

UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
PUBLIC WORKSHOP - HEMOSTATIC MEDICAL DEVICES FOR TRAUMA USE

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September 4, 2014  
8:00 a.m.

FDA White Oak Campus  
10903 New Hampshire Avenue  
Bldg. 31, Room 1503A (Section A of the Great Room)  
Silver Spring, Maryland

INTRODUCTORY SPEAKERS:

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SESSION IV - CHALLENGES IN EVALUATION AND VALIDATION

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SESSION V - CASE STUDY: XSTAT'S REGULATORY JOURNEY

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SESSION VI - INTERACTIVE SOLUTIONS

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MEETING

(8:00 a.m.)

DR. ASHAR: All right. Well, if everybody could go ahead and have a seat, I think we can get started on Day 2 of this FDA hemostatic device public workshop. I just wanted to thank you for an exceptional session yesterday, and I also appreciate the fact that you came back. So thank you for being here.

Just a few things I wanted to mention this morning before we launch into our keynote speaker this morning. As I mentioned to you yesterday morning, there was a team of FDA people across various centers that have been involved in the planning of this workshop, and I just wanted to take a minute or two to recognize them. If they're in the room, then it would be great if you could stand up or wave your hand. If you're participating remotely, then, of course, we can't do that, but just to acknowledge their work and effort here.

And, of course, you all know Allison Kumar. Maegen Colehour. She together with Allison were the ring leaders for all of this. Carolyn Yong, Joshua Crist, Suzanne Schwartz, Betsy Ballard, George Gibeily, Roxie Horbowyj, Jitendra Virani, Steven Wood, Nisha Jain, Sam Arepalli, Karen Manhart, Ken Cavanaugh, Jeremiah Wille, Ann Farrell, Edvardas Kaminskas, Nicole Verdun, Peter Hudson, David Krause, Pablo Morales, Charles Durfor, and Ron Kaye. So you can tell it was very

much a group and team effort, and I think we can all agree that it was. It turned out better than we could even have hoped.

(Applause.)

DR. ASHAR: And I'd also like to thank all of you for attending. Because I know that we all lead busy lives, there's an opportunity cost, right, in all of these decisions. You could be doing any number of things. You could be taking care of patients, you could be furthering your business in different ways, but you've chosen to spend the time with us at both expense related to time as well as cost, in some cases. So thank you for taking the time to attend and participate, because we do need your input, and we're certainly going to ask for it this afternoon.

So with that, I want to launch into Dr. Bijan Kheirabadi. He is going to be giving our keynote talk this morning. He is a research scientist at the U.S. Army Institute of Surgical Research.

Dr. Kheirabadi.

(Applause.)

DR. KHEIRABADI: Good morning. I would like to express my gratitude to the organizer for inviting me, and it's really an honor to present you with this talk. And I hope, by the end of this talk, I can convince you that well-designed animal studies can be very informative and perhaps improve or increase the confidence level that we were taking to move product from the preclinical to a clinical trial.

Before I start, I have to say that these are my opinions and not reflecting DoD or U.S. Army. And I think there is another important distinction I want to make. I have no conflict of interest with any of the companies, any of the products that have been developed, whatsoever. I'm completely independent and a government employee.

I think this is the least of what we consider the Army's ideal hemostatic agent. First and most importantly, it had to be FDA cleared at least, or perhaps approved. And I think the second item is we were hoping to have this agent actually stop arterial and venous bleeding and soft tissue bleeding in less than 2 minutes. And then you can go down the list of the important aspects of what is considered to be a most optimal hemostatic agent for use on the field, at least.

Early 2000, one of the earliest products that came online, courtesy of FDA clearance, was what you remember, what's called QuikClot zeolite granules. This product was essentially -- the efficacy study that was done was using this particular model, which was a transection taking the scalpel a little bit, cutting through the vessel artery and vein in the groin area, and pouring the material in there and see whether it stops the bleeding or not. This was a basic model that was used to prove the efficacy and also showing that actually the temperature that is caused -- because it causes exothermic reaction -- does not increase more than 15°C on that level. Therefore, it seemed to be also safe.

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But the result -- actually, if you read the paper or you look at it, they couldn't really show any blood loss differences, whether they treated with the QuikClot -- what the QC stands for -- or using actually a standard dressing. The efficacy that actually proved that the product works is in the survival result. And if you look at it, the survival with QuikClot was 100%. That was a comparison done with no treatment.

If you look at it in the same model -- SD stands for standard dressing, which you're just putting gauze on that particular wound -- it actually provided 66% survival. So the difference was only significant when they compared the product with no treatment.

But if you were just looking at it compared with the regular dressing -- you're just putting a few gauze in there -- the QuikClot wasn't much better than a gauze. Certainly, they didn't show any difference in the blood loss, and the fact that it was convincing that the temperature never really rises beyond 50°C, this product got FDA clearance and moved on and very quickly was deployed and was being used mainly by Navy and Marines in the battlefield.

The subsequent studies by Air Force actually was a survival study, a similar model, groin injury that they treated with QuikClot, but they clean it up and let it go for a couple of weeks, and that wound site, within 7 days, becomes necrotic. They see the injuries, the internal injuries, first-degree burn on the skin, and it eventually led to abscesses.

So, clearly, there was a safety issue with it. Even the efficacy data that was provided, it wasn't that convincing. But, nonetheless, they set a very low bar, that everything else becomes predicate to get approved because they could prove it's as effective as QuikClot.

And, by the way, we are better because we don't produce any heat, our product doesn't generate heat.

So we get a flood of material after that, coming in. All get clearance, and all essentially claimed that they are very effective material, and we placed them to see which one of these are really best, which one should be fielded.

Another product that also came out early was that HemCon dressing. This was the first time a chitosan -- a carbohydrate complex was used, which was a shellfish from the shrimps, and they made it into this material. The material essentially was once you get wet, it would stick well to the tissue, and that was the property. It wasn't hemostatic, and I'll show you data. Basically, it has this mucoadhesive effect. So when you put it on the wet tissue, when it gets wet it, would stick, and that's how they stopped the bleeding. So that was the second product that came online and with -- of Army support.

I think the test that really proved the efficacy was using the model that Colonel Holcomb -- Dr. Holcomb now -- developed at that time, which was a Grade 5 liver injury using this particular blade. But you have to

recognize, it was proved to be effective, and actually the prototype proved to be effective in this model. But this really represents a venous bleeding, and it's really an internal injury. The product, HemCon or any of these dressings, were really meant to stop arterial bleeding for extremities. So the model that we were using, even though it shows efficacy in this model, it doesn't necessarily prove it's going to stop arterial bleeding. So it was becoming important to recognize what model you're using, and what are you actually trying to prove, what product, what the indication is. If that product is indicated for arterial bleeding, that's what we really were testing it on.

Anyhow, based on the efficacy data that developed here, that was the second product that went to the field as a product that Army believed -- and by the way, the nice thing about it, it didn't generate heat, so at least it was safe and didn't cause more damage.

So, at that time we sort of came up and said, what do we think an ideal model would be for compressible hemorrhage, for those products that you actually put on the top of the -- what is a topical agent? What could be the model we will develop, or should we develop, that's considered to be an ideal model? And we can go back and test all of these new products that keep coming to the market and prove whether they're efficacious or not.

So this was what we kind of figured out. Should it be a consistent injury with a reproducible outcome of bleeding? It should have a nice high blood loss so we can use actually the change of the blood loss as our

primary endpoint, because if you're just using survival, then you need 200 pigs to really show the difference statistically. But using blood loss, it was a very good endpoint to determine the efficacy.

We wanted a very high mortality rate in this, and most importantly, I thought, we wanted a model that using gauze would not work, because if gauze works in there, then there's no reason to put anything better or more expensive material. So it had to be a model that gauze, by itself, would not stop it. So we wanted to find something better and hopefully then mimic the injury of extremities with junctional bleeding.

And I think one other thing that we later on add to this, we wanted to have a resuscitation protocol in the model that would be compatible with what is actually being used in the field or a standard of care, which was low-volume hypotensive resuscitation. So that was another ideal thing.

And, most importantly, we always want to find a positive correlation between blood loss and mortality. The higher blood loss, the higher mortality; the lower blood loss, lower mortality. So that's the point that I'm continually looking at, to other models. We go to see if that's maintained, because if we don't show both of them simultaneously, sometimes it could be misleading. So endpoints were important to us with blood loss, survival, percent survival, and some other measurements.

This was another early model that was developed by

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Dr. Sondeen: very, very severe arterial bleeding, a 4.4 mm hole in abdominal aorta. This was one of those all or none working. If you put it in, if it works, it works; if it doesn't, animal will die. There's no question about it, the bleeding was so severe. And the only thing that seemed to be working in this aortic injury model was the stuff that actually adheres or sticks to the tissue, such as fibrin sealant or even some chitosan dressing, could stop the bleeding in this model. Anything that would actually start forming a clot, it would fail because the bleeding was so severe it would wipe the material away.

We actually take that model and we look at one other thing, very early studies, to see how this HemCon dressing that we're talking about, adhesiveness, works in that model versus a fibrin sealant, which was another adhesive dressing. It turns out that HemCon, at least some of the good batches, doesn't stop the bleeding and stick to that hole and seal the hole and stop the bleeding.

But the point that we noticed after a while, these things, they lose adhesiveness; they become gelatinous and it comes off. So the animal only lives an average of 48 minutes. After that, the dressing will come off and it will bleed to death. So even the chitosan was a good adhesive, but the adhesion had a time limit, and that time limit was below what we consider to be an ideal dressing.

So that led us to what we now consider to be a standard arterial hemorrhage model that we developed, and that is essentially

isolating a femoral artery, putting some lidocaine on it that will dilate the vessel, and then we realized, any time if we cut, transect it, the vessel retracts both sides and constricts and bleeding stopped by itself. You really don't need to put any hemostatic on it. So the only way to maintain that bleeding is to make actually a gigantic hole in it, but maintain the vessel integrity.

So the 6 mm hole is made. We allow it to bleed, and then we pack the wound with whatever material we have and give it a couple of minutes' compression. In this case it happened to be a Combat Gauze or regular gauze, and we went through a whole host of testing, nearly 10 or 12 studies in new agent -- I'm sorry -- simultaneously, Navy were doing similar studies in some of the other models.

By the end of the study, we were looking at these particular two agents that seemed to be the champion of our model, which one was the Combat Gauze you have heard about. It's a surgical gauze incorporated -- kaolin incorporated into it. And the other material we call WoundStat. WoundStat was basically smectite clay, and it literally comes as a clay material that you pour it into the wound.

These two products seemed to be the best products, and compared with the two that already existed and already fielded, which was HemCon dressing and QuikClot granules, they seemed to be significantly better. You can see, the blood loss comparison to those were reduced, and

that blood loss corresponded to the survival within the 3 hours: WoundStat 100%, Combat Gauze 80%, versus the HemCon and QuikClot, which was much significantly lower. By the way, standard gauze in this model will fail 100%.

So we now recognize two new products. Both are FDA approved and substantially better than what was already fielded in the field. So that led to the gradual replacement of HemCon and QuikClot with a new product, which we'll now consider possibly Combat Gauze and potentially, maybe, WoundStat as a backup.

So we have a nice arterial injury model as our model of testing for arterial bleeding, which coming back, we're still using that venous bleeding that Colonel Holcomb and Dr. Pusateri developed a long time ago. The only thing we have done is that we realized this type of injury, which only involved a path exam cutting, is not a fatal injury, it was not a lethal injury, and the only way they could make this lethal injury, by giving an enormous amount of fluid at very high rates. So you're overloading the animal and that hematically then will die. So we want to avoid that particular limitation.

So Colonel Holcomb, in a subsequent paper, he suggested, let's do a way to deficient the coagulation function of a pig. They seem to cross over, so even that injury is survival. What can we do to bring the coagulation capacity to a lower level so the bleeding was more severe and possibly would die? So this was the model that they have, and I'm continually using it to develop a coagulopathy in the pig prior to the injury and, in this situation,

essentially using 50% of the blood from the pig and you infuse an equal volume of colloid -- Hextend in that situation -- and you bring the body temperature four or five degrees. So you're creating a hemodilution, a hypothermia, which, by the way, is really effective. You can see the hemoglobin drop to half of normal. Fibrinogen dropped to the half of normal. Interestingly, platelet count actually dropped to one-third because Hextend actually decreased the platelet count; and so forth and so on. So the model, now you've essentially reduced the capacity, the coagulation, to half of its original values.

And, by the way, the bleeding time in a normal pig is about 3 minutes. Once you lose coagulopathy, it's over 10 minutes. So it clearly has -- now the bleeding becomes far more sensitive. And just looking at some of the early results in a normal pig, unless you have resuscitated a significant amount of fluid, your no treatment group, that's the only time when no treatment is 16%. If there was minimum resuscitation, they will all survive. And in the case of packing, which is essentially the wrapping of the gauze, you saw 100% survival in the normal pig. Once you make the animal coagulopathy, wrapping it with the gauze, putting gauze is no longer effective with the animal; 100% die.

So that provides the venous injury model, so severe now. So we now can go back and see what can be better than packing, what can be better than a standard of care and gauze treatment. We recently used that.

For instance, in this case we actually look at two different fibrin sealant products versus gel foam, all of them intended for use of internal bleeding and surgical bleeding. And, as you can see, gel foam, essentially as a control -- and even fibrin sealant dressing, which both are made from fibrinogen, a very similar composition -- can have a hugely different result, one only 25% survival versus 100% and significant differences in the blood loss.

The advantage of the model was now we have a venous bleeding. Not only a venous bleeding, but a model that we can test the material that surgically will be used for internal use, possibly for implanting it and not removing it. And (b), by doing the coagulopathy, we no longer need to go through this large volume of crystalloid resuscitation. We only have to give the animal about a liter of Hextend, and that's all we need to raise the pressure. If the material stopped the bleeding, it would have stopped it and no more fluid needed. If it bleeds, it would bleed to death. So it was a fairly good robust system now for testing surgical material for mild or moderate bleeding. So that was one model. This is the second model.

And, finally, Colonel Blackburn one day came and said, you know, we have this type of bleeding. These are large soft tissues and the patient becomes coagulopathy and these are IDE injuries and you can go back in and clamp the main arteries, but the soft tissue continues losing, and it was really very hard to stop it. Can it become an animal model to actually address this type of bleeding?

So we developed this model, which was essentially putting the animal on the side, clamping the aorta temporarily, and then removing, nicely, about a big chunk of its buttocks muscle, and then we open the clamp and you can see on the other slide that this produces a mixed arterial and venous bleeding. Fairly slow. Not a major artery; it's small arteries and small veins. But, you know, the pig has a great advantage because they have much better coagulation than us. This bleeding that seemed to be very significant, you put a piece of -- wrap it with the gauze and see that 3M sterile sealer or plastic, and the bleeding stopped within 5 minutes. So it wasn't really making such a massive injury that we wanted to test.

So the way we made that to a lethal bleeding is again back to that coagulopathy induction, which was making -- once we make the animal hemodiluted and hypothermia, the same injury no longer could be treated with regular gauze. Now it would actually continue bleeding until the animal died because it just didn't stop because of coagulopathy.

So we used that model to show an advantage of possibly using negative pressure wound therapy as a way of providing hemostasis. We found that if we actually dress the wound with the gauze -- or, for that matter, combat grade; it doesn't matter -- now you put a strong negative pressure on the wound to constrict the blood vessel, constrict the tissue. The bleeding that was non-stoppable with anything else, now the combination of gauze and negative pressure, we could stop the bleeding, and within 3 hours

the bleeding -- even when we removed the material and stopped the pressure.

The result was the same thing. We see a significant reduction in blood loss when we combine either Combat Gauze or regular gauze with negative pressure -- well, either gauze or Combat Gauze was not effective. So it kind of -- maybe negative pressure can be used as an adjunct to hemostasis in a situation that you have a soft tissue with slow bleeding.

So that was essentially the three models. And, by the way, here, the survival -- again, the survival corresponded to blood loss, high survival with the combination versus not.

So this is as far as I'm talking about the efficacy model. We have arterial and we have venous and we have soft tissue. What about safety? How do we know these products are safe? I mean, we saw what happened with QuikClot, you know, the potential with other things, that is, you get FDA clearance and come to the market, but it still may not -- may still have problems.

So there are essentially five issues that we want to know. Do they cause thermal injury? Do they cause thrombosis? Could they be actually embolized and enter systemic circulation and cause emboli? Could they have cytotoxicity? Are they actually toxic against the cells? And, finally, what would be the long-term effect in terms of tissue healing?

This has started from the very preliminary stuff that we were

doing on the product I mentioned to you, WoundStat or smectite. This product, when we look at it histologically, despite of really nice debridement of the wound removed, we noticed there are particles of this smectite or WoundStat remained on endothelial cells in some of the tissue samples that we recovered, and that was concerning. Also, it wasn't just the smectite. We even found some of the residue of kaolin, which was part of the Combat Gauze, being present in some jugular vein. So, if you have those things, should we have reflow of the blood? Could they actually cause thrombosis? And that's how basically they all start.

I must mention, we also developed some in vitro way of assaying these materials. This is just thromboelastography. If you look at the line that is sort of a baseline -- and I'm looking at the control -- it's the green line. That's if you take the blood and just put it in there without doing a whole lot. It takes a while to start clotting, and then the clot starts fairly slowly -- on the green line you see it -- and it reaches some clot strength.

This machine essentially measured elastoviscosity of the blood. As it gets clotted, these curves form, and if you look at the blood that is being treated either with WoundStat and kaolin, which are the two curves on the very left side -- it's the blue line and the white line -- you can see the time that these processes starts becomes much faster, the clots form faster and even actually make it stronger. So these agents, both kaolin and WoundStat, were highly stimulating clotting coagulation. So, if they're left in the blood

vessel, could they actually cause thrombosis, and what would be the effect of it?

So we designed this study. We said, this is maybe a way we could figure out if these cause local thrombosis and could they be actually embolized. So we developed this model of injuries in the neck. So we will open the neck, isolate carotid artery and jugular vein, make injuries, and then treat it with this product and then we remove it. And I will show it. The reason we're choosing the neck was this: We said, if there is emboli formed or embolism, the chance of -- if it's arterial, it will end up in the vein, and if it's the venous, it will end up in the lung. We can go back and take this tissue out and look to see what will happen to it.

So this is how the model was. We isolate the blood vessels, jugular and carotid artery, make the injuries and then pack them -- in this case it happened to be Combat Gauze -- for 2 hours. And we also pour WoundStat, which was basically clay material, leave it there for 2 hours, then we went back and take this material out. We remove, as best as we could -- debrided that wound by 2 L of saline and clean up anything we could see. And then once we clean it up -- by the way, at that time the vessel is clamped -- we repair the vessels and let it reflow for a couple hours, and we close it and wait for 2 hours to see what happened during this period of time and what we're going to see.

By the way, at 2 hours, we sacrificed the animal and took the

brain out, we took a lung out, and we start cutting these and look to see if we see any potential material trapped in these two organs. Sure enough, we saw something in the lung. We could see residual of the WoundStat that had apparently traveled through the jugular vein, end up in the lung, and actually caused thrombosis. Well, okay, a small thrombosis.

But the most interesting is that when you look at the CT of this result 2 hours after reflow, you can see the arrow pointing to the area that was actually treated and later on repaired. With the gauze, there seemed to be no problem. With the Combat Gauze, the vessel regained the flow. But if you look at the WoundStat, there is no flow. The vessel is gone, and you actually see a residue that is left over of WoundStat. That was the artery.

And the same thing happened with the vein in the gauze and Combat Gauze. The vein was constricted with the WoundStat; it's completely ablated. And when you open those 2 hours later and compare the Combat Gauze with WoundStat, the vessel treated with Combat Gauze was nice and clear, there was no thrombus seen in it histologically and also microscopically, but the wound that was treated with the tissues -- those vessels treated with WoundStat was clotted with the blood clots completely, and there was no flow, at least in many of them -- majority of them.

