters per se; they are built under the same build parameters but obviously that the geometry had a significant effect. We sort of built a regular ring cage and then one we did some topology optimization on and that is I think a significant factor.

But I think -- and we brought up in the previous breakout session looking at fatigue standards. And I don't think we necessarily have to have special standards for 3D printing materials but just can we test those 3D printed devices under the same fatigue standards we test other devices although there may be some -- the biggest consideration may be some anisotropy effects.

MR. BERNAL: Andres Bernal, Bioniko Consulting. I have a general comment about the breakout sessions format. And I believe the breakout sessions in your conference has been pretty general and broad questions because additive manufacturing is pretty broad.

But there are practically three main families; FDM or extrusion, powders and photopolymers. Just a suggestion maybe some format of tracks or breakout sessions on each family because each will have more commonality and people have practically focused their research or their manufacturing in one of them. I would be more interested in specific settings or specific processes for each because what applies for powders does not apply for polymers and does not apply for FDM so it depends, it depends.

DR. LEE: And we are used to saying that actually quite a bit. It depends. So yeah, thank you for making that point. But please go ahead.

MR. KUMAR: I'm Mukesh Kumar with Biomet. To answer your original question on what kind of tests one could do for a patient specific device. So the questions becomes what is this device intended for. That is the first question we ask. So we have some experience with patient specific guides for example. And in those guides the way it is acted is the surgeon will use that guide to put it on a bone and then put the guide needle through it. So the amount of loading on something like that is very very small. There it is more about dimensional accuracy. So in the industry blue light scanning, white light scanning, or laser scanning is becoming very common in its use now. So as a suggestion people could look into that.

But also it has got to be functional for example. What is critical to quality on your device; right? So if a doctor is using it as a guide and putting it in through it but your hole is much bigger than what it should be then the hole could have a very different angle; right. So we have general quality tests that people perform with gauge pins and whatever to determine if you are in the go, no-go gauge of the gauge pin that has been designed for this particular device. So that is the first thing, a couple of things there.

The other thing is will it be mechanically strong. And if you think about how

most of these parts are made yes even though the doctor may not use any load on it but during the manufacturing process it goes through quite a bit of handling. It goes through tumbling; it goes through blasting with high water jet, whatever. So it does see a lot of forces that give you the confidence that it will not break in the OR and of course during machine validations people do tensile tests and during maintenance and after maintenance we do all kinds of test to demonstrate that the machines have come back to where we wanted it to be or where we want it to be.

To the other point that the person from Layerwise was bringing about. With metals I think it is the same thing. I mean at the end of the day, yes, there could be anisotropy. But at the end of the day let's say there is a factor within the z axis and the x axis and the y axis but as long as those axes are meeting the minimum requirement whether that be of standard A or standard B, doesn't matter, or is meeting a functional requirement it doesn't really matter if you are slightly stronger at one end or the other end.

DR. LEE: Okay. Does anybody have any comments? I think we want to try to capture as much as we can at this point. But I think maybe this is actually probably the start of a discussion. It is not really the end product. So I think he was making the point that there might be use in having future breakout sessions maybe with more focused topics and certainly that is a possibility. Just recognize that this is the beginning of the conversation.

So then does the panel have any other final comments or -- sorry, I didn't see that one.

LT. COBURN: You are over the podium so you can see.

DR. LEE: Yes, it is kind of blocking.

MR. BONINI: Julius Bonini from Lucideon MMP again, metallurgist. One thing I

forgot yesterday for the session regarding whether you verify what you plan to make is what you get the very unique aspect and benefit of ALM materials for medical implant applications has been this porous coating. You can create this unique porous coating that has this great structure that will allow us to integrate better than the conventional ones. The problem is how do you validate you are getting what you asked for. And the typical thing in conventional devices is to use ASDMF 1854 for wire bead or anything else which we can apply. When we see your porous structures, the ALM stuff, it looks nothing like those. And we can't even apply 1854, the best thing we can do is measure the thickness and say, that is the thickness. But everything else we can't. I think it was Andy Christensen who has some information about what ASTM is doing. Is ASTM looking at that as well in any way shape or form? Is he still here?

MR. CHRISTENSEN: I don't know the answer to that question.

[Laughter.]

MR. BONINI: Great.

MR. CHRISTENSEN: I do think is the one standard you are referring to though for porous surfaces?

MR. BONINI: Yeah.

MR. CHRISTENSEN: So in our experience it has abrasion as one of the tests in it.

MR. BONINI: Right.

MR. CHRISTENSEN: Those kinds of things. I mean we've seen customers take and follow that same standard for porous surfaces that are additively manufactured even though they are not coatings but follow the same standard. I think it is a safe thing because you are probably could 3D print things that wouldn't meet that abrasion standard say for particulate debris. And it is something that there is no reason why we shouldn't follow the exact same

standard for that purpose.

MR. BONINI: That part works well.

MR. CHRISTENSEN: Yeah

MR. BONINI: The abrasion and tensile strength whatnot but it is that cross sectional evaluation of the amount of void and how thick and what the surface is, that just doesn't apply. And I think ASTM needs to work on --

MR. CHRISTENSEN: Somebody that works with me might have a better answer here.

MR. ROBBE: Hi, Nick Robbe (ph), 3D Systems. Can I ask -- they are wanting to evaluate morphological characteristics of the porous coating?

MR. CHRISTENSEN: Yeah, right.

MR. ROBBE: Then instead of evaluating the part you can build like a test coupon of the porous structure so it is large enough that you can evaluate those. You are right you need a certain size sample to do stereology or micro CT or whatever technique you'd like.

MR. BONINI: It is still very difficult. I think and maybe we should get involved with the ASTM committees more and see if they can get something directly for ALM because the structures we see are so different than plastic wire bead.

MR. ROBBE: But still it is a pore size, strut size volume porosity. It has got to be able to be measured.

MR. BONINI: Yeah.

MR. ROBBE: We do it for several customers.

MR. BONINI: Good.

MR. ROBBE: Maybe we can talk off line.

MR. BONINI: Great. Thank you.

MR. BOLT: Kind of addressing that same issue. You mentioned ASTM and Standards. ASTM does have a committee F42 strictly for additive manufacturing. I would say if there is a need, an industry need for a standard, specific test methods that are not addressed by existing standards that whoever is interested join F42 and propose new work items to do this because that is the forum where you are going to get all the people involved in the test method element.

DR. DI PRIMA: Matthew DiPrima FDA. I actually have a follow up question. So FDA has a porous coating guidance and I was wondering if for people printing porous coatings if there are challenges specific to additive manufacturing in complying with that guidance.

DR. LEE: I am not seeing anybody volunteering. Do the panelists have any comments on the question?

Okay. We will just leave that one for the docket then.

Just pointing out that the commenting period I believe ends in what November, end of November. Yes, 30 days. So you do have sufficient time for those in physical attendance as well as video.

So with that let me just thank the panelists and the audience for their very useful contributions. Thank you.

[Applause.]

BIOLOGICAL CONSIDERATIONS OF FINAL DEVICE: CLEANING, STERILITY, AND BIOCOMPATIBILITY BREAKOUT SESSION OVERVIEW

LT. COBURN: I'd like to ask the panelists for the Cleaning, Biocompatibility, and Sterility Session to come up. One, two, three and I believe Dr. Yoo wasn't able to say for this

day. Nope there he is.

I will also go through the questions again. Are we good? All right.

We had an interesting panel yesterday with our four panelists, Dr. Yoo, Bill Brodbeck, Ed Kanegsburg and Jayanthi Parthasarthy, no, that was close. I'm sorry. Let me get this right. Parthasarthy, yeah.

DR. PARTHASARTHY: Parthasarthy.

LT. COBURN: Okay.

DR. PARTHASARTHY: J, that is fine.

[Laughter]

LT. COBURN: And J.

The questions that we asked related to these three topics. There were four questions so one of these topics got two questions.

Are standard biocompatibility and IO tests sufficient to determine bioactivity or biocompatibility of additive manufacturing materials? You can already see that these questions overlap with some of our discussion that we've had today.

How do we verify that sufficient excess material is removed from complex structures including post-processed contamination?

How do classic sterilization methods or do classic sterilization methods need to be adapted for 3D printed products? We had several different examples or sub-questions under that.

Lastly how does sterilization affect the device material characteristics and performance?

Rather than answer all the questions in order I consolidated some of the

feedback because it ended up being very similar for different questions. And we came to the conclusion that there are a few unique challenges posed by additive manufacturing but only a few.

And that for many of these topics, sterility, biocompatibility, and cleaning many if the standard approaches and standard metrics still apply. However, you may need to use different methods or find another way to get at the standard metric. So if you are using a standard and you have to meet a specific criterion then you may not be able to do it in the standard way. And to get at that we discussed using a risk based approach to define your testing and the levels of testing that you need; and then also consulting obviously the consensus standards, FDA guidance, best practices and recommendations.

Lastly to be familiar with the most likely points of failure in your device by doing something like a failure mode defects analysis or some other method of looking at your device critically both before you create it and then as you're making them and testing them.

These will allow you to access the different aspects of the device which we get to in the next point which is complex geometries enabled by additive manufacturing do actually create challenges to biocompatibility, sterility and cleaning. Again standard metrics apply but when you have some sort of a torturous channel, if you have a deeply porous structure the ability to get into that structure and inoculate it for sterility testing or clean it effectively or determine that you have cleaned it effectively is not always very easy and it not always very straight forward. So those are the challenges that one has to be aware of when making an additively manufactured device. It is not necessarily that the device or the process itself makes things not apply to the standard but that the new things that you are doing with the device and the new things that you are doing with the printer allow you to have these factors you have to

take into consideration.