So that was a question. That became a situation. You know, we know there's a little bit leftover material, and that may be causing it, but this is really a significant problem. So this is the time that Dr. Bowman, one

of our colleagues, brought us to attention an earlier cytotoxicity study, and they actually showed aluminum silicate, which basically is a kaolin and smectite, actually have toxicity, but not against most cells, but most important cell, the endothelial cells; a test that required, as cytotoxicity for tests, approval of most hemostatic agents, testing the material against fibroblast. Well, we said fibroblast is really not here. What we need to see, if these materials are actually damaging endothelial cells.

So we set up this study to use three different cell cultures: HeLa cell, which represents more epithelial cell; macrophage-like cells; and finally human umbilical material cell cultures. And we exposed them to different materials. To make a long story short, HeLa cell showed no toxicity of any of the material. On the other hand, macrophages began to show toxicity at a concentration of 50 µg/mL. And when it came to the endothelial cell, even the lower concentration showed toxicity against the kaolin, which is a pure kaolin, and WoundStat; and for that matter, bentonite, which was a component of WoundStat.

So we kind of find out a toxicity test, now in vitro toxicity, which was very important to look at some of these materials, because if they can cause -- kill the endothelial cell, this might be really the reason why we see all of those clotting formations.

And, by the way, we tested another way. The way that I showed you is by directly putting the material into the tissue culture. Well,

what if we actually put the material in a filter and suspend it in the media? Not direct exposure because they actually have toxicity. It turns out that they don't. So it's not something comes off the material extracted or washing out that caused toxicity. It's actually exposure of material directly to the cell that causes toxicity, and that you could see in phase contrast. Even after 1 hour of adding WoundStat, that's the control and you can see on 1 hour, when you look under, the material actually attracted these aluminum silicate materials to stick to the membrane and began to break down the cells and the pyknotic of the nuclei.

So we came back to say, if we want to really see the cell studies, how toxic is it? It's not like to use fibroblast. We have to really go back and use endothelial cells because this material very much comes into contact with endothelial cells when you put them in the wound. So this was our in vitro.

Finally, one other thing I want to talk about is do we have a long-term effect? We proved at that moment these resolved; essentially removed WoundStat as possible use at all. It was eliminated, and no longer that product is being now made at all. So now remained Combat Gauze. It becomes the number one product that was fielded and replacing both QuikClot and now all three forces was using it. But, remember, even in Combat Gauze we saw residual healing, and it was important to see if those residuals can have some long-term effect.

So we did essentially the same model we did, except instead of stopping the experiment at 2 hours, we let it go for 2 weeks. And you can see, within 2 weeks, the vessel that was treated with Combat Gauze completely healed, and the blood flow remained after Day 1, 7, and 14. There are no differences. CTs of blood vessel showed the same thing happened to the venous site. Again, the injury -- there is a constriction of the vein, but after 14 days the vein came back to normal and the flow reestablished, but there was no long-term effect.

And if you take it out and look at the vessel, essentially we saw no differences to the vessel that was treated with gauze versus Combat Gauze. They looked clean and nice and flow maintained. So we're really looking at the Combat Gauze in the short term and in the long term. No effect on thrombogenicity in the short term and no effect in the long term.

And, by the way, the best way we knew these pigs are doing well is when we measured their weight, and you see their weight gain is essentially the same as the control. So metabolically they are the same, they are normal. So the Combat Gauze happened to be good and effective and is a safe agent.

I'm not quite sure how much time I have, but let me just kind of show you work I spent on -- the approaches are now -- so far, what I have talked is about the topical agent. What about the new development of this noncompressible bleeding? And which you heard about it. There are

essentially three ways to stop this type of bleeding: intravenous injection of hemostatic drug -- that's already been done and those materials have been developed; so REBOA, that you heard yesterday extensively; I want to talk a few points about intracavitary administration of these agents.

So this is the approach that Colonel Holcomb suggested a long time ago. And, in fact, I was one of the early people who were trying to see if we can develop a fibrin sealant foam for this material, and I will give you some of the data.

So this material comes essentially in three different ways: either it's foam or fibrinogen based -- we heard about it yesterday; fibrin clot was an example of that, which essentially is a fibrin that is formed in the abdomen and hopefully will stick to the tissue and stop the bleeding. The other one is a product coming along; it's a chitosan-made foam with the same idea. You inject it into the abdominal cavity, and if it comes into contact, it seemed to stop -- stick to the tissue and possibly stop the bleeding. And, finally, a product that you're probably going to hear much more about it is the non-hemostatic foam. We call it tamponade foam, which is the Arsenal foam that you will hear later on. So these are the three different types of the foam that we will see.

Now, what kind of model should we use as ideal model for treating -- for testing these materials? It's not much different than what we talk about, you know, a compressible model. Essentially, we want to have a

truncal injury with severe bleeding. We want to have a bleeding. There is no access to be treated with topical agent. We want to have a large blood loss, again, to use as an endpoint with a high mortality when we do not do any hemostatic intervention because really there is no way of reaching it.

And, finally, most importantly again, I will say, we want to see this correlation between blood loss and mortality. If we use something, it should reduce the bleeding and increase the survival rate. And hopefully, whatever we use, we want the model to be compatible with that principle of a small-volume fluid resuscitation, which is the only way that it's going to be treated, a patient on the field, on the battlefield. They're not going to get liters and liters of crystalloid. They're going to give a very minimal amount of colloid. So that we would consider to be an ideal model.

And, by the way, you can essentially use whatever I mentioned to you, as far as liver injuries, splenic injuries. There are two ways of doing it: You can open the animal and make the injury. This happened to be a rabbit model. We cut the liver, and once the bleeding is stopped, we close the abdomen and we inject it with the fibrin sealant foam in that manner, and we look to see if the bleeding slows down or not. And you can do that in any of the pig studies as well. The liver injury can be done, the model that we use, close the animal and inject it. So that was the only way of administration of material that would be different.

But one of the early things we learned about this is the

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difficulty to stop this bleeding is much harder. You can have a material that you can put directly on the tissue and it can stop the bleeding very nicely, including fibrin sealant foam. But when you inject it into the abdomen, you have a problem because the material cannot penetrate everywhere, and it cannot reach the area that actually bleeding has started.

Not only that, we always recognize that the treatment will come later on. So when we let the animal bleed for 15 minutes and then we inject the material, we found that material distributed nicely, but the blood that is actually pooling around the injured organ becomes an obstruction, becomes physically obstructing and wouldn't let material to get to the injury site. So then you have a very nice hemostatic material. When it came to the closed abdomen application, they would not work. They would not work because that pool of blood, that clot becomes a physical stoppage and wouldn't allow it to reach. So we had material that worked perfectly well in an open abdomen. When we closed the abdomen, we saw no result.

I'm just going to quickly mention about this model that you probably will hear a lot more about. And this is an elegant model, the injury produced in a closed abdomen, and is a lethal model, Grade 5 liver injury. The difference between this one and the one we described is in here. Not only hepatic vein has been cut, we go in and actually pull the vein, which is the main vein that comes to the liver is also injured. So the bleeding is far more faster and puts animal in exsanguination much, much sooner. This is a

lot more bleeding and much more dangerous bleeding. In people, this type of injury can be very much lethal, very fast. However, the authors believe that to make this model lethal, they really needed to add to this, this high resuscitation fluid. So they're giving the fluid, crystalloid, for up to -- 10 liters may be necessary for this model to make it, at least in the control, the untreated, to have 90% mortality. And that's the design of the study.

So we were at some point, possibly, that we actually may be doing some confirmation study, testing the foam in ISR. So we said that -- going back to our ideal model, we said, can we actually modify this model as minimal as possible, but make it compatible without a small-volume fluid resuscitation? Can we have a still lethal model and closed abdomen with the limited fluid? And the limited fluid was basically what has been recommended on the field, which is about one liter to the normal casualty, and we extend it down to 15. So we limit our fluid resuscitation to about 600, 700 mL.

And what we found out, if we actually do the same injuries that they were doing, we couldn't even get to the resuscitation. Your animal will exsanguinate very quickly, because we actually weighed them for at least 10 minutes before we started resuscitation. So we said, well, maybe we have to tune down this, and the only thing we did, we maintained the portal hepatic vein injury essentially the same. We made a smaller injury on portal vein and more reproducible and giving a small amount of fluid resuscitation to see how

we're going to do it. And guess what? Our initial review showed that the pressure dropped very rapidly, but magically seemed to be -- with some of these animals, as soon as we give them a little bit of fluid, their blood pressure came back, and they seemed like nothing happened to them. They survived very nicely. So we said, wow, look at this. This small resuscitation fluid is a magical thing.

So let's take the fluid away. We'll just do the injury and do nothing and see what happens. We did the same thing, and the same results. Some of the animals -- a majority of these animals sort of began to come back, and they improved pressure and they began to survive.

So we were beginning to believe that actually we need to give a lot of fluid to make this bleeding more significant, until we look at some of the data, data of these animals. If we look at it and we compare and we look at it and see these animals, in average, lost about 56% blood. And this 56% blood, we look at it to see what -- and platelet count and fibrinogen level at the end, right? And we noticed the amount that actually dropped is only about 25%. So how come? The animal is losing 55% blood, but the final hematic is only 25%. So where did they get this extra blood? And, obviously, this extra blood makes them to survive. So something else is coming to the plate, and that's something that we've always been doing in the past, but we didn't do that because we want to be as close to the model that has been presented.

So what we said, there's only one thing, this pig has -- they have this nice big spleen sitting out there as a reservoir. As soon as they get stressed out, as soon as the pressure of the spleen contracts and gives them an auto-transfusion, gives them a fair amount of blood. And could that be actually responsible for the fact that this animal recovered? Sure enough, we did it, take the spleen out and look at it. Our blood loss slightly increases, about 63%, but not significant to the previous one. But on the other hand, our mortality now was significantly increased. We had only about 15% survived. And now if you look at the hemoglobin platelet count, all correspond to the loss of blood loss. We do not see that.

But we think a splenectomy or a spleen plays a major role in pig and lower animal. We don't have that, we don't have that reservoir. So, if we want to make a model that's compatible with the human, we really need to take the spleen out so we take that confounding effect out. So now we have this model, and that perhaps hopefully in the future will be used for other things.

Okay, that's the efficacy study. What about safety? Can we come up with safety evaluation of intracavitary agent? I said, well, the same thing that we talk about topical stuff, it also applies to the noncompressible or intracavitary situation. We have to look at that thrombogenicity effect, the embolism, all of those questions should be answered. But there are two other factors that should be kept in mind, and that is what would be the

respiratory effect and what is the hemodynamics? At this time we're injecting these materials into the abdomen. Could they actually have some problems, some reservation, in this situation? The reason I say that, because we did a study early. We were aware of the possibility that a couple of studies came out showing that actually by putting air into the abdomen of the pig, you can actually reduce the bleeding. So just the pressure, a small amount of pressure.

But when we look at two of the studies, we notice all of those pigs were ventilated on mechanical ventilation. What if they are not ventilated? What if you have a patient in the field and you're stuffing it into the patient? If they increase the abdomen, could they actually change the respiration? Could they put him in trouble? You can see, we actually could not show any difference between the animal that was hemorrhaged only -- by the way, the hemorrhage is uncontrolled hemorrhage. We cut the spleen, let them bleed, we close the abdomen, and we inject the air. We inject air up to 10 mm/Hg, and that was nitrogen essentially. But the animal left on spontaneous bleeding, we found that when we put the air, we couldn't actually change the blood loss. We can see the blood loss is almost identical.

On the other hand, look at the survival. The animal that just bled only, they live -- 71% of them live much longer. But the animal that actually got hemorrhage plus abdominal insufflation plus that 10 mm, they start dying much faster and sooner. And the reason was this: because once

you put the pressure in their abdomen -- these are spontaneous bleeding -- their respiration starts falling. That's RR, respiration rate. Their  $PtO_2$  increases because no longer they can expel all the  $CO_2$  from their bodies. So that will build up. What happened to pH? Falling, the pH falling in those animals and the lactate levels increased. So they not only had metabolic acidosis from hemorrhage, now we're adding respiratory acidosis because of the pressure that we put in the abdomen. So mechanical ventilation becomes an issue. If it's not present, then anything you put in the abdomen could have a respiratory effect.

But what about another? This was much earlier stuff. What about the pressure that we put in the abdomen, could that actually reduce the blood flow to the heart? Could that actually collapse the vena cava? This was in a study done in the rat a long time ago, with the help of Colonel Holcomb, that would suggest that, could that insufflation of the abdomen with pressure actually change their hemodynamics? And this is a rat study.

You can see, these are the blood pressures of the animal basically after we put in -- we take blood out of them. This is a controlled hemorrhage. This is the animal that was not hemorrhaged. We put, for 15 minutes, either 5 or 10 or 15 mm/Hg of pressure in the abdomen, and then we open it and let it go out and we just see what happens with this animal. If you look at it, down in insufflation, you can see, at that moment there is a

soft pressure drop. When you desufflate, we let the air go out, the pressure comes back and all of these animals survive. So they can tolerate, under known loss of blood, up to 15 mm/Hg of pressure. But what happens if this animal hemorrhaged earlier? Could they have still tolerated that site on that kind of pressure?

So here is the next. This is the animal we first took 15 mL of blood out of them so their blood pressure is lower. You can see it fall and then recovered and stayed around 60 mm/Hg. Now we put the pressure. Those who didn't get pressure, 0 mm/Hg or 5 mm, they seem to do fine; they survived the entire time. But those who got 10 and 15, now 10 and 15 mm/Hg dropped their pressure and then we desufflate them; they did not recover. Now, that was enough that potentially completely cut down the blood flow, and those animals died.

So this here, what it's really telling you is that the pressure that we generate into the abdomen and the effect of it, a lot depends on how much that patient has bled already and what -- that becomes very critical because that can be a component of -- now extra pressure can kill them or can save them. It depends on where it goes.

I must acknowledge a group of patrons, including some of them who are present here, as my mentors and lead the work to do, and this was really with the help of many people that were involved at ISR.

I thank you very much for your attention, and I'm open for any

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questions.

(Applause.)

MS. KUMAR: We have about 5 minutes for questions, if anyone has any.

DR. KHEIRABADI: Yeah, I went too fast to finish on time.

UNIDENTIFIED SPEAKER: Bijan, that was a great overview of a lot of work over a number of years. On the negative pressure Wound V.A.C. study --

DR. KHEIRABADI: Yes.

UNIDENTIFIED SPEAKER: -- did you just do negative pressure by itself?

DR. KHEIRABADI: Yes. Actually, we had to combine it with the gauze. In other words, if we would have just put negative pressure -- by the way, the negative pressure also, we found, is not the low negative pressure that they use for wound healing, which is like 80 or 120 or so. We actually have to put in a very high negative pressure with a suction line in the OR, which was about 500 mm/Hg. But if we would have just put that one on, which is basically connected to the suction line in the OR, that pressure and the Wound V.A.C. alone, it did not stop the bleeding. We continued seeing the blood going. It only worked when we actually first dressed the wound with either Combat Gauze or gauze and then put the negative pressure. And that really helped that clot begin to form on the junctional --

UNIDENTIFIED SPEAKER: So how does the negative -- how do the two combine? How does it work? Why does it work?

DR. KHEIRABADI: Really, the best way I could say it is, when you put it initially in there, there's a lot of blood coming, too. But then, as it pressurizes, it seemed to be actually constricting. The wound becomes smaller and smaller, and as it's constricted, it constricts the blood vessel. So the pressure is high enough to make this constriction happen and also bring that gauze much closer to the wound site. And the combination of the two seemed to be producing the clot.

UNIDENTIFIED SPEAKER: Bijan, a good talk. As you know, those of us in military labs, there's a lot of discussion about standardizing the models we use for testing these various products. Yet, many would say that having multiple models showing similar results would be more robust and would translate the data better to human. So I was wondering if you could comment on that.

DR. KHEIRABADI: I totally agree with that. I think as long as we meet those initial criteria that I mentioned, it doesn't have to be -- because, clearly, every wounds are different, the wounds are different. But as long as we have a model that produces large bleeding and the treatment is consistent with what might be used in a standard of care, I don't think what model we use is important. In fact, I think the different -- if you can prove a product in a different model, the validity of your experiment, the validity of

product will be much greater because it really shows that versatility of the product. If you show it only under one condition, one condition and only one condition, you can't really guarantee that it works in a situation with a different type of wound.

DR. ASHAR: You showed some pretty impressive slides demonstrating that the CT scans in the animal model that was treated, I think, with plain gauze, Combat Gauze, and WoundStat; there were cases, I think, in the WoundStat right where there was obstruction or thrombosis of the carotid artery and vein.

DR. KHEIRABADI: Yes.

DR. ASHAR: And so that caused the decision, I guess, to find one product more preferable than the other --

DR. KHEIRABADI: Yes.

DR. ASHAR: -- at least based on the animal studies.

DR. KHEIRABADI: Yes.

DR. ASHAR: I'm wondering, because of the difference in the coagulation capabilities in the animal model versus the human model, you know, how that translated in the experience in humans once the product was released.

DR. KHEIRABADI: I think the product -- I think there were only a very few of them used in people in some circumstances. And, secondly, we have the same question, and I think that's what led us to look at the tissue

cultures, and that was actually human endothelial vein cells. So this wasn't really specifically damaging the vessels in the pig. It actually even kills endothelial cells in the human cell cultures. So I'm pretty confident that that damage that we saw, it would easily be translatable to the human, if there was any vein patient treated with that.

Oh, by the way, we found out that if you just put it outside of the vessel -- which we did, actually -- actually causing the injury, we didn't do injury. We just load that on top of the vessel, it didn't cause any. So it didn't really kill the outside tissue of the vessel, but it only caused thrombosis when there was any injury and the material reached inside the blood vessel and inside the material --

(Applause.)

MS. KUMAR: Okay, at this time we're going to begin Session IV, and Session IV is entitled Challenges in Evaluation and Validation. And the objective of hosting this session during this workshop is to really gain a better understanding of the advances in preclinical bench testing, so what novel advances have been made in these studies and the various -- continued discussion on the various translational animal models that are being done.

So I would like to invite Mr. Adam Rago, who is a senior scientist with Arsenal Medical, to begin this session.

MR. RAGO: Good morning. I'd like to start by extending my thanks to the FDA and the meeting organizers for really bringing together

such a group of people, and for the opportunity to share some really exciting work that we've done in collaboration with Dr. David King's lab at Mass General Hospital.

So, in this morning's talk, I will kind of cover two things at a high level. The first is our work in preclinical animal models, and then I'll pass the torch to Dr. King to talk about a very interesting translational study that's ongoing in the lab.

So as Dr. Sharma mentioned yesterday, we're developing an expandable polyurethane foam technology for treatment of noncompressible hemorrhage, and this is something that we've studied extensively in animals and on the bench.

Before diving into a bunch of data, we wanted to really recognize an outstanding advisory board that we've had the privilege of working with. This group of clinicians and subject matter experts have been really critical in developing these animal models, interpreting the results, and helping us translate our results in swine to humans.

You certainly see Dr. Kheirabadi up here. It's a nice transition from his talk into the requirements, that we set out to test a self-expanding polyurethane foam. So some of these things you've already seen. It's very consistent. We prioritize testing in large animal models. We also prioritize testing this technology for noncompressible hemorrhage in a closed cavity model, and that was largely based on the experience that some interventions

worked well in the open abdomen but worked poorly in closed abdomen models.

We prioritize testing in multiple trauma or hemorrhage scenarios, specifically an arterial bleeding scenario and a venous bleeding scenario. And we really focused on models that were lethal so we had that binary signal, live or dead, mortality. We measured a variety of secondary endpoints as well. Obviously, they need to be consistent and reproducible, and of course, results need to be compared to a control group.

Additionally, we felt the material or essential testing was in a large animal survival model to understand the long-term tolerability of the material and the intervention.

So at the time -- this is somewhat historical data -- in May 2010, we surveyed the animal models that were available and had been developed in the literature. We classified them kind of broadly into two key factors. The first is whether it was an open or closed abdomen model, and the second was whether it's lethal or non-lethal, and as you can see from the table, there was no existing model that was both lethal and closed cavity. So we took various elements of many of these animal models that have been used extensively and combined them to generate a new animal model for the evaluation of foam.

So we've used animal models extensively throughout this testing. I'll go into detail on our work in a lethal liver injury model and a

lethal iliac injury model. But as Dr. Sharma mentioned yesterday, we've also tested, in additional animal models, to select the material that worked and to determine that it was safe.

And, finally, a note for this forum. We are using the biocompatibility testing according to the ISO 10993 standard to augment the safety profile and to confirm biocompatibility.

So our injury models, we think, are best shown by a video, which I'll show here.

(Video played.)

MR. RAGO: So the MGH lab has developed a technique where wires can be placed percutaneously and then -- or placed through an open laparotomy and externalized through the skin, such that pulling them leads to a robust closed cavity injury. So it doesn't look like much here, but as we cut away, just looking at it from an open cavity, you can see a very robust bleeding and this pool of blood that forms around highly variable anatomy, shown here in a liver injury.

The foam system is deployed 10 minutes after that injury. You see it here being delivered from an early prototype, but again looks like a caulking gun. It mixes those two components together, and they react to expand the abdomen, as you'll see in a moment.

We followed these animals for 3 hours, looking primarily at vital signs. And then when the material was removed at 180 minutes or the

time of death, we also aspirated and quantified the amount of blood in the cavity as a blood loss measurement.

You'll see Dr. Duggan at MGH removing the foam. It comes out as a solid block, and it conforms to that abdominal anatomy. As you can see, it's removed quite rapidly. It's typically taken us about a minute to remove the material.

(Video ended.)

MR. RAGO: So these are the results from that model. First, just the animal model itself. We see very rapid mortality in the control group, which is shown in red here. The intervention is at 10 minutes. We see rapid mortality of the animals within that first hour, down to about 8% survival at 60 minutes. The foam intervention is shown in the blue curve. This resulted in a significant survival benefit and a reduction in hemorrhage relative to the control. So the baseline case had about 95% survival at 1 hour and about 70% at a 3-hour time point.

We augmented this data by testing different doses of the foam. As you can see on the Kaplan-Meier, we established dose dependence of this effectiveness, where more foam led to improved outcomes. And, again, all of the doses that we tested over this profile demonstrated significant benefit in both hemorrhage rate and in survival.

So that's a venous injury model. One of our priorities, as I mentioned earlier, is studying an arterial injury model as well. So here we

have a brief video to get a sense of what transection of the iliac artery looks like.

(Video played.)

MR. RAGO: Here we show it in the open abdomen, but again, this is a closed abdomen model when we're testing our materials and when we're testing the control group. If you recall the video Dr. King showed yesterday of intra-abdominal bleeding, this tends to look quite similar, although it isn't a swine. It leads to robust rapid arterial bleeding that is lethal without intervention.

(Video ended.)

MR. RAGO: That's shown nicely by the red curve here. Again, survival is a function of time. In the control group alone there's very rapid mortality. The intervention with the foam again supports survival, significant at a 1-hour time point and then out to 3 hours as well.

So we didn't touch on it in detail in this presentation. We've also looked at a survival model and used that to demonstrate the long-term viability of the treatment. The work has been published extensively. You can see the references at the bottom here, and we'd be happy to point people in the right direction there.

I think the other note that I'll make is that we are planning on working with an outside CRO to confirm all of this work in studies according to good laboratory practices, and that work will take place this fall.

And so with that, we've done a great deal of work in swine, and I presented a small portion of it here today. And one of the things that our group and the MGH group has been thinking about extensively is how you take these promising results in swine and translate them into something that's safe and effective in humans. So I believe we designed a very interesting and unique study to address that concern, and I'll pass it off to Dr. King here to take you through what that study looks like.

DR. KING: Thanks, Adam.

So, if you look back at this body of work, almost 600 animal experiments all together. And this is not all of it, by a long shot. We're really good at learning how to save pigs. Well, first, we're really good at killing them and then really good at creating interventions to save them. And if you happen to have a pet hog that gets hit by a car or something, we can fix that and in a very reliable, reproducible way. I have largely concluded, from years of this animal work, that we have an intervention that has an extremely favorable risk/benefit profile for reducing mortality and hemorrhage-related death in pigs. So that's great. But pigs aren't war fighters, at least not yet. And I don't see a big push from thought leaders in the United States, related to civilian trauma care, pushing for a new hemostatic intervention in pigs.

So somehow we have to get from here to human beings, and at the end of the day, anything we do and anything Bijan does and anything anyone does in the animal lab is still in the animal lab. And making the

successful transition is a challenge. As Dr. Kheirabadi pointed out, sometimes things go awry, right? They appear to work perfectly well in the animal lab, and then you get to human beings, and the first few out of the box, you realize that granular zeolite makes burns. Just a variety of unforeseen stumbling blocks that probably, maybe, you conceived of in the animal lab.

So we contrived this pathway to get from pigs to humans, and there's a variety of ways to do this. Initially, we brainstormed a whole bunch of pathways for it, and you can imagine the ideas that come up. You think about non-human primates. You start doing non-human primate work, and you still suffer from the same problem, that there's obvious significant anatomical differences between non-human primates and humans. It's still an animal, and it's not a human being.

We thought about using cadavers, as in fixed donated cadavers. So we did that. As it turns out, the tissue compliance is terrible. When you have an intervention that's heavily dependent on normal human tissue compliance, that's a no-go. We thought that changing compliance was related to temperature and fixation. So we took some cadavers and we warmed them up, which made the lab smell fantastic, and as it turns out, warming them up doesn't change the tissue compliance very much at all. And we tried un-fixed, we tried perfused cadavers, so warming them from the inside; that didn't work well either.

So we've been down this road a variety -- tried a variety of

approaches to try to make a logical anatomic leap from animals to human beings. And along this brainstorming pathway, we came up with this, what, at the time, I regarded as a ridiculous idea. And the moment I thought about it, I dismissed it until everything else failed and then, of course, you come back to moments of desperation and innovation.

And the idea was to take human beings, patients who had just recently passed and test your -- test this intervention in them, which, of course, would have representative tissue compliance and representative anatomy to human beings. But, of course, to my knowledge, it had never been done before, and the major hurdle, I thought, would be who in the world would ever consent to this, right? Your family member is dying in the ICU, and you're going to walk up to them and say hey, by the way, after grandma passes, we'd like to perform this crazy study. And so I thought the hurdles were probably too many to overcome, but we decided to proceed anyway. And that's what we're terming the recently deceased study, and I'll go into some details on exactly what that is in a moment.

So making this transition from animal anatomy to human anatomy is a big deal. We learned a lot and based many of our mathematical assumptions on dose translation based on a fairly large existing body of literature on abdominal gas insufflation, particularly during laparoscopic surgery, right?

So you take human beings -- and this is widely published --

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undergoing elective laparoscopic anything. You can measure the gas insufflation and the pressure/volume relationship that exists, and we compared that back to swine and did many, many iterations of this, created mathematical relationships and tried to predict what the right dose would be, and took that dose and brought it to the so-called recently deceased in an effort to bridge what I think is an extraordinarily large gap, right?

The idea that you're going to take an intervention as unusual as intraperitoneal injection of a foam that undergoes a phase change from liquid to solid and leave it there for a few hours, I mean, it's a pretty big leap to propose going straight from animal models, which at the end of the day are just a set of contrived circumstances that we create, to a live human being. It seems largely unethical, and this was our natural conclusion, is that that probably was unethical. There had to be some intermediate step, and we think this recently deceased study represents the appropriate intermediate step.

Probably we're learning a lot from this study. Let me frame it for you. The idea was to take what we thought was a mathematical assumption or a mathematical derivation of the appropriate dose for a human being based on gas insufflation data and take that to patients, recently deceased patients, with naturally representative anatomy. This has a variety of significant issues. It's not just the fact that the organ sizes are different or the colon is located in a slightly different place or the omentum is

bigger and more robust in humans. But it's also the abdominal wall, right? Pigs are quadrupeds; they're on all fours. As they grow, their belly gets bigger and bigger and hangs lower and lower to the ground, and the abdominal wall compliance ends up being a pretty significant issue versus humans, who are upright and, you know, depending on how much you work out, you may have this distensible abdominal wall or not. And these things needed to be looked at.

So the population is human beings with virgin abdomens -- so no prior abdominal surgery or abdominal pathology -- who have recently died. We consent the families once patients are made comfortable or the decision to withdraw care has been made. After they pass, we rapidly meet them at our center, in the morgue, but the site where the procedure is performed varies by institution. I think Houston is doing it in the ICU and Oregon with three sites. Oregon is doing the procedure in some holding room adjacent to the ICU that they have, and we're doing it down in the morgue.

So we engage the recently deceased patient within 3 hours of death. Usually the entire procedure is done within 3 hours of death. And 3 hours comes from the forensic literature. Around 3 hours is when actin and myosin start to cross-link and rigor mortis and tissue changes start to set in.

So our experience, so far, has been that the tissue handling feels entirely normal, as you would expect very recently after death. Most

importantly or equally as important is that because these are patients who have just passed, they are so-called normothermic. They're not perfused, naturally.

This is a variety of our inclusion and exclusion criteria. As you can imagine, it's important that they don't have free intra-abdominal fluid because this changes tissue compliance, especially, for example, patients who are cirrhotic, who may have liters in. So we screen for that.

Importantly, before we inject foam in the recently deceased patients, we have to have a representative fluid volume present in the intraperitoneal space, representing what would be, we think, significant blood loss. So any time you put a volume into an expansile space, the pressure/volume relationship is affected. So it wouldn't be appropriate to inject an intervention into the abdominal cavity that's intended for hemorrhage without somehow simulating what that hemorrhage volume would be because it changes the pressure/volume relationship. So we instill 1500 mL of crystalloid into the abdominal space and then inject foam subsequently to have an adequate representation of what the pressure/volume relationship would necessarily be for someone who is bleeding to death.

The foam is injected, and we wait for it to set up, and after 15 minutes, we characterize the pressure/volume relationship with intravesicular bladder pressure monitoring, and we know from the wealth of

animal data what the pressure/volume relationship should look like from the bladder pressure monitoring. Then we laparotomize the recently deceased patient. At laparotomy, we assess foam contact with a variety of organs -- extent, how many loops of bowel are engaged in the foam and so on -- and we can compare that back to a wealth of animal data relating to tissue contact and so on.

So we're using this study largely to compare back to what is a fairly huge database of animal data, and I think this is allowing us to create an ethical pathway forward to bridge what I think is a fairly enormous gap between animals and our so-called first-in-human -- what our first-in-human experience might look like.

So now, so far, we have three sites that are enrolling patients. Every case, every patient that's enrolled gets reviewed by the entire medical advisory board to determine if dose is too high or dose is too low or problems that have come up and solutions and so on. You think you can conceive of what you might learn from a study like this, but when you actually start doing something as unusual, you start learning things you never knew -- you never expected you might be learning. And this study, as ill conceived as I would have suggested to you when it first crossed my lips years ago, as it turns out, is wildly valuable for us in understanding what foam utilization in human beings looks like.

So far, we've been at this about a year. We've injected foam in

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10 recently deceased human beings. Getting there was not so easy, though. When you go to the IRB with a study like this, they scratch their head and say, you want to do what? So it took a little while to push through, particularly especially at my institution.

It's shocking, though. What I thought would end up being the most difficult part of this, obtaining consent from families, as it turns out was not very difficult at all. When you approach families who have a loved one dying, they are seeking us out. You tell them that you're interested in some research, and they say yes, I want to know. My grandmother would love to give back to society like that. Please tell me about it. I continue to be shocked, really, at the willingness of people in fairly unfortunate circumstances, the willingness of a general population to give back to a greater scientific cause. You know, I'm not sure if my family would be able to make that decision, but the evidence suggests they do because, by and large, families are very open and very willing, assuming their loved one is a candidate.

Important and incumbent upon this process was that we naturally not interfere with the organ donation pool, right? You can't start injecting foam into patients who would have otherwise been a candidate for organ or tissue donation, so we work closely with the organ procurement agencies to make sure that they screen away these patients first. So we wait for them to decline. Once they decline, then we can engage families and

approach.

And I think that's about it. I hope this gives some insight to a very unusual approach.

(Applause.)

DR. FALUS: I have a few questions. That's a large number of animals and several protocols, but having shown the tables compare controls, we don't know the number of efficacy. We understand that there's only one single parameter, which is survival. I would like to know what is the efficacy percent touching the p-values. I would like to know if these are GLP studies. I would like to know if you have conducted safety studies and which status that is. And I would like to know how can you go to an IRB without having an IDE?

DR. KING: So the short answer is -- so we don't get too off the schedule -- all of those questions can be answered by going to PubMed and putting in King, D.R. This is all published in the peer-reviewed literature, all the p-values, all the other surrogate endpoints, like blood loss and ends and so on. I mean, naturally we can't present the entire body of literature here, so we're trying to give you a flavor of the highlights that are very high level. But the details are all in the public domain. I'll be happy to send you copies of all the manuscripts.

Each of the models have model development manuscripts that are in the public domain, and then each of the individual experiments are also

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written up separately. And a variety of other studies that are just coming out and are in various phases of production answer some of your questions specifically related to safety. Adam didn't dwell on that today, but one of the more -- I think, more significant studies we've done is foam injection in animals with a splenic injury, foam explantation and survival for a month, and then we've redone that same series of experiments for survival out to 3 months, looking at a whole variety of safety endpoints.

DR. FALUS: Which one? Which?

DR. KING: Say again?

DR. FALUS: Which kind of safety? What pharmacological values have you studied? Have you studied carcinogenic, mutogenic values, toxicity?

DR. KING: Yes.

DR. FALUS: Adverse events?

DR. KING: Yes and yes, and looked at all manner of end-organ function or dysfunction or lack of or appropriate function, even sort of organism-level endpoints like weight gain and behavior and so on.

DR. FALUS: Right. Is this a GLP study?

DR. KING: All of these acute studies are non-GLP studies, and a variety of these have been and are being reproduced in GLP in a GLP lab.

MS. KUMAR: Okay, I'd like to introduce our next speaker.

Dr. Mike Ramsey is the CEO of CardioCommand.

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DR. RAMSEY: Good morning. This was my original talk title, but after hearing a few comments yesterday, I decided to recast it:

"Ballistics, Blood, and Balloon Tamponade: Testing in 50+ Gunshot Wounds Guides Development and Refinement of an Exovascular, Low Weight and Cube Device by Using Focused Empiricism."

(Laughter.)

DR. RAMSEY: I wish Todd Rasmussen was here to hear some of that.

CardioCommand is a small company in Tampa, Florida. We're in the transesophageal cardiac pacing business fundamentally, but an accident happened a number of years ago to a friend of mine; he was killed in a hunting accident. Another good friend was the first responder and attempted to stop the bleeding, both entry and exit, by stuffing it with strips of cloth torn from a T-shirt. I was moved by that. And that day we decided we were going to develop a device for treating that type of hemorrhage. It was not our business, but it became our mission and it still is.

Reviewing the scientific literature, trying to figure out what method of action we would use, balloon tamponade became the candidate of choice for us. It was often successfully used in penetrating trauma, even though the actual balloons used were improvised or repurposed. There was nothing designed in the balloon tamponade technology to deal with penetrating trauma, but they were still being used.

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The first report that I am aware of, of penetrating trauma being treated with balloon tamponade is Morimoto from Brazil, and he tied a piece of Penrose drain around a Robinson-type catheter, put it into the liver, blew it up and blew it up firmly enough so that the ends bulged out and actually locked it into place. That's a phenomenon that you will see in some of the things I will show later.

Jugular and carotid artery gunshot wounds and stab wounds treated using a Foley, they were successful in five out of eight cases. That was percutaneously introduced. Pelvic and rectal gunshot wounds, also successfully treated at surgery with an improvised device: a Foley catheter.

These are the two devices that are available commercially that are largely involved in the many reports of using balloon tamponade to control hemorrhage of many different types and in many different locations in the body. And in that regard, I highly recommend David Feliciano's two publications, spaced 10 years apart, about the utility and safety of balloon tamponade.

The Foley catheter dates back to 1930 and Sengstaken-Blakemore to 1950. These are, as I said, the ones that are used, even though they're not designed or cleared, from a regulatory standpoint, for treating hemorrhage.

Like direct pressure, balloon tamponade is effective if it can get to and compress the bleeding. But the existing devices are inadequate. Our

goal is to build -- is to design a balloon catheter that, number one, can be used in the field to be inserted transcutaneously and navigate completely the wound track of a ballistic injury and, once navigated, has enough potential volume to tamponade the entire track.

Our first-generation prototypes. Here are some of them.

There actually were a number of others, but these are representative, and basically, they're fairly delicate devices: a 10 French catheter and a 5 French catheter with a 25 cm balloon of 2 cm in diameter. We have a stiffening stylet to help get it into the wound. And they look good on paper, they look good in prototype form, but will they work? So we're going to test them in some wounded dead tissue.

Pork and beef were our dead tissues of choice. They were shot with a .38 Special, and you can see that in this particular pork roast, one of the exits is a nice round exit; the other two are linear. We don't know exactly what to make of that, but we were able to navigate those wounds and insert and inflate our prototype balloon catheter; similarly in an eye of the round.

When we opened the wounds by inserting a long knife and slicing, we weren't too impressed with what we saw. As you can see, there's a little roughened tissue there. There are a couple of what I call catch points here and here. But, basically, the bullet has not done much damage. Those little catch points, however, did make it very difficult in some cases to get the catheter through. It just simply hung up on those little points.

Well, as a summary of the first tissue tests, all the wound tracks were successfully intubated, but as I said, some were very difficult. Balloon inflation at 250 mm/Hg did not tear any tissue, and that pretty much confirms the safety that we read of using balloon tamponade in the literature. However, the first tests do show that improvements are necessary. In both our test methods and in the improved catheter navigation, it was very hard to get it through the wound.

On the wound ballistic side we went to school, literally, with Martin Fackler, who is a well-known ballistics expert. And this slide contains a lot of data. It is taken from Fackler's work, and its shots fired into ballistic gelatin. Now, the ballistic gelatin is not human tissue, but it has been established and sort of calibrated -- and literally, it is calibrated -- to mimic human muscle tissue. And when you fire various bullets into ballistic gelatin, you get various types of temporary cavities, which are the dotted lines, and permanent cavities, which are the solid areas. Fackler describes the solid area of the permanent cavity as tissue that's been crushed and the temporary cavity as tissue that's been stretched.

Obviously, the depth that the permanent cavity develops is variable, but typically it's way out of the distance that you can reach with a finger; the thigh depth, 12 cm; pelvis depth, 25 cm. We wanted to make sure that TourniCath, our balloon tamponade device, would reach into an area deep enough to actually get into the permanent cavity.

Interestingly, if you're not familiar with wound ballistics, the major portion of the permanent cavity is caused because the bullet is unstable in the tissue and it tumbles and crushes a lot of tissue before it typically exits rear first.

We knew we needed something more powerful than a .38 Special, and so we selected what Dirty Harry would choose, a .44 Magnum. It has roughly six times the power of a .38 Special and, in clear ballistic gelatin, it makes an impressive impact. You can see this very large temporary cavity. The bullet completely penetrates the gelatin and comes out sideways. The question is, what kind of wound would it produce in tissue that we could study?