Another theme that came up as has come up quite a lot is that validating your cycle at the most probable locations of failure is extremely important. Again in the case of sterility it would be inoculating the most difficult to sterilize location; for cleaning it would be to insure that the deepest crevice or smallest tunnel or smallest passage or smallest pore is reached by your cleaning solutions and then, of course, that your cleaning solutions are removed.

We had a couple of comments about when cleaning you are using surfactants and solvents to remove material. Then, of course, you have to use a different solvent to remove the solvent and the cleaning material. And sometimes you need to use another solution to remove that third solvent. So it is this iterative process but you have to insure that all these steps meet again the same standards.

One point came up this morning as well as in our session was that the biocompatibility data for existing materials is not easy to come by and that seems to be a gap that users have. That is a gap that as a group here with industry and academia and the players in the industry that there may be some synergy to fill but we were not able to come to an easy solution at the breakout session. One of the comments about this specifically was that for polymers biocompatibility is sometimes reported in say a monomer but not in the polymerized state so there is that gap. So then the point, of course, was made that testing has to be done on the finished products as well so if biocompatibility data isn't readily available testing the finished product as is will help provide some of that data.

Back to some cleaning, the intricate geometry as I mentioned makes cleaning more difficult. Some of the variety of methods sonication, powder blasting, using solvents and

surfactants came up again. Because of the general nature of the session there wasn't a specific part to that. The porosity of a device may be changed with different kinds of techniques you are using and, therefore, may change the ability to clean or remove cleaning solutions from your device. So that was a point.

So that brings up the point that device designers should account for this cleaning process when they are designing the device so when you are making this torturous path, you are making this crevice porous structure on the outside you should be aware that cleaning has to be done, that there are certain limits to what cleaning can be done and work with your total product team to make sure that you meet all the standards and meet all the limitations of all the other processes.

So this is a little bit different I guess than traditional manufacturing in that the processes are a little bit more defined. This is just removing some of the design limitations and, therefore, making it more incumbent on the designers to be aware of where they are in that process and where the limitations for the rest of the manufacturing process are. One of the comments was that that doesn't only include outside contaminants and bioburdens that are brought in or machining oils that are brought in but also residual powders and residual monomers that are part of the manufacturing process.

Lastly one of the questions was about how does the sterilization and cleaning process change the device itself. And it was agreed that sterilization and cleaning can change material especially when oxidation or different kind of polymer effects occur. But this is not specifically an additive manufacturing concern. And really it gets back to this knowing your process, knowing your device and that the ability to make rapid changes in your device or rapid iterations in your design process makes it all the more important to know the pressure points in

your system, to know where the failure modes are most likely to happen and to define those so that you can check for them throughout your design, cleaning and validation processes.

I think that was basically all we got. I would throw it to the panel to see if they have anything to add.

DR. BRODBECK: I think one thing we really didn't discuss in too much detail yesterday that I put some thought into after hearing some discussions earlier today is when we were talking about unique devices per patient where it's a customized device what kind of challenges would that provide when we are talking about sterilization or cleaning even. And any thoughts on that would definitely be helpful.

But my one suggestion obviously would be work with FDA as well as your design team to figure out okay what is our worst case scenarios, try to get a bracket going. If you have customized devices, you are not going to be able to figure out every single possible scenario but hopefully you can encompass that in some type of bracketing in your studies. But any other thoughts would definitely be interesting.

DR. KANEGSBERG: That brings up a good point because with the additive manufacturing you can probably bracket a little more easily by actually making parts at the ends of your bracket as well as in the middle and testing them with relatively low cost of actual manufacturer. So that might be a good way in the development stage of testing. Change the porosity for instance and where the details of the design and do your worst case both large and small.

LT. COBURN: That is a good point. If I can summarize to make sure I've captured that right. Is that you would say that in this bracketing that you would produce a part that meets your minimum tolerance and your maximum tolerance as well as producing the parts as

intended. And then test on those because in additive manufacturing you can actually do that more easily.

DR. KANEGSBERG: Right. Or even go outside your minimum and maximum tolerances just a bit, give you that extra margin.

LT. COBURN: Great. Now I would go to the audience. Again all the feedback that you can provide here really helps inform our decision making processes, our thoughts processes and any feedback you have on these aspects especially from the people who are in the red lanyards who were not in the discussion.

DR. HOLLISTER: Scott Hollister, University of Michigan. I wasn't in the session. But a question I have and maybe it came up in the session was obviously we have these raw materials that are being handled, that are being put in the machine, they are being built into a part and they are sterilizing the part and especially if you have resorbable material are there other standards to look at or ways to test or want to test sterility during the whole process and how do you address those issues from the raw material on up?

DR. BRODBECK: That is a good question. I guess from our standpoint and well at least where I am at it would be useful information to know throughout the build of the device where your sterility stands. Obviously our main focus is end device. I mean is it the final device because that is all that matters to us. I am not going to say -- I am not speaking for FDA just to clarify. But is the device sterile? And there might be easier methods for components, maybe not, but really you have got to devise and develop and verify and validate your methods for final device. Is that final device sterile? Prove it and is it reproducible?

So although and if you are having consistent failures then definitely look at the components and try to determine where your failure is. Do a failure investigation of the

components. But I think final device is definitely the most important.

LT. COBURN: That does bring up a good point that came up that I did not put in the summary which I probably should have. That Dr. Yoo did mention for in his case where he prints biologics and you can talk to this a little more if I miss any points. That in his case sterility is important throughout the entire process. And most or a lot of that has to do with the fact that he will print cells. So obviously a cell coming on a non-sterile material is a lot more impactful in that kind of process.

DR. YOO: Yes and in addition well you know that is when you print cells and you plan to implant it in vivo. However, we sometimes print biodegradable or polymers alone and use that as an implant. And when you implant it you do expect the material to degrade over time. And the final product may be sterile but, however, as it degrades if there are toxins or contaminants they would be released as the material degrades over time. So that is why testing final product is important but also testing -- sterilizing the raw material is also important as well as the entire process.

LT. COBURN: Thanks very much.

MS. KANEGSBERG: Barbara Kanegsberg, BFK Solutions again. Since I wasn't in that session and since some people are sort of confounding sterility and cleaning from comments that I've heard the best analogy to make if I could take a second if say you put devices in an autoclave and you open the door of the autoclave and you find a mouse. You then have to pick up the little mouse by its tail and look at it and you say maybe it is sterile but you still have to remove that little mouse from the vicinity of the devices. And soil itself can interfere with sterility. It can also interfere with performance of the devices and if there is out-gassing or if there is leachable residue it can do things like kill the host which is not pleasant.

In the case of implantable devices that are done by additive manufacturing the removal of particles is something that I think we need to consider carefully in both how we do it and how we demonstrate removal of particles. So in my experience particles keep leaching off of the parts. And you can clean, you can clean five or ten times and then if you switch to a different cleaning agent maybe one that is less or more polar than what you've used you'll remove a totally different selection of particles and the number of particles will jag up, the particle level will go up. And then you have to keep going again and again. And so how do we assure that we've removed all the particles? Do we assure? I guess that would be for Jay or for Ed or anybody.

DR. KANEGSBERG: Well I don't think you can assure that you've removed all. You do have to again as Barbara mentioned you do have to make sure that you assess the risk and determine okay what is going to be an acceptable level. Keep in mind that once this device has been implanted it is there, it is there for the duration, we certainly hope, and so you want to make sure that either the rate of leaching of either organics or particles is at an acceptable level or that the total amount over time again that goes into your risk analysis.

DR. BRODBECK: One of the things that we talked about yesterday is we were talking about extractables or leachables from the devices that the way we resolve that through the ISO 10993 standards is through exhaustive extraction. And really what that is supposed to capture is whether or not in a simulated environment with the experienced in vivo are you really getting everything out of that device through the exhaustive extraction. But it is not going to be 100% one-to-one ratio here. So you really have to devise your experiments or your verification studies to really simulate what you believe that the device is going to experience in vivo. And, therefore, obviously we have as we talked about different vehicles for the

extraction, et cetera. But we just have to be practical. We have to make sure that we are actually doing what we intend the device to do inside the body; what it will be experiencing.

MS. KANEGSBERG: So Brodbeck I'd sort of like to build on that a teeny bit. The 10993-17 or 18 are more geared toward the toxicity of -- it is more thin film, it is more geared towards things that we've done toxicity studies on animals and we know is a poison. Particles are a little bit different and in some cases I think so that just the presence of them you don't want the physical particles there. Might we be able to still adapt the risk approach that they use? I don't know. Or maybe show that you've used more than one solvent because if you do exhaustive extraction with a solvent that is not taking the dirt off you haven't quite gotten there.

And I guess I am concerned because some people who might be with the FDA who have been asking for assurance and I'm not sure I can give anybody absolute assurance. I don't think anybody can. Just --

DR. BRODBECK: No, that is a very good point definitely. The exhaustive extraction is step one. Identifying what comes out of that extraction is another step that should be something you identify elsewhere where there'd be a risk analysis etc to say these are potential leachables; this is what we need to test for; and set it up that way. But just using the exhaustive extraction as the starting point in order to try to get something and obviously expanding from that; try to figure out again what is the most practical. And if you use everything that you possibly can and you still see nothing then you have to rely on long term biocompatibility studies or your implant studies to determine whether or not -- you are not going to determine whether or not something is leachable or what is leachable, you are going to determine whether or not something that is leachable is causing an adverse reaction. So I

mean you have to address it one way or another.