We ended up using a .44 Magnum to shoot a pork shoulder roast, and as a way of examining what it did, we used a gastroscope and actually intubated it, and this is a video that shows what we saw.

(Video played.)

DR. RAMSEY: This area on the right that's very bright and the area on the left that's bright, that's actually broken bone. We're looking into the entrance, and it's just cleaved a spot through the bone and we're inserting into the wound cavity. You can see the tremendous permanent cavity that it's created. The exit wound in the back there is about the size of a quarter.

(Video ended.)

DR. RAMSEY: So we knew we needed bigger balloons. We also knew we needed better ability to navigate the wound. If a bullet made the hole, maybe a bullet would be a good thing to use as an exploring tip. So we got various different types of bullets, put them on the end of our metal stylet, which now goes totally through the catheter, and it allowed us to introduce the bullet, the exploring tip, pushing on the stylet, advancing the bullet and then, using a Seldinger-type technique, push the catheter to join the bullet. And then, inching it along in that way, we felt like we would be able to navigate tissue wounds much more easily than the original designs.

We developed a test model to test these new devices. It was going to be dead tissue. We were going to use pork hindquarters. We were going to actually use gravity fed arterial pressure, a captive bolt gun to inflict injury, and quantitate the rate of blood loss before treatment, insert the catheter, and then inflate and determine the tamponade effectiveness.

Our proposal unfortunately was not funded. However, at an ATACC meeting where we had a poster showing the results of the first live tissue -- excuse me -- the dead tissue tests, we were offered the opportunity to piggy-back, so to speak, on a medic training course field day where a porcine model with 200-pound sows and wounds inflicted by modestly powerful handguns, we would be able to test.

We did 15 wound track placements in 11 subjects, 5 subjects living, 6 freshly dead; encouraging results and observations -- encouraging

results, but observations -- a lot of wounds involved bone. All attempts were successful to navigate and the time to track -- I mean, time to complete the insertion and inflation was about 10 to 90 seconds. Most were without difficulty. With the exploring tips that I showed, it was really pretty easy. Interestingly, there was really no difference in the feel or process between dead tissue -- between freshly dead tissue and living tissue.

Based on those experiences, we went to a third-generation design: shorter, square shoulder balloon; inner and outer telescoping sheaths; larger, same diameter sheath as the tip. We now have a tip that is attached to the balloon rather than to the stylet. And as you can see, there is the final design at the bottom. Third gen looks pretty close to it.

Another live tissue testing session; the same thing, but in this case we had two sows that were devoted to us exclusively. Twenty-two percent of the balloons actually were punctured by bone. We were very successful, but two of the balloons were punctured by bone. The vital signs were not measured, but the subject survived 2 hours to sacrifice and necropsy. At necropsy, there was no balloon tamponade injury. There were no major clots. It appeared to be working quite nicely, but we need to improve balloon puncture resistance, and we need to measure vital signs to prove tamponade.

In order to test puncture resistance, we constructed a cylinder that had screws that went into it and we put in various types of balloons and

inflated to where they were punctured, and it turns out, two walls are the best, and at 250 and 300 mm/Hg, that's what it took to puncture these balloons with screws punching on them. And still, we never had -- once we went to two balloons, never had a balloon failure.

This is the final device. It's about the size of your little finger in diameter. It's 12 inches long. It weighs 1.3 ounces and occupies 39 cc worth of volume. So it's a very small device. But when inflated, it has a potential volume of 405 cc.

This is the device inflated. This is a wound track model that we made to model a .30 caliber AK-47, and when the device is inserted and inflated, you can see that it conforms to fill the entire wound track.

We had our fourth round of live tissue testing and final design: three subjects, 12 gunshot wounds. One animal died from a pulmonary contusion and pneumothorax on the fifth shot. The other two survived and with stable vitals.

This was our data-taking form, and we had someone from the University of South Florida, a thoracic surgeon, Bill Marshall, there to record. A wound inserted -- I mean, a TourniCath inserted into a through-and-through wound in the shoulder; a wound in the groin; .45 cal. The fact that this bulges out doesn't matter at all; it never comes out.

(Video played.)

DR. RAMSEY: An axillary wound with a 20-gauge slug and a

video of a pretty impressive 20-gauge slug in the groin, which both the surgeon and the big game hunter said, we don't think that one is going to be successful. We installed anyway, pulled the sheath off, inflated, and the animal did well and ended up being experimented on a couple of more times. As you can see, that wound totally swallowed the entire device. That's what it looked like afterwards.

(Video ended.)

DR. RAMSEY: And I mentioned the captive bolt gun. This is a modified captive bolt gun that we also used that day.

And our observations are that large subject, live tissue testing in the field is, we think, pretty good and likely the best simulation of actual field use. Wounded dead tissue is useful. We believe that our artificial circulation model could be useful, and we really feel like a laboratory model is needed that produces massive hemorrhage, 100% lethal early and real-world limited access to the actual wound being treated.

Thank you very much. And thank you, FDA.

(Applause.)

MS. KUMAR: Thank you, Dr. Ramsey.

Our next speaker will be Larry Martinelli, who is a Director at Materials Modification, Incorporated.

MR. MARTINELLI: Thank you. We appreciate the invitation here. We have a little bit of a different type of device than what we have

seen already. Also, with our work with the Army and DARPA, we were focusing on open wounds, open-style wounds versus closed cavity, though we did do some closed cavity experiments.

This program was initiated at the Quick Reaction Fund at OSD. The Medical Research and Materiel Command, they were kind enough to provide some bridge funding, and it was also funded by the U.S. Army AIDE program.

I would like to say that in reality this whole program really began around 2003. We were doing a program with DARPA on brain bleeding and methods of stopping that. That program manager moved on and so did we. And at that point we became more involved with the open wound style models. We focused on the femoral model primarily.

But, basically, GRO-KLOT is an externally applied wound treatment. It produces -- and you can read it through. It's a two-part system. It conforms to all of the wound surfaces. The primary initiator for the expansion of the product is oxygen, so it helps form the polymeric matrix. It conforms to wound surfaces and stops the bleeding. We specifically were directed to stop the bleeding without use of any direct pressure in an open wound. So that was the style, and that was the direction that we were given from the Army.

The pressurization is unidirectional -- omnidirectional. It conforms to difficult wound surfaces. It is used with a hydrocolloid cover

bandage, which offers an additional order of protection. We specifically designed the cover bandage and the hydrocolloid to work in wet and also blood-soaked conditions. Primarily, though, it frees up time for the possibility of treating multiple injured, perhaps reengage in combat, and also has good application in mass casualty civilian scenarios. It is easily and completely removed from the wound site.

This was our development team at MMI. Kris Rangan is here. Dr. Sudarshan couldn't make it this morning. I was on the team, and we had our financial. Surgical was actually provided later in the program by Dr. Grant Bochicchio, who talked yesterday. We also made extensive use of Dr. John Vlazny at a local Barton's West End Facility. And, by the way, Colonel Burris at USUHS was the primary developer and helped us with the early stage models, which were more moderate bleeding.

This is the product. We had some very specific rules we wanted to follow and that the Army had actually wanted us to focus on. First of all, the finished product had to be small enough to fit into a pack along with other types of medical hemostatic-type devices and other medical gear that the medic would carry along. It had to fit easily in a side pocket on a backpack or even on your pants area. So it's a five by six by a little under two-inch package. It weighs around 4.5 ounces. Weight was an extremely important portion of this. And the dose that we are using here -- you can use multiple doses, but to keep it compact, we were looking at a 44 mL dose of

product. It expands to about a 150 mL volume at this point. You can see the wound barrier shield as well.

Essentially, there are six easy steps for this. I have the video. I'm not certain how that might start up. I'm sorry.

(Video played.)

MR. MARTINELLI: Okay -- but essentially prepared a device. It's a self-turbulator that's on there, injected into the wound, as you see in number four. You peel back the wound shield product, and you place it over the wound itself.

This is the typical femoral model. It was used extensively at the time. We were using a 6 mm punch. The product is inserted into the blood area. There's a lot of expansion here, and basically, you put down the cover bandage and we proceeded with the test. This is on the removal. It conforms to the wound. You can see that.

(Video ended.)

MR. MARTINELLI: We started with our rat models, mainly to get our techniques down, to understand the process, to understand the formulation. We did about 62 rat subjects. Of those, we took about 10 or 12. They actually all lived pretty long, over a month, before they were euthanized. Really, this tests the efficacy of the product. We were using 89 -- we went through 89 porcine models and then we were doing final comparative and validation tests with 26 subjects.

In our Phase II, we were doing a fair amount of laboratory bench trials. This was primarily measuring expansion rates. We were looking at temperature, we were looking at pressures that were developed, and we were also looking at getting the proper feel. Yesterday we talked about the use of empirical observations to really determine the best outcomes. And so empirical observation was extremely important, how the product was delivered by hand. There was a lot of feedback on the D.V.M.s on that, to getting the pressure right and getting the formulation and viscosities correct as well, so you can again have hand-delivery.

In the early stages, we did some femoral transection models, and those were fine. We had very good survivability with that. But later, it was determined that the transection model may not actually be the best because it could have some retraction. There were other issues where you could also have some collapse of the vein. So we converted over to the -- from the 4 mm over to the 6 mm punch-style injury. These were the usual Yorkshire porcines, 34 to 38 pounds. They were used throughout all of these trials.

We did two styles of tests. One was more of a moderate bleed test, which was popular at the time that it was being done. HemCon and others were all on that style of test. So those were about -- a top of about 7 mL/kg per minute with the free bleed time. The controls we used were no treatment at all, and those were 27 and 20, as you could read there.

We did, however, then -- in speaking with Dr. Kheirabadi, who at that time was actually developing his high bleed model and a more rigorous model, we then realigned our test practices to conform better to this high bleed rate, more of a failure model so you could differentiate the product from other products in the field. And we had lesser results than we did without the moderate bleeding; however, the results were still very acceptable. The Army was extremely interested in at least that 1-hour survivability, and many of these tests went on to 2 hours and 3 hours.

As we saw in the video, just quickly running through it, the product basically expands into place in approximately 25 to 35 seconds. The hydrocolloid is put in place at about the expansion point, about a little over a minute. And in the 3-minute mark, it's completely cured out and the plug is in place.

Removal we saw in the video. This is a little bit more detailed. It tends to come out in large pieces, and the basic style of the product itself and the coloration actually had enough contrast that it never was confused with the surrounding tissues.

We went through the usual biocompatibilities. These were all produced -- these were all done by NAMSA -- and, you know, going through all the cytotoxicity. You could read through the list on this. No adverse effects were found from this, including the hemolysis. They had their scientists go over all of our constituents and the formulations to do an overall

biological risk assessment, and those conclusions came out positive.

Now, we deviated a little because we knew there was great interest in the liver injury style model. We used more of a macerated approach, which you saw yesterday in great detail. This was performed by Dr. Bochicchio.

We did a number of animals, but here are three of the typical. In the top side you could see, after the foam had expanded, all achieved the hemostasis. And we'll see some results in a moment. Removal, again, was shown to be very easy and very clean, and that's in the lower grouping.

We also did a stomach injury model, and we did some basic tests on that, just as a proof of concept. This was a proof of concept. And, again, the product went in, the bleeding stopped; it was removed very easily.

We used two styles of Grade 5 liver injury, one coagulopathic. You see the results on that. We had 100% survivability at 1 hour and 64% at the 3-hour mark. The non-coagulopathic subjects with free bleed, we were looking at 3-hour survival rate, 100%. We had an hour-and-a-half survival rate -- that was the cutoff on the stomach injury -- with 100% survival.

We're also very happy with the FDA, not only for giving this conference, but they have given us some tremendous guidance. We were in Q-Sub meetings with them. They gave us a very, very good idea where we needed to go. This work is ongoing. We will be taking up our GLP studies shortly and everything that goes along with that. So these were our models

and how we worked and how we developed the product. So, basically, we feel that for us, the de novo process does present an appropriate path for regulatory acceptance.

(Applause.)

MS. KUMAR: Thank you.

Our next speaker will be Dr. Peter Kofinas from the University of Maryland.

DR. KOFINAS: Good morning. I'm Peter Kofinas. I am Associate Dean in the Clark School of Engineering at the University of Maryland, and also Professor of Bioengineering. Our Fischell Department of Bioengineering has a relationship with the FDA, with our CERC center.

The research I'm going to present is very much at the early stage of research. It's a collaboration between us at the University of Maryland, Adam Behrens, who's here in the audience -- he's a graduate student who's leading this research; and we're collaborating with Dr. Anthony Sandler, who's the vice president in Children's National Medical Center and Professor of Pediatric Surgery; also Dr. Brendan Casey, who's also here in the audience. Here at the FDA we're all doing this project together, and I'm going to present you some of our research results on a different approach, which is blow spun biodegradable fibers for surgical applications, but also you'll see how these can be used for other things, like trauma.

So the motivation for our work. It's because it's technically

difficult surgical procedures that lead to increased costs and risk, and there are limitations to conventional techniques, the conventional suturing techniques. So we'd like to use a polymer that helps seal wounds and provides additional strengths in different wounds. This would apply in different procedures, ear, nose, and throat, cardiovascular, and all kinds of procedures. What I show here is intestinal anastomosis, which I'm going to show you a picture of, a video where we tried this, and I can show that our material can withstand quite high of a pressure.

So there are other commercial products for surgery, and we had the various presentations here, too. Similar products are used for trauma. Their main characteristic is that they're biologically active. Most are fibrin-containing products, so that makes them expensive, upwards of \$500 per application. And also some have short shelf life, so they're difficult to store in the field.

So our technology is a synthetic polymer blend, so it's a product that's stable. We use a very simple technique. Here you can see on Figure A, this is a paint brush that you can buy off Amazon for less than 10 bucks, and we have a polymer solution that's applied in the reservoir and a compressed gas source. We're actually using carbon dioxide as a gas source because this gas is actually in the OR. In the field, you can think of this as being in a canister with a compressed carbon dioxide gas. On the bottom left picture you see a latex glove that's coated with these polymer fibers. So the

use of pumping this polymer solution blend and with the compressed gas, we can make nanofiber mats and we can coat irregular surfaces. That's the advantage of our technology.

So here is a fiber morphology, as we can see, with scanning electron microscopy. We make nanoscale fibers, and they're non-woven fiber mats. The interesting property of our material is that the material becomes more adhesive as it contacts tissue, and there is a transition that we have determined through differential scanning calorimetry that happens around 37 degrees. So, at body temperature, we get this transition where we change the morphology of these fibers, and it's activated by the body temperature. So that's a really interesting feature of our material, which makes it more adhesive as it contacts the tissue.

We also have some preliminary biocompatibility studies with human coronary arterial endothelial cells, where we've shown that we have no difference on a live/dead assay, and we show that our product, in the preliminary, is compatible.

These fibers also degrade -- and I show you here some SEMs -- that this polymer will degrade over 30 days or more. So you can potentially leave it in the wound and it will degrade and it will be absorbed. We have not done studies, long-term studies, in animals yet for this, but this is just showing you in vitro studies of the degradation and the morphology of the fibers and how the molecular weight of the fiber decreases. We monitor that

through gel permeation chromatography.

(Video played.)

DR. KOFINAS: Here I show you, in the Children's National, we have a surgery where we have a femoral vessel bleed in a piglet, and we apply the polymer solution, and you see it is applied, and there is carbon dioxide pushed through. And as you see, slowly, the wound is coated. I was going to use some of the sound here. I don't know how to change the sound.

Anyway, I'll show you what happens. After 2 or 3 minutes, we have completely coated the wound and the bleeding has stopped. So this acts as a sealant in a femoral bleeding. This is now applied to a six-suture anastomosis. You can see here the anastomosis, and we want to see how much pressure our material can withstand. You may be able to hear the surgeon actually counting the pressure. So we're applying, first, our material and then injecting saline, and we want to see the burst pressure. Oh, it's not showing on the screen. So this is Dr. Sandler. He's really happy that this works very well on the anastomosis.

(Video ended.)

DR. KOFINAS: This is a graph here of the pressure. You can see the six-suture anastomosis. If we add our polymer sealant, it can withstand much higher pressure than if you just have the suture. So this material can seal femoral artery bleeding. It also can be applied to withstand pressure. It also sticks to tissue. It conducts the -- that's the advantage, it sticks to wet

tissue, and we have demonstrated that with these preliminary experiments.

Another way we can apply that, this is on the skin of a piglet. For wound care, we were able to spray the skin, and we can apply that and leave it on the skin for wound care.

So this is just the preliminary results that we have on our research. We have developed a material and an application technique which is very simple, and it allows an in situ deposition of polymer fibers. You can go into cavities, you can coat anything you'd like. That has potentially wide clinical application and also potential in trauma. We have demonstrated some effectiveness in acute animal models, and right now we're continuing the biocompatibility characterization and trying to look at the adhesion testing. In collaboration with the FDA, we're also looking at putting antimicrobials into the mixture. It is a solution of various polymers. And we're trying to also see the potential for antimicrobial use.

So this is my short presentation. I'd be happy to entertain any questions. Thank you.

(Applause.)

MS. KUMAR: Okay, we'll be able to take questions during the panel session.

I'd like to introduce our last speaker, who is Dr. Charles Durfor of the Division of Surgical Devices at FDA.

DR. DURFOR: Well, very simply, I'd like to thank the organizers

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for this meeting, for giving me an opportunity to speak about using some creative thinking in dealing with preclinical models in this particularly appropriate patient population.

What does it mean to think outside of the box? I'll give you my definition, and that definition is using good science and a thorough understanding of medicine to design your studies in an appropriate manner. What does that mean? It means sometimes you're going to be outside the box. Sometimes you're not going to be following ISO 10993. But it also means that you fully understand the value of your model, what its strengths are and what limitations.

With all of that said, what you're going to hear from me this morning is not another paragraph. Instead, I think I'm underlining the excellent work you've already heard presented in this session and others.

Okay. There's a basic inherent challenge that we've heard over the last 2 days, and that is can one size fit all? And this slide begins that discussion. There is a broad diversity of composition of hemostatic materials. But then over the last 2 days, we've also heard issues about is it exovascular? Is it endovascular? Are you dealing with venous bleeding? Are you dealing arterial bleeding? Is it a standalone product? Is it working as an adjunct? Is it used for compressible bleeding? Is it used for junctional bleeding, noncompressible bleeding? Is it severe and life-threatening bleeding, or is it moderate bleeding? All of those factors fit into designing your study and

thinking outside the box. It doesn't mean that you can't have broad models, but it means you just have a whole series of different checkboxes you have to think about before you're designing a study and saying this means this.

Then we have to add one more thing, of course. Anyone who is obtaining material either from animal or plant sources has to deal with the variability there. My first job outside of a postgraduate situation, I was in a lab and we were studying rhodopsin from bovine cows, and we learned early on, there's a seasonal variation in that, depending on the time the animals went to slaughter, whether it was before or just during sunrise.

So you have this inherent variability in your source material that also points out, perhaps, the value of these nonclinical studies. Some of them, as we've heard many of them are, they're proof of concept. But others can be for different reasons, for example, comparing different products, different treatment regimens, maybe you're changing a supplier, maybe you're doing it as lot release. So well-designed nonclinical studies have great applicability in this area, and I think that's a great thing.

We've also heard yesterday to consider other issues when you're designing outside the box, and if you're going into the battlefield or trauma situations, you need to consider the environment. And I thought there was an excellent list there that included a couple that I didn't present on this, such as ruggedness in weather. So that's important.

Another important issue when you're thinking about outside

the box is who is going to be the end user? Is it a buddy, is it a medic, is it a surgeon? But that also plays back into how we do our nonclinical studies, because there may be value in these nonclinical studies actually helping us think about or test what's the best way to write our labeling and write our instructions for use. So when we're thinking outside the box in preclinical studies, that's another issue to consider.

Now, let me back up. My way of doing this talk is the following. I'm actually, as you can tell, citing from some draft guidance that the FDA has published. That is not to set foreign policy. That is not what draft guidance does. Instead, I'm doing it for two reasons. The first is it's sort of written documentation. The FDA is wrestling with these same outside-the-box issues, and we're at least offering our comment.

But the second point of referencing these draft guidances, not final guidances, is it's an opportunity to ask you to provide comment. And for each of these guidances -- and on the last slide you'll see web links -- there is a docket. And so as you think through your products, as you think through your experiences, this is a chance for you to comment back to the FDA on both the guidance I gave you on medical devices made from animal tissue and for our new biocompatibility guidance.

Now, the table on the right is the standard ISO 10993 chart. For those who are not familiar with it, it's a list of nonclinical tests that can be performed, and generally they're driven by means of the type of tissue

contact and the duration of tissue contact. It works for many biomaterials, but not all. And I think we're seeing that today, so let's explore that a little bit more as we think outside the box.

In this guidance there are several topics that I think are very important for this area. I'm not going to cover all of these. I will cover a few. But they're important to think about. And once again, FDA wrestles with this issue with you. So I think we're partners in trying to move science forward.

Before we talk about specific issues, I also want to drop back. I'm a part-time archeologist as well as a scientist, and I've learned, just as in science and archeology, it's important to work smart and then work fast. And so part of working smart is not repeating studies and collecting data that already exists.

And so there are many sources of information as we go forward, and FDA certainly looks forward to either hearing about your in-house studies referencing master files from other suppliers of materials you may be using. There's obviously published literature and there are other sources of information. The reason this is important for you is not only that you read it, but we read it and we may come back and say, gee, I read something in the material safety data sheet. Have you thought about this? So all of these sources of information are important for you and may actually streamline some of your approaches.

So I'm going to go ahead and hit a couple of quick specific

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issues in biocompatibility testing that in some respect we've already discussed, and I'm just flying over it at the 30,000-foot level.

Animal tissue is an issue, and sometimes it just doesn't make sense, and the whole point of these next couple of slides, sometimes doing what ISO 10993 tells you to do doesn't make sense. I thought Dr. Kheirabadi gave us an excellent example of that today, where he was talking about using endothelial cells rather than fibroblast cells to look at the cytotoxicity of a hemostatic product. A perfect example: you step outside the box -- scientifically and medically correct.

Another issue with animal tissue that you can run into if you have a human-derived product, does it truly make sense to be doing immunogenicity sensitization testing in a guinea pig? Already the immunogenetic issues are going to play a role. So how do you deal with this? Well, you first recognize what are appropriate standard approaches and you think it through, and then you come up with the best approach. And as we heard from Dr. Krause's talk yesterday, there is a Q-Submission process so that you can engage with the FDA. Before you spend a lot of time or money on a test, approach us, discuss it. Does this make sense? And we can have a discussion.

I'm going to talk about in situ polymerization in a minute, but I also want to just dwell a minute on the surgical instrument models for transmissible spongiform encephalopathies. To me, this was a remarkable

outside-the-box setting, and what happened here, the model that's used for looking at transmissible spongiform encephalopathy is intracranial implantation in hamsters. And so you had companies that were developing reagents that would inactivate TSEs on scissors. Did that mean the company had to go out and develop microscopic scissors they could put in a hamster's brain? No, that didn't make sense.

So what they did is they analyzed the circumstance. They said, what are the essential elements where the product may or may not function? And it came down, in the case of scissors, of thinking about where the two blades come together. That's probably where the cleaning wouldn't be the most effective. So a model was developed, and in that particular case they were wrapping pieces of wire around, and that was the model that was implanted.

So sometimes it's always desirable, it's always optimal, if you can, to test the final finished sterilized product. But there may be times when it just doesn't make sense and you have to think outside the box.

The FDA has had the great pleasure and opportunity to work with a number of companies over the last 15 years in developing in situ polymerizing devices, and we've learned a lot from that, and I think some of that translates directly into this area, whether or not your product reacts in the body. We've heard a lot of these issues today.

So my approach to this area, when I'm dealing with a product

that's in situ polymerizing -- but we've even heard issues here in terms of non-polymerizing products.

Consider the toxicity and the safety of the reagents. A lot of that can be done from the published literature, and that's very helpful.

Consider the reaction. Today we've heard about problems with heat generation in some products. So the reaction is another aspect that one needs to consider. Other products generate reactive molecules that can be a challenge.

Consider the product. Consider the decomposition product. And here we have concerns that as the product comes apart, is it all of a sudden being able to migrate throughout the body? Are there new reagents that are becoming systemically available?

And then consider the kinetics of resorption, because that may influence not only the way you do your nonclinical studies but the way you do your clinical studies.

I'm not going to dwell on nanotechnology because I didn't hear much of it discussed today, but it is another classic example where things are falling outside the normal realm. We accept the fact that nano- and microtechnology, or even products that are rationally designed to influence host cell response, they're a little different and they require thinking outside the box. And FDA is eagerly trying to engage and do that as well. I do find that sometimes it's very helpful to be somewhat tutorial to the FDA. You say,

hey, this is what we're thinking, this is what we know, this is what we think is the best, and the FDA can come back and tell you their experience as well.

And once again, not only are you thinking about the product, but you're thinking about how the tests are done, are you doing the right extractions, things like that. Nanotechnology as well as many of these other products raise interesting issues.

So with that said, I'm leaving you with a couple of references that hopefully will help in your thought process, and I look forward to working with you. Thank you.

(Applause.)

MS. KUMAR: Thank you.

Okay, we're going to begin our panel discussion. I would like to invite our moderator to come up, Joshua Crist, who's a scientific reviewer in the Division of Surgical Devices, as well as inviting Dr. Kheirabadi up, as well as Dr. Keith Hoots from NHLBI, Karen Manhart-Byrnes from FDA. And let's begin.

MR. CRIST: Hi. First, I want to acknowledge all our speakers here. Thank you for coming and presenting all of your work voluntarily and participating in this collaborative discussion. And also thank you to the other panelists here to discuss.

So there are a number of animal models available or that have been developed for hemostatic products for trauma use, for many different

patterns of injury, different anatomical locations. So I'd like to start the discussion off discussing the value and the limitations of existing animal models in predicting clinical outcomes for different wound types; also where can we improve in our animal models and where do we need to improve.

DR. KHEIRABADI: Do you want me to start?

MR. CRIST: Sure.

DR. KHEIRABADI: I think every animal model has its own advantage and disadvantage, and we really have to recognize how we set it up and that it meets what would be a general practice in the field. When we test a product under circumstance that is irrelevant to how it's going to be used, then that animal model loses its value.

And I'm going to emphasize another thing. For every product that we're going to test, we got to make sure we got a control and a control that is similar to what we're actually testing to make sure we really do make a difference and do get something different. Otherwise, some of those bleedings that I see here, it could very easily be stopped by using a gauze. Why do we actually develop a new product if actually gauze is going to work? And doing a controlled experiment is really, really important to demonstrate what you have in making a difference or not.

So I agree with you. How we can improve the models? Improve them by increasing that level of a difficulty of stop that bleeding. That's how you make it more difficult. That's why we need to provide

something that is more effective.

DR. KING: So I just want to agree with that and add this point. Yes, our animal models should have some reflection of what we are likely to do clinically, so the so-called clinically relevant animal model. On the other hand now, the model has to be developed to answer a specific question, and sometimes answering the question may require either a model that doesn't exist or a model that has a set of conditions imposed on it that may not be clinically relevant but are useful to answer the particular question, and around that framework is having the appropriate controls. Having the right controls -- and not just standard of care controls, sometimes you may even have a negative and a positive control -- is really fundamental to interpreting the results of any trauma hemorrhage animal model, is having the right controls and asking the right question out of the model.

DR. KHEIRABADI: On the same issue, I think we have to be very careful. Sometimes, as investigators, we tend to like to prove what we have is good and efficacious. Sometimes we manipulate our models to some way that it gives you the better and more positive result and that's how we proceed with that situation. I think I'm cautioning a lot of you, especially those who have financial interests or even as a scientist. You spend time and you're working on something, you're hoping to get something that works, and whether intentionally or unintentionally, you try to manipulate the system, set up the system in such a way that you get positive results. Nobody wants

to see negative results. Nobody's going to publish the paper that is negative.

So you're going to have to be very careful that -- watch where you're walking and the line that you're walking -- you don't become -- you know, artificially produce data that it looks great, but in reality, when you put it in the hand of the medics or the one who actually is going to use it, will find, oh, this is not working.

DR. KING: I agree, Bijan. That's the strength of testing in multiple animal models in a variety of different circumstances. We should continue to do that.

DR. FALUS: Our product was designed for a trial by using in military and civilian settings. The strategy was defined by FDA by setting up a regulatory path. The product needed to be tested as an adjunct to hemostasis in three different models and then it would be tested as primary treatment, which we believe is the right way to do it. The models are basically conditioned by the need to follow a regulatory path.

UNIDENTIFIED SPEAKER: Do you think there's value in getting them out of your hands so at some point it's not multiple models within the same potentially, you know, favorable lab? I mean, we've been guilty of this -- you know, we're prone to this, even in our own labs where we -- the best thing is to say, okay, we've got it to a point where it works. Now, let's give it to somebody who's not a medic initially. Let's give it to another model -- another lab and see if they can make it work, you know, before it goes too far

because, I mean, would you see value in that, Bijan?

DR. KHEIRABADI: Absolutely. And we often get a product brought to our door, and they said, you know, we think we have a good product. We have done some preliminary studies. What do you guys think? You know, we will gladly take those products, put them in a small animal test, and we give them very honest opinion. A majority of them, unfortunately, doesn't work as well as they wish and then we would recognize it. We're not releasing that data to the public. We're not trying to destroy the company by any means. We're sharing our finding, our information, our way of seeing how the team works with them and we say, maybe if you take this path, perhaps we'll improve it. But as of now, we don't think it's really been better than what we already have inside. So I totally agree with that.

UNIDENTIFIED SPEAKER: And I think you can -- then you can tweak the -- I mean, then you can make changes. It's really the first and initial and really safest way of validation, is to say we have this product, it works well in our lab. We've got it as good as it can be. Let's see if it will work in somebody else's hands in another animal, the same animal model, maybe just a different lab with people who aren't quite so invested in its success.

DR. KING: I enthusiastically agree. I also want to make sure that -- what you first said, I think, is equally as important, and that is none of these things can be developed without appropriate input from the end user

and by, I think, studies that include the end user, right? I understand, yesterday, we were talking about pathways and how we might conceive of how things could initially be tested in a controlled environment and in the trauma room or something. But eventually, it's going to get out there and out there -- to get things out there safely, you have to have some studies that involve end users and usability. You know, it's not going to be a surgeon doing it all the time, and you have to engage those guys early in this whole process.

MR. CRIST: Charles.

DR. DURFOR: Yeah. Dr. King, I thought your study in recently deceased persons really speaks to this issue because it says we've taken animal studies where we can take them and now we need to do the next step. So I'm wondering if you could maybe generalize your thought process in looking at that study and saying what was it in that particular product that was valuable to do it and are there -- what other criteria would make it a good idea or not a good idea.

DR. KING: So the problem with studying any intervention for someone who's dying is the high risk of that population to begin with. So by definition, it is nearly impossible to do some kind of a randomized trial with a reasonably powered endpoint for anything less than the entire GDP of the country, right? There's so much noise in that signal for randomizing a prehospital patient who has a blood pressure of 40. This is impossible data to

get.

So when you're talking about that kind of population, you know, our feeling was that, because you can't get that, you need some other reasonable surrogate, which is how we wound up where we are in this recently deceased study. I think this is a potential pathway, not just for this particular foam, but this pathway could potentially be utilized by a whole variety of other tech going forward. It just depends on what population you're planning on studying. You know, if this was a topical gauze bandage or something, there is conceivably probably better and more efficient ways to study that. But when you're talking about trying to study a group of patients who are largely impossible to consent, who have an extremely high mortality to begin with, to power a study to create an endpoint that is useful is almost impossible.

DR. KHEIRABADI: I also think that we have to recognize the limit of the information that we can get this type of a study. These patients are not patients; they're dead. So when you're sticking something into them, the best result you're going to end up to find out is what kind of pressure do you generate? You really don't see whether it's going to work or not or whether it's going to be safe or not. It's dead. Dead is dead.

So we have to be very careful of what information we're learning for doing that. I mean, it's very valuable in terms of finding what pressure perhaps generates, what potential danger you will have, but it's not

definitive studies. It does not definitively tell you the product works or not or whether it's safe or not.

DR. KING: Agree. So efficacy and biologic safety have to be established in a biologic model. They have to be, right? And that's why you do animal work in a variety of models, not just one in many, and you put it in many people's hands. Again, coming back to with an intervention that's designed for an extraordinarily high-risk population, it's almost impossible to study in human beings. And so I think this not an unreasonable surrogate and stepping stone.

DR. DUBICK: I have a question. So as we discuss animal models -- and yesterday we heard a lot about the difficulty in performing a lot of these studies in humans, especially trauma patients, in a timely manner and with the cost. I wondered if the FDA panelists could address the animal rule and how that might play into getting some of these products out faster.

DR. KOFINAS: Well, I was going to -- yeah, I was going to comment on what you said about having negative results that are never published. I think it is important, if you're a place that tests many products, to kind of compile that data and publish it because that tells the community, right? You don't really need to reproduce the wheel. If you're working with a certain material or your product is based on some material and you know this material has these limitations, it is important to get guidance on -- you know, you need to demonstrate -- if this is based on this material, you need to

demonstrate this specific experiment because we know this has these limitations.

DR. FALUS: Well, first, if you are conducting a regulatory study, you cannot hide your bad results. Number one. It's all documented. It's GLP studies, and they have been conducted in a certain way. Publication is not to go with it. We have, in our product, developed two types of models, those that would allow us to follow a regulatory path and those who would allow us to show that it has a military indication or a trauma indication in the civilian life. It's a little bit different than what is supposed to be because we use three standardized models and three different organs, liver, spleen, and kidney, which we perforate, crush, and really hurt very badly.

And in addition to that, we do a mix of wounds, a combination of wounds, between those organs, adding perforations on the gastric tract and the -- and although not everything is standardized, only the single organ models are standardized, we tend to say that if the vast majority of the outcomes are positive, then the model is applicable in such a valuable situation as the battlefield, which is extremely valuable.

DR. KHEIRABADI: To answer your question, essentially lots of the materials brought to our door, long before, actually get to FDA. These are really a prototype. These are the things that -- an idea that somebody developed and made it bench top and worked something and developed. Publishing this thing, the material is really not finalized, it's not ethical, and it

doesn't have any value. Even if I publish it, this material, before it actually comes to the final stage, it can be completely changed.

And, secondly, we have this confidential agreement with the companies. So we want to have that close relationship. If I give negative data and tomorrow I publish it, no other company will approach us to say, by the way, take a look at it, because we're not there to put people out of business. We really want to help them to develop it and we sort of put it in our model and say, you know what? You have maybe a good product, but this is not for trauma, this is not for severe bleeding. Maybe you should follow another path. So that way we can be helpful. I'm not looking to publish multi-papers, but I like to know if I can help them to move it along a large path. And as I said, most of them are really prototypes. So that's why we're not going to publish.

MR. CRIST: All right, I'd like to pose another question to the panel. So as we discussed a lot yesterday, for many of these hemostatic devices, clinical data can be very difficult to obtain. And so I wanted to propose a theoretical situation. So say you had two devices. Similar risks, similar value can be obtained from animal models. For one, you have a population that you think you could readily study. For the other, you anticipate it being very difficult to obtain clinical data. Would your animal testing plans differ for these two products, and if so, how?

DR. KHEIRABADI: Obviously, again, you try to mimic the

situation that you will have in that trauma. Actually, I think the animal study can be really, really helpful because as, for instance, Dr. King pointed out, if you're trying to get a certain population of the patients that are coming to the ER, they're near death, there's a very limited number of people, even if you put them -- test them. Whether they're going to make it or not is still not going to be certain. So you set up your animal model based on the clinical scenario that you see. In this situation, you have the advantage, you can see what exactly it does, and it's not unethical not to do the standard of care versus the animal model that is perhaps more moderate. So those two, yes, have to be different.

DR. KING: I agree. And I think you also have to look at that material or potential solution, perhaps, in more than one model or more than one set of circumstances. You can't just do the same experiment over and over and over and over again. You need to change up the circumstances because, naturally, as we talked about yesterday, the patients are inhomogeneous.

And as much as we like to control everything in the animal lab, sometimes having multiple somewhat unrelated models, like low pressure/high flow venous bleeding versus a model of high pressure/high flow arterial bleeding versus a model of hypotensive resuscitation versus one with over-resuscitation or coagulopathy and no coagulopathy -- now, demonstrating usefulness under a whole range of circumstances adds power

and reassurance that (1) the signal, the efficacy and safety signals are real; but (2) some ethical reassurance that when it finally does get to a very inhomogeneous patient population, it's reasonable to expect somewhat similar results.

Now, as a wise man once told me, a fool can ask more questions than a wise man can answer, right? So you can't keep asking questions ad infinitum. At some point you have to make the leap. When do you cut it off, right? When do you say we have tested in five circumstances? Why not six? Why not eight? Why not 10? So I don't know. But at some point there is an inflection point, right, of diminishing returns. I don't know that there is a concrete way to establish where the point of diminishing returns is, but it exists. And maybe that point of diminishing returns is related to funding or time. It shouldn't be, but sometimes it is. But, more importantly, I think it should be related to usefulness of data.

DR. MANHART-BYRNES: As an animal --

MR. RAGO: I'd just like to -- sorry, sorry. I'd just like to build on Josh's original question point there. I think if you have a device with a challenging population and a device with a straightforward population, your initial testing in demonstrating safety and efficacy can be similar. But when there is this really challenging clinical population, it may be useful to have some level of intermediate steps before you test in the patient who really needs it. We've heard great examples with junctional tourniquets tested on

healthy volunteers, certainly not the patient that really needs that device. With our material, a different risk/benefit profile, we've chosen to use a recently deceased study as an intermediate. So I think there are steps between truly intended clinical use and your animal models that can be helpful.

DR. MANHART-BYRNES: And just to throw in, as an animal studies reviewer, we really look carefully at the indication for use for the device and just to make sure that the animal study has addressed that sort of issue and what the device will actually be used for.

DR. KHEIRABADI: I just want to give an example of how the Combat Gauze became suddenly the choice. This was completely by coincidence. We were invited to one of those Tactical Combat Casualty Care, and I was presenting the data after doing a comparative study of 10 products, and we know that Combat Gauze and WoundStat were the best result. And right after me, Dr. Arnold got up. And this was an independent study, a different model. They were using a Navy and they presented, and I was amazed seeing actually we're kind of coming to the same conclusion. We just pick up essentially the same good data. And at that moment, that was probably the best data we could show. We showed a different model, a different institute reaching the same conclusion, and I think that probably was the most forceful fact, that eventually Army decided -- also Navy -- let's put the thing away. We have something better and more effective. We

should switch it. So that really showed the power and the strength of using one technology being tested in a different animal and reaching the same conclusion.

DR. SHARMA: Yeah. So I wanted to come back to Dr. Dubick's question that was directed towards some of the folks from the FDA, about the use of the animal rule and given some of the challenges we've talked about with studying these devices clinically, how that may or may not apply here.

DR. DURFOR: Is the word "animal role" or "animal rule"?

DR. SHARMA: Rule.

DR. DURFOR: Maybe you can tell me your definition of the animal rule. I'm not as familiar with it as I should be, and I apologize.

DR. SHARMA: So as I read it, the animal rule states, in cases -- and I think one of the classic examples is the H1N1 scenario. But in cases where it's very difficult to establish efficacy -- efficacy and, I think, potentially even safety in a human clinical population -- animal data can be used as that body of establishing probable benefit relative to risk.