MR. BOLANDER: Thomas Bolander from UTEP. I also wasn't in that discussion yesterday with part of it. And you brought up a point earlier saying looking at monomers. Now a lot of people who do photo polymerization the monomers are often very toxic obviously for obvious reasons. And I think very few people probably propose to actually photo polymerize the device. They would have to make sure there is no more monomer in there. But let's say somebody would like to photo polymerize a mold for a device. What do you think and there was concerns that maybe ANO active monomers are now in the final device that leach out from the mold into the device and shouldn't that be some biocompatibility testing actually off a molded device and what are your thoughts about that?

LT. COBURN: Panel?

DR. BRODBECK: I don't want to keep on talking here. But anyway that is a very good question. Yes I think well first you have to hopefully we all identify that in your final device if there is a monomer in your device you are going to find that through your A taxus siphon -- pardon, toxicity studies. So toxicity studies very early on will identify that and hopefully through a logical approach or risk based approach or failure investigation you'll find out where the source of that toxicity is and can trace it back possibly to the mold. And, therefore, obviously employ some type of cleaning or some additional aspects to your mold in order to come up with a final product that is free of the potential toxin.

MR. KUMAR: Mukesh Kumar with Biomet. I think I heard three things over here, porosity and cleaning, particle leaching and of course sterility. So I am going to try to see if I can address some of those points over here.

So in the medical device industry resorbable polymers have been around for

about 15 plus years now. And normally in my experience raw materials are never sterilized. And of course in the industry we have not seen that not sterilizing the raw material or every step of the process causes any clinical problems. What is insured is that you are manufacturing it in a relatively clean environment so you are not doing it where there is a dust storm going on. You might know that. But of course the final device is always sterilized. Whatever it is the right method of sterilization or whether it is ETR or hydrogen peroxide or gamma, whatever that is to be decided.

On particle leaching at least from my experience on metals I've noticed that most of the time you can clean it out with mechanical agitation with maybe some supplementation of say ultrasonic and water. But most of the time with blast of air, blast with mechanical agitation, ultrasonic, ultrasonics in some kind of liquid like water or isopropyl alcohol does take most of the particles out at least on metals. I do not know about resorbable polymers; I do not know about polymerizable polymers and cannot attest to that.

The last question that I am going to address is about porosity and if you change porosity what happens. In our opinion if you change porosity you have changed the device and that is a completely different -- I mean I might let FDA answer that but in my mind it is a new device; we'll have to do a new submission. So we know from the FDA guidance document that you have to be within this parameter, I don't remember the exact numbers, but there is a range that is allowed in that guidance document and that is where we stick with it.

LT. COBURN: Thanks very much. Dean you've been waiting.

DR. DEAN: David Dean, Ohio State. Just picking up on the question of porosity a lot of discussion of porosity is surface porosity or through and through porosity and this is a discussion that is a very clinical topic. Like talk to physicians, they'll be very familiar and have a

concern about surface porosity as to whether it is going to produce a biofilm which could then become infected. And the thinking about the sterile field just from the point of view of you are giving them something sterile, maintained in the body but then the infection can come from within the body itself so we've lost that. It doesn't matter anymore because we've created a site that can become infected.

And the same thing can be with internal porosity. The internal porosity that only fluid can get to bacteria and virus that is called a cyst. So we have to be very careful when we are 3D printing about creating spaces that the immune system can't reach.

LT. COBURN: That did come up a little bit in the discussion. I am glad you brought that up again. Where parts can be fully dense or not fully dense, they can have a residual porosity, they can have a design porosity and knowing what your part is again is integral to this process in that you have to know what you intend to print, know what you have printed and then analyze that based on whether or not it can be reached by fluids, if there is a diffusion gradient that is different than a standard material or different than you expect.

And I'd like to go back to the things that we mentioned earlier which is the things like a FMEA where you're identifying your failure modes and what those are based on your specific device. Or you can use a phenomenological identification of risk type of approach, PIRT, P-I-R-T, and that really allows you to take into account a lot of these phenomena for your specific device and then be aware of them and be ready to test and be ready to analyze them when you get to the stages of that process.

MR. WAN: The previous comment was a good prelude to my question. Jason Wan, NIH. What are people's thoughts on incorporation antimicrobials into the products?

UNIDENTIFIED PERSON: Combination products.

LT. COBURN: Panel? I defer to them.

DR. BRODBECK: Well being part of a sterilization company I think it is a terrible idea. I think you need to sterilize it.

[Laughter.]

So, no. I think it is a good idea. It is definitely a combination product. I don't know how it is currently viewed. I know we were looking at that from one of my previous past lives. And there is a reason why it is previous. But I'll defer that.

LT. COBURN: I will also defer on what to do about antimicrobials but if anybody in the audience or attendees would like to comment on their thoughts about that specifically remember one of the things we are looking at here is how does additive manufacturing change in adding something like an antimicrobial to the process. So is it any different than adding it another way?

DR. YOO: Yeah, you know there are products or studies that have incorporated antimicrobials into devices, implantable devices especially for like orthopedic areas where infection cannot be controlled so those are controlled release products that antibiotics or other growth factors may be released over time in a controlled manner. So why not?

DR. KANEGSBERG: I think that it is a why not. But again it would be basically a new device and the same would go to someone putting on a some sort of a nano coating to make the device hydrophobic so that it doesn't have to be cleaned. There have been developments in that area but I don't think we're quite there yet. But again it requires a lot of knowledge of what you are doing especially knowledge of what you are not doing.

DR. BRODBECK: One other thing to consider there are I know different surfaces that have claimed to be antimicrobial so that is one thing. But as soon as you introduce

anything within the device itself and you still plan on terminally sterilizing that device that just brings up another point to consider if you have antibiotics in there you can't really use steam or heat or anything that is going to denature that. So it is definitely a good idea. Whether or not it is feasible at this point?

LT COBURN: Is there a comment from the audience?

MS. STEPHENSON: You have a patient gentleman over here.

MR. BONINI: So again I'm -

LT. COBURN: Behind the podium. I couldn't see.

MS. STEPHENSON: Are you going to a different topic?

MR. BONINI: Yeah.

MS. STEPHENSON: Okay. Well I do have one short comment on this. A long one I'll take after yours.

LT. COBURN: We have one over here too.

MS. STEPHENSON: One possibility that additive manufacturing -- sorry, Kate Stephenson, Stanford University. One possibility additive manufacturing does is allows you to actually integrate things like surfactants and antimicrobials into the build process itself. This is particularly interesting if you are looking at resorbable materials. You could have staged releases as the part dissolves away inside the body which is not something you can do in injection molding. So you can actually affect your print orientation so you have very discrete bursts of exposure.

MR. BONINI: I want to go back to the particle discussion. Julius Bonini, Lucideon MMP again.

LT. COBURN: Before you go back to the particle. Do you have a comment on the

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MS. STEPHENSON: It can wait.

MR. BONINI: Particles are a big issue for us and specifically for titanium and metals. Much like you every time we ultrasonically clean we collect more particles. I've not had -- well let me preface this statement most of the devices we've seen that are brought in that are ALM we can continue to look at them, I've got pictures of particles that will scare you. The one time we don't see it is when the parts are HIPped afterward. And I think Ernesto from the company EBM and then applying HIPping afterwards I think that is a great idea. And if I can send a message to the FDA in this greatest of all worlds as Matthew was asking for if I could send you a message is require titanium ALM porous coated devices to be HIPped. That will solve 90% of the shedding problem. My colleague still thinks he can get a few more out but that will solve 90% of the problem right there.

The cleanliness issue is the other one and this whole discussion about cleanliness is great because it convinces me that you guys are on the right tract. You are addressing this issue, it is an important issue. These porous coatings are very unique and addressing it this way is a good way to do it. And you are all on the right track.

And adding the shedding particles to it is another aspect of it.

MS. VORVOLAKOS: So I am wondering if people have been in a standard way or non-standard way incorporating particle aggregation studies into their protocols. For example if you take two hydrophobic surfaces and you bring them close together in air they will stick to each other. But if you do that under water, let's see how do we do this, so if you take two hydrophobic surfaces put them under water and bring them close together they will spontaneously stick to each other at the exclusion of water, there actually will be a cavitation.

So there might be some simple tests that folks can do. You can have a battery of washing media or solvents or whatever, take the kind of particles that come out of your device, sprinkle them in there if they aggregate that is probably a bad idea, a bad washing medium. If they tend to disburse, it means that they are wettable and that the medium can get in between the particle and the surface of the device that you are trying to remove it from.

So just an idea.

LT. COBURN: Thanks so much. I think Reuben and then back to Kate.

MR. WAUTHLE: So my name is Reubin Wauthle from 3D Systems Layerwise. I would like to comment on the suggestion to HIP porous structures. I've been doing my PhD on porous metallic structures and I do not agree and I don't think we should fully discuss this topic. I would like to discuss this after this session with you.

LT. COBURN: Sorry, Reuben, before you go back you said you don't agree with which part?

MR WAUTHLE: With HIPpig that that is necessary to make sure that there are no particles that come loose.

LT. COBURN: Thanks for the clarification.

Then Kate?

MS. STEPHENSON: Kate Stephenson, Stanford University. A lot of emphasis of the discussion has been on final products, use of additive manufacturing in final devices. A significant part of additive manufacturing's value is going to be part of the design process during prototyping and so I want to get insight on potential other situations for example animal clinical trials.

A lot of times you will take ESA laser early prototypes into an animal trial for

testing in which case you are under the review of an internal review board. And I wanted to know if you had any feedback or insight from bringing additive manufacturing devices or prototypes into animal trials and dealing with the printing protocols that involve those devices?

LT. COBURN: I throw it to the panel first?

No special insights from the panel, then the audience. Do you have a --

MR. KUMAR: No I don't have an answer to her question. I was going to address --

LT. COBURN: Let's try and answer the question first and then we'll --

DR. DI PRIMA: Matthew DiPrima, FDA. There is a lot on sort of the clinical trial approval process going on at the FDA. We have an entire enterprise group right now working on how to simplify and clarify what is required for the FDA approved pre-clinical trial.