DR. DURFOR: Right. I'll offer a general comment because the whole point of my talk was this is a very broad area, and I hope others will add as well.

There are clearly products that are on the market that have animal data supporting them and limited or no clinical data. But that really

depends on a lot of things. It depends on the product, the patient population, how much information we have on the value of the animal model.

So is it impossible to come to market without human data? No. But there are a lot of different factors that factor into it. It allows me to maybe ask the question that maybe I shouldn't, but I think it's interesting. We spent a lot of time yesterday talking about databases, and this is a session on thinking outside of the box. So I wonder, is there information in our databases that will help inform us about animal models? Can we learn, can we look back and say -- I think, Dr. Kheirabadi, you just did that with Combat Gauze. But are there other ways we can think about the data we have to help us make better knowledge about the predictive nature of animal models?

MR. RAGO: I think there is. So it's not a database, but there's a good paper that's referenced in the materials for this meeting. It was written by Dr. Pusateri and his colleagues, entitled "Making Sense of Preclinical Literature." They looked at a number of different animal models and performance of the same device in different models and, I think, drew some pretty insightful conclusions. But maybe the panel could expand. I'm not aware of any systematic database for different animal model testing.

DR. DURFOR: I was actually thinking about the experience we've had in humans with these products and then looking back and saying, well, this is what happened in humans. How well did the animal model do it?

DR. RASMUSSEN: I'd like to make a comment. I'd like to step back now as we sort of finish this panel that's called Thinking Out of the Box. You know, yesterday I mentioned two categories of hemostatic devices, exovascular and endovascular, and I think I view them as not competitive but part of the toolbox, and it's a toolbox that two of the portfolio managers in our program, Tony Pusateri and Sylvain Cardin, are really in charge of filling that toolbox. Right now I think the exovascular part of that toolbox is 95% full. I see really nothing in it with endo.

And I think that we would be remiss if we left this working group without recognizing that we -- from the external compression standpoint, we're going at it again and again and again. We have really two approaches intraperitoneal, two for cavitory, several for topical compression. The exovascular part of our toolbox is full, and at some point we're going to -- there will be a working group that we convene and people will say you have a 95% solution to the exovascular approach. You have a 5% solution to endovascular. Remember, the exovascular approach offers no inherent capability for cardiac support, for circulatory support or translation to ECMO or any other extravascular -- I'm sorry -- endovascular types of support, organ support or resuscitation.

So I would really challenge us to think about that. And this is a great group of thinkers and a great group of innovators, and I think we would want, in a working group like this sometime in 2017 or 5 years from now to

really be talking about endovascular solutions which also offer inherent circulatory support, transition to ECMO, resuscitation capability, and such.

And I just offer that comment.

MR. CRIST: We have a few minutes left. One more comment.

UNIDENTIFIED SPEAKER: Yeah, just a comment for the group.

We saw some data today and I know there are folks in the audience who have more data. I would, thinking outside of the box, really encourage the companies to publish their data. I know there are reasons not to publish data when you're a small company.

What I would tell you, as a user, when you get approached by a company with an FDA-approved device with no published data, it's problematic. These companies can publish data along the way in the peer-reviewed literature and in the *Journal of Surgical Research*, *Journal of Trauma*. They're not great high-impact journals like the *New England Journal of Medicine*, but they get peer reviewed by folks who would use them, look at them, take them out of people whatever you're going to put in; extremely useful to do that -- and just as a comment to the group -- looking at all of the data and not being able to see much of it published.

Thanks.

DR. KING: Can I just make a comment about that? You know, as an academician, publishing is -- you know, it's part of our job and our lifeblood. However, there's a much greater importance here. If you're going

to propose to someone to do something -- this is called outside the box. If you're going to propose to a clinician that you want to make an intervention that is way outside the box, it's hard to get clinical buy-in without a group of your peers, your clinician peers who have seen it, reviewed it, and also support it. No one is going to take you at your word, right? You have to have buy-in from the community at large, the community of end users or end removers or whatever. I mean, there are some chuckles, but it's important. Just because you say so doesn't make it so. I mean, we're a group of scientists. We want to see the data. I want to see the data.

UNIDENTIFIED SPEAKER: Let me address some of that from the standpoint of a very small company, and we are a small company and self-funded at this point.

In the early stages, there's always a huge hesitation to publish any type of data because you're always worried about the confidentiality and what have you. I think, as you continue along your animal studies and you start generating very consistent data -- because in our case we were -- you know, we're developing a formulation. We were using a very consistent model so we could, you know, see how the product worked from one to the other. You know, we finally reached the point, for example -- and this month we will have two patents that will be issued on our products. On my desk I have three different papers that are ready to be reviewed. So I think it's where you are at in the process as a small company.

For us, now, we're confident in what we have and we're confident in how it worked. You know, you're showing negative data as well as positive data in a paper, but we understand the outcomes, and we're confident the outcomes are very positive. But I think a lot depends on what protections you also have in place. So when you have a patent in place or two patents in place, that makes a huge difference as to when you can lay it out there and not lay it out there.

DR. RAMSEY: Coming back to animal models and consistency, multiple different animal models, to me it doesn't, in a sense, matter how well it works in the lab. How well is it going to work in the field? And there's a diversity of injury in the field that usually means something has punched holes into soldiers or civilians and there's a variety of different size holes, shaped holes and injuries, arteries, veins. I think again, as I suggested in my talk, that in the field, true ballistic injury, given all of its inconsistencies and varieties, provides a slant and an opportunity to test reality as to how it's going to actually perform in the field. That is essential before it gets to human use.

And regarding human use or human testing, I would appreciate if people from the FDA or other panelists could give us an overview of what kind of human testing was done in the existing hemorrhage control devices that are FDA approved, before they were approved. I'm not aware of that, and I would be interested to know what human testing was done in order to

-- I mean, because we're talking preclinical, as if human testing has got to be done. The existing devices. Was there human testing done?

DR. DURFOR: If I could offer a quick answer to that.

DR. RAMSEY: Okay.

DR. DURFOR: The top resource is called device search engines, and that allows you to search a product by its name, by its company, by its application. There is an obligation for PMAs and for 510(k)s to give you a summary of the data. So that would be my place to start, would be to use those search engines. I mean, I don't want to stop anyone here from talking, but if there's a particular product later on that you're interested in, that search engine will take you to that.

DR. RAMSEY: I will do that. We have many of the world's experts in the room, and I was actually hoping that someone would opine as to what human clinical testing was done before FDA approval, if there ever was any done.

MR. CRIST: We're going overtime. We need to wrap up. So thank you for your comments, and we'll have to conclude the preclinical panel.

DR. ASHAR: So we have several of these devices, and I'm not quite sure which ones you're referring to, and I actually hate, in this forum, to call out any one particular manufacturer. But as Dr. Durfor pointed out, you know, this information that is present in our 510(k) summaries and in the

summary of safety and effectiveness is often not published in the peer review literature. So this is -- you know, I don't think -- I think you would be ill informed if you only went to the peer review literature and looked for this information. So you should look at FDA's websites to find this, you know, the justification for how we got to where we got.

Now, with the 510(k) summaries for 510(k)s, you know, the Class II devices, that information in the summaries in previous years is, I have to confess, not great. But in recent years we have made a real effort to make sure that the performance testing justifying the decision that was made is included in that summary. And I think even more robust are the PMA products, where the summary of safety and effectiveness goes into all of the bench, animal, and human testing that was done.

You know, Ken Cavanaugh can speak specifically for the clamps. There is a specific website that I think either -- I think Dr. Krause demonstrated for the XStat device, so you can look there. So I'd go to the individual products and see what they did.

You know, I have to say that it's -- we face this problem every day. You know, companies come to us. They say people are dying. We need a product. All of our tests look to indicate that this is going to be beneficial. They find or seek a niche indication where potentially the benefits of product use outweigh the risks and then we're asked to make a decision. And so based on the information provided, the indication that's been given, the

benefits and risks, when we put all of that together, all of those things come together to make a decision. So it's to simply say, did they have clinical or did they not? It's a whole assessment of all of that.

And I think you could probably, with anything, find questions, ask questions, find flaws. But hopefully this conference, and especially all of the input from everyone here, helps establish some uniformity with the different indications that are -- you know, we have two foam products. We have a balloon product, we have a spray nano product, and yet we have the same animal models, we have the same tools available. And so how can one person or how can a group of individuals at FDA find commonality to make sure that there is a level playing field and that we're making the right decisions that are beneficial to patients? So I think that if, in our breakout sessions, we could discuss some of that, I think that would be helpful.

MS. KUMAR: I'd also like to touch on one more resource, [clinicaltrials.gov](http://clinicaltrials.gov), which is a search engine that provides visibility to all of the ongoing clinical trials that are supporting IDEs and PMAs. So that is also a resource to find that information.

Okay, so we are going to take a break, and we are going to convene at 5 after 11.

(Off the record.)

(On the record.)

MS. KUMAR: Okay, we're going to get started with our next

session. Session V will be a special treat for everyone. It's actually going to be a case study looking at the recently granted de novo application for the XStat, so we'll hear a little bit about the product. We have a special voiceover presentation from SOCOM, and we'll follow up with the FDA's perspective of this regulatory journey as well, followed by a short question and answer period. So I'd like to turn this over to Andrew Barofsky.

MR. BAROFSKY: Thanks, Allison.

I'd like to again thank the organizers for inviting me to come and introduce the XStat product and talk a little bit about the regulatory journey that we took to achieve our recent de novo approval. I'd like to start with an acknowledgement.

The XStat project, which started about five years ago, has been funded with the generous support of the U.S. Special Operations Command and the U.S. Army Medical Research and Materiel Command. They've been both generous in their funding, but also in the collaboration. This has been truly a public-private partnership to develop this technology and bring this capability to the battlefield.

I won't linger too long on the problem. I think this was discussed very extensively yesterday by clinicians and end users who have far more experience than I do in this particular area. In fact, I'm going to quote one of our audience members, Dr. Pusateri, here. What I really want to just point out here is that the XStat device was designed specifically to treat

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junctional hemorrhage, and it is focused on that particular type of injury.

So to introduce the device itself. It's a first-in-kind, non-absorbable, expandable hemostatic sponge for temporary internal use. That's the actual -- FDA's actual description of the device. Each one of the XStat devices is a syringe-like applicator that is filled with approximately 92 small compressed chitosan-coated sponges. And what happens with these sponges as soon as they come into contact with any type of aqueous liquids such as blood, it essentially triggers them to expand to their uncompressed dimension, and it's essentially a spring-like expansion that occurs.

As you can see with the picture of the little sponges outside of the applicator there, each one of them contains a little blue X on it. That's actually a radiopaque thread that's been attached to the end of the sponge, and that allows the sponges to be observed under x-ray so that a surgeon can ensure that none of the material will be left behind. These are not bioabsorbable. These are not intended to be left in the wound. They are equivalent to a more traditional type of wound dressing, and they have to be removed.

I described a bit of this, but how exactly this works. So one thing I failed to mention about the applicator. One feature that it has -- and this is actually a design feature that was specifically requested with the combat medic in mind. It has a telescoping handle. And so when you remove it from the package, it comes in a compacted state. And so the first thing you

need to do with the device as you pull it out of the package is pull on the handle and click it into place, and at that point it becomes a syringe-like applicator. Once you've done that, you insert the tip of the applicator into the wound track and simply push out the sponges into the wound track.

And, again, once the sponges come into contact with blood, they're going to expand extremely rapidly, within a matter of seconds. You can see in that gif image of the sponges being injected into a glass of water with some food dye in it that the sponges basically pop open in seconds. And, again, the sponges do need to be removed from the wound before -- during a definitive surgical repair procedure, and a radiograph is required to ensure that none of the sponges are left in the wound.

Moving on to the topic at hand, which is our journey through the regulatory cycle, the XStat device was recently approved under a de novo petition. The approval date was back in April. There's a new regulation number, 21 C.F.R. 878.4452. It is a Class II device. It has a product code of PGC, and we're very proud to have a functioning submission number that we can talk to people about.

This is the actual indications for use for the XStat device. It's a hemostatic dressing for the control of bleeding from junctional wounds in the groin or axilla that are not amenable to tourniquet application in adults and adolescents. It's a temporary use dressing. It can be used up to 4 hours. And it's intended for use in the battlefield, and then there are several

contraindications, which are pretty much different sites. Again, this is directed towards the junctional zones.

Here's our FDA timeline. April 9th, 2009 was our first successful animal use of an early, early stage prototype of this device. It was done in a swine transected femoral artery. And approximately a year later we had an informal sort of introductory meeting with the Agency that was a collaborative meeting. That was actually accomplished through the military relationship with the Agency. And then in December 19th, 2011, we filed a pre-IDE submission for the XStat dressing. The intention there was actually to solicit feedback from the FDA regarding a 510(k) application, and so that was essentially our pre-sub submission. We spent a couple years -- and what's, I guess, missing from this timeline are several discussions and phone calls and in-person meetings with the FDA in between these time points.

And so really filing the pre-IDE submission and really engaging with the FDA, the engagement with the FDA and then obviously with our military collaborators, became much more substantive, and it was during that two-year period which the FDA gave us guidance and feedback on our proposed studies. We were able to accomplish the preclinical work on the device, and we also determined the regulatory pathway, which was, again, we intended to go approve the device under a 510(k) application, but based on our discussions with the FDA and the guidance from the FDA, we decided to avail ourselves of a de novo petition, and we filed that in January of 2013 and

we received approval under that petition about a year and a quarter later.

This is a very broad overview of the supporting data that we submitted with our de novo petition. Bench studies. We did the ISO 10993 biocompatibility studies. We did stability studies, sterility, validation. We submitted significant data on mechanical performance, both mechanical performance with respect to the sponge and its ability to expand under different conditions and mechanical performance with respect to the applicator and the application system, the ability of the sponges to be deployed from the applicator. We also submitted data with respect to the radiopacity of the sponge.

With respect to the animal data that was submitted in support of the application, the pivotal data was a GLP study that was done in a swine femoral model. It was essentially a version of the standard ISR model. The real, I think, only significant difference is that this device works in an enclosed wound environment, and so we made the entry hole to that injury site smaller.

We also did submit some additional non-GLP animal data, testing the device in a subclavian model, and that was to show its efficacy up in the shoulder region as well as the groin region.

And then, to round out the supporting data, we submitted human factors. We did a human factors study to show that combat medics, military medics, and EMTs could effectively deploy the device on a manikin

under somewhat adverse conditions, which are to simulate some of the conditions that would happen in a stressful environment such as a battlefield application.

And then this is actually the last slide. We are certainly looking forward to submitting future 510(k)s based on the XStat device that's now approved, with an intent to expand the indications to hopefully clear the device for civilian trauma down the road.

And then we've also developed a smaller version of the device. So the XStat that's been approved now is actually a 30 mm outer diameter device. It's intended for a narrow entrance, but albeit somewhat large holes -- exit wounds, if you will. And we've also developed a smaller version, which is called the XStat 12. It has a 12 mm outer diameter that uses the exact same sponges that are in the larger XStat device, but in obviously a smaller format to be able to deploy the dressing into a smaller wound.

And that concludes the introduction to the device. I believe that we've got a presentation from Kyle Sims from SOCOM -- yeah -- that we can --

(Audio recording played.)

SGM SIMS: My name is Sergeant Major Sims, and I'm going to give you an overview of my office's interaction with the FDA during the review of the XStat dressing. And I apologize for not being there in person, but I'm traveling overseas right now. Hopefully this audio recording will kind

of convey how important our interaction was with the FDA.

The standard disclaimer applies. This is not the opinion of the Department of Defense or the Department of the Army. This is my personal opinion. The next slide.

I'll start out by giving you a little bit of background about my role and what it is that I do. So I am pretty much the representative of the end user. As the developer, I make sure that the product that we field meets the needs of the actual combat medic on the battlefield. So I am a special forces medic with quite a bit of experience treating patients from the point of injury to the medical treatment facility. I work solely prehospital and handle primarily urgent operational needs. The next slide.

I represent SOCOM on a number of different research and development committees. I won't go into detail about them. I have them listed here. But it gives us input for our primary area of concern, which is the prehospital environment.

Hemorrhage control has really been the cornerstone of our portfolio for more than a decade now, and junctional hemorrhage, in particular, is something of a particular concern. Standard normal tourniquets have been incredibly effective at treating extremity hemorrhage. But, basically, from the uppermost place where you can effectively place an extremity tourniquet to the edge of the body armor, those are the junctional areas, and those are large vessels that create a tremendous amount of

bleeding when they're injured and lead to a very high mortality.

So we developed a number of external compression devices. And in parallel to that, we were looking for a dressing which would allow us faster, more effective, maybe a little bit longer term, less painful treatment of a bleeding. So the external compression devices -- I won't mention them here because these were all devices that we provided in a letter of expedited review for, and were very successful at getting them rapidly roughly cleared and fielded to the force, whereas the XStat dressing was a much longer development and was developed in parallel. I'll go into that more in the next slide.

So XStat was developed in order to address deep track wounds, and the standard of care now is really packing with the hemostatic gauze and then putting a good solid pressure dressing in place. The problem with that -- especially with the smaller narrow track wounds that were difficult to pack, just because of the size of the entrance wound or the size of the exit wound -- often the cavity was deep enough. It was hard to find exactly where the bleeding was. We were looking for a blind solution in order to inject down into the wound and rapidly stop the bleeding. Kind of the road we were traveling down was we were looking for a fixed blood-type solution, either an injectable foam or gel that we could inject down into the wound track and rapidly gain hemorrhage control. And that was when we discovered the sponges, which developed over a couple of years into what became the XStat

dressing.

So for purposes of this presentation, I'm going to focus on just the interaction with the Food and Drug Administration on the review of the XStat dressing.

What I've got illustrated here is our previous process. So on the very left bottom left-hand corner, the technical subject matter expert, that is myself. And, historically, what I would have had was interaction with the vendor. You see the Food and Drug Administration represented on the bottom right-hand corner, and you'll notice that everywhere on the left-hand column, contracting program management and myself down on the bottom, we all have direct lines of communications to each -- you know, lines of communication with one another and to the vendor. But you'll notice the other government entity on the far right-hand side. The Food and Drug Administration has no interaction with us whatsoever, and that is really the shortcoming of our whole process. Prior to that, our only interaction with them was articulated in a one-page letter for expedited review that we would provide the vendor and want for them to submit their packet.

Bear in mind, this is a project that was totally government funded. So the entire development was designed to fulfill a military operational need funded by government research dollars, and we're not even talking directly to the other government agency.

So about halfway through the development process, I started

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interaction with Dr. Schwartz's office, and that really changed how we -- the flow of information and how we handled this and, I think, expedited the process considerably.

So the new process. Here you can see the two black lines on the right-hand side going from myself to the vendor and to the FDA. Once we did this, what it did was open up an actual avenue of communications. So when the vendor would come to me with their feedback from the FDA after going over their notes and address, say, the instructions for use, you know, change -- proposed changes that they wanted to see in the instructions for use, I would take a look at those and I could go, you know what? This is not going to work for me.

And rather than giving them a set of changes back, to go back to the FDA with and then the FDA come back with another round of changes to the vendor, for them to come back to me, it actually opened up an avenue for me to pick up the phone and contact Dr. Schwartz's office and go, hey, look. This is in the reviewer's notes regarding what they want to see changed on the instructions for use. So, if I understand you right, if I understand these notes right, your concerns are X, okay? And that may be -- I understand that's one of your concerns, but if you word it like that, these are my concerns, that the user is not going to understand this, they're not going to understand that, or it's going to force them to train to use the product in a manner that's not consistent with how it should be used.

So I think this is a reasonable approach and we could have a good thorough discussion and come up with what we felt was a mutually agreeable set of wording to hand back to the vendor to present back to the FDA. And what that did, I think, is cut us down considerably in the number of go-betweens back and forth between the FDA and the vendor. So I really think that mitigated the process quite considerably. And now I'll blow it up a little bit on that next slide to give you a little bit of a cleaner illustration of that interaction with the FDA.

This is just a little bit of a blowup on the new process, particularly with how we interact with the FDA. You see the vendor has a direct line of communication with the reviewer. They exchange all of their notes back and forth. The same with their phone calls. Whereas I would interact with the vendor specifically on -- especially if it required design change to the device or changes to the instructions for use. And then I would -- if I had concerns with how the proposed changes would affect our application or our training on the device, then I would go back to Dr. Schwartz's office at the FDA and speak to her. She may or may not consult with the -- she may consult with the reviewer or provide her opinion as to what would be a reasonable course of action or plot out if it's non-negotiable and we're going to have to come up with our own solution for how to get around it, you know, how to come to terms with what the FDA was comfortable with negotiating on and what they weren't.

But you see, I think if you've ever had a communications class, this is a much more effective structure to get where we wanted to go. And what it does, on the right-hand side there, that line between the technical SME and the FDA is a direct government-to-government line so that we don't waste a lot of time, months and months of interaction, going back and forth over problems that we could have sat down and just discussed and sorted out a mutually agreeable solution up front, in order to field devices that much quicker to our combat medics.

So I apologize for this short presentation, but I guess, in conclusion, communication is really the key to successful outcome. I think it's key for the vendors to understand they don't need to be afraid to communicate with the FDA. And for the government, I think we have a duty. If we're really going to be good stewards of the taxpayers' dollars, I think we have to communicate, government agency to government agency, a little bit better than what we have in the past, because ultimately, you know, my salary comes from the same pot of money that everyone down at the Food and Drug Administration comes out of. So, if we don't communicate with one another and we spend an extra, you know, 100 man-hours on a review process just because we can't pick up the phone and have a 10- or 15-minute conversation, I think we're being negligent, you know?

So, if there are any questions regarding our interaction and the process here and what we were able to do, you can contact me. My contact

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information is at the bottom of the slide here with my office number and my e-mail.

And, again, I apologize for not being there in person, but I thank you for the opportunity to give you a short overview of what we were able to accomplish with the fielding of the XStat dressing.

(Audio recording ended.)

MR. CRIST: All right. So this is Joshua Crist again. I am a reviewer in DSD. I just wanted to provide a quick overview of the XStat device, to highlight the de novo process and also to reiterate some of the resources that are available to you, if you're thinking about pursuing that.

So as Dr. Krause talked about yesterday, starting in 2012, you can submit a de novo directly without being NSE with the 510(k). And so we do currently have a draft guidance document about the de novo process that explains our current thinking but is also open to comment. So please go check that out, and if you have any comments and feedback, please provide it.

Also, another resource that the previous two presenters highlighted, and that is early communication with the FDA through the Q-Submission process. And I think that's really helpful. So, if it's something you're thinking about, talk to us in a Q-Submission.

So, real quick, just an overview of why we thought that XStat was appropriate for de novo. So XStat comes in -- they are a sponge, a

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cellulose sponge. And so looking at existing regulations, we have these Class III absorbable hemostats for surgery, and we also have hemostatic wound dressings for external use that go through the 510(k) process. So looking at XStat, you know, it's not really an external use device because it's used in these deep wound tracks. There's a variety of small individual pieces that have to be taken back out of the wound, and they expand and they can generate pressure. And also the indications are different than these existing regulations for these devices.

So, because of the differences in technology and indications, we agreed that there isn't really a good predicate for this device, but we think that the benefits and risks of it could be easily enough identified that we could develop the general and special controls to mitigate them. Then we could proceed with the de novo path.

And so the granted de novos have a de novo summary that's published, and if you're thinking of de novo, I would recommend taking a look at some of these, or especially if you're thinking of submitting a 510(k) to show that you're substantially equivalent to one of these. And it has more details than either of our presentations have been showing and are available in this de novo summary that talks about the testing that was done and the risks and the special controls. And I'm just going to quickly go over that at a high level, but go check it out in the de novo summary for more detail.

And as Andrew said, you know, they did pretty standard testing

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that you would expect: biocompatibility, stability, sterility, performance testing on the bench, characterizing the mechanical properties of these sponges really well; absorption capacities, swelling, expansion forces and pressures and several models, and also the mechanical testing of the device that's going to be used in the field; forces to deploy the device and testing in different environments. And also just reiterating, several animal studies and human factor studies were important in the performance testing of this product.

And I just wanted to highlight a couple of examples of risk mitigation. Again, you can go and look at all of their details in the public de novo summary.

So an example of a couple of identified risks would be collateral tissue damage, paralysis, or nerve damage from the expansion or having to do reoperations due to material being retained in the body. And as you can see, there are multiple mitigation methods for these risks. One such would be in vivo performance data. And so you can see there's a special control where it dictates in vivo performance data should evaluate characteristics such as deployment, control of bleeding, radiopacity, and retrieval and assessment of local and systemic effects.

And just another example, a little simpler risk such as adverse tissue and allergic reactions could be mitigated with biocompatibility testing, infection with sterility testing, and stability assessment. And so those are

also examples of special controls that were written. And you would want to or would need to address if you were to submit a 510(k) to try and demonstrate that you are substantially equivalent to a de novo device.

Another thing to highlight is that in the de novo evaluation, we do consider benefit/risk, and we have a non-draft of a published benefit/risk guidance document that you should take a look at if you are considering the de novo pathway. You know, there are many factors we consider in that evaluation, such as the types of benefits, the probability of the patient experiencing multiple benefits, durations of effects; also the severity types, rates of harmful events associated with the device separately and the aggregate effect of such adverse events; and then a variety of additional factors such as uncertainty, for example, as to the result of poor study design, availability of alternative treatments, risk mitigation, postmarket data, whether it's a novel technology addressing unmet medical needs. And, again, that can all be seen in more detail in the benefit/risk guidance document.

And back to the de novo summary. It also contains a good discussion of our benefit/risk evaluation for the XStat device. And I really can't go into much detail on that because there's a decent amount of information. But long story short, we decided that the benefits of this device would definitely -- the probable benefits would outweigh the probable risks for this device. And in addition to the factors such as the benefits and risks, there are factors such as the limitations of the animal study designs, the

clinical expertise required to use the device, and the lack of alternative treatments. And that all went into the benefit/risk evaluation.

So probably the most important slide. So after the de novo is granted, it creates a new regulation to which you can submit a 510(k), and that's listed right here again: non-absorbable, expandable hemostatic sponge for temporary internal use. And so you could submit a 510(k) citing this device as the predicate.

And now I'd like to open it up a few minutes for questions.

DR. SHARMA: So I think this is really a helpful example, but a question for you, Andrew. One of the things we face as the challenge in being a completely funded program is that as questions come up through the Q-Sub process and new studies are brought to bear, funding isn't immediately available, and there is a contracting cycle you have to go through, and so it can take a while to actually be able to generate that data.

Can you talk about your experience with sort of the interface between getting the feedback and having the contracting piece and the funding piece as well?

MR. BAROFSKY: Sure, I can talk a little bit about it. It can be nerve-racking, but the bottom line is, I think that I probably can't emphasize enough that -- and this is, I think, also something that Kyle mentioned, is that communication is key. I think that as soon as you, the device developer, feel you're ready, go and start having that conversation with the FDA and avail

yourself of their pathways for doing that, because the sooner that you engage with them, the sooner you're going to get that early feedback which will allow you to develop your project plan and allow you to stay on budget and on a timeline, et cetera. And so, I mean, that was critical for us. And, again, our timeline in that period was that pre-IDE submission and the feedback that we got from that.

You know, the sooner that you know that yes, this -- you know, the animal study design that you are proposing to do and the feedback from the FDA is that that appears to be the right study to do, then you can set the wheels in motion to go actually do that and find the funding and find the time and the resources and the expertise and the laboratory, et cetera, to do it.

And yeah, you need to -- you know, I think that one of the panelists yesterday mentioned certainty as a key word to discuss, and I think that's what the companies look for, some level of certainty that if I'm going to invest all of this time and resources that I have that are precious, that what I produce at the output of that is going to be acceptable and it's going to actually, you know, support the regulatory petition.

MS. KUMAR: So I have a question for the FDA team. We saw, when the indications for use were shown, that there's a battlefield use only that was included, and I think that was done for a reason, and I think it's a valuable reason to share with the audience. And I think that we've heard here that nobody likes that indication. So I think, from the FDA side, we've

heard that loud and clear, but there was a method to the madness, per se. So maybe I think that might be valuable to share.

DR. KRAUSE: I can talk about that a little bit. I don't want to get into a whole lot of detail and start a debate because I know I've heard the conversations. However, at the time that we were coming up with the indication for use and weighing the benefits and the risks, I think the benefit of battlefield use versus the risk of battlefield use were much clearer and easier for the FDA to agree with than a general use of the device in the general population. And at the time, that seemed to expedite getting it done. You know, certainly, the company could have come back, they could have made more arguments, and I think the company agreed that getting on the market was important and getting the product out there was important, and the path of least resistance at the time was to indicate it for battlefield use and just get it done.

So, again, we've heard everybody's comments, and we think they're important. And, you know, nothing is stagnant. We don't like to sit around in our offices and come up with ways that we can block people from getting really good useful products on the market. So, you know, realize that.

Another thing to realize is the -- I'll kind of make a general comment about the de novo process. Years ago when -- you know, the de novo process is relatively new. So we're talking 1997. Before that, if you were NSE, you were PMA, and Congress realized that that was not a good

thing. So Congress wrote modifications to our law, to where we could do the de novo. But, you know, as Congress is wont to do, laws are not always written that clearly, and implementing things are difficult, and some of the original de novos took years. I mean, we're not talking one year; we're talking many years, three, four, things like that. This product took about a year from the time that the de novo was submitted to the time it was approved -- a year and a quarter -- which is actually pretty good.

And I think the comments that have been made about early contact with the FDA, talking to us, discussing the path forward, providing your plan and letting us comment on it, discussing the type of information, I think all of those things play into it and in the end make the process easier. And, you know, there are various offices in the FDA that can help you and that can be used. In the end, it comes to the division and the division provides you with input. So taking advantage of those other offices at the FDA is a good thing, but in the end, you're going to need to deal with the division. So finding the most direct path to the division where your device is going to be regulated is the best path forward.

So I mean, I think we want to work with you, and hopefully you want to work with us.

MS. KUMAR: Okay. Well, if there aren't any other questions, we're going to go ahead and wrap up this session and move on to actually getting some work done.

DR. KRAUSE: Oh, Allison, could I say one more thing? I just wanted to let -- I mean, a couple of people were very important in getting XStat done. One of them was the lead reviewer, Kelley Burrige, who is now in drugs. So I just wanted to let that be known. Kelley had a lot to do with this. Joni Foy, our Deputy Office Director -- the interactions in the FDA, right at the end, in order to get XStat, the regulation written and everything, was really an excellent job. And I have to say, the division working with the front office, the lead reviewer, and the company, we were able to accomplish in a couple of weeks an amazing amount of work, writing the regulation, the benefit/risk document, which Dr. Ashar had a lot to do with, and the team really worked together very well.

And I think that's important to know, is once we have all the information we need and we feel comfortable with what we're doing, things can move pretty fast. And the company was very helpful, Kyle was very helpful, all the people at the FDA, and the process really streamlined for those last couple of weeks to get it done. So, you know, I think once we get to that point where we have all of the information, we can really push it forward.

Thanks.

MS. KUMAR: Okay, thank you.

(Applause.)

MS. KUMAR: All right. For this next session, I'm going to come in the middle

of the room. So we have put together two questions which we think are still outstanding as far as what FDA has heard and what we had wanted to have answered at the conclusion of this workshop in order to begin the next round of discussions.

So what we're going to do now is break up the room. So I'm going to go ahead and do that now, and what I would like you to do in your smaller groups is just pull your chairs together and try to answer these questions, and I'm going to give you about 10 minutes or so to do that. If you could designate one person within your group to take notes from the group -- and that person will also be your spokesperson because, at the end of the 10 minutes, I'm going to ask that person to come and represent your conversation and provide us with a brief answer to this question. What we're going to do is we'll have someone recording each answer from the different groups.

And we want to see where the conversations have overlap, where there is consensus that is built, where there are differing opinions, and then let's have a broad group discussion and talk about these differences or the consensus that has been reached so that we can, you know, jump off that point and continue to move this ball forward.

Okay. So let's have these three rows get together.

(Off microphone discussion.)

MS. KUMAR: And then just all you guys. Maybe so. A little bit

of movement, and I'll give you maybe a minute or two to rearrange yourselves, and I'm going to set the timer for about 10 minutes.

The first question is -- so we've discussed ethical -- well, I'll let everyone get arranged and then we'll do the question.

(Pause.)

MS. KUMAR: Okay, here we go. The first question gets back to where do we start? So there was a lot of discussion yesterday about the logistical constraints around collecting clinical data, the ethical considerations for collecting clinical data, regardless of when it's collected, but getting that data, human data on the first experiences that we can for some of these novel devices, whether they're exovascular or endovascular. However, I think we've heard a lot about the exovascular, that there's the 95% solution. I think what we'd like to hear about is the endovascular solution.

So, if we could, I would make a request, and if it's okay with Dr. Ashar, to focus on those particular devices. Where is she? Not here, okay. No head nod.

So considering all of these constraints -- we've heard about those -- using your expertise, your research experience, your physician's background knowledge, what group of patients should we start with? So what does the patient population look like, the environment, and what are the pros and cons of performing testing within this group? And if any of my FDA colleagues would like to expand on that question.

UNIDENTIFIED SPEAKER: Endovascular is definitely a special group, but what about intracavitary exovascular? That's another new area that might be worth discussing.

MS. KUMAR: Okay, that included. Okay. Ready, set, go.

(Whereupon, the first breakout session was held.)

MS. KUMAR: Okay, time's up. Who wants to go first? You guys are all sitting here quietly. I'm going to let you go first. Everyone else seems very still stuck in discussions. Okay. So we're going to have the first group give a brief overview of what they discussed. We're going to capture notes so that we can have it for the remainder of the discussions.

Who is your spokesperson?

DR. BENNETT: I'm Dr. Brad Bennett, retired Navy captain. I served on Tactical Combat Casualty Care with John and others in this room for over 12 years. I am an end user of the products, a lot of the external products, both as an end user, as a researcher, and as a live tissue instructor.

And I started off with my group, and I said, let's not exclude this little 95% figure that's been thrown out the last day and a half. I have been a major advocate against going from a safe laboratory, whether it's the Army or Navy or other academic laboratory that does hemostatic agents, and you go from that experienced surgeon's hands and then it's given to the conventional medic or corpsman, which are the majority, that has zero or very limited clinical experience and the first time they ever see trauma may

be on his staff sergeant, who now has multiple fragmentation injury. And let's just use a junctional injury. He may or may not have any live tissue experience, so he may have not have used that new gauze.

And so we are making a major transition. There are a few academic centers that like to do those intermediary steps. I would like to see the FDA looking for those intermediary steps before we make this major transition, that the efficacy in the laboratory is going to have the same effectiveness by a young conventional medic.

The intracavitary and endovascular. We think that the FDA, the vendor, and academic clinical trial centers need to come together and start discussing, looking for that efficacy data, animal based, what has potential for multicenter clinical trials, and to get that first Level 1 trauma patient with these two different categories, the intracavitary and endovascular. And that kind of discussion needs to start very early.

That's kind of our discussion points.

MS. KUMAR: Okay, I'm going to go counterclockwise. You guys are up. Who is your spokesperson?

MR. RUSSO: Well, I am a non-physician --

MS. KUMAR: And I need --

MR. RUSSO: I'm Richard Russo with a medical device firm -- here we go -- and we made a decision to see if we could use the 50.24 approach and said that this is really difficult to generalize about because the

patients and the wounds are so variable and the product types would be so variable or difficult to compare that a single approach is probably not going to be possible.

But we looked at patients in extremis, particularly in large vascular wounds, and we thought that patients could be studied without informed consent, on a limited basis, to test feasibility in the resuscitation room. The benefit to the patient would be to try to buy time for the standard of care and to lower morbidity by lowering the blood loss. The benefits would be that if we did it in the controlled setting, we would be able to develop data that would be sufficient to see if this approach was feasible and would merit additional study. We thought that it should be carefully documented, maybe by video, and that it would obviously need protocol metrics and community involvement.

And there was some discussion about also having this type of study done OUS maybe, but the same ethical issues and the same documentation issues exist, though outside the United States, the patient population would not have availability of the same standard of care that they might in the United States, so therefore there would be less of an ethical issue.

There was some concern raised by our attorney here, who --  
(Laughter.)

MR. RUSSO: No, he was thinking ethically, and that was a joke.

He was thinking ethically, and he said, "We have to make sure that we're not denying anybody what could be an effective standard of care." So it has to be carefully constructed.

MS. KUMAR: Thank you.

Okay, Group 3, I'm going to need somebody to travel. If you could give your name.

MR. WOJCIK: Hi, my name is Jerzy Wojcik. I'm part of industry.

Our group had quite a bit of discussion, first, to talk about -- I guess, from a logistics perspective, we were discussing that it was very important to really understand what your intended use is for the product, and based on that, you would take a look at what kind of intentions do you want for your product to perform in this particular situation. From there you define what kind of models would be appropriate from a clinical trial perspective and then based on that, again, clinical relevancy of each model.

From determining what kind of patient we would want to include, we basically said any patient, and the reason for that being that in this type of situation, you're really looking for feasibility, and from that perspective, if any patient is included, you can lower the number of variables from the clinical setting, what you're looking for, and really take a look at just the performance criteria that you want for feasibility to be successful.

And then also we had definitely agreed upon a controlled operating room setting. And following on, I think both groups mentioned

that this is a very controlled environment. So, again, collection of data from that perspective would help feasibility again.

MS. KUMAR: All right, thank you.

The next group.

MR. DAVIS: Hi. Dan Davis, also from industry. This is going to be short and sweet.

We were under the assumption that this is for traumatic injuries, primarily looking at high-risk patients that may not otherwise survive, and really kind of took a similar approach to what was done for XStat and a little bit beyond that, looking at potentially postmarketing opportunities, postmarketing studies, in patient populations that would primarily start with soldiers on the battlefield and then the indication could be expanded through a future 510(k) for the general population.

MS. KUMAR: Okay, the next group.

DR. SHARMA: And I was just getting to consensus. We didn't quite get all the way to consensus, so we had a lot of discussion. I think there were two patient -- we were trying to be more specific about the patient groups, and there were two groups that were specifically discussed. Well, actually three groups. We talked about the ED, starting in the ED. We talked about the military and starting with the military. And then we also had a lot of discussion about are there elective procedures in which we could try the device out first, and what the ethical implications of that would be for the

patients in those procedures. And so we came up with a lot of options but didn't really get to consensus. Those are the three. Yeah.

DR. KING: I think the question is wrong.

MS. KUMAR: Okay. Well, rephrase.

DR. KING: No, I think you're asking -- you may be asking the wrong question.

MS. KUMAR: Rephrase. What do you think?

DR. KING: Yeah, the question implies that everything needs some kind of human testing, and I think the first question you have to ask is does it need human testing?

MS. KUMAR: Sure.

DR. KING: Maybe you could define what testing means.

MS. KUMAR: Um-hum.

DR. KING: Meaning, is it an efficacy signal, is it a safety signal, is it a feasibility signal? You have to define what you mean by --

MS. KUMAR: Okay, thank you.

DR. HOLCOMB: So we had no consensus.

(Laughter.)