If your study doesn't have to go through the FDA and it is just under the purview of the IRB I think the best you can do is point to the FDA guidelines for what we do require for the FDA regulated clinical studies. But if your clinical study just goes through your IRB that is unfortunately really going to be just between you and your IRB.

LT. COBURN: Thanks. And I guess also you were asking about animal studies too which has I am sure a different aspect. I am not personally an animal testing person so I don't know much about the rules that go into that so I won't talk about those.

If anybody has any specific comments on the animal part in sterilizing cleaning for animal tests?

No specifics. Okay.

MR. KUMAR: So to address the question on HIPping. I have had the luxury of evaluating additive manufacturing for metals for quite some time from different technologies.

The question is not whether you need to force HIPping on it. The question is how do you design your pore structure. If you evaluate your particle size, and if you evaluate your pore structure, and if the pore is bigger than the particle, there is a way to take it out. The way to take it out is you have to figure out how much energy you need to put in for an ultrasonic or some kind of vibration or energy method that dislodges the particle. I think the lady over asked the cleaning lady had asked the question how do you demonstrate that porosity has been cleaned of particles. I mean there is x-ray method; there are micro CT methods that we have used and can be used to demonstrate that.

The problem with HIPping is if you rely on HIPping as a method to ensure that particle doesn't come out then you are also insuring that you are occluding your pores. So I would rather say that clean the particle, design your pore structure, remove it with ultrasonics and you don't have to rely on HIPping.

LT. COBURN: Thanks very much.

It does seem like there is some contention about the methods and ways to clean which I think is actually a really good discussion to have though I don't know that this is the forum to have it. But it is something that obviously everybody here now is well aware of the intricacies of cleaning your products especially if you are doing something with porous coatings or torturous tunnels or any kinds of channels like that, therefore, you should really be aware of your design of your product and examine your risks, examine the design and then examine the protocols that you are using subsequent to those examinations to really get at how much cleaning do you need, how much cleaning can you do and then how do you accomplish that.

So while we won't necessarily find the answer to this is definitely how you do it I think we have established that those three things are the important aspects of it.

MS. KANEGSBERG: Barbara again. I hope we haven't beaten the subject too much to death. I think I'm a little concerned about what we don't know yet. And I'm learning more and more about what I do not know about particle removal. I think we have to, all due respect to the proponents of water and isopropyl alcohol, they are both fairly polar solvents and there is a limited ability to wet the surfaces. So for metals cleaning we may need to look at the density, the surface tension, the viscosity a bit more and just be a little bit more creative in what we do use. It is partly design, it is partly the pore size, but it is also the particles getting trapped and sticking to surfaces.

There wasn't a question in there but I did have a question, different question. I know in PhRMA we're looking at life cycle, you are looking at life cycle, you in general, not you personally but you in general of the FDA. Any thought about that for medical.

LT. COBURN: Are you talking about total product life cycle?

MS. KANEGSBERG: Yeah, basically life cycle in the sense of design, development, pre-validation, validation, monitoring, revalidation. Sort of a vicious cycle of -- they are talking much more about that in PhRMA. I wondered if that was in the works for medical and how that might be appropriate for additive.

LT. COBURN: I personally actually don't know exactly what is going on in that arena. But I can say that from the discussions we've had here we can say that the experts that we've had on the panel and then from the audience agree that validation is very important for all aspects of this process. So it seems like that is a very important part based on the feedback we've gotten here.

MR. MATHERS: Derek Mathers, from Worrell Design. My question is for Dr. Yoo. Do you see sterilization being a hurdle for the commercialization of the skin and living tissue

process? And what components do you really have to think about in terms of sterilization of that machine as it proceeds that are going to be essential to it being widely adopted?

DR. YOO: Very good question. Sterilization should not be a hurdle. So your final product is like any cell based products, like tissue engineering products; so because your product includes the cells obviously if the material -- your end product is toxic the cells will die. So it prescreens itself. But I do think that sterilization during the process is very important. I think as far as the final product is concerned it's pretty similar to other cell based products.

LT. COBURN: Thank you very much.

Are there any other comments or questions from the audience?

MR. HOROWITZ: Eric Horowitz, FDA. I have a cleaning question for kind of the room that is from a slightly different prospective. Has anyone had any experience with what potential residues there may be specific to the different types of additive manufacturing processes that are important to incorporate into your in process cleaning to insure that subsequent post-processing like machining or polishing or anything like that isn't adversely affected?

LT. COBURN: Okay. Thanks. It is a question about specifically to additive manufacturing what residues should be incorporated into your analysis for in process cleaning.

Comments from the audience? I see one, possibly two.

MS. KANEGSBERG: You know that is a great question and I would say that additive -- it's not just additive. It's additive as a function of the fact that you've got -- it's basically a product where you have a lot of surface. So there is just the potential for more things to get stuck. And it is not necessarily that it's a whole new beast, it's being a little more, I hate to use the word mindful, it sounds like I should be doing a Yoga class, but you really do

have to be a little bit more mindful of planning the processes, thinking what might be there.

I think certainly particulates and NVR are the classic ones. But then you have to go on and speciate and it is just like anything else. It is not a whole new beast.

LT. COBURN: Okay. Another comment from the audience.

MR. HIGGINS: Come on, Barbara, you're killing me. 3D printing is supposed to be making things easier; right? I am just kidding.

I'm Sean Higgins from Boss Instruments. We make mostly all reusable stainless steel, titanium things, they are all cleanable. And we do a lot of cast titanium which almost always gets HIPped and almost always gets sealed. It is additive but it is not 3D printing. I think a lot of the same things, Ed Morris, kind of nailed it you still are using the tool. I think the moniker printer got put on this and it makes us think plug and play and everyone just things -- it is still a tool. As he said you need to know how to design your part properly.

If it is going to get sterilized and be used, the same principles apply. You still need to just use common sense. You're not going to replace a designer who knows how to get something cleanable and that is why all parts in the OR are still very simple.

Like I said we have 20,000 something individual SKUs we don't revalidate every time. I mean we put through a validation cycle, basically set a standard vice grips, looks like standard vice grips but you base the fact that you can get that clean and sterilized in a hospital and then people consistently reprocess that and we kind of keep in mind that we are dealing with the FDA and they are reasonable people, so if we can show you a validation for that and then we can show you a simple hand retractor that has much simpler surface area we are not going to go back and reinvent the wheel or reinvent the new coating process. I mean the same things I think still apply to 3D printed parts. And you are not going to make a Sparspel plastic

part FDM and then think you are going to autoclave it and sterilize it because you've just made a water balloon of bacteria. So you've just got to start using the common sense and I think understand your printer, your platform, and what it can actually be used for and just design around that.

LT. COBURN: Thanks very much. One more, yeah.

MR. KUMAR: To answer your question on -- this is Mukesh Kumar again with Biomet. I think I am hogging the mic over here. I feel bad about it. But anyway to answer your question the industry, medical device industry at least in the metals work we have been machining porous structures for quite some time. And the way we go about figuring out in what like for polishing compounds or whatever we have, what materials will be used to dissolve this. And so let's say you have acetone or isopropyl alcohol or whatever that is; that is the first thing that we do. Once we know how to dissolve it there is a way to take it out. How do we know we have done that? The STM standards on cleaning is quite extensive. It tells us to look for these parameters which we do that and then it tells us how to demonstrate that our parts are clean.

So I see in additive manufacturing no other difference. You are still making a porous structure, still machining it at the end of the day, you are still using the same polishing compounds whatever and you are evaluating with the same STM standards.

LT. COBURN: Thanks very much.

Well I think that will bring our session -- oh wait, one more comment.

DR. DI PRIMA: Sorry, James. Matthew DiPrima, FDA. A lot of the cleaning discussion has been on metals and powder based printers. So I am really curious with people doing SLA and DLP printing when you pull it out of the vat how do you make sure you have all

the excess material removed. I realize you can just throw it in a UV chamber and cure everything on there. But if you have features you are trying to pull out and you want to make sure all the excess material has been removed from there?

Thank you.

LT. COBURN: Thanks so much for that. Follow up comment? Please.

DR. DEAN: David Dean, Ohio State. That is a challenge. We are always fighting to get enough green strength of the part coming off of the plate so that we can handle it and it can survive as we were talking about before what kind of cleaning can it survive. So are we going to use ultrasonic alcohol bath or air to blow it out because we can't leave the unpolymerized polymer in there during the post curing that will fill in all the porosity we've tried to render. So that is a struggle and we also have to worry about polymers drying if we are using alcohol or acetone as that vaporizes it is going to make the part more brittle or start degradation or those kind of things.

So those are -- it is a big struggle.

MR. CHRISTENSEN: Andy Christensen, 3D Systems. We have some experience with stereolithography so it's a good question and it takes validating a good cleaning process to remove the residual material. And in case of SLA it is residual resin that is on the parts and typically you are not curing before, you are using some other solvent and then you've got issues of solvent and getting a solvent off. So you go through and you validate a process to provide that you have a part at the end that is solely the material you want it to be which in most cases is the resin that it was supposed to be made in but without extra resin encasing it.

LT. COBURN: Thanks very much.

Well I think that will bring the session to a close. I appreciate the comment that

the FDA is full of reasonable people.

[Laughter.]

And I appreciate the participation of the audience and I would like to thank our panel members.

[Applause.]

DR. DI PRIMA: All right. So we are actually a few minutes ahead of schedule unlike yesterday. So we are going to go to a break for lunch and we'll reconvene at one o'clock.

And at one it is going to be a little bit different because it is just going to be some FDA people sitting up here and we are going to be talking about where people see technology going and what is sort of the next technology hurdles are going to be.

So thank you. And we will see you guys at one.

LUNCH

DICUSSION AND FUTURE TECHNOLOGIES

DR. DI PRIMA: This is the future technologies and discussion section. So this is going to be a little bit different than anything else we've done so far.

So it is just going to be FDA people sitting up here and we have some questions for the audience about future technologies and technical limitations that you either think need to be addressed or you are working to be addressed. And we are hoping this is going to be a little bit more of a fun conversation.

Again please let me emphasize no policy. We are not going to be talking about specific submissions or applications. We just want to get a sense of where the technology is going to make sure that our thoughts and efforts are aligned with what everyone else is doing.

And again I want this to be kind of open and fun and an opportunity for you to

really get to interact with the FDA.

With that do we have the first question ready? Almost. It is in SharePoint.

People are coming in and we are having some software version issues which is kind of ironic after all the talk we had this morning about inoperability and validation. No, we are good.

LT. COBURN: Yes, my computer is not responding at the moment. Give me one more second, figurative second.

This one is going to be a nice broad question. I know how everybody here has chastised us a little bit for asking broad questions but I think this one will be more amenable.

The question is where do you see, you being the attendees here, 3D printing being in two to five years. So in two years what do you think will be done in 3D printing and in five years where do you think we will be with 3D printing. Obviously we see a lot of the hype through different kinds of media but we are talking technical reality, two to five years.

MR URDANETA: Could you clarify in terms of capability or in terms of what's in the marketplace?

LT. COBURN: I would say either. But I would say capabilities is probably more relevant to this discussion.

MR. URDANETA: So, Mario from Weinberg Medical Physics. My last name is difficult to pronounce, don't worry about that.

So based on conferences and such that I have attended what I've seen is there is a push towards multiple materials. So you will start seeing, we can already see different colors and different young modules and things like that. You are also seeing machines that are bigger. I saw an extrusion machine making chairs. I don't know why you would do that but

you've seen that.

And myself as well as other smaller entities I think more in the five to ten year range you are going to see technologies coming out that incorporate multiple processes within the same machine. My particular case I have some free form fabrication and then some laser sintering and then some spray coated, things like that within the same machine. There are different groups and various universities that do that and they also add components as the machine is being built.

So I see that is what I have seen in my experience.

LT. COBURN: Thank you very much.

Any other perspectives?

MR. BULLEMER: Martin from US. Probably I can add to that a little bit. If you look at the marketplace you definitely will see very much increased marketplace for additive manufacturing. So you will see new OEMs out there, coming up with new machines also with what we call hybrid manufacturing which has been mentioned here; so combining technologies. That will change a lot because you will have different questions again here on that podium like how do you handle the milling and laser sintering machine at the same time?

When it comes to the established players who can see right away if you walk through the enormous show that at the moment the tendency is to have way bigger machines at the moment. I am sure that is applicable for the medical because the parts have a certain size matching the body. But you will see bigger machines and you will also see for academia some smaller machines coming up.

All these machines which are then newly in the market they will have much more controls, much more sensors in there to answer all the questions you might have during

the risk assessment. And you will see the old machines that have been used for prototyping vanishing from the market.

LT. COBURN: Thank you. Over on the other side.

MS. MATSUMOTO: Jane Matsumoto from Mayo Clinic in Rochester. From a clinical side we make medical models. We don't do implants. But our creation of those has grown dramatically over the last year. We have it in-house in the hospital. We have it where the surgeons can come down and when you introduce these models to surgeons we take CT MR data. They find it so helpful because a virtual 3D model is still 2D so to have a three dimensional model your brain comprehends it more. The surgeons invariably pick up the models, quit talking to you, rotate them, think about them, talk about where they are going to cut, what they are going to do with them. They help them in their surgeries. They make the surgeries shorter. They feel the outcomes are better.

When you have what we have are multi specialists surgeons working together on one case. They can have that model and talk about it. Much better than having a flat screen image.

The patients really like it. This is for complex surgeries. It is not for simple surgeries. It is for complex surgeries. The patient -- to show the patient this is a model it is not a model of anybody, it is a model of you. This is you. This is what we are going to do. This is what we can't do. The patients absolutely think it is great. This is them. I mean it really is like wow they have -- talk about individualized medicine, this is it.

So from our prospective apart from implants that is a whole new discussion and bioprinting is a whole new discussion for us. We are just growing exponentially with what we are doing and it is through demand they are bringing to us. Not what we are bringing to them.

So we see as this becomes more available medicine is really going to pick it up.

I mean I know there is medical stuff now but I think in two years from now it is going to be so much vastly expanded from what it is now.

What the FDA does with these kind of medical models we are really interested in because again they are not implanted. But we see this being such an additive thing -- I mean additive for patient care, for quality of care, for quality of outcomes. It is just this value added.

As one of our orthopedic surgeons said you know you used to have plain film, then you got CT, he says this is the next step. It really adds quality. So from our prospective that is where it is going and that is where we are aiming.

And I think this also kind of came at the same time where you have this high resolution imaging that is now available that wasn't available five years ago. So you can take these images and make them into SDL, you can converge images. Imaging is only increasing more. You have PET scanners, you have functional MRI. And to take some of this information that is coming and overlie it and use it for surgical cases.

And that is just surgical cases. The application in education is huge. So I see this as we are on the cusp of something that is really going to -- when we look back at now we'll say this was like the Model-T. And in five years we will be on a Chrysler or something -- or two years.

So that is what we see from our prospective.

LT. COBURN: So in terms of surgical models what sort of new capabilities are your surgeons looking for? We've seen the multi-colored, being able to print multi materials at once, differentiating nerves from bones versus arteries. What sort of technological improvements with surgical models are you also sort of looking for?

MS. MATSUMOTO: I think we're looking for the people that make the material and the printers to really come to us and say what do we need because we are not making jet engines, you know, we are not making cars. We need something that more simulates the human body. So I'm not saying we are going to have something exactly like it but we need different materials. We need materials that don't break as easily. We need materials that you can ultrasound through, that you can put needles in, that you can cut, you can glue. We absolutely need colors. We love colors. And those are the things.

So I see that from the manufacturing side that's the need that you are going to see if you want to start selling to medical centers for this kind of thing those are the things you are going to have to develop. You are going to have to maybe not think quite so much about jet airplanes and turn it to humans. They are not square and they are not circle, they are a lot of curves, there are a lot of intricate pathways. There is a lot going on there. So I see that as a need that the industry should meet. And if they meet that, they'll grow with it because I think that is where the demand is from us.

LT. COBURN: Thank you very much. I would also like to follow up on that same vein that any of the people in the clinical realm in the room would talk about the things they are looking for or their surgeons they work with are looking for in devices that are not just models, that are the other kinds of models, the other kinds, so guides, implants and the device companies that make those, are there trends that you see that I guess are, of course, non-proprietary. So from the clinical people are there trends that you see?

UNIDENTIFIED PERSON: Just a quick comment on some of these technologies that will be coming down the pipe for sure in five years with respect to what you are asking. The clinical folks not only want to see something in their hands because they've been able to do

that for a number of years now. They also want to interact with these devices. So we are talking about platforms and devices that are not going to be inside of people but are going to be used to analyze and to train future orthopedic surgeons, physicians, et cetera. So they want feedbacks developed into these systems so these 3D printed models will also have circuits printed into them which we are working on right now. So those are the different type of aspects of how we want feedback. Say, oh, I just nicked the artery, oops, that is what they want to see is that really because there is a big push for that because in the UK for instance they have banned the use of cadavers. So you can't use cadavers to train. So you are going to be telling me that you are going to be trying to train on live people for the first time. It is important to get these really high tech smart devices and I think that is where the big trend is on the training side.

But definitely on the modeling side they are going to get more sophisticated, more intricate yet they will also need to see that integrated technologies. Not just 3D printing but how do we take that 3D printing technology and use the other systems that like electronics and feedback mechanisms within those models.

LT. COBURN: Thank you very much.

MR. GRANT: We've been making medical models and parts for about ten, 12 years. So color is very important but I will tell you what they are really looking for is being able to make things that have tubes in it without having to deal with supports. A lot of veins types of things for arteries and flow studies and things that are going on with modeling. Materials that are water clear that aren't affected by liquids and other types of things like that. And again we are looking at some simulation as well so color for actual prosthesis fabrication is a big deal. Layering technique to be able to layer color in sections kind of like the Home Depot thing where

I pick a color, put it where I want. Layering color within a prosthesis. And materials that are inert for use in prosthesis. This layer type of technology with additive is excellent for being able to do those kinds of things because you can place things where you want them. You can place materials where you want them as well. And you can kind of scatter around the density of those materials so it gives you more lifelike. So that is what is plus and that is kind of where we really in the medical side I see as an area where we need to move more forward towards.

Right now we have no elastic type materials that have color unless I want black or red or some bazaar color but nothing in that field. Now there are newer printers that are coming out that have color wheels that you can kind of adjust the color with but that is kind of where we kind of see things going.

MR. MOONEY: I'm Jim Mooney. I'm a pediatric anesthesiologist at Penn State, Hershey. I can't tell you where it is going. But I can tell you where I am pretty sure it is not going anytime soon. And that is in the pediatric market. Pediatrics are the epitome of where Bespoke modeling is necessary. And we saw the great work with the tracheal bronco malaysia that is done. But bringing that model to pediatric care where every patient is individual based on size, based on congenital malformations or deformations, that is not something that is going to be happening any time soon.

And part of it is because of the regulations, the FDA drugs are a great example, once a drug is approved everything I use in my pediatric pain clinic is essentially off-label; that is going to be an issue for manufacturing. But also the validation studies, things like that that are currently required that are limiting Bespoke production is going to be a barrier there too.

And until those issues are resolved just like medical research in pediatrics, until the proper research is done every child is an experiment.

MR. HIGGINS: Sean Higgins, Boss Instruments. I kind of follow up on that. We offer some pediatric instruments and we're a general device manufacturer but we're seeing a trend towards we need not a one off but something that is so low volume we really don't want to put in the time and effort because the money is not there to develop something that goes through full validation. Like pediatrics is tough because it is a small volume market and for me as a designer the barrier to actually get clinical feedback you need to make something that is a one off and you need to start getting feedback. So a 3D printer is nice for show and tell.

And kind of another application all of our requests are kind of smaller incision, smaller instruments but also used on larger and larger patients. So laparoscopic for instance they need to be longer but they also want them smaller so that kind of works against each other because now it is getting weaker material where you are putting more demand on it.

So from my standpoint it would be nice to have a single use device even though you could really reprocess it; it would be worth it for us to start getting some feedback before we go through and lock down a design from a pediatric surgeon or someone else to develop a device that we might be able to sterilize and use once, get some feedback and then get our products better so we don't get so far down the road and lock in a design that is not optimal for the clinical use but by the time you are there you are not going to go -- it is not practical to go back and change your design at a certain point. So a 3D printer can be helpful for us if we have like a material and process and can use a onetime gas sterilization or something and get some clinical feedback but actually get it used beyond just the anatomic model or the teaching model, like actually put it in a surgeon's hand and get him to use it without putting the patient at too much risk.

Also no affiliation but as far as where the technology is going I think there is a

machine tool company Mori Seiki that made this new plasma deposition. It is a five access subtractive machine that also lays down metal where you need it. It is a cool video. It is online. But yeah it kind of leverages both additive and subtractive so I think kind of falls what mine does. It is one machine that's doing more processes within the same envelope. It is just a really crazy video if you want to watch it.

DR. DI PRIMA: Thank you. That is actually I think the last couple of comments are a good segue into my sort of future question. What new materials are going to be available in the two to five year range both polymers, metals and I'm also really interested in the idea of functional materials. I've talked with people trying to make FDMable magnetic and conductive material, so the idea that you could actually print a working engine. So anyone who has any thoughts on where material availability is going to be in two to five years, please share your thoughts.

MR. BINKLEY: I'm Peter Binkley from e-NABLE. And I don't work for a Taulman, Taulman 3D but they are doing a lot of innovation in terms of different types of filament printing filament. They have a few different nylons that are available. But they also have some PET, some number one plastics which are very human friendly. And they are I think constantly developing new materials for FDM type printers, so that would be one to watch. T-A-U-L-M-A-N. They are doing good things. And they've donated quite a bit of filament to our volunteer organization so we can provide free devices.

DR. DI PRIMA: Thank you.

In the back.

MR. FUERST: Jacob Fuerst, ESI. This goes to more of a metallurgical answer. But going upon what I've seen come out of industry now it's additive manufacturing of materials

that we know very well, Ti64 is a good example. The work that I did in graduate school that has continued on we blended materials, functionally graded layers was a big deal with us and we actually used our powder depositor system to create an entirely new series of alloys. We ranged through titanium tantalum from 10% tantalum up to 90% tantalum. We figured out how to fuse tantalum 2 titanium keeping it in that melt range. We did dental implants from Ti15 Moly which is important to note that there is no commercially available Ti15 Moly powder. We actually used CP grade for Ti and CP Moly and blended it by stacking parallel powder depositors and just getting all the tuning parameters right and could actually produce the alloy on deposit.

We did similar things with Niobium and so the idea and this is going to get into a regulatory issue but you can use powder deposition to create new alloys, to vary your parameters. We could produce a hip implant for example a femoral component that is full strength Ti64 grade 5 ELI in the core and then work our way out so that by the time you got to the bone porous surface interface we gotten either down to a Ti15 Moly or a Ti60 Tantalum that very rapidly dropped the modulus of elasticity and increased the biocompatibility so we could improve tissue adhesion while maintaining full strength in the core. So we really just kind of extrapolated upon instead of just building what we know, let's play with it and see what we were able to create is functionally graded layers.

We did a lot of titanium diboride on the surface of metal on metal implants which substantially brought down the wear resistance. So we were able to avoid a lot of the issues normally associated with Cobalt Chrome metal on metal wear by switching to an ultra high boride which is titanium based and incredibly biocompatible.

So it is really a matter of experimenting and kind of I hate to say cliche thinking

outside the box but not just see additive manufacturing as a let's take an existing material and figuring out a new shape. But let's see how we can alter the material properties, what alloys we can create through the process.

And I know that that is a little scary from a manufacturer's idea because now we are getting into these are materials that may not have been approved from a regulatory standpoint. But now it is in the FDA's court on that to how do we go about encouraging research groups to do more experimentation in alloy blending, functionally graded groups, ceramic metal matrics composites which are all things that are easily done and accelerate that approval process so it doesn't take ten or 15 years to make a boride metal on metal wear resistant device a reality.

DR. DI PRIMA: Can I get your name and affiliation one more time. I just want to make sure I have it down right?

MR. FUERST: Jacob Feurst, Engineering Systems, Incorporated.

DR. DI PRIMA: So for my medical device companies out there how interested are you in something like functionally graded alloys for your implants. Or are you just too scared of that right now?

DR. HOLLISTER: Scott Hollister, University of Michigan. One of the new materials we think might be coming down the pike is shape memory materials and can we 3D print with shape memory materials. We've developed a biodegradable polyglyceryl dodecanoic acid which is a shape memory bioresorable polymer that we are trying to look at for catheter based delivery application. And we can mold it right now but we'd like to develop a way to 3D print it. We've tried to make micro particles. We've done some basis laser sintering with it but those are some materials we'd be interested in.

DR. DI PRIMA: Thank you.

MR. MORRIS: Ed Morris, America makes. Some of the things we see our members doing particularly in the universities at very high level certainly a lot of mixing of nano materials into traditional materials to alter the characteristics, alter the strengths in some of the applications of course a defense related so you alter the signatures of the materials used in applications.

I see the concept of integrated competition on materials engineering becoming very very real where you are able to compute the material properties you want and have designer materials almost on demand. Of course that makes a whole huge challenge in terms of the amount of simulation capabilities to predict the performance of these materials that are invented on demand for indicated computational materials engineering.

The graded materials are coming along strongly. The gentleman talked about so it is almost unpredictable where all this is going to be going but it is going very fast.

DR. DI PRIMA: Thank you.

MS. STEPHENSON: See a lot of possibilities in catheter manufacture, PTFE and Teflon derivatives. Right now in catheter manufacture we're stacking a lot of different derometer materials and laminating them so being able to have a 3D printed catheter where you can actually tune the cross linking to have direction flexibility or changing the derometer across the length of the catheter it would be a great thing.

DR. DI PRIMA: Thank you.

Dr. Dean?

DR. DEAN: David Dean, Ohio State University. You asked about graded metal materials and that is most of the metal materials we are looking at now are qualified in their

monolithic form and if we are blending materials we should be able to characterize what they are capable of, basically bracket what they can do. And then maybe the qualification will have to involve preclinical applications where the FDA will be able to understand what the risks are as they see how we are trying to change function, function coming into the design, function coming in by what the materials can do and then what happens in the animal model so you can assess the risk.

DR. DI PRIMA: Thank you.

MR. MORRIS: I forgot another piece with the materials extrapolating from the shape memory materials MIT has done work on what they are calling 4D printing where it is self assembly structures.

The other piece that intrigues me in terms of innovation applications and particularly what it might mean in the medical community significant work being done to combine the printing and mechanical or electronic parts. So you are using the right materials for the metal, the right materials for the electric circuitry and so forth so that perhaps you can do some simulation of nerve circuitry by the combining of electrical and mechanical printing.

MR. FOULDS: Geoff Foulds from Affinity. You were asking about what sort of trends you might be seeing in the printable electronics. So I think what you want to do is you want to watch industries that have very low barrier entry compared to medical devices and a lot faster cycle times as a result. So pay a lot of attention to consumer electronics, photography and the fashion business, they are going to tell you what is happening in those area a lot sooner and you'll see it happening in here.

DR. LEE: Okay. In the context of the whole emerging thing and I think we are getting at achieving novel properties and novel materials and things like that enabled by the

additive manufacturing. So I am kind of wondering within this audience I am wondering how many of you have kind of started moving toward the combination products space. By that I mean you've started incorporating maybe drug components or biological components along with your -- as a part of additive manufacturing process. Does anyone want to share their experience or at least show hands of have you done it or are you considering doing so in the near future? For research phase.

And would any of you be willing to kind of give us a brief description, non-proprietary but something like what kind of things are you doing.

MR. YOO: My name is Jae Yoo from GlaxoSmithKline. I am actually -- as my qualification reflects from Pharma industry. One of the things that we are interested in is making drug delivery devices. GSK is heavily involved in inhalation devices. So one of the ideas that we are thinking about and actually exploring is can we make the plastic versions of the device using three dimensional printing and to be assembled with the components that will contain the drug. So that is one of the areas that we are interested in.

And there are some other drug delivery applications that could be interesting such as micro needles, once again containing the drug; and although this is not related to combination products there are other companies in the three dimensional printing industry that are actually thinking about pharmaceutical products such as oral drug delivery platforms.

DR. LEE: Okay. I thought I'd seen another person volunteer in the back there.

LT. COBURN: So we've heard a lot about what the clinician are interested in, what some people are doing and trying with the different advanced technologies or mixing polymers. And again remembering this is about technical aspects and all things like that. What do you see as either an OEM or device manufacturer or a researcher even, what do you see as

the biggest hurdles to achieving the things that we have just heard here as far as the needs of the clinician. Please refrain from answering the FDA.

MR. BULLEMER: Martin Bullemer from EOS. I think we had this discussion in material session a little bit. I really appreciate that everybody comes up with cool ideas and new materials, that is what Mike Lee called the academia and I see a lot of possibilities. You get butterflies in your stomach talking about it because it might change the world.

However, in a regulated industry like we are here in discussing that to have a mature product out on the market takes time. So if you are talking about what is happening in the next two to five years you won't see I would say rarely any of these materials in the market because it takes time.

I will give you an example. If you take a new material with an experienced engineer, 25 years experience in developing an alloy and making it happen at the mature level would take us at a very good level that we can bring it to the medical industry it would take a year. And you can do that in the academia, you can test and try and whatever but how do you bring that to the market is a different question.

And again as trust my triangle you have to have it on the right machine with the fine condition, you have to have it with right parameter sets, and you have to validate it. This takes time.

And so if anybody of you have a good idea and there is a market for that, I do business development for my company, come to me and we will see if we can make it happen.

LT. COBURN: Thank you.

Another comment.

MR. KARPAS: Les Karpas, Metamason. So one of the issues getting a medical

device startup off the ground is you are stuck in a circular trap of you've got investors you are trying to pitch to who want to see validation but you're pre-clinical and pre-regulatory. So your ability to show anything tangible to them that doesn't violate the direct rule book of what you are supposed to do from a regulatory prospective kind of spins you around in circles for a little while. Eventually you find a few people who are willing to take the risk based on whatever data you can produce or whatever prototypes you can produce that you officially have not put on any humans because that would be bad.

But there is a reason why there aren't more medical device startups who are hoeing that road the way that I've decided to. It is because you get into this nobody wants to take the risk because you have a threshold that is as fairly expensive one to cross before you have any very tangible or marketable data that you can use to really to pull an investment. And so it is food for thought for you guys as to how to alleviate that if you want to see more innovation and more new entries into this space.

LT. COBURN: Thank you very much.

MR. RIOS: Ernesto Rios from Renovis Surgical. I think from a medical manufacturing standpoint when you are developing a product line and there is so much design that needs to go into it from the beginning of design all the way to when you launch it, you try to incorporate additive manufacturing it's very difficult for a device manufacture like us when we want high volumes of product to do development of materials at the same time.

So from the device manufacture it is very difficult for us to develop new materials. So we are really count with the OEMs to do that work in advance. And we just piggyback on their development, what materials they have developed and we then integrate that into our design. So as a medical device manufacturer it is very difficult for us to develop

product the same time as develop the materials.

The technology is very advanced, it is very complex so it is kind of on the OEM to develop that and have it available for us and then we can incorporate that into our product.

Thank you.

LT. COBURN: Any other comments on that question? Tentative? I see some movement. No.

DR. DI PRIMA: I'll ask the next question then. For either device manufacturers or the OEMs or even the clinical people what's sort of the number one technical barrier or challenge you would like to solve tomorrow. What is that one thing if you can just do with additive manufacturing, you could change the world.

MR. RIOS: Ernesto Rios again from Renovis Surgical. I think that if we could have a very smooth surface, have better surface finish I think that we could make parts and forget about traditional manufacturing at that point. I mean we don't have to do any post machining, any post processing, maybe some heat treating. If we could have a perfect surface or the surface that we want on every surface of the part from the actual machine, I mean I think that would be a beautiful thing.

MR. URDANETA: Mario Urdaneta, Weinberg Medical Physics. What would help me would be a really good database of material properties. And I believe that this is something that the Department of Energy has signed an initiative on. But that would -- yes, that would be very, very helpful.

DR. DI PRIMA: I'll share mine. I'd love to be able to 3D print embedded electronics within a structural elements. I'd love to be able to put strain gauges wherever I want inside a test fixture and then be able to remotely monitor them as well as a number of other

awesome applications if you could 3D print a component with embedded electronics.

MR. BERNAL: Andres Bernal, Optics. Would be really great and but not light guide type optics or any 3D because Look Excel is doing that but imaging optics that is really difficult because of the layering nature of additive manufacturing. You get scatter on the surface. So it would require some sort of new technology to curved surfaces.

MS. STEPHENSON: One thing I would like to see is a complete accurate anatomy database of three dimensional anatomy all the way down from fetus to elderly with accurate demographic data going from the 5th percentile up to 95th percentile, just to be able to have -- and make that open source.

LT. COBURN: Thank you very much. We actually have a separate initiative on the digital library of modeling and simulation for both medical imaging and medical modeling which sounds like that is a very good topic for that and we're working on collaborating with industry and academia to create a database of models that wouldn't be in this case 3D printable directly but it would at least create a database and there are efforts underway to do that. SO hopefully we will be able to give more updates as the efforts come to fruition and then somebody most likely in this room will find a way to post them in STL or AMF format and they'll be able to be 3D printed as well.

MR. BOGHOSIAN: My name is Ara Boghosian. I'd like to see an export format where it is not just STL but also incorporates the step where I just information within the STL all in one hybrid file because I get a lot of files from non-experienced users and I need to modify but they don't have the original CAD file. So I'm curious to hear if anybody knows of any software out there currently or someone doing research in that area that will make STL files modifiable or some type of hybrid.

Thanks.

LT. COBURN: I'm imagining someone in the room can talk to that. Not pointing any fingers. Or not. That is okay.

MR. ZANDBERGEN: With the Materialize Magics and 3-matic software you can modify STL files. It is something that we do every day.

LT. COBURN: Yeah, there are actually also several other packages, engineering packages that allow STL modification especially through conversion to NERBs or some other form of deformable modeling that way. Art has a lot of, art as in Artistic, the field of art, not a person names Art, has a lot of experience in that because they do a lot of modeling and deformable modeling so this would be one of those cross-silo kind of things looking into that field much like somebody mentioned the consumer electronics and photography. It is a way to look at these deformable models as well.

Follow up? And then you sir.

MR. BOGHOSIAN: Yes, just a quick comment on that if the person is exporting low resolution then you are stuck with ISO and Geomatic, you are just allowed to, whoever is familiar with it, modify whatever is there. So it would be nice to have the native information kind of zipped inside the STL file so that if an experienced CAD user wants to extract that and recreate the STL file.

LT. COBURN: Thanks so much for the clarification. That is actually very similar to a raw file for cameras. Going back to photography it encodes all of the information about the situation instead of just compressing it to a Jpeg.

Over there.

MR. ADZIMA: I was just going to say -- I am Brian Adzima from Autodesk. But

MeshMixer does allow you to modify STLs and it is free.

LT. COBURN: Is that a comment in back? Yep.

MR. BONINI: If we are still addressing that question on the world changing technology. I saw two presentations yesterday, the on-patient printing of skin cells following burns and the other one involving printing microstructures so organs and one of the ones that was completed was muscle. Really thinking into the future the ability to do multiple body structure printing as trauma repair theoretically being able to print an entire hand or arm or face following amputation or severe trauma; not just being able to print a piece of jaw and implant that but actually on patient make a face, make a limb. I think maybe 50 years down the road would be a worthwhile application.

LT. COBURN: Thank you. And that, of course, when we start talking about 50 years down the road does get into where as we've seen through some analysis of the media that is sometimes where people think we are today. So it is actually true. So if you go out and read the media people might think that we can actually do that next year.

So obviously in this room of experts and people in the field we know that that is 50 years down the road. So I'm glad to hear the gamut of everything and that we know where we can go and the steps to get there. So thank you for all those.

MR. KARPAS: Still throwing out wish we coulds or wish we hads. Les Kapas, Metamason. I've been chasing after this for a while and I think it is maybe chasing after it for a long time still the ability to finely control durometer and elasticity within a part from a Shore 10 to a Shore 90 and would still be biocompatible and durable and fastenerless and binderless. So that make whatever you want, you can do it all in a single build and have it actually be a useable, functional part when you are done.

It is going to be a while but wish list; right?

LT. COBURN: Absolutely. Thank you.

MS. KANEGSBERG: So under general wish lists, Barbara, BFK Solutions. Wouldn't it be wonderful if 3D additive manufacturing could be used to shortcut the need for animal studies perhaps so that you could emulate, do something a little more sophisticated than in vitro but not be faced with the variability of species of rats and other animals. And that could perhaps be used specific in vitro testing could be used to speed up development of devices.

DR. DI PRIMA: Okay. This next question is still going to be along the wish list but it is going to be a little bit more practical. In terms of standards what would you like to see? I know we've touched on this a little. But we'd be more than happy -- okay, so remember FDA does not make standards but this is sort of for the industry. What sort of standards do you want to see? Where do you see a need? Thank you.

DR. LEE: Actually maybe a follow up. How many of you participate in the existing standard practice, development practice? Okay.

Are there any barriers for those that didn't raise your hands to participate in that process or are you aware of it?

Okay. Well maybe that is not a type of a questions that I can just post to the crowd. Okay.

DR. DI PRIMA: I am still interested to hear more about the standards people wish they had.

MR. MOONEY: Jim Mooney, Penn State, Hershey. I would just go for free and open. ASTM charged me about $40 for a three-page PDF that cost them zero to send me.

[Laughter.]

I think it is disturbing and if we take a look at the global picture it's atrocious. A lot can be done across the globe if people had access to information.

DR. DI PRIMA: Thank you. I'd like to point out that we don't control ASTMs pricing model.

[Laughter.]

Thank you.

MR. BOLT: Fred Bolt, TechPlas Consulting. I don't work for ASTM but I am a member and have been for 20 some odd years. I share your pain there, even as a member except for the fact that I'm on a few committees I would have to pay for them too if I needed something. However, bear in mind that ASTM is pretty inexpensive compared to ISO if you've ever --

[Laughter.]

If you've ever bought any ISO standards. And also bear in mind that the funding or income for these groups, ISO and ASTM, SAE also, any standards organization, comes from the sale of their publications even though they are electronic now. So keep that in mind.

However if you are active in ASTM and join specific committees you will at least have access to the latest balloted documents. You are also allowed access to one volume of documents each year which you can download any of those that you want for free.

MR. HIGGINS: Sean Higgins. I'll put in one vote for no new standards; end use still isn't changing unless you are going to change the requirements for the final application. I think we probably have all the standards we need. If you can't use a 3D printer to meet the requirements, then you just can't use a 3D printer. My opinion.

LT. COBURN: On the other side.

MR. BONINI: Yeah, already -- Julius Bonini, Lucideon. I've already talked about the need for standards and to answer your question. Yes, I need to join F46, was it F46?

LT. COBURN: F42.

MR. BONINI: 42,

MR. BONINI: That is good. I should join that committee. The problem is I don't have the time. My company wants to make money. I don't have time to join these committees and do that kind of stuff; that is the real problem. But a lot of us should whenever -- especially academia, they have a lot of time.

[Laughter.]

They should definitely affect those committees because they know and understand the material. But I'd love to so I should really attempt to join it and try to work with them but that is really the problem is the amount of time that is involved with the committee work.

LT. COBURN: Here's I guess a less directly additive manufacturing question but for the organizations that are involved in the development of the standards or have been involved in development of the standards speaking directly to the I guess the business case have you found it worthwhile to develop those standards or help with the development of standards?

MR. BOLT: Fred Bolt again. There is a saying somebody told me once that if you don't get involved in the development of standards somebody is going to do it for you and you are going to wind up with standards that you may not like or have a hard time meeting. Yeah, it takes time, it takes -- it can take time, it can take a commitment to be involved directly in standards development. And if you can afford the time it's certainly well worth it. It is not that

expensive at least for ASTM it is $75.00 a year I think and that allows you to join any number of committees for free beyond the $75.00.

But further you don't have to go to all the meetings and stuff, although it certainly is a big help, you still have the right to review the ballots, review the work that is going on and provide comments which are recognized, have to be addressed. So you know the time participation doesn't have to be all that great. It is up to you whatever you can afford to do.

MR. COMEFORD: Hi, Pat Comeford, McCarter & English. I'm a trial lawyer and that usually gets a reaction, a defense trail lawyer. So I defend manufacturers. And what I'll say is exactly to that point. If you don't get involved that is what I use in Court is your track record of how you built it and what the standard is. And I don't know a lot about witness coupons but I do know a lot about plaintiff's attorneys and they usually don't let science get in the way of their case. So if there is a standard out there I can point to, if there is a standard out there and your track record we can point to that is what you have to go on. Otherwise if you leave it up to judges or you leave it up to the jury and that can get really scary depending on where you are. So I would say as a business proposition long term you want to be involved because whatever you are doing under your bushel if you are keeping your light under a bushel you don't want to start telling people about it when you are in court.

MS. KANEGSBERG: Barbara again. So I've been involved in a number of standards setting committees and overall even though sometimes it feels like I've become part of the flat earth society it is better to be involved because just the give and take makes for better standards.

It is also true that it's easier to develop defendable processes if there are standards. And sometimes I have been able to keep clients away from going to trial or getting

sued just by showing that they are using the standards. So, yeah, I'm in favor of them.

LT. COBURN: Thank you very much.

MR. FOULDS: Geoff Foulds from Affinity again. As far as the business case for standards in medical devices I'm not so familiar with that because I come from computer graphics for the past 20 years. But if you pull out your cell phone and you look on the display of your cell phone you'll see a little Blue Tooth icon which is the result of a standards process. You see little Wi-Fi icon which we've all been enjoying getting our FDA guest access, also the result of a standards process. So I can tell you that in other industries standards are really what drives things forward and in a big way. So it's often times the process is too opaque and that it is too closed a shop where there is one organization in the standards process that gets to be too powerful. And then -- you need to have some creative tension in the group.

So if you think about document standards like PDF, adobe has really dominated that standard and it has kind of stagnated. So the reason that Blue Tooth and Wi-Fi are still very active is that there is still quite a lot of tension within those communities about who's pushing and pulling. So that is what you want to try and drive for in this community.

And you've got a harder problem because the ultimate risk factor, of course, is a lot more extreme than in the telecommunication, the computer graphics business but if you can strive for that, that is where you want to go.

LT. COBURN: Thank you very much.

DR. DI PRIMA: So we asked about standards because that is a technical space that the FDA can openly participate to help technologies and companies be more innovative and sort of ease through some of these problems. So since we didn't get a lot of feedback on standards sticking within the technical space now is there something the audience would like

the FDA to do or participate in to sort of ease the use of additive manufacturing as a way to make medical devices? And again technical area only please.

All right. So what I am hearing right now is FDA is doing the absolutely perfect job right now in additive manufacturing which based on some conversations I've had with people I know is not true. So please let us know technically what you'd like us to do.

MR. FESTJENS: Hi, Neils Festjens from Materialise. It is not directly related to additive manufacturing but we see issues specifically for patient specific device industry is in the imaging world, it is all in the medical imaging and that is where we believe that a push from FDA would definitely be nice to make sure that different manufactures of different scanners that they are aligned. And I think that would also be beneficial for the patient specific devices.

DR. DI PRIMA: Thank you. That was a very good technical area we could look into.

LT. COBURN: Seeing no further comments, we'll close that question. But there is the docket so if you do have any areas submit to the docket.

All right. Well that actually brings us to the -- see you always say something like that and somebody comes up.

ARA BOGHOSIAN: This may have been already discussed in the materials session which I wasn't here but just a real general question about materials because it is the most common question I get for people who are not familiar with the medical device industry in terms of how to answer this. What materials has the FDA approved? That is what they ask in general. And it is a very difficult answer to explain to them because they are not familiar with the processes and validation and so forth. So how do you recommend answering that question to a novice or non-experienced user?

DR. DI PRIMA: We have a great deal of experience in answering the question. The answer is the FDA does not regulate materials. We only approve devices which then usually requires another half hour of explanation of the regulatory process.

MS. ISAYEVA: Well I guess I should stay this way directing my comment. My name is Irada Isaveya from FDA and Office of Science and Engineering Labs. And I just wanted to add to Matthew's question, comment where would you like FDA to help. And in terms of -- I would like to just kind of inform everybody that we do have a research arm of FDA that is involved in research activities. So many of you don't know that but we do research and it is mostly to address regulatory technical questions. And so maybe that is where the disconnect is coming and that is maybe why people are so quiet. We are not -- we are here to do some of that research. The research in itself and the research that industry doesn't want to be investing too much into or academia is not interested in because it is not fundamental. But there is an area of applied regulatory science where we can help. So if you want to bring that up back to your industry or think about that more we would really appreciate your feedback on that.

MR. KARPAS: So along the lines of things that FDA might be able to do to help, I've had a number of discussions with different regulatory consultants, other medical device startups about if I take a predicate device that was not 3D printed and I want to 3D print it can I still get a 510k because I am changing manufacturing process so have I annihilated the prior predicate. And so more clarity on as you combine additive manufacturing predicate and a device predicate that would be relatively different in terms of let's say I want to take a knee brace and I want to take an SLS machine. And the SLS machine was used to do I don't know an orthotic, so you are taking some knowns of -- bad example because that is not -- orthotic is not regulated by you guys. But you know what I'm saying. You take one manufacturing process

that has got a 510k, you take a product that's got a 510k guidance on how you can combine those to stay within the framework would be useful.

DR. DI PRIMA: All right. So that is a little bit more on the policy side. However the 510k summaries for all clear devices are publicly available and they do list the predicates.

LT. COBURN: Also we can work on clarity because as we know we are not always perfectly clear with things. We can take that point home for sure.

Are there any other comments or concerns or questions?

DR. HOLLISTER: Scott Hollister, University of Michigan. I guess I have a question that there is obviously a tension with additive manufacturing between stuff you do as a baseline and then stuff that becomes customized out of it. And I am wondering if you would comment on in different standards, let's say ISO 10993 there are things that you with the very standardize shapes and things that are always the same. And then there are things you do with the final device. Is there a delineation in these standards where you can say okay, if you did one device with the same process, on the same parameters, on the same machine, the same material all of the tests that you did on that previously with the standardized shape are okay and then you just have to do these tests again because the device structure or shape has changed. If you can sort of address that issue?

LT. COBURN: I don't know that we can address that other than to say our stock answer which is it depends I'm sure. But I think it is definitely something that we can bring back and think about.

Thank you.

DR. DI PRIMA: Okay. Well we have the room until I'm going to say 3:30. So we will be here and more than willing to talk with people individually. But with that I'd like to thank

everyone for coming and participating. And again please, please send any further comments you have to the docket. Friends, co-workers, let them know about it. We want to get as much and as broad of a feedback as we can about the questions we raised and the conversations we had. And if we had a question and you want to answer something a little bit differently than what we asked or discussed, please let us know.

LT. COBURN: And the last thing is we talked about standards and what can we do, what are the hurdles and people talked about sharing information I think everybody here is in the right space because we are all here sharing information across the different silos with OEMs, vendors, standards organizations, medical device manufacturers, academia and government. So this is a great space in this hour to cross those barriers and find out where you can really interface.

Thank you very much.

[Applause.]

(WHEREUPON, the public meeting concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

State of Maryland

My commission expires:

Notary Registration No.:

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I, CHERYL LaSELLE, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

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Date CHERYL LaSELLE

Transcriptionist