DR. HOLCOMB: Everybody's shaking their heads up and down. So we talked a little bit about human factors, extensive training, truncal hemorrhage. And we didn't really talk about this, but one of the things that is true about truncal hemorrhage, when you're talking about indications, when

you're looking at a patient who is bleeding to death, you've identified they need a laparotomy. You don't know what is injured. You don't know if it's iliac artery or spleen or liver or what have you. You don't know. You're going to go to the OR, you're going to open them up and fix it. So getting closer down from an indication of them bleeding in the abdomen is impossible for these devices.

We, as a group, kind of split on this early feasibility study, which requires an IDE, 50.24 consent mechanism, resulting timeline, for a sum total of five patients. Five patients is not going to really give you safety or efficacy. It's going to give you hints of how the thing works.

On the other side of the equation is a postmarketing approval with very rigid controls: five centers, 40 patients, registries, websites, reporting, discussion back and forth with the FDA, trying to get the FDA to have control in postmarketing, but with a large enough sample to really get some hints again of efficacy and safety, merging timelines and public need and risk and benefit. And I would just say that our group, in the time provided, could not come to consensus on those two options, both of them having benefits and --

DR. KHEIRABADI: The third option would be a combination of the two.

DR. HOLCOMB: Even less consensus.

(Laughter.)

DR. HOLCOMB: Not disagreed, but obviously -- so those are two extremes, I think, what Bijan is saying. And we actually said yesterday several times that the final solution is going to be someplace in the middle of those things, balancing the benefits of one approach and the risk of one approach with the benefits and risks to the others. You know, in an ethical fashion, risk and benefit, risk and benefit, you keep coming back to risk and benefit. And when people talk about safety and efficacy in this population with 5 patients or 40 patients, you know, that's a difficult thing to translate into reproducible results. It's a tough problem you gave us.

MS. KUMAR: Well, we gave it to you because it's a tough problem for us.

Okay. So does anybody have any comments about what came out of this? It sounds, I think, your last comment really was reflective of everyone. It's a really hard question to answer, so maybe it wasn't completely fair to ask. But I guess, from my viewpoint, for products that would require testing -- and, first, that would need to be established and made clear, you know, whether that happens in a premarket setting or a postmarket setting. It sounded like, from yesterday, there was some sort of evidence that people would like to see on use. You know, it was loudly echoed postmarket, but I'm not sure that's the point of this conversation. So that's, I think, what we were trying to get at with -- you know, the evidence of performance, I suppose, was what we were trying to get at.

So there were a lot of different -- some similarities with the 50.24s and the postmarket studies and elective procedures versus military versus emergency department. I think those were all echoing the conversations that were held yesterday.

Heather, did you have a comment?

MS. PIDCOKE: Yeah. I'm not sure anybody's advocating doing -- you know, trying to push everything on postmarket studies. It's just that doing everything in the premarket study is time consuming and expensive and a real barrier. And so maybe some of that can be shifted, some of that burden can be shifted to postmarket. I don't know if other people agree with that or not.

MS. KUMAR: Thank you.

DR. BENNETT: I just want to follow up with the postmarketing data. There's a dearth of literature published in peer review journals on the external devices, all except for one, thanks to John Craig, who I call the father of modern tourniquets. And his colleagues have done tremendous studies on retrospective and prospective studies on tourniquets, externally applied extremity tourniquets. But when you look at the hemostatic agents and dressings, they're limited to a few case studies. They just don't even compare, nevertheless, with the junctional devices, the external pelvic slings that have been around for a while now, with SAM Medical having a dual application of uni- and bilateral junctional as well as a pelvic sling. So we

really need to continue the focus on that postmarketing peer-reviewed data, in the image of John Craig and others from the ISR.

DR. KHEIRABADI: I think categorizing all hemostatic having the same kind of safety probably is incorrect. If you're looking at a basic dressing that is going to be put on external wound, it's not an issue, it's not going to be a huge safety issue, it's not going to kill a patient. On the other hand, if you have a product that you're pushing internally into the abdominal cavity, that is a highly risky procedure. So that maybe really requires to be much more intensely checked before it's being marketed versus a simple dressing that is put on external wound.

So I agree with what Dr. King said. It really depends on what are we trying to push through? What is going to be tested? And each product may have to be tested different. Some may need pre-approval testing to make sure it's safe in a few patients before it's put out, and then they'll put postmarket testing and some may not. You could put it out and just follow it and see what happens.

DR. KING: Yeah, Bijan, that's the point I was trying to make about the first question that we should ask is, does it need human testing? So was there human testing before the first CAT tourniquets were put in theater, right, premarket testing, randomized trial of exsanguinating wound injuries with or without the CAT tourniquet? Of course not, because the risk/benefit profile for that was so favorable that it's absurd to propose it.

And so I think, for any device -- or any intervention, for that matter -- the risk/benefit to the specific population will be what dictates how you have your initial first-in-human experience. When you have an intervention that's very high risk with moderate benefit, that might -- you might want to generate a little more data before you start intervening widely, than if you had an intervention like a CAT tourniquet or an external bandage that, based on the animal literature, you suspect has extremely low risk and moderate or even significant benefit.

So I don't think you can just put, you know, a lot of different shaped widgets and not all the holes are the same size. You need the triangle in a triangle hole and a square in the square hole and so on.

MS. KUMAR: Thank you. And I agree, I think we have existing paradigms for a lot of the tourniquets and a lot of the exovascular 95% solutions. And, you know, it's really been novel technologies that I think is one of the main drivers for why we're all here today and some of the answers that we're trying to get at.

Okay. Well, in the interest of time, because I don't want to keep you all from lunch and getting it at 1:00 p.m., we're going to move on to the next question. And just to give everyone an idea of where we're going with collecting all of these answers is we would like to provide a follow-up to the meeting in a written format and to embellish on the white paper that we put out for the discussion points prior to the workshop. We'd like to have a

way to round that out with comments from all of the stakeholders of the groups. So this is really one way to get at that.

So moving on to the second question. Within your same groups and 10 minutes of time, one of the issues that we have brought up in the *FR* notice and in the discussion paper was really getting at a bleeding scale and the definitions around bleeding severity. There were some questions brought up about that yesterday, but that is something that we've also struggled with. What is a mild -- you know, an indication or a submission --

(Laughter.)

MS. KUMAR: -- to address mild, moderate, or severe bleeding. We need to know what that means. Yes.

UNIDENTIFIED SPEAKER: Is this internal or external? So are the medics going to see this or is it hidden inside the truncal?

MS. KUMAR: I need someone from the branch or division to address that question.

UNIDENTIFIED SPEAKER: And the reason I ask is we've trained a lot of -- we've trained medics on tourniquets and some of these external devices. If it's bone wraps, you put gauze on. If it's spurting, you put a tourniquet on. So, if you can see it, it makes a big difference -- it's a big difference if we're talking --

MS. KUMAR: So Carolyn or Josh, do you --

UNIDENTIFIED SPEAKER: I prefer to talk about truncal.

(Laughter.)

UNIDENTIFIED SPEAKER: I don't want to put words in your mouth, but -- because that's much more difficult and that's why we're here, is truncal --

MS. KUMAR: Okay, I'm cool with that suggestion. Anybody else?

UNIDENTIFIED SPEAKER: I would say this is visible bleeding, either visible operative bleeding or visible bleeding on the surface of the trunk extremities, et cetera.

UNIDENTIFIED SPEAKER: No, it can't be extracavitary. Nobody needs help there.

(Simultaneous comments.)

MS. KUMAR: Okay.

(Off microphone comment.)

MS. KUMAR: Okay. So I would like you all, in your groups, to have these discussions and then --

(Laughter.)

MS. KUMAR: -- bring forward and we'll see -- you know, I think that's where we'll see some of the consensus come out. If you want to tackle bleeding within certain areas, that's obviously what is most important to the conversation, and maybe we'll all have the same conversations within your

group. Ten minutes.

(Whereupon, the second breakout session was held.)

MS. KUMAR: Okay, let's hear what you guys had to say. Who wants to talk this time?

DR. BENNETT: Brad Bennett again.

I didn't want to deviate between external and internal too much, only because the retrospective studies and the case reports that have been done by Craig et al. show that a lot of our patients in the battlefield who get tourniquets get thrown on because, you know, they train up, they get very good at it. They see a distraction injury unlike they've ever seen in their life and they throw it on. Many of them get removed once they get into the triage centers and because it's a venous-type blood. So we have lots of that.

So, in our training, we really distinguish arterial, and most of it is not spurting because that's an exposed artery. It's going to be a running type where you sweep the skin and does it well up and swell and run off quickly? We try to distinguish that as severe versus mild venous oozing that may only need a dressing or a light pressure dressing. And so I really wanted to emphasize, in our group, that we still get a lot of tourniquets, external devices, put on for something that's not severe arterial.

We're going to just pass the truncal one because that's very difficult. There are multiple indicators of internal bleeding. A lot of them are very hard to detect, as we heard from Dr. Alcorta early on, our EMS state

director here in Maryland, talk about the challenge they have on a daily basis. Is this a surgical patient or not? And there's no easy one answer for that. I'll let Dr. Holcomb and others tussle with that one.

MS. KUMAR: Thank you.

Next group.

UNIDENTIFIED SPEAKER: We'll have to say that we had a lot of --

MS. KUMAR: You've got to talk into the microphone.

UNIDENTIFIED SPEAKER: -- anti-consensus steps.

MR. RUSSO: Well, what we did say was that there was a concern that if we just made a decision to test people, to offer innovative devices to people without a clear indication for use, that people might get -- be exposed to risks that were unnecessary. But the medical opinion was that the best way of identifying internal bleeding that needed to be treated surgically with a device such as the ones we've discussed was hypotension. That's limited by the fact that hypotension is not exclusive or specific to bleeding, but that's where I think we ended up. Did I miss something? With many caveats.

MS. KUMAR: Do you want to share a few caveats?

UNIDENTIFIED SPEAKER: The caveats to that were mainly other potential causes of hypotension, and for internal bleeding, the inability to specifically know that it's due to bleeding. And I think Heather definitely has

more to say.

(Laughter.)

MS. PIDCOKE: Just echoing what the last group found, that prehospital setting is such a difficult environment to make this judgment call about truncal bleeding. I think that that's why there's been a focus on, you know, starting these things in the hospitals, because we really don't have a good way of differentiating patients. And there are so many causes of hypotension in the field that, you know, this is very different from a biologic study where giving a unit of plasma to somebody who might not need it is not ideal, but it's not going to commit them to a trip to the operating room.

MS. KUMAR: Thank you.

Okay, Group 3.

MR. RAGO: Hi. Adam Rago speaking for team back corner.

We talked about both surface bleeding and -- you know, bleeding that you can see and external -- sorry -- internal bleeding. I think the point that we'll add on external bleeding is that we agree that it should be assessed and based on a system that is relevant to, kind of, people from all walks of life and is intuitive to people with different perspectives. So a medic and a surgeon should be able to look at something and get the same score.

We then kind of transitioned our discussion to internal bleeding; a lot of good points made in the short period of time. I think, to summarize, we talked about bleeding scores, we talked about ABC score in

some level of detail. For those that don't know ABC score, it looks at penetrating mechanism, systolic blood pressure, heart rate, and positive FAST exam as a predictor of massive transfusion, scores like this easily applied, you know, straightforward and not complex, that we think would add value.

I think with regard to what the right score system is, there is some work that can be done in looking at the data and looking at registries. But with regard to that, I want to echo two important points that were made yesterday. The first is that there's not a lot of time dependence in those registries, which is important for understanding bleeding. And the second is that they're infrequently linked up with outcomes, what was done and what happened. Until those two things happen, I think a really definitive evidence-based score is still going to be somewhat elusive.

Thanks.

MS. KUMAR: Thank you.

Next team.

UNIDENTIFIED SPEAKER: So we pretty much started with what we saw the utility of the bleeding scale as, and one is in a clinical trial setting. If you can actually figure out how to put a clinical trial together for some of these devices for stratification purposes, that would be helpful. And in the clinic, essentially, what's your indication for your device? If the bleeding is severe, you know whether you can or cannot use the device.

However, the problem was that most of the discussion we were

having, the clinicians, surgeons, medics, whomever, they determine whether to use a device, not necessarily on a bleeding scale, but more based on experience. So it's more of the I know it when I see it and how you would translate a bleeding scale into the clinical environment. None of us really truly knew how to do that. And I think that pretty much sums up where we got stagnated a little bit.

MS. KUMAR: Thank you.

DR. KING: So the answer for extracavitary hemorrhage is easy and I'll give you the -- and I don't think you need a scoring system, and the reason you don't is because if you wait for your score to register as high or severe at the point of injury, you've already lost three-quarters of your blood volume. So you'd likely want to intervene before the score is bad, and you'll know that because the blood will squirt you in the eye. And when the blood is squirting you in the eye, you should intervene regardless of what the score is.

The example I'll give for this is in Boston. In Boston, there were 66 limb injuries, almost all of them with bad bleeding, and almost all of them had tourniquets put on, over half of those by non-medical providers. Why? Because they knew it when they saw it. They knew what severe bleeding looks like. They're not medical people. But it's like porn; you know it when you see it.

(Laughter.)

DR. KING: So I'm not sure you need a scoring system for severe extracavitary hemorrhage. Now, what do you do for mild and moderate? Much more problematic. But arguably maybe we don't -- if you're looking for interventions for severe or life-threatening bleeding, then you only need to positively identify severe or life threatening and maybe not worry about the mild parts of the scale. That same principle can be applied to -- although much more complicated -- intracavitary hemorrhage.

So I would argue, the real solution is some kind of multi-signal based automated integration of a lot of data streams, right, to try to predict who has internal bleeding. So that's fantasy land. Lots of folks working on that. It's not going to happen today or tomorrow, so you're stuck back in the Stone Age, right? You're stuck with clinical gestalt, which is based on -- that gestalt is based on a bunch of routinely available or sometimes not available vital signs, and that gestalt is based on experience, and the experience of the practitioner is wide and varied, right? So the green medic perhaps cannot identify somebody with moderate or moderate to severe bleeding. The very experienced medic or surgeon can probably very successfully identify the guy with moderate to moderately severe bleeding. But what they can both identify are the patients with life-threatening hemorrhage.

And that construct has to exist with a couple of caveats. One is the absence of another cause for the hypotension. So when a leg is blown off and it's gushing, you would not propose that that patient first has internal

life-threatening bleeding as the cause of their hypotension. Now, they may have both, but it's probably inappropriate to assume it's one and not the other. And so we're stuck back with using the same screening tools that you used for your clinical gestalt, which is going to end up being standard vital signs and how poorly they look.

And I would argue the same for extracavitary hemorrhage. We're pretty good at identifying guys who are about to die, because their blood pressure is undetectable or extremely low, and at the high end of the scale you probably don't care, right, because you're not going to intervene for life-threatening bleeding when the blood pressure is 90 because maybe that will progress later on to a blood pressure of 50. But at the point of 90, you don't know and the uncertainty is too much to propose an intervention, I think.

So I would say we don't care about the high end of the scale -- high-low. We don't care about the mild and moderate end of the scale. We just care about identifying guys who are about to die, and I think, based on our existing data streams, we're pretty good at that.

MS. KUMAR: Thank you.

Last up.

DR. HOLCOMB: So we had consensus this time. We dispensed with external bleeding for the reasons that already have been articulated.

We thought that the scale of mild, moderate, and severe -- we

translate it into Class 1, 2, 3, and 4 shock. Class 1, 2, 3, and 4 shock uses normal accepted vital signs, mental status, et cetera. It's taught worldwide. It's in ATLS. It's in every trauma book, emergency medicine book. It's not perfect, but it's what is out there.

Much like David said, mild we would classify as 1 and 2. Who cares, really? They're going to do pretty good. They might turn bad later, but for the most part, those patients do fine. Class 4 shock, everybody recognizes it. That's the guy with a hole in his abdomen with a pressure of 50, and that person needs all of these interventions because they have a 50% mortality in the best of places, at Level 1 centers. What's interesting is the Class 3 shock.

So Class 3 shock. So I'm on call Saturday. If a guy comes in in Class 3 shock, I'm not sure I would use these products. If a Class 4 shock patient came in, I would instantly, with no hesitation, even though I can be in the operating room in 10 minutes, from the ED to the OR. We showed the paper the other day that showed each additional minute increases mortality in these kind of patients. So, if I can tamponade bleeding, stop bleeding, even for those 10 minutes it takes me to go from the ER to the OR, I should help my patient in Class 4 shock.

Class 3 shock. So, if a guy comes in in Class 3 shock and I'm in the ED and we go to the OR in 10 minutes, I wouldn't put it in. But if I'm in the operating room and my fellow is in the next one and my resident is in the next one, which happens pretty routinely, then I might tell the ER guy to put

it in because I can't get to the OR for an hour in those cases.

If the patient is at a Level 2, 3, or 4 or non-trauma center, which are the vast majority of the hospitals in the United States -- 4,800 hospitals would fall in that category -- and they're in Class 3 shock, I would have them put it in, because it's going to be an hour to get from one hospital to the next even in an urban center. And it's going to be another 10 or 15 minutes to get to the operating room.

So Class 3 shock, to me, means kind of triage of people, time, that Bijan talked about, and personnel for Class 3. Class 4 goes in immediately. Class 3 you triage. What's your situation? How far away are you -- using an accepted score. The scores that are out there right now that we use routinely, the ABC score uses heart rate, vasc exam, blood pressure, and penetrating truncal mechanism. We used it in our prospective randomized study to enroll. It's pretty effective. We use it routinely in our center. Our medics use the ABC score. If you want a score on the helicopter, they do ultrasound in the helicopter and then everything else is easily done.

Tactical Combat Casualty Care that Brad and I have been involved with for over a decade also uses a score, if you will, and it's weak or absent radio pulse. It's been used on the battlefield for a long time. There's published data on this. If you come in as a trauma patient and you've got an absent pulse, I'm taking you to the operating room because you are really hurting in a world of hurt. If your pulse is weak as well, with the right

mechanism, then I'm really worried about you. I teach my residents that every day.

So there are scores out there that are published in TC3, that are published in the literature with ABC, and then Class 1, 2, 3, and 4 shock. I think this is doable, actually. It won't be perfect, as David said, until we get some crazy thing that integrates big data with molecular status, you know, that we all want and we all have research projects trying to do it right now because it's really cool, but it's not available yet.

MS. KUMAR: Thank you.

Final comments?

DR. ASHAR: Yeah. You know, I just wanted to thank all of you for deliberating over these very -- I guess I heard the first one was a difficult question and the second one was confusing. And so welcome to our world here at FDA.

(Laughter.)

DR. ASHAR: And I think you've given us great advice. We are going to have a transcript where we're going to be considering all of this and figuring out, you know, actually how to best advise you. But these are the types of questions that we face all the time. And it's not just that we want to develop a scoring system that's validated for use out in the clinic. That's not necessarily the case. But we want to at least have something where we parse out what patients we're studying during that phase that we're studying

patients, so that way our words, in a clinical trial, of how we define these patients can be translated into the labeling to inform users. Because if we, as a community, don't understand who we're studying and what we're talking about for a device, how can we expect the end user to do so?

So thank you for your thoughtful deliberation. I think that the firepower in this room is enormous, so we'll take all of your words of wisdom and try to integrate that.

MS. KUMAR: Okay. Well, I think that was all the torture we were going to make you guys go through this morning, and now we're into the afternoon and I know it's late. So thank you, everyone, for attending. I hope that you are as pleased with the investment and time that you put into it as I think the FDA team is. And it's been a tremendous day and a half, and we've enjoyed the conversations that have been held, and thank you for participating.

(Applause.)

MS. KUMAR: We are going to try to have the presentations available on the workshop's website. So, if you were a presenter and do not want your presentation shared, please e-mail me directly. Some of you already have let me know. The webcast is also recorded, and that will also be available on the public website.

So thank you.

(Whereupon, at 12:54 p.m., the workshop was adjourned.)

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

